แอลฟาโบรมิเนชันของคีโทนโดยใช้เฮกซะโบรโมแอซีโทน

นางสาวทิพากร แสงระวี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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α-BROMINATION OF KETONES USING HEXABROMOACETONE

Miss Tipakorn Sangrawee

A Thesis Submitted in Partial Fulfillment of the Requirements

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ทิพากร แสงระวี : แอลฟาโบรมิเนชันของคีโทนโดยใช้เฮกซะโบรโมแอซีโทน (α-BROMINATION OF KETONES USING HEXABROMOACETONE) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ดร.วรินทร ชวศิริ, หน้า.

ได้พบวิธีการสังเคราะห์ใหม่สำหรับแอลฟาโบรโมคีโทนภายใต้ภาวะที่ไม่รุนแรงภายในระยะเวลาสั้น โดยใช้เฮกซะโบรโมแอซีโทน (เอชบีเอ) ใช้โพรพิโอฟีโนนเป็นสารต้นแบบ ได้ศึกษาปัจจัยหลายอย่าง เช่น โบรมิเนทิงเอเจนต์ เวลา การใช้ยูวี ตัวทำละลายและอัตราส่วนโดยโมลระหว่างโพรพิโอฟีโนนกับเอชบีเอ โดยใช้โพรพิโอฟีโนนกับเอชบีเอ 1:1 โดยโมล ในเททระไฮโดรฟูราน ภายใต้ยูวี 5 นาที พบว่าได้ผลิตภัณฑ์ 2-โบรโมโพรพิโอฟีโนนเพียงตัวเดียวในปริมาณสูง ได้นำภาวะที่พัฒนามาใช้กับคีโทนอื่น ๆ เช่น แอซีโทฟีโนน 2-ไฮดรอกซีแอซีโทฟีโนน 4-ไฮดรอกซีแอซีโทฟีโนน 4-เมทอกซีแอซีโทฟีโนน แอลฟาเททราโลน ไซโคลเฮกซาโนน และ 2-เฮกซะโนน ได้ผลิตภัณฑ์ปานกลางถึงสูง นอกจากนี้ปฏิกิริยาแอลฟาโบรมิเนชันของคีโทนบางกลุ่มกับเอชบีเอสามารถเกิดได้โดยทำปฏิกิริยาที่อุณหภูมิรีฟลักซ์เททระไฮโดรฟูรานแทนการฉายรังสียูวี นอกจากนี้ประสบความสำเร็จในความพยายามขยายส่วนปฏิกิริยาแอลฟาโบรมิเนชันของโพรพิโอฟีโนน ได้ 2- โบรโมโพรพิโอฟีโนน

สาขาวิชา ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์ ลายมือชื่อนิสิต .....

ปีการศึกษา 2557 ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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TIPAKORN SANGRAWEE: α-BROMINATION OF KETONES USING HEXABROMOACETONE. ADVISOR: ASST. PROF. WARINTHORN CHAVASIRI, Ph.D., pp.

The new synthetic method for α-bromoketones under mild conditions with short reaction time using hexabromoacetone (HBA) is disclosed. Propiophenone was used as a model substrate. Various factors including types of brominating agent, reaction time with UV-irradiation, solvents and molar ratio of propiophenone: HBA were scrutinized. The optimum conditions as the ratio of substrate to HBA (1:1) in THF at RT for 5 min under UV (254 nm) was uncovered. 2-Bromopropiophenone was obtained as a sole product in almost quantitative yield. The developed protocol could be successfully utilized for other selected ketones, such as acetophenone, 2-hydroxyacetophenone, 4-hydroxyacetophenone, 4-methoxyaceto-phenone, α-tetralone, cyclohexanone and 2-hexanone with moderate to high yield. Furthermore, α-bromination of certain ketones with HBA could be conducted in refluxing THF instead of using UV-irradiation. The scale-up of α-bromination of propiophenone into 2-bromopropiophenone was also attempted with success.

Field of Study: Petrochemistry and Polymer Science Student's Signature .....

Advisor's Signature .....

Academic Year: 2014

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LIST OF ABBREVIATIONS

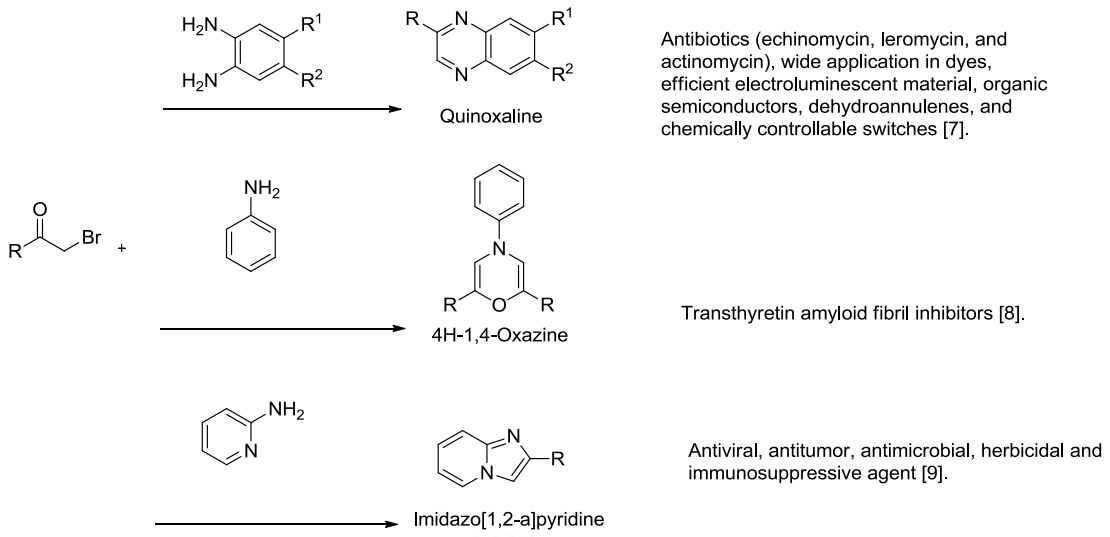
Ar-H	Aromatic proton (s)
DCE	dichloroethane
g	gram (s)
GC	gas chromatography
h	hour (s)
HBA	hexabromoacetone
Hz	hertz
J	coupling constant
MB	mass balance
min	minute (s)
mL	milliliter (s)
mmol	millimole (s)
µL	microliter (s)
NBS	*N*-bromosuccinimaide
NMR	nuclear magnetic resonance
ppm	part per million

q	quartet (NMR)
R_t	retention time (min)
RT	room temperature
s	singlet (NMR)
TBME	*tert*-butyl methyl ether
THF	tetrahydrofuran
TLC	thin layer chromatography
t	triplet (NMR)
UV	ultraviolet
W	watt
%	percent
α	alpha
δ	chemical shift

CHAPTER I
INTRODUCTION

Halogenated organic compounds play a very important role in chemistry, they are essential in organic synthesis as starting compounds and synthetic intermediates, as designer molecules for material science, industrial chemicals and bioactive compound [1, 2].

α-Bromination of ketones is one of important transformations in organic synthesis [3]. **α**-Bromoketones are useful synthetic intermediates and their high reactivity makes them prone to react with large number of nucleophiles to provide a variety of biologically active or value-added compounds [4]. Selected instances for the synthesis of biologically active compounds from **α**-bromoketones are given in Scheme 1.1. In addition, **α**-bromoacetophenone derivatives have been investigated for their active participation in the inhibition of protein tyrosine phosphatase such as SHP-1 and PTP1B [5]. In the preparation of Naproxen (a nonsteroidal anti-inflammatory agent), **α**-bromination of alkyl aryl ketone is an important step in the 1,2-migration of the aryl group to get the product in very good yield [6].



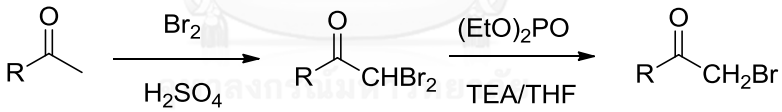
Scheme 1.1 Selected examples for the synthesis of biologically active compounds from **α**-bromoketones [7-9].

Previously, **α**-brominated carbonyl compounds could be prepared by using Br_2 in a protic solvent in the presence of Lewis acid [10]. Nonetheless, Br_2 is very highly toxic reagents, handle and hazardous and cumbersome for chemical reaction. Recently, various methods have been reported using $CuBr_2$ [11, 12], NBS–NH_4OAc [13], NBS-photochemical [14], NBS–silica supported $NaHSO_4$ [15], NBS–ionic liquids [16], and NBS–PTSA [17]. However, the disadvantages of those procedures are in some cases the substrates or products being intolerance to acid, requiring high temperature and forming undesired by-product(s).

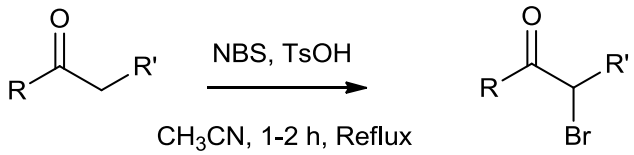
1.1 Literature Reviews on α-Bromination for Ketones

The development of new methods for α-bromination for ketones can be summarized below.

In 1998, Diwu and co-workers [12] reported the bromination of 4′-dimethylaminoacetophenone using different procedures such as Br_2 in HOAc, dioxane dibromide, $CuBr_2$ and NBS in CCl_4 furnishing the desired product in 9-96% yield. Selective dibromination of arylmethylketones with Br_2 in H_2SO_4 could be achieved in 96-100% yield and selective debromination of the resulting 2,2-dibromomethylarylketones with diethyl phosphite in the presence of triethylamine (TEA) in THF giving target product in 92-96%.

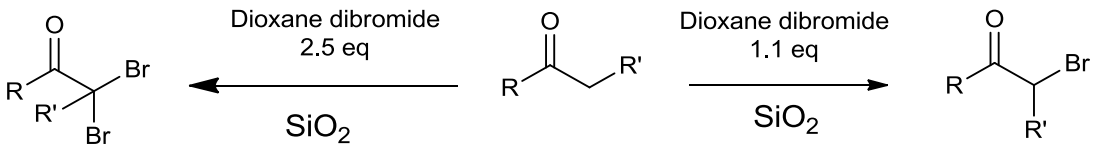


In 2002, Lee and co-workers [18] addressed the synthesis of bromoketones using a combination of NBS and TsOH in CH_3CN for 1-2 h at reflux temperature yielding the target products in 72-96%. In 2004, Lee and co-workers [19] studied α-bromination of carbonyl compounds using [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB) and followed by MgX_2 (X = Cl, Br, I) under solvent-free microwave irradiation for 4 min giving 61-94% yield of desired product.



In 2003, Tillu and co-workers [20] reported the bromination of active methylene compounds with a mixture of hydrogen peroxide (H_2O_2) or *tert*-butylhydroperoxide (TBHP) and HBr in 1,4-dioxane. Substituted acetophenones, benzocyclic ketones provided **α**-bromo-keto compounds in high yield (72-95% isolated yields).

In 2003, Paul and co-workers [21] reported the synthesis of **α**-bromoalkanones/ cycloalkanones and dibromoalkanones using dioxane–dibromide and silica gel under solvent-free conditions and microwave irradiation for 1-13 min in 72-95% isolated yield.



In the same year, Paul and co-workers [22] synthesized **α**-bromoalkanones by the reaction of alkanones with hexamethylenetetramine-bromine complex (HMTAB)

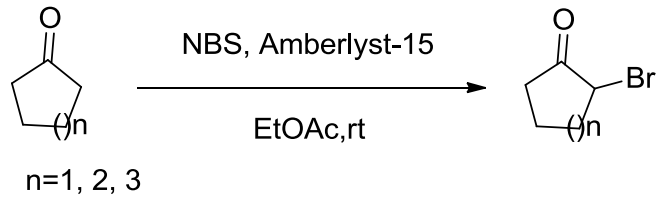
and basic alumina under solvent-free conditions for 5-10 min yielding the target products in 70-83% under microwave irradiation.

In 2004, Tanemura and co-workers [13] examined the bromination of various cyclic ketones using NBS catalyzed by NH_4OAc in Et_2O at 25°C to give the corresponding α-brominated ketones in good yield (81-99%), while acyclic ketones were efficiently brominated in CCl_4 at 80°C (10-81%).

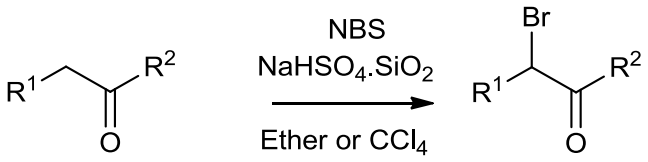
In 2005, Kavala and co-workers [23] reported the bromination of cyclohexanone and acetophenone with 1,2-dipyridiniumdibromide-ethane (DPTBE) under solvent free condition for 1 h furnishing 80 and 85% isolated yield, respectively.

In the same year, Meshram and co-workers [24] reported α-halogenation of various cyclic ketones with *N*-halosuccinimides using Amberlyst-15 as a heterogeneous solid acid catalyst. Because of its simplicity, high selectivity, short reaction times (20-30 min), high yields as 86-92% isolated yield were obtained. This

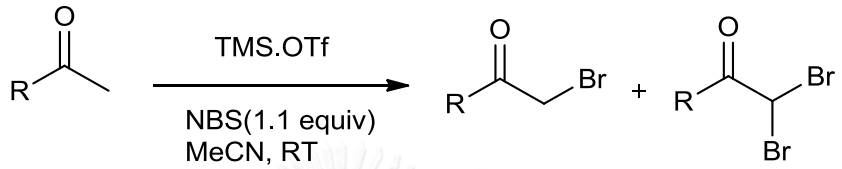
method in addition was simple and convenient using an inexpensive and recyclable acid resin.



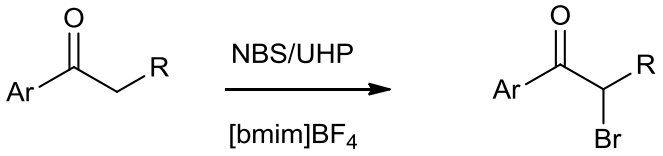
In 2005, Das and co-workers [15] developed a mild, simple and efficient method for α-bromination of carbonyl compounds (cyclic and acyclic ketones, amides and β-ketoesters) using NBS and catalyzed by $NaHSO_4/SiO_2$ in Et_2O or CCl_4 furnishing α-bromoketones within 0.5-2.5 h for 61-91% isolated yield. In 2006, Das and co-workers [25] developed on α-bromination of carbonyl compounds for 0.5-2 h in 72-99% isolated yield.



In 2006, Guha and co-workers [26] synthesized bromoketones using a combination of NBS and trimethylsilyl trifluoromethanesulfonate (TMS·OTf) in CH_3CN for 1-4 h giving 63-93% yield.

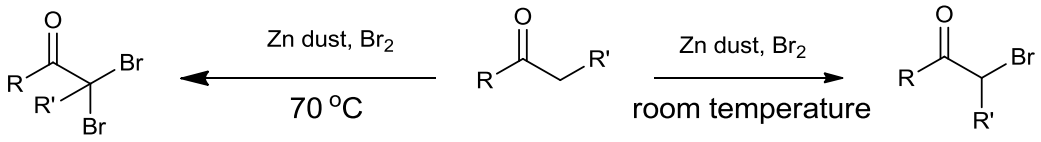


In the same year, Lee and Park reported the efficient method for **α**-chlorination and **α**-bromination of carbonyl compounds using *N*-halosuccinimides/urea–hydrogen peroxide, UHP) in 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim]BF_4, an ionic liquid medium at 60°C for 1– 20 h providing 74-97% isolated yield [27].

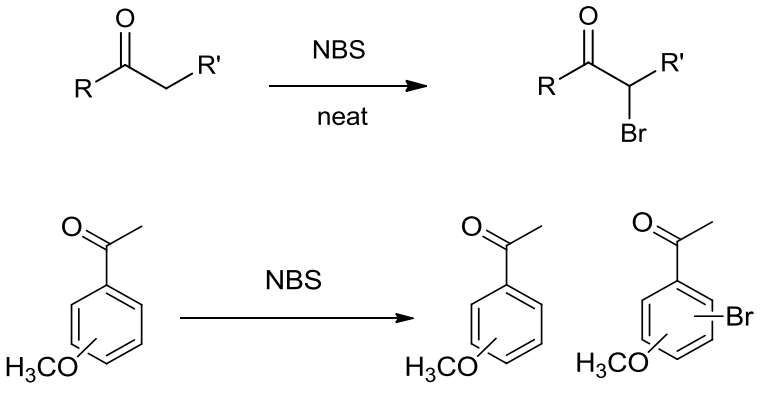


In the same year, Juneja and co-workers [28] reported **α**-bromination of alkanones with Br_2 catalyzed by *in situ*–generated $ZnBr_2$ from zinc dust and bromine. Bromination with dioxane-dibromide using water as solvent and provided selectively

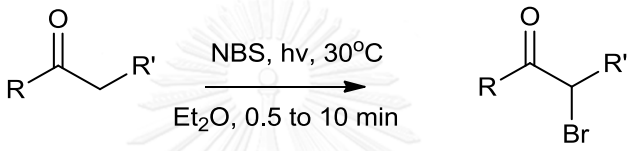
α-monobromination at RT for 0.1-4.5 h in 79-94 % and α,α-dibromo products at 70°C in 74-93% isolated yield.



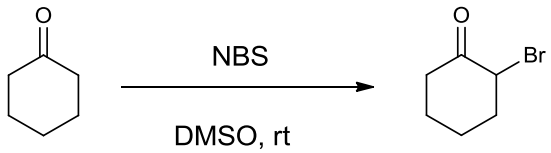
In the same year, Pravst and co-workers [17] reported the reaction directed the site of functionalization of ketones with NBS and catalyzed by PTSA under solvent-free conditions. α-Bromination was the exclusive process at 20°C for 3 h in 75-95% yield, while in water, ring functionalization occurred in the case of methoxy substituted aromatic ketones at 60°C for 5 h in 72-95% yield.



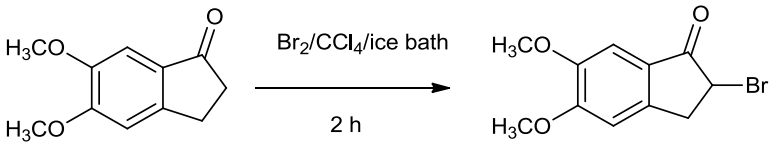
In 2007, Arbuj and co-workers [14] demonstrated α-bromination of cyclic and acyclic ketones with NBS in the presence of UV–vis irradiation in Et_2O under N_2 atmosphere giving the corresponding α-brominated ketones in good yield (15-84% conversion) at 30°C without any catalyst, catalyst support or radical initiator within a short time (0.5-10 min).



In the same year, Sreedhar and co-workers [29] described α-halogenation of various carbonyl compounds such as cyclic ketones with *N*-halosuccinamides in DMSO under catalyst-free conditions. The reaction proceeded very smoothly to give the corresponding α-monohalogenated products in good to excellent yields (72-95% isolated yield) for 10-85 min.



In the same year, Choi and co-workers [30] studied the α-bromination of 5,6-dimethoxyindan-1-one using Br_2 for 2 h furnishing the desired product in 14-35% yield.



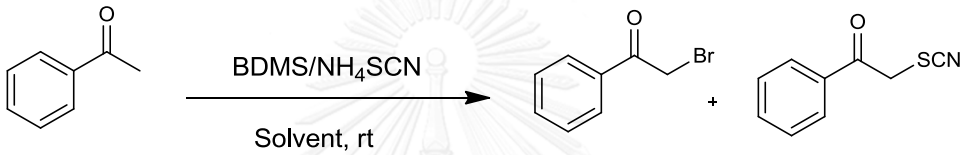
In 2008, Pravst and co-workers [31] demonstrated the effect of reagent and catalyst on halofunctionalization of acetophenone with *N*-halosuccinimides catalyzed by PTSA under solvent-free reaction conditions at 20°C for 3 h in 95% conversion.

In 2009, Podgorsek and co-workers [32] displayed the brominating system for the regioselectivity of bromofunctionalization of benzocycloalkanones in water. A comparison of reactivity and selectivity of both brominating systems revealed the H_2O_2–HBr system to be more reactive than NBS for benzyl bromination and for the bromination of ketones.

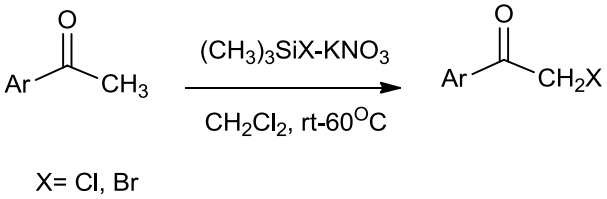
In the same year, Ngatimin and co-workers [33] addressed a mild method for α-halogenation of α,β-unsaturated carbonyl compounds based on the use of bisacetoxyiodobenzene (BAIB) and hydrohalide salts of pyridine.

In 2010, Patil and co-workers [34] synthesized α-bromoketones from alkenes with HBr-H_2O_2 at RT for 5-30 h in 20-94% yield.

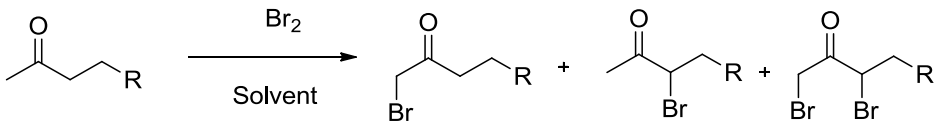
In the same year, Bhalerao and Akamanchi [35] developed an efficient and convenient method for α-thiocyanation of ketones and β-dicarbonyl compounds using a reagent combination of bromodimethylsulfonium bromide (BDMS) and NH_4SCN in CH_3CN. The developed method was mild and gave good yield of bromoketones at RT for 5 h in 70% yield.



In 2011, Prakash and co-workers [36] developed the system for α-bromination of acetophenones with $(CH_3)_3SiBr$-nitrate in CH_2Cl_2 at RT for 16-48 h in 35-73% yield.

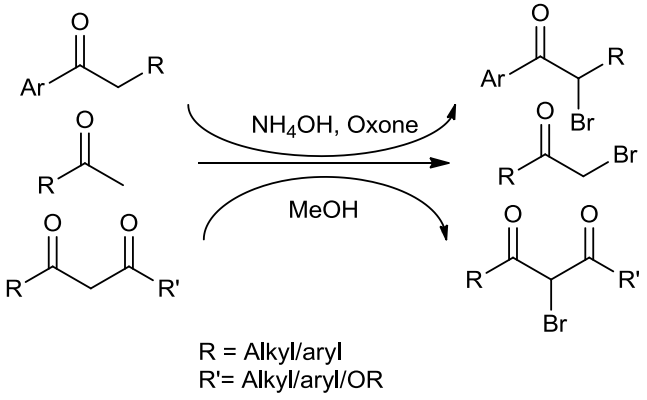


In 2010, Zavozin and co-workers [37] reported the bromination of methyl ketones with Br_2 in ionic liquids and organic solvents to produce 3-bromoketones which are typically formed in organic solvents.



In 2011, Salama and Novák [38] used the combination of *N*-halosuccinimide and $SiCl_4$ in CH_3CN for **α**-monohalogenation of carbonyl compounds. This system was found to be an efficient system for selective **α**-monohalogenation of carbonyl compounds at RT for 5-7 h in 81-92% isolated yield. In addition, the system could extend for benzylic halogenation for 6-11 h in 67-84% isolated yield under mild conditions.

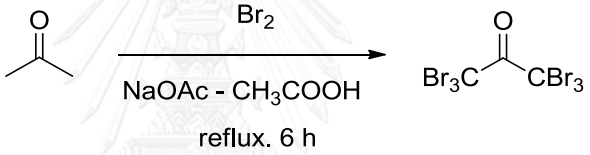
In 2012, Macharla and co-workers [39] addressed the bromination of various cyclic, acyclic and aralkyl ketones using NH_4Br and oxone in CH_3OH at RT for 40 min - 48 h in 8-98% yield or reflux temperature for 5 min -2.5 h in 21-98% yield.



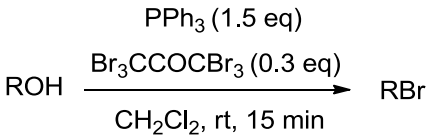
However, the disadvantages of those procedures are in some cases the substrates or products being intolerance to acid, requiring high temperature, long reaction time, use of hazardous chemicals and forming undesired by-products.

1.2 Literature Reviews of Hexabromoacetone (HBA)

In 1969, HBA was first synthesized by the reaction of acetone and Br_2; nevertheless without utilizing as a reagent in organic chemistry [40].



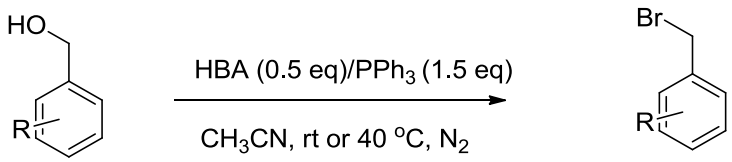
Up till in 2008, Tongkate and co-workers [41] described a new and efficient method for the bromination of alcohols utilizing $Br_3CCOCBr_3/PPh_3$. Various alcohols can be converted smoothly into their corresponding alkyl bromides in high yields under mild conditions with short reaction time.



In 2009, Menezes and co-workers [42] employed HBA as an alternative tribromoacetylating agent of primary alcohols and amines and as mediator in the conversion of carboxylic acids into amides and explored the utilization of this reagent coupled with PPh_3. The reactions could be performed under mild conditions with moderate to good yields.

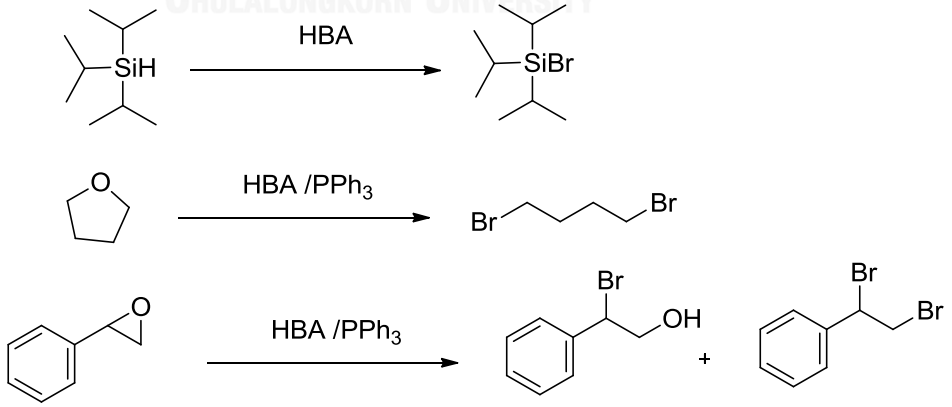
In the same year, the synthetic method for halogenation of benzylic and allylic alcohols using a combination of PPh_3 and a halogenating agent, such as Cl_3CCONH_2, Br_3CCO_2Et and $Br_3CCOCBr_3$, was disclosed. Primary benzylic and allylic alcohols appeared to be reactive alcohols for transformation to the corresponding halides *via* S_N2 mechanism without the formation of by-products. For secondary benzylic and allylic alcohols, the desired halides were attained in good yield [43].

In 2011, Joseph and co-workers [44] addressed the preparation of benzyl bromides from alcohols with high conversion rates at low temperatures under neutral conditions and short reaction time.

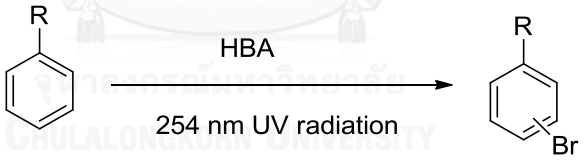


In 2012, the bromination of hydrosilanes, ethers and epoxides using UV irradiation or reflux temperature in THF furnishing bromosilanes in excellent yield

within 15 min. Under these optimized conditions, various hydrosilanes such as triphenylsilane and dimethylphenylsilane could be applied. In the case of the cleavage of linear ethers, dibenzyl ether was transformed to benzyl bromide using HBA/PPh_3 with a molar ratio of HBA/PPh_3 1:2 at reflux temperature in toluene for 4 h. For the opening of cyclic ethers, excess THF was cleaved using HBA/PPh_3 with a molar ratio of HBA/PPh_3 1:2 at reflux temperature in THF for 15 min to produce 1,2-dibromobutane in quantitative yield. In addition, the same reaction could be achieved under microwave irradiation at 130°C for only 1 min to produce high yield of the product. For the opening of epoxides, the formation of bromohydrin and dibromo products could be controlled using undried and dried CH_3CN and a molar ratio of HBA/PPh_3 0.5:1.0 and 2:3, giving bromohydrin and dibromo products in quantitative yield [45].



In 2014, the bromination of aromatics using HBA was addressed, anisole was used as a model substrate. Several factors including UV radiation, temperature, time, the substrate concentration, a molar ratio of anisole: HBA and additives were explored to search for optimum conditions which led to the selective production of the corresponding 4-bromoanisole in high yield using short reaction time. Several chemical probes including allylbenzene, safrole, flavone and pinostrobin were selected to investigate the scope of this reaction. The trend of the reactivity could be observed in order for the bromination towards unsaturated portion > aromatic with activating group > α-carbonyl group. The reaction pathway was believed to occur *via* Br_2 generated *in situ* from HBA [46].



R = EDG and EWG group

Up to date, HBA has not been employed as a brominating agent for α-bromination of ketone. In this research, a novel, mild and high yielding synthetic method for α-bromination of ketone using hexabromoacetone (HBA) was systematically explored.

CHAPTER II

EXPERIMENTAL

2.1 Instruments and Equipment

Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel (Merck Kieselgel 60 PF_{254}). Column chromatography was carried out on silica gel (Merck Kieselgel 60, 70-230 mesh).

The ^{1}H -NMR spectra were performed in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference on a Varian nuclear magnetic resonance spectrometer, model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ^{1}H. The chemical shifts (δ) are assigned by comparison with residue solvent protons.

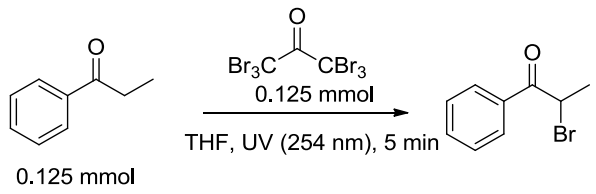
Gas chromatography (GC) was performed using CP-3800 gas chromatograph instrument equipped with a flame ionization detector (FID) with N_2 as a carrier gas using SGE BP21 column (30 m length, 0.25 mm outer diameter, 0.25μm film thickness).

2.2 Chemicals

All solvents were purified by standard methods before use unless those were reagent grades. The reagents for synthesis were purchased from Fluka or Sigma-Aldrich chemical companies and used without further purification.

2.3 Optimum Conditions for the Conversion of Propiophenone to 2-Bromopropiophenone Using HBA

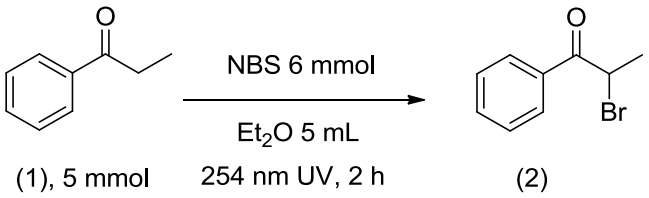
General procedure:



In a quartz cell (cylinder tube 2.5 x 13.5 cm), propiophenone (17 µL, 0.125 mmol) was mixed with HBA (67 mg, 0.125 mmol) in THF (1 mL). The reaction mixture was stirred at RT under the irradiation of UV light (254 nm, 6W) for 5 min. The reaction was monitored by TLC and at appropriate time was quenched by adding $NaHCO_3$ (1 mL) and extracted twice with Et_2O (5 mL). The product yield was analyzed by GC using naphthalene as an internal standard.

Synthesis of 2-bromopropiophenone

To a mixture of propiophenone (0.67 g, 5 mmol) and NBS (0.89 g, 6 mmol) in Et_2O (5 mL) was added. The mixture was stirred at RT for 2 h under UV-irradiation. After completion of the reaction (as indicated by TLC) diluted with Et_2O, washed with H_2O, dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column using hexane–EtOAc (10:1) as eluent to obtain 2-bromopropiophenone. The ^1H NMR spectrum of the target product is presented in Figure 2.1.



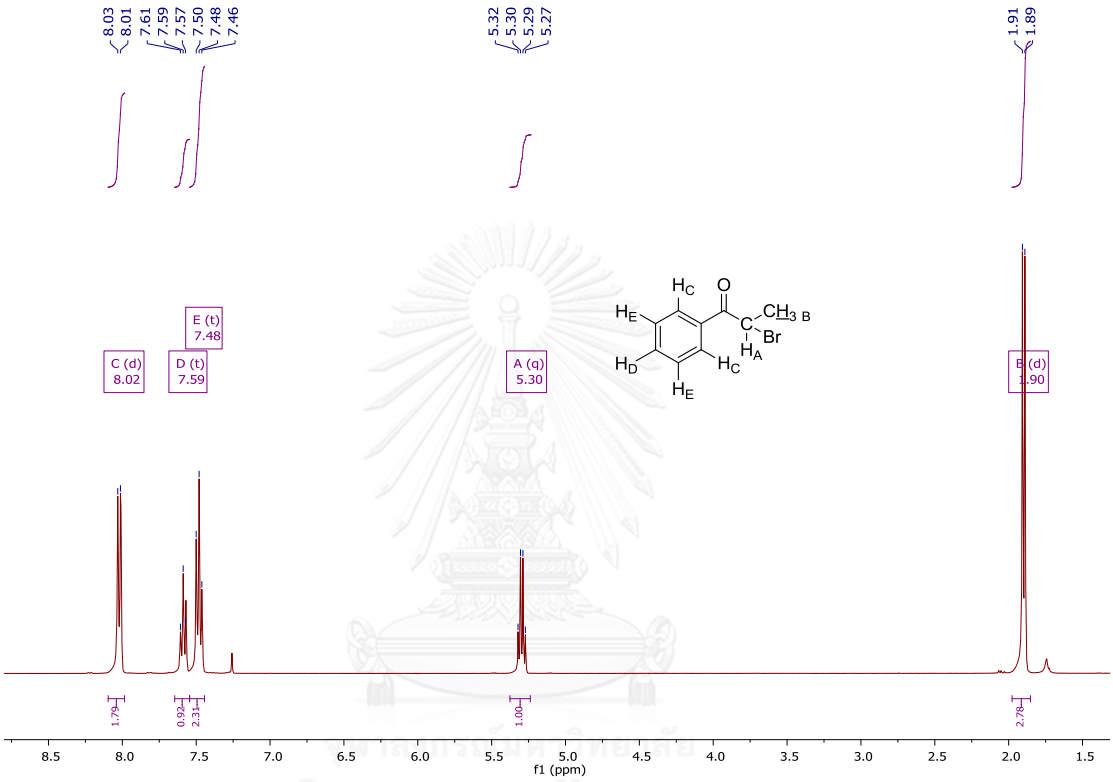


Figure 2.1 The ^{1}H NMR spectrum of 2-bromopropiophenone (**2**)

^{1}H NMR (400 MHz, $CDCl_3$) **δ** (ppm) displays the methyl protons at $\boldsymbol{\delta}_H$ 1.90 (d, *J* = 6.7 Hz, 3H, COCHBrC$\underline{H}_3$), the aromatic protons at $\boldsymbol{\delta}_H$ 8.02 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.59 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.48 (t, *J* =7.6 Hz, 2H, Ar-H) and the **α**-carbonyl protons at $\boldsymbol{\delta}_H$ 5.30 (q, *J* = 6.6 Hz, 1H, COC$\underline{H}$BrCH$_3$),

2.3.1 Effect of Types of Brominating Agent

Six different brominating agents: hexabromoacetone (HBA), *N*-bromosuccinimide (NBS), carbon tetrabromide (CBr_4), tribromoacetic acide (Br_3CCO_2H), bromoethane (C_2H_5Br), bromotrichloromethane ($BrCCl_3$) were utilized to observe the efficiency of this bromination.

2.3.2 Effect of Reaction Time with UV-irradiation

The general procedure was carried out except for the reaction time used was altered from 5 min (without UV) to 10 and 15 min with UV-irradiation at RT.

2.3.3 Effect of Solvents

The general reaction was performed using seven different solvents (1 mL): Et_2O, 1,2-dichloroethane (DCE), dichloromethane (CH_2Cl_2), hexane, acetonitrile (CH_3CN), tetrahydrofuran (THF) and benzene with UV-irradiation at RT for 5 min.

2.3.4 Effect of Molar Ratio of Propiophenone: HBA

The general reaction was carried out using four different molar ratios of propiophenone: HBA as 1:1, 2:1, 3:1 and 6:1.

2.4 α-Bromination of Selected Ketones Using HBA

The general experiment was performed except for using other selected ketones namely acetophenone, 2′-hydroxyacetophenone, 4′-hydroxyacetophenone, 4′-methoxyacetophenone, cyclohexanone and α-tetralone instead of propiophenone.

2.5 The Regioselectivity Study on α-Bromination of 2-Hexanone Using HBA

2-Hexanone (15 µL, 0.125 mmol) and HBA (67 mg, 0.125 mmol) in THF (1 mL) or Et_2O was mixed. The reaction mixture was stirred 5 min at RT under UV. The yield of products were analyzed by GC using naphthalene as an internal standard.

2.6 The Comparative Reactivity Study on α-Bromination of Selected Ketones

2.6.1 Effect of Molar Ratio of Propiophenone, Acetophenone and 4′-Methoxyaetophenone: HBA

Propiophenone (17 µL, 0.125 mmol), acetophenone (17 µL, 0.125 mmol) and HBA (67 mg, 0.125 mmol) were mixed. The molar ratio of propiophenone: acetophenone: HBA was varied as 1:1:0.5, 1:1:1, and 2:2:1. In case of 4′-methoxyaetophenone, the molar ratio of propiophenone: 4′-methoxyaetophenone: HBA was varied as 1:1:1 and 2:2:1. The product yield was analyzed by ^{1}H -NMR with naphthalene as an internal standard.

2.7 Optimum Conditions for α-Bromination of Propiophenone Using HBA Without UV-irradiation

2.7.1 Effect of Brominating Agent on α-Bromination of Propiophenone

The α-bromination of propiophenone was performed under two different conditions. Firstly, propiophenone (17 µL, 0.125 mmol) was mixed with *p*-toluenesulfonic acid (PTSA, 10%mmol) and two different brominating agents: HBA or NBS (0.125 mmol) in THF (1 mL). In the case of HBA, the reaction was carried out at RT for 15, 30 min or 1 h whereas that of NBS at RT for 1 h. The yield of product was quantified by GC using naphthalene as an internal standard.

2.7.2 Effect of Solvent on α-Bromination of Propiophenone

The general reaction was carried out using eight different solvents: Et_2O, CH_3CN, THF, CH_2Cl_2, *n*-hexane, 1,4-dioxane, *tert*-butyl methyl ether (TBME) and benzyl ether without UV-irradiation at RT for 1 h and reflux temperature for 30 min.

2.8 α-Bromination of Selected Ketones Using HBA Without UV-irradiation

The same general procedure was carried out at reflux temperature without UV-irradiation. After completion, the reaction mixture was extracted twice with Et_2O. After evaporation of solvent, the reaction mixture was analyzed by ^{1}HNMR with naphthalene or toluene as an internal standard. The selected ketones studied

included acetophenone, 2′-hydroxyacetophenone, 4′-hydroxyaceto-phenone, 4′-methoxyacetophenone and α-tetralone.

2.9 Scale-up of α-Bromination of Propiophenone Using HBA Without UV-irradiation

Propiophenone (68 µL, 0.5 mmol) was mixed with HBA (0.27 g, 0.5 mmol) in THF (10 mL). The reaction mixture was stirred 30 min at reflux temperature. The reaction was monitored by TLC and at appropriate time, the reaction was quenched by adding $NaHCO_3$ (1 mL) and extracted twice with Et_2O (5 mL). The residue was purified by silica gel column using hexane–EtOAc (10:1) as eluent to obtain 2-bromopropiophenone 72 mg (68% isolated yield).

CHAPTER III
RESULTS AND DISCUSSION

α-Bromination of carbonyl compounds is one of important transformations in organic synthesis since **α**-brominated products are useful synthetic intermediates. In this research, the optimum conditions for **α**-bromination of ketones were scrutinized using propiophenone and hexabromoacetone (HBA) as a chemical model and a brominating agent, respectively. The developed protocol was then applied for other selected ketones to observe the scope and selectivity of the reaction.

3.1 Optimum Conditions for **α**-Bromination of Propiophenone

Various parameters including type of brominating agent, reaction time with UV-irradiation, solvents, molar ratio of propiophenone: HBA were examined.

3.1.1 Effects of Type of Brominating Agent

Six different brominating agents: hexabromoacetone (HBA), *N*-bromo-succinimide (NBS), carbon tetrabromide (CBr_4), tribromoacetic acid (Br_3CCO_2H), bromoethane (C_2H_5Br) and bromotrichloromethane ($BrCCl_3$) were chosen to screen for a proper brominating agent. The results are exhibited in Table 3.1.

Table 3.1 The effects of type of brominating agent on **α**-bromination of propiophenone (**1**).

Entry	Brominating agent	%Recovery of 1	%Yield of 2	MB (%)
1	HBA	34	65	99
2	NBS	94	0	94
3	CBr_4	90	17	107
4	Br_3CCO_2H	88	10	98
5	C_2H_5Br	97	0	97
6	$BrCCl_3$	99	7	106

Reaction conditions: Propiophenone (**1**) (0.125 mmol), brominating agent (0.125 mmol), Et_2O (1 mL) 5 min, UV, RT

Table 3.1 reveals the effect of type of brominating agent on the conversion of propiophenone (**1**) into 2-bromopropiophenone (**2**). The authentic sample of 2-bromo-propiophenone (**2**) was prepared by bromination of propiophenone with NBS [9] and characterized by ^{1}H NMR. The target product was light green liquid. ^{1}H NMR (400 MHz, $CDCl_3$) **δ** (ppm) displays the methyl protons at δ_H 1.90 (d, *J* = 6.7 Hz, 3H, COCHBrC<u>H</u>$_3$), the aromatic protons at δ_H 8.02 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.59 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.48 (t, *J* =7.6 Hz, 2H, Ar-H) and the **α**-carbonyl protons at δ_H 5.30 (q, *J* = 6.6 Hz, 1H, COC<u>H</u>BrCH$_3$),

Under the same reaction conditions, the reaction with HBA provided a high yield of the desired product (entry 1), while other common brominating agents

(entries 2-6) gave lower yields of the target molecule. Thus, HBA was selected for further study. According to previous reports, most common used reagents for **α**-bromination of ketones included Br_2 [10, 30] and $CuBr_2$ [11, 12]. Recently, various methods have been addressed using NBS–PTSA [17], NH_4Br and oxone [39]. However, all these methods suffered from one or more disadvantages such as long reaction times, preparation of catalyst, use of hazardous chemicals, and intricate workup procedures.

The use of HBA is a better alternative for Br_2 and NBS, which did not produce HBr in the reaction and long reaction times. This reagent under UV irradiating generated bromine radical easier than NBS. Up to date, HBA has not been employed as a brominating agent for **α**-bromination of ketone. The amount of 2-bromopropiophenone (**2**) was determined by GC using naphthalene as an internal standard. An example of calculation method for %yield of product is exhibited Figure 3.1.

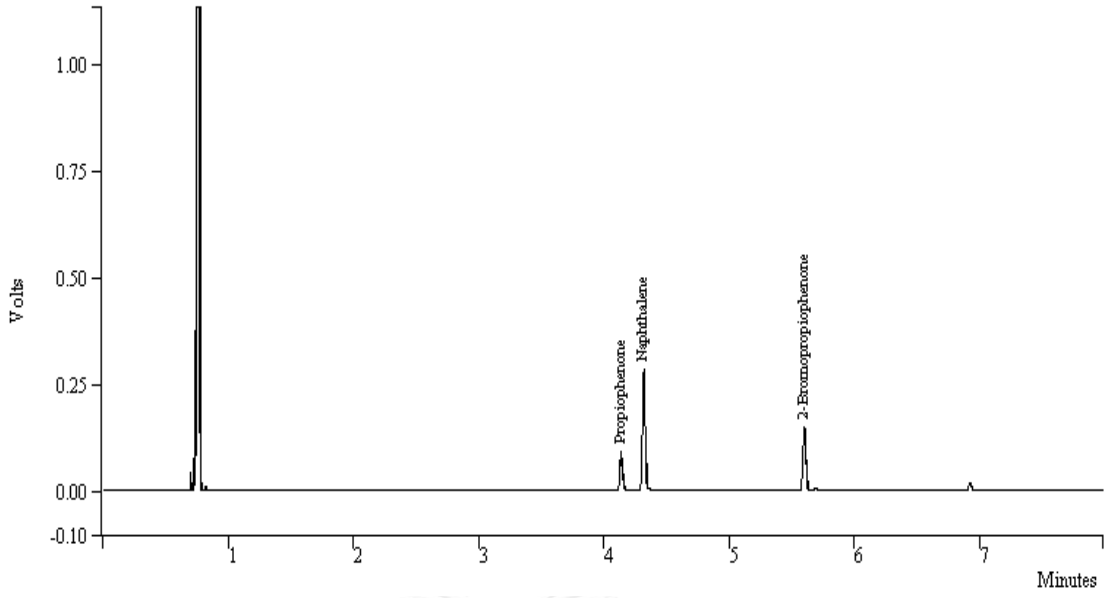


Figure 3.1 Chromatogram of the crude mixture for bromination of propiophenone (1)

$$\frac{\text{Area of Internal standard}}{\text{Area of Sample}} \times \frac{\text{Mol. Of Sample}}{\text{Mol. Of Internal standard}} = \text{IRF}$$

$$\frac{\text{Actual mole of product}}{\text{Expect mole of product}} \times 100 = \%\text{yield}$$

The product with R_t 5.59 min was obtained in 65% yield with 34% recovery of propiophenone (**1**) with R_t 4.13 min. It should be noted that there was no signal of 2,2-dibromopropiophenone (R_t 6.46 min).

3.1.2 Effects of Reaction time with UV-irradiation

Four sets of experiments to observe the effects of reaction time and UV for α-bromination of propiophenone (**1**) using HBA were investigated. The results are exhibited in Table 3.2.

Table 3.2 The effects of reaction time with UV on α-bromination of propiophenone (**1**).

Entry	time (min)	% Recovery of 1	% Yield of 2	MB (%)
1	5 (without UV)	98	5	103
2	5	34	65	99
3	10	4	100	104
4	15	6	94	100

Reaction conditions: Propiophenone (**1**, 0.125 mmol), HBA (0.125 mmol), Et_2O (1 mL), reaction time and UV (vary), RT

As presented in Table 3.2, the reaction in the absence of UV light (entry 1) generated the target product in poor yield. The yield of this product increased when the reaction was prolonged. The optimal reaction time was observed to be 10 min (entries 2-3). Increasing reaction time with UV-irradiation from 10 to 15 min did not provide the yield of 2-bromopropiophenone (**2**) (entry 4). This result clearly demonstrated that irradiation by UV light was important for this reaction.

3.1.3 Effect of Solvents

The attempt to gain better yield of 2-bromopropiophenone (**2**) from **α**-bromination of propiophenone (**1**) was carried out using different other solvents such as 1,2-dichloroethane (DCE), dichloromethane (CH_2Cl_2), hexane, acetonitrile (CH_3CN), benzene and tetrahydrofuran (THF). The results are exhibited in Table 3.3.

Table 3.3 The effects of solvent on **α**-bromination of propiophenone (**1**).

Entry	solvent	% Recovery of 1	% Yield of 2	MB (%)
1	Et_2O	34	65	99
2	DCE	94	6	100
3	CH_2Cl_2	95	4	99
4	hexane	75	11	86
5	CH_3CN	62	38	100
6	benzene	100	5	105
7	THF	3	97	100

Reaction conditions: propiophenone (**1**) (0.125 mmol), HBA (0.125 mmol), solvent (1 mL), 5 min, UV, RT

As displayed in Table 3.3, the reaction in CH_3CN, hexane, DCE, benzene and CH_2Cl_2 generated the target product in poor yield (entries 2-6), while Et_2O and THF provided the best results (entries 1 and 7). THF was found to be the most suitable for **α**-bromination of propiophenone (**1**).

To observe the efficiency of THF as a reaction media, the decreasing reaction time with UV-irradiation from 5 to 2 min in THF was conducted and the results are exhibited in Table 3.4.

Table 3.4 The effects of reaction time under UV on **α**-bromination of propiophenone (**1**).

Entry	Reaction time (min)	% Recovery of 1	% Yield of 2	MB (%)
1	2	36	69	105
2	5	3	97	100

Reaction conditions: propiophenone (**1**) (0.125 mmol), HBA (0.125 mmol), THF (1 mL), UV, RT

Attempting to reduce the reaction time in THF to 2 min did not give good yield of the desired product. Thus, the optimal reaction time should be 5 min in THF with UV-irradiation.

3.1.4 Effect of Molar Ratios of Propiophenone: HBA

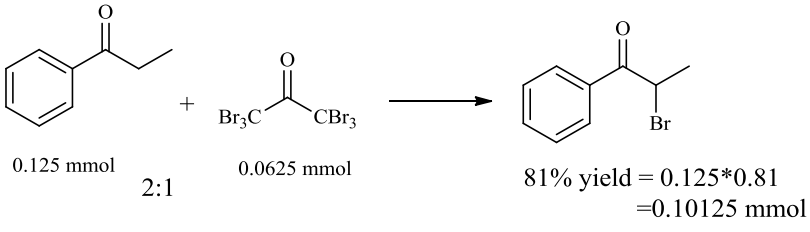
The optimum molar ratios of propiophenone: HBA was studied using four different molar ratios of propiophenone: HBA as 1:1, 2:1, 3:1 and 6:1. The results are presented in Table 3.5.

Table 3.5 The effects of molar ratio of propiophenone:HBA on **α**-bromination of propiophenone (**1**).

Entry	Molar ratio of propiphenone: HBA	% Recovery	% Yield		MB (%)
			Based on propiophenone	Based on HBA	
1	1: 1	3	97	97	100
2	2: 1	14	81	162	95
3	3: 1	32	57	171	89
4	6: 1	36	63	379	99

Reaction conditions: propiophenone:HBA (vary), THF (1 mL), 5 min, UV, RT

Table 3.5 reveals that when the ratio of propiophenone (**1**) to HBA was increased or using less HBA, the yield of the desired product was decreased. This was clearly demonstrated that the amount of HBA was essential for this reaction. Considering the yield of target product based on the amount of HBA, the formation of 2-bromopropiophenone (**2**) was increased when low amount of HBA was employed. In addition, this experiment was set up to observe the efficiency of HBA. In entry 1, with the molar ratio of propiophenone to HBA 1:1, the target product could be attained in very high yield based on the mole of brominating agent used. These results displayed a good efficiency of this brominating agent.



HBA has more than one bromine atom. The reason that the molarity of the desired product was more than that of HBA was that HBA could brominate more than once. The theoretical yield based on HBA is 0.0625. Therefore, % yield based on HBA is 100 x 0.10125/0.0.625 = 162%.

3.2 α-Bromination of Selected Ketones

In order to explore the scope of this developed system, seven diverse ketones were selected. The results are collected in Table 3.6.

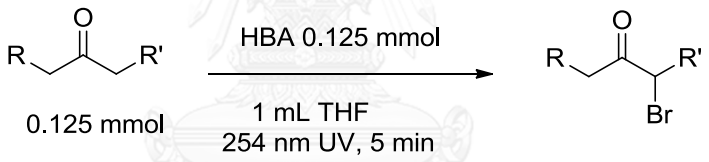
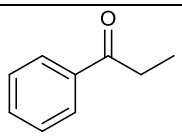
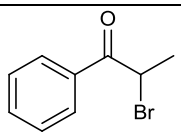
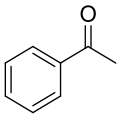
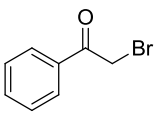
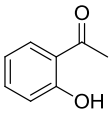
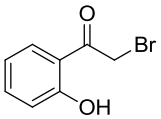
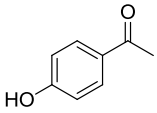
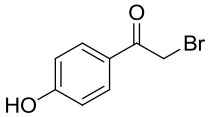
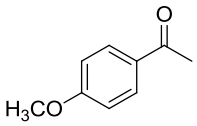
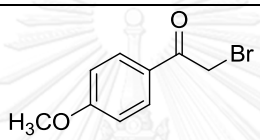
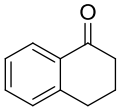
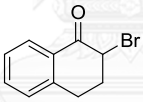
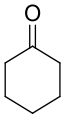
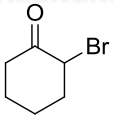
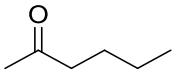
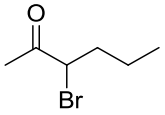
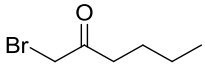


Table 3.6 α-Bromination of selected ketones.

Entry	Substrate	Product	%Recovery	%Yield	MB (%)
1	 **1**	 **2**	3	97	100
2	 **3**	 **4**	32	66	98

Entry	Substrate	Product	%Recovery	%Yield	MB (%)
3	 **5**	 **6**	74	26	100
4	 **7**	 **8**	58	34	92
5	 **9**	 **10**	40	61	101
6	 **11**	 **12**	39	65	104
7	 **13**	 **14**	57	47	100

Reaction conditions: substrate (0.125 mmol), HBA (0.125 mmol), THF (1 mL), 5 min, UV, RT

Entry	Substrate	Product	%Recovery	%Yield	MB (%)
8	 **15**	 **16**  **17**	13	69 13	95

Reaction conditions: substrate (0.125 mmol), HBA (0.125 mmol), THF (1 mL), 5 min, UV, RT

The synthetic method for **α**-bromination of propiophenone (**1**) into 2-bromopropiophenone (**2**) was obtained as sole product with success under mild condition with short reaction time. This method is very fast compared to other reported methods in literature. For instance, the **α**-bromination of acetophenone using NBS catalyzed by PTSA under solvent-free conditions resulted in 75% yield of 2-bromopropiophenone (**2**) product in 6 h [17], and in combination with NH_4Br and oxone in CH_3OH at RT for 26 h in 10% yield or reflux temperature for 7.5 h in 58% yield [39].

When acetophenone (**3**) was used as a substrate, the yield of the product, 2-bromoacetophenone (**4**), and %recovery of substrate were determined by ^{1}H NMR with naphthalene as an internal standard. To illustrate this, the two-proton signal of 2-bromoacetophenone (**4**) at δ_H 4.45 and the methyl proton signal of acetophenone (**3**) at δ_H 2.6 were taken to calculate the percent of product formed and the percent recovery of acetophenone (**3**), respectively. An example of the ^{1}H NMR spectrum of the crude reaction mixture of the bromination of acetophenone (**3**) is presented in Figure 3.2.

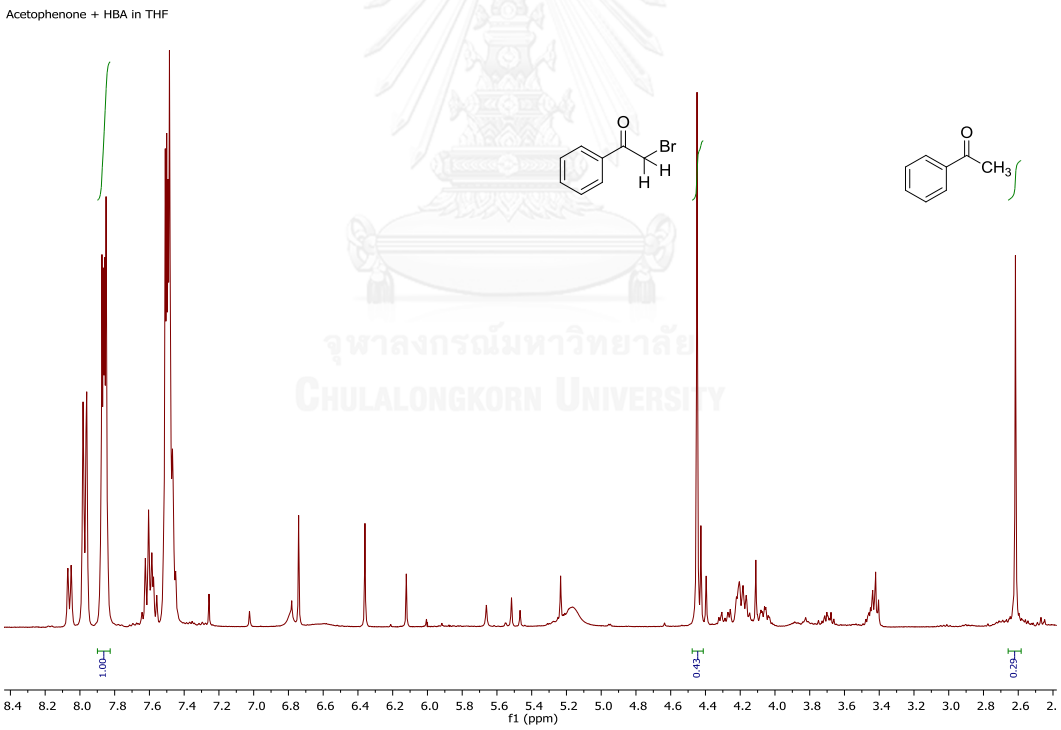


Figure 3.2 The ^{1}H NMR spectrum of the reaction mixture of acetophenone (**3**) using HBA (from entry 1, Table 3.6)

This reaction gave 66% yield of 2-bromoacetophenone (**4**) and 34% recovery of acetophenone (**3**). This method is very fast compared to other reported methods in literature. For instance, the **α**-bromination of acetophenone using NBS catalyzed by $NaHSO_4/SiO_2$ in Et_2O gave 72% isolated yield of 2-bromokacetophenone (**4**) product in 2 h [15], catalyzed by PTSA under solvent-free conditions resulted in 95% conversion in 3 h [17, 31], and in combination with trimethylsilyl trifluoromethane-sulfonate (TMS·OTf) in CH_3CN produced 85% yield in 24 h [26].

For 2′-hydroxyacetophenone (**5**), the **α**-carbonyl protons at δ_H 4.41 of 2-bromo-2′-hydroxyacetophenone (**6**) product and the methyl proton at δ_H 2.6 of 2′-hydroxyacetophenone (**5**) were used for the determination. The results showed 26% yield of 2-bromo-2′-hydroxyacetophenone (**6**) and 74% recovery of 2′-hydroxy-acetophenone (**5**). The ^{1}H NMR spectrum of the reaction mixture of the bromination of 2′-hydroxyacetophenone (**5**) is presented in Figure 3.3.

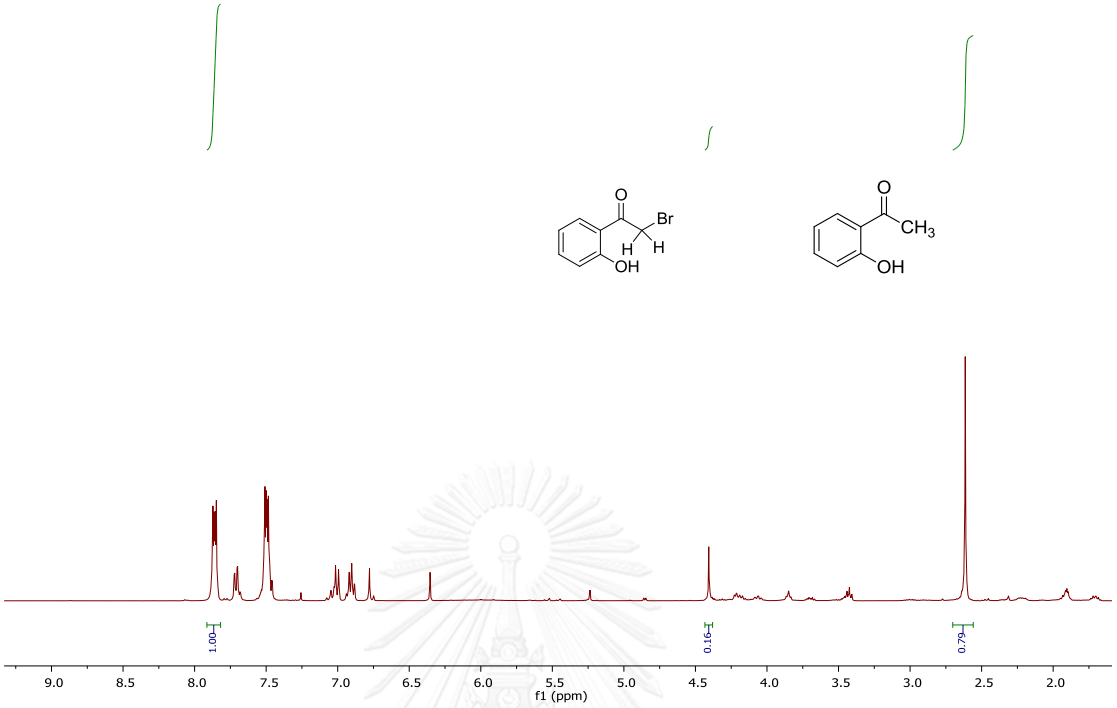


Figure 3.3 The ^{1}H NMR spectrum of the reaction mixture of 2′-hydroxyacetophenone (**5**) using HBA (from entry 2, Table 3.6)

The ^{1}H NMR spectrum of the crude reaction of the bromination of 4′-hydroxyacetophenone (**7**) is displayed in Figure 3.4. It revealed only 34% yield of the desired product and 58% recovery of the substrate. The ^{1}H NMR with toluene as an internal standard at δ_H 4.41 of **α**-carbonyl protons of 2-bromo-4′-hydroxy-acetophenone (**8**) and at δ_H 2.62 of the methyl protons of 4′-hydroxyacetophenone (**7**) were used for the calculation.

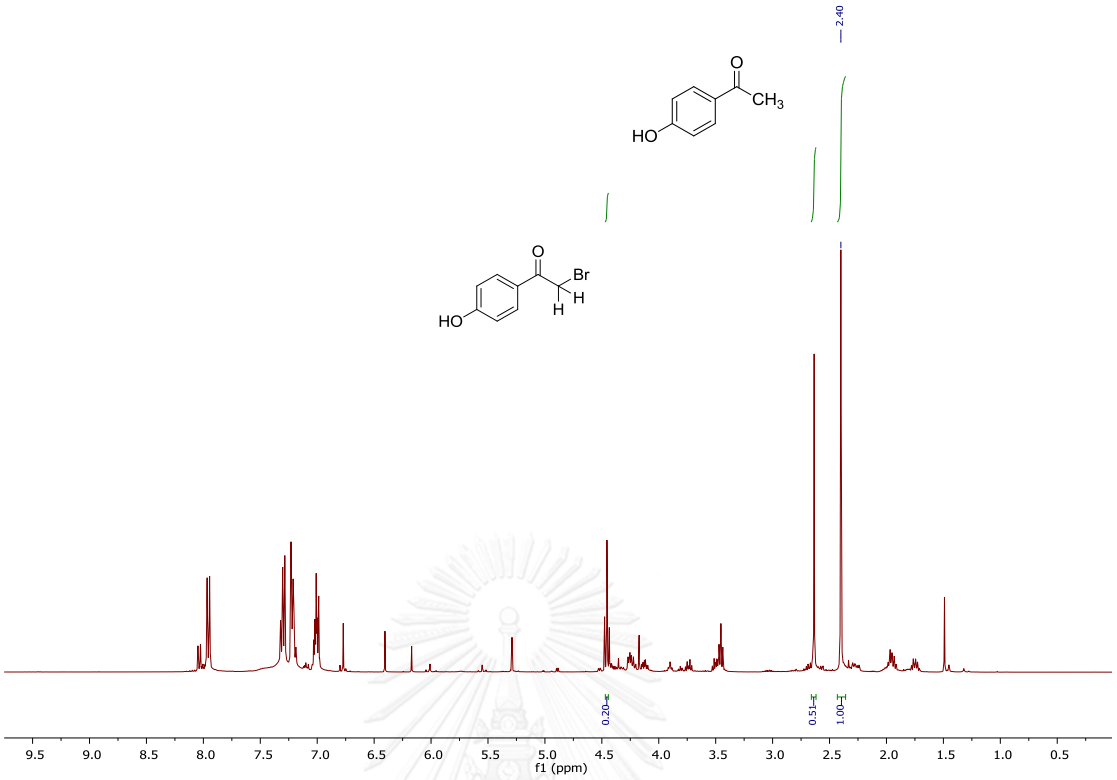


Figure 3.4 The ^{1}H NMR spectrum of the crude reaction mixture of 4′-hydroxy-acetophenone (**7**) using HBA (from entry 3, Table 3.6)

From entry 4, the yield of 2-bromo-4′-methoxyacetophenone (**10**) was 61% the recovery of 4′-methoxyacetophenone (**9**) was 40% based on the peak areas of the two **α** protons at δ_H 4.37 and methyl protons at δ_H 2.51. The ^{1}H NMR spectrum of the crude reaction mixture is exhibited in Figure 3.5.

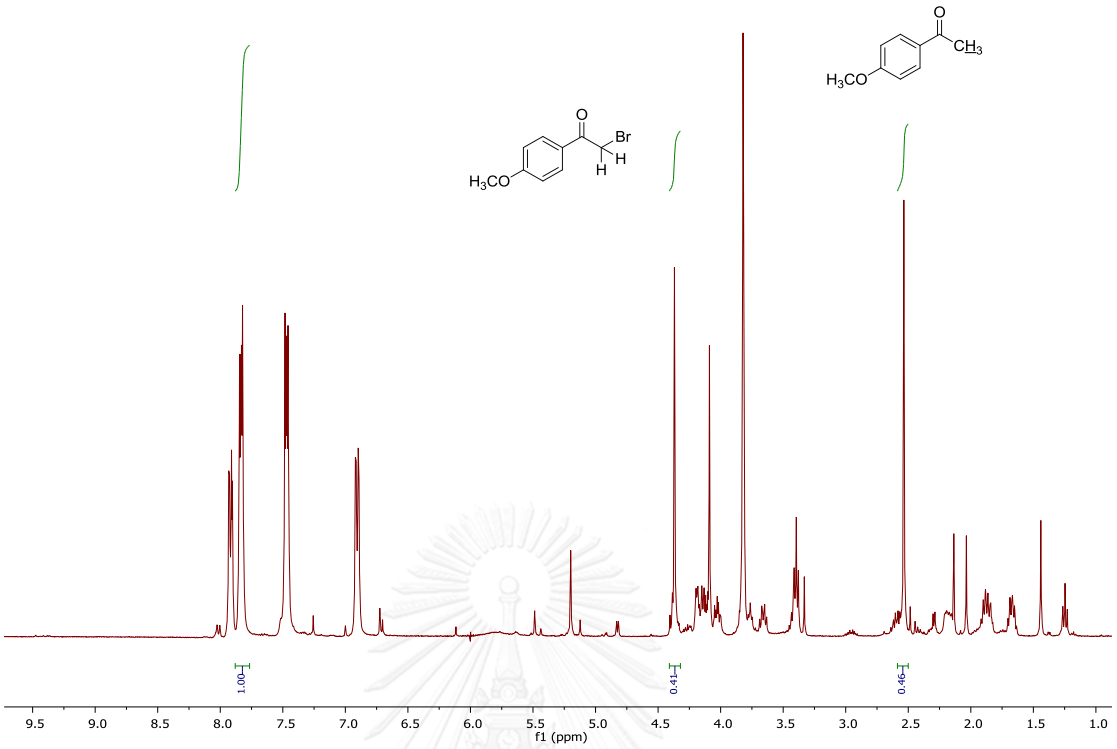


Figure 3.5 The ^{1}H NMR spectrum of the crude reaction mixture of 4′-methoxy-acetophenone (**9**) using HBA (from entry 4, Table 3.6)

The investigation of 2′-hydroxyacetophenone (**5**), 4′-hydroxyacetophenone (**7**) and 4′-methoxyacetophenone (**9**), which have different substituents on acetophenone (entries 2-4), were to show the effect of substituents on the phenyl ring on the bromination of acetophenone. The presence of highly activating groups on the phenyl ring favored nuclear bromination, whilst moderately activating groups favored the **α**-bromination [31, 39]. The methoxy group was less activating than the hydroxyl group and in this study both 2′-hydroxyacetophenone and 4′-

hydroxyacetophenone consistently produced around 26-34% yield of products while the product of 4′-methoxyacetophenone was 65% yield.

For **α**-tetralone (**11**), as displayed in Figure 3.6, the ^{1}H-NMR of the **α**-carbonyl protons at δ_H 4.73 of 2-bromo-**α**-tetralone (**12**) and the aromatic protons at δ_H 8.15-8.21 of **α**-tetralone (**11**) was used for the determination and the yield of 65% for the bromination at **α**-positions was observed (entry 5).

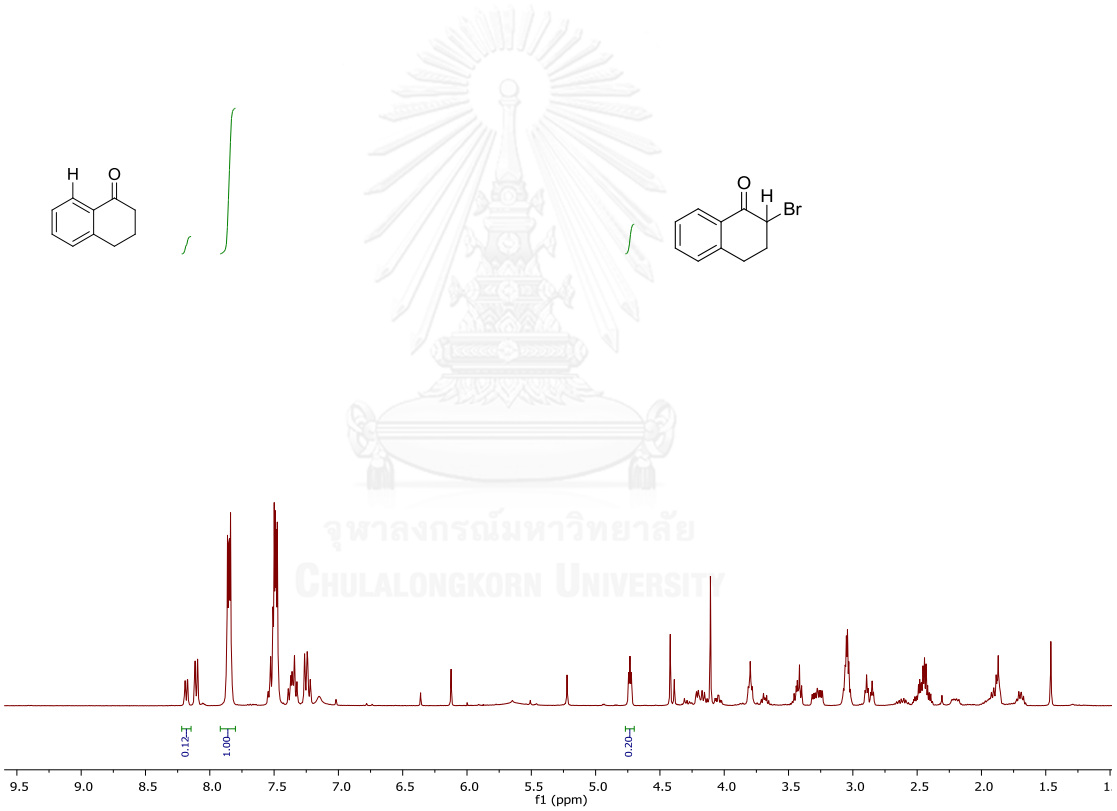


Figure 3.6 The ^{1}H NMR spectrum of the crude reaction mixture of **α**-tetralone (11) using HBA (from entry 5, Table 3.6)

From entry 6, the quantification of 2-bromo-cyclohexanone (**14**) was carried out by GC using biphenyl as an internal standard. The product was obtained in 47% yield with R_t 6.04 min by SGE-BP21 column as displayed in Figures 3.7. The derived product was characterized with ^{1}H-NMR displaying the proton of the brominated **α** carbon at δ_H 4.14-4.06 as displayed in Figures 3.8.

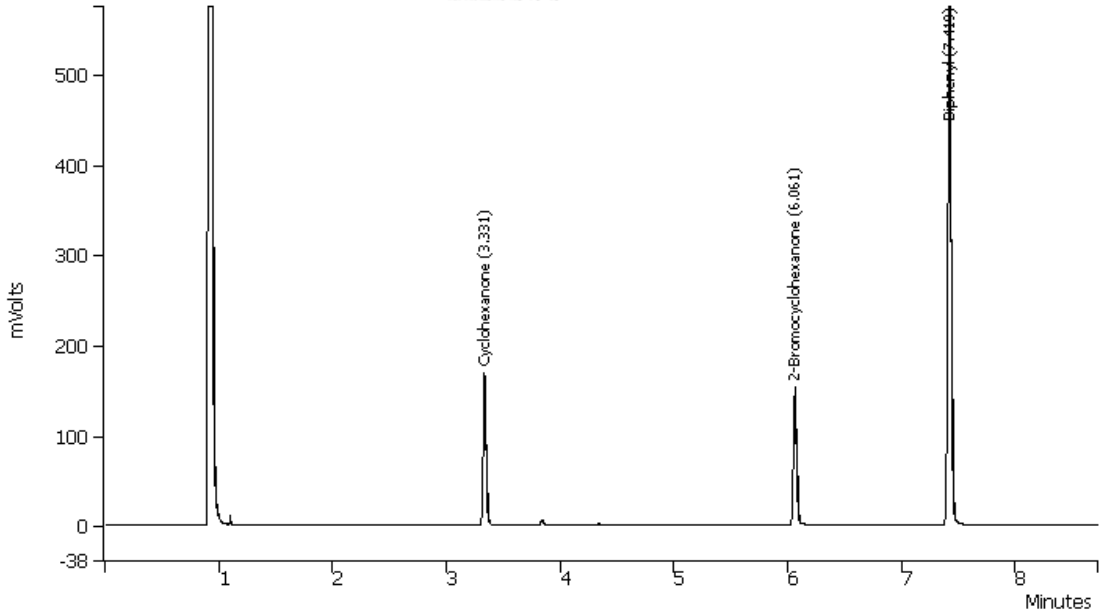


Figure 3.7 Chromatogram of the crude mixture for **α**-bromination of cyclohexanone (**13**)

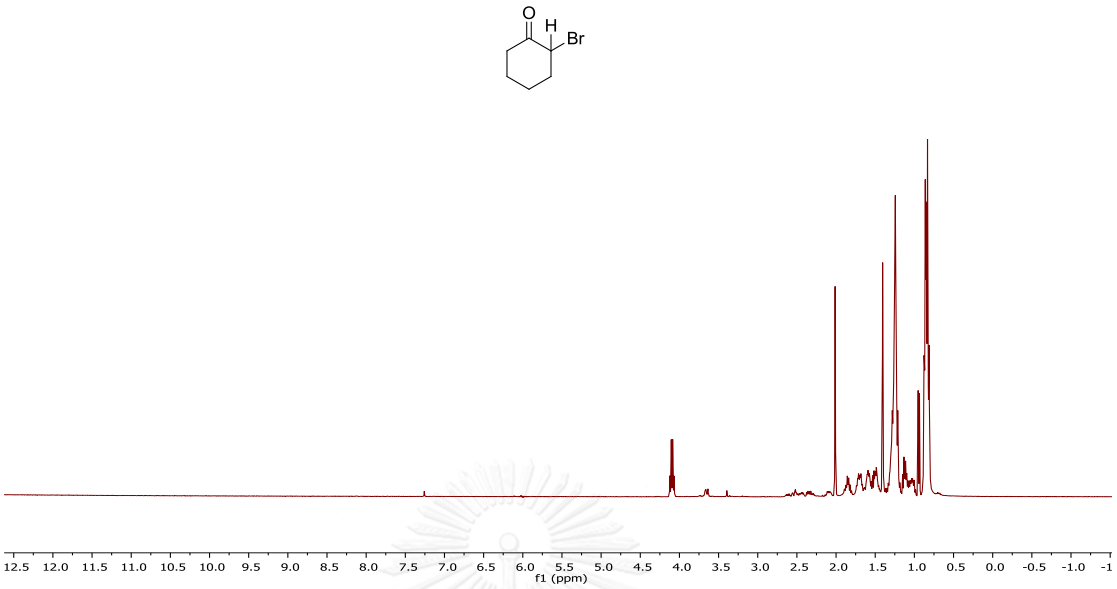


Figure 3.8 The ^{1}H NMR spectrum of 2-bromocyclohexanone (**14**)

2-Hexanone (**15**), an unsymmetrical acyclic ketone (entry 7), was recovered at 13% with R_t 1.72 min by SGE-BP21 column and two products were formed from monobromination at the two **α**-positions. The reaction was completed with 65% yield (R_t 3.20 min by SGE-BP21 column) of 3-bromo-2-hexanone as the major product and 13% yield (R_t 3.71 min by SGE-BP21 column) of 1-bromo-2-hexanone as the minor product. The reaction was also carried out under the irradiation using sunlight. Similar conversions and selectivity were recorded, indicating the general nature of the photoinitiated bromination [16]. Previously, the applicability of some **α**-bromination method was reported for acyclic ketone [15].

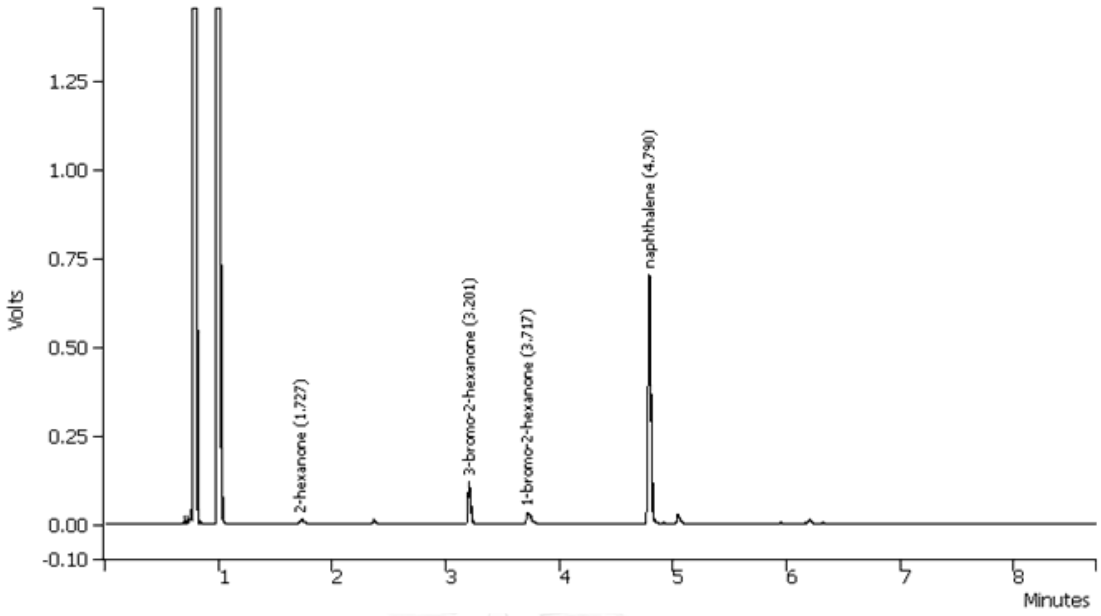


Figure 3.9 Chromatogram of the crude mixture for **α**-bromination of 2-hexanone (**15**)

The developed protocol could be successfully utilized for several ketones such as acetophenone, 2′-hydroxyacetophenone, 4′-hydroxyacetophenone, 4′-methoxyaceto-phenone, **α**-tetralone, cyclohexanone and 2-hexanone with moderate to high yield under mild reaction condition with short reaction time using HBA as a brominating agent.

3.3 The Regioselectivity Study on α-Bromination of 2-Hexanone Using HBA

2-Hexanone (**15**) was chosen as a substrate to explore the regioselectivity of the developed system. The results are exhibited in Table 3.7.

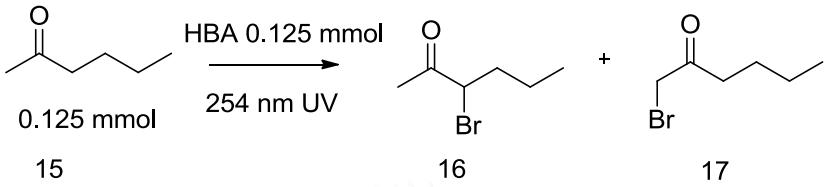


Table 3.7 Effect of solvent on α-bromination of 2-hexanone (**15**).

Entry	solvent	% Recovery of 15	% Yield of 16	% Yield of 17	MB (%)
1	THF	13	69	13	95
2	Et_2O	0	98	0	98

Reaction conditions: 2-hexanone (**15**) (0.125 mmol), HBA (0.125 mmol), solvent (1 mL)

α-Bromination of 2-hexanone (**15**) was found to form two products, 3-bromo-2-hexanone (**16**) and 1-bromo-2-hexanone (**17**), with different extent. According to the literature, acyclic ketone was brominated using NBS and catalyzed by $NaHSO_4/SiO_2$ in Et_2O and CCl_4. The α-brominated products were obtained in high yield [16]. Using less polarity solvent such as Et_2O (entry 2), none of 1-bromo-2-hexanone (**17**) was found. This result shows that the regioselectivity of reaction can be controlled as 3-bromo-2-hexanone (**16**) was detected in high yield. Application to

the preparation of chiral epoxides or imidazolin-2-ones. The products were analyzed by GC using naphthalene as an internal standard.

3.4 The Comparative Reactivity Study on α-Bromination of Selected Ketones

3.4.1 The Reactivity Study on α-Bromination of Propiophenone and Acetophenone and 4′-Methoxyacetophenone

From previous results, both propiophenone (**1**) and acetophenone (**3**) were very reactive towards the bromination with HBA. The experiment was set up to compare the reactivity of both substrates. The results of two expected products are exhibited in Table 3.8.

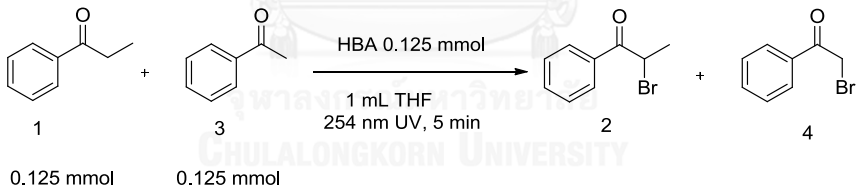


Table 3.8 The reactivity study on α-bromination of propiophenone (**1**) and acetophenone (**3**).

Entry	Molar ratio of 1: 3 : HBA	% Recovery of 1	% Yield of 2	MB	% Recovery of 3	% Yield of 4	MB %
1	1:1:1	0	102	102	36	46	82
2	2:2:1	26	75	101	73	22	95

Reaction conditions: propiophenone (0.125 mmol), acetophenone (0.125 mmol), HBA (0.125 mmol), THF (1 mL), 5 min, UV, RT

From previous results, at all molar ratios, the amount of the product derived from propiophenone (**1**) was higher than the target product of acetophenone (**3**) under the same reaction conditions even though α-carbon was brominated for both compounds. The yield of both target products was increased at higher molar ratio of substrate:HBA and decreased at lower molar ratio of substrate:HBA. The experiment implied that the active bromine species producted from HBA should be Br_2. The reactivity towards the α-carbon groups was in the order of methanediyl group > acetyl groups. In addition, for the synthesis of the yield of 2-bromopropiophenone (95% isolated yield) was higher than the target product of 2-bromoacetophenone (85% isolated yield) with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent, HTIB) followed by magnesium halides under solvent-free microwave irradiation conditions is described [18].

3.4.2 The Reactivity Study on α-Bromination of Propiophenone and 4′-Methoxyacetophenone (9).

From previous results, both propiophenone (**1**) and 4′-methoxyacetophenone (**9**) were very reactive towards the bromination with HBA. In this section, the molar ratio of propiophenone (**1**): 4′-methoxyacetophenone (**9**): HBA at 1:1:1 in THF with UV-irradiation for 5 min was examined for the yield of products. The results are presented in Table 3.9.

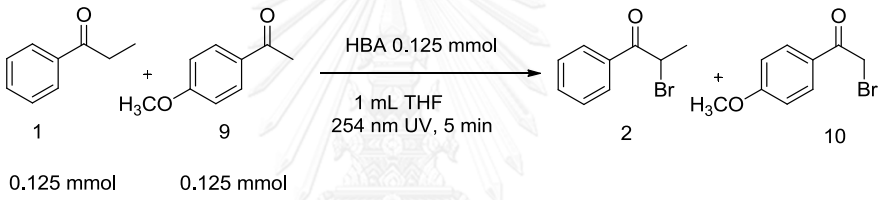


Table 3.9 The reactivity study on α-bromination of propiophenone (**1**) and 4′-methoxyacetophenone (**9**).

Entry	Molar ratio of 1: 9 : HBA	% Recovery of 1	% Yield of 2	MB	% Recovery of 9	% Yield of 10	MB %
1	1:1:1	9	90	99	45	53	98

Reaction conditions: propiophenone (0.125 mmol), 4′-methoxyacetophenone (0.125 mmol), HBA (0.125 mmol), THF (1 mL), 5 min, UV, RT

As shown in Table 3.9, the product derived from propiophenone (**1**) was higher than the target product of 4′-methoxyacetophenone (**9**). Based on this result, the effect on the reactivity towards the α-carbon groups was in the order of methanediyl group > methoxy groups.

3.5 Optimum Conditions for α-Bromination of Propiophenone Using HBA Without UV-irradiation

In this section, other reaction conditions were explored for the conversion of propiophenone to α-bromopropiophenone using HBA especially without UV-irradiation as an alternative including the addition of PTSA, variation of solvent, and the reaction temperature.

3.5.1 Effect of Brominating Agent on α-Bromination of Propiophenone

First, the general reaction was carried out using *p*-toluenesulfonic acid (PTSA) as an additive (10 mol% of propiophenone) for the bromination using NBS and HBA. The additive reported on the literature indicated that Lewis acid is well known as a good catalyst on bromination of ketones [17, 31]. For two different brominating agents: HBA and NBS. The results are exhibited in Table 3.10.

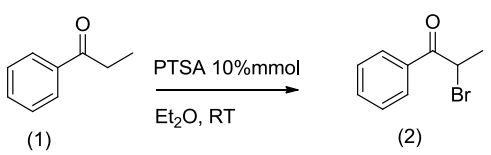


Table 3.10 Effect of brominating agent on **α**-bromination of propiophenone (**1**).

Entry	Brominating agent	Time (min)	% Recovery of 1	% Yield of 2	MB (%)
1	HBA	15	59	41	100
2		30	19	83	102
3		60	0	101	101
4	NBS	60	65	35	100

Reaction conditions: substrate (0.125 mmol), HBA (0.125 mmol), Et_2O (1 mL), RT

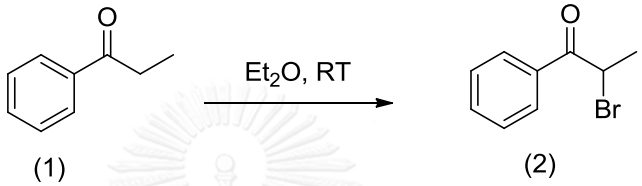
Yield determined by gas chromatography (GC) using naphthalene as an internal standard.

As displayed in Table 3.10, the yield of the desired product when using HBA increased as the reaction time increased. At 15-30 min, the reaction was not completed and propiophenone (**1**) could still be detected in the reaction (entries 1 and 2). The reaction was complete within 60 min and provided a high yield of the desired product (entry 3)**.**

NBS has been known as a good brominating agent for synthesis of many brominated carbonyl compounds [15-17]. Under the same reaction conditions, comparing the yield of 2-bromopropiophenone (**2**) from HBA and NBS, the reaction with NBS provided a poorer yield of the desired product (entry 4).

3.5.2 Effect of the Additives on α-Bromination of Propiophenone

The reaction was carried out using *p*-toluenesulfonic acid (PTSA) as an additive (without and with 10 mol% of propiophenone) for two different brominating agents: HBA and NBS. The results are exhibited in Table 3.11.



(1) (2)

Table 3.11 Effect of the amount of PTSA on α-bromination of propiophenone (**1**).

Entry	Brominating agent	PTSA (% mmol)	Time (h)	% Recovery of 1	% Yield of 2	MB (%)
1	HBA	0	1	0	100	100
2		10	1	0	101	101
3	NBS	0	1	86	14	100
4		10	1	66	24	100

Reaction conditions: propiophenone **(1)** (0.125 mmol), brominating agent (0.125 mmol), Et_2O (1 mL)

Table 3.11 reveals that in the event of HBA as brominating agent, the amount of PTSA (without and 10 mol% of propiophenone) high yields of the desired product (entries 1 and 2) were recorded indicating that the amount of PTSA has no effect on

α-bromination of this reaction while for NBS the results showed that reaction generated the target product in poor yield (entry 3). When PTSA was added, the amount of the product increased indicating that PTSA promoted α-bromination of propiophenone using NBS.

3.5.3 Effect of Solvent on α-Bromination of Propiophenone

The effect of different solvents on α-bromination of propiophenone (**1**) at RT and under reflux was studied and the results are summarized in Table 3.12.

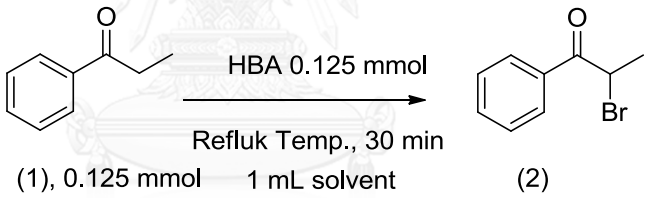


Table 3.12 Effect of solvent on **α**-bromination of propiophenone (**1**).

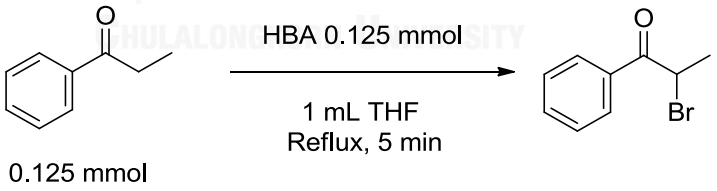
Entry	solvent	Temperature	Time (min)	% Recovery of 1	% Yield of 2	MB (%)
1	Et_2O	RT	60	0	100	100
2		Reflux	30	13	87	100
3	THF	RT	60	0	100	100
4		Reflux	5	0	95	95
5		Reflux	15	0	101	101
6		Reflux	30	0	102	102
7	CH_3CN	RT	60	97	2	99
8		Reflux	30	93	7	100
9	CH_2Cl_2	Reflux	30	74	28	102
10	n-hexane	Reflux	30	57	42	99
11	1,4-dioxane	Reflux	30	69	31	100
12	TBME	RT	60	37	62	99
13		Reflux	30	36	64	100
14	Benzyl ether	RT	60	0	99(1*)	99
15		Reflux	30	1	96(4*)	97

Reaction conditions: propiophenone (**1**) (0.125 mmol), HBA (0.125 mmol), solvent (1 mL), 5 min.*% Yield of benzyl bromide by GC using naphthalene as an internal standard.

As displayed in Table 3.12, the conversion was attempted with different other solvents and CH_3CN, CH_2Cl_2, 1,4-dioxane, *n*-hexane and TBME generated the target product in poor yields (entries 7-15), while Et_2O, THF and benzyl ether provided the best results (entries 1-6). Benzyl bromide is unwanted side product in benzyl ether (entries 14-15). THF was found to be the most suitable for **α**-bromination of propiophenone (**1**) using HBA without UV-irradiation.

It should be noted that the reaction temperature had an effect on the bromination. High yields were obtained at reflux temperature in short reaction time compared to RT.

The experimental results indicated that the optimum condition is the ratio of substrate to HBA at 1:1 in THF at reflux temperature for 5 min without UV irradiation.



3.6 α-Bromination of Selected Ketones Using HBA Without UV-irradiation

According to all trials and condition optimization on the bromination of propiophenone (**1**) with HBA, the optimum condition is with the ratio of substrate to HBA at 1:1 in THF at reflux temperature from 5 min to 30 min without UV irradiation. This condition was applied to other substrates. The results are shown in Table 3.13.

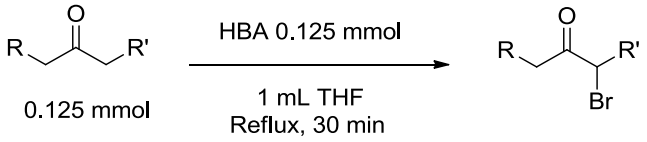
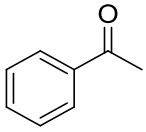
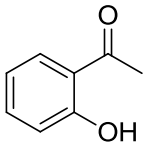
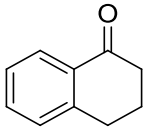
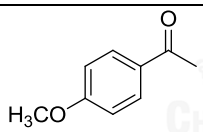


Table 3.13 α-bromination of selected ketones without UV-irradiation.

Entry	substrate	Temperature	Time (min)	% Recovery of substrate	% Yield	MB %
1	 **3**	Reflux	30	0	42	42
2	 **5**	Reflux	30	49	68	117
3	 **7**	Reflux	30	91	12	103
4	 **9**	Reflux	30	42	57	99

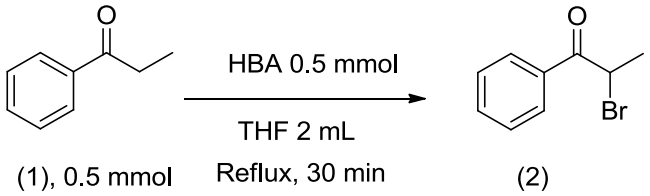
Reaction conditions: substrate (0.125 mmol), HBA (0.125 mmol), THF (1 mL), reflux temperature

When comparing the results in Table 3.13 with those under UV-irradiation (Table 3.6) entries 1, 3 and 4 gave lower %yield of target product than the reaction under UV irradiation. While for 2-hydroxyacetophenone (entry 2) %yield of target product was higher than when performed under UV-irradiation. In the same way,

other reported methods in literature. For instance, the **α**-bromination of 2-hydroxyacetophenone (**5**) using NBS under UV-irradiation in Et_2O gave 15% isolated yield of 2-bromo-2-hydroxyacetophenone (**6**) product in 10 min [7], less than using NBS catalyzed by PTSA under solvent-free conditions (91% isolated yield in 2 h) [8], and in combination with Br_2 at reflux temperature in CH_3CN produced 85% yield in 45 min [7].

This result showed that **α**-bromination of certain ketones with HBA could be conducted in refluxing THF instead of using UV-irradiation with moderate to high yield.

3.7 Scale-up α-Bromination of Propiophenone Using HBA Without UV-irradiation.



Propiophenone (0.5 mmol) was mixed with HBA (0.5 mmol) in THF (2 mL) for 30 min and the reaction mixture was stirred for 30 min at refluxing temperature. After completion, monitored by TLC, the reaction mixture was extracted twice with Et_2O (5 mL). The residue was purified by column chromatography over silica gel using hexane-EtOAc (10:1) as eluent to obtain the pure α-bromopropiophenone in 68% isolated yield.

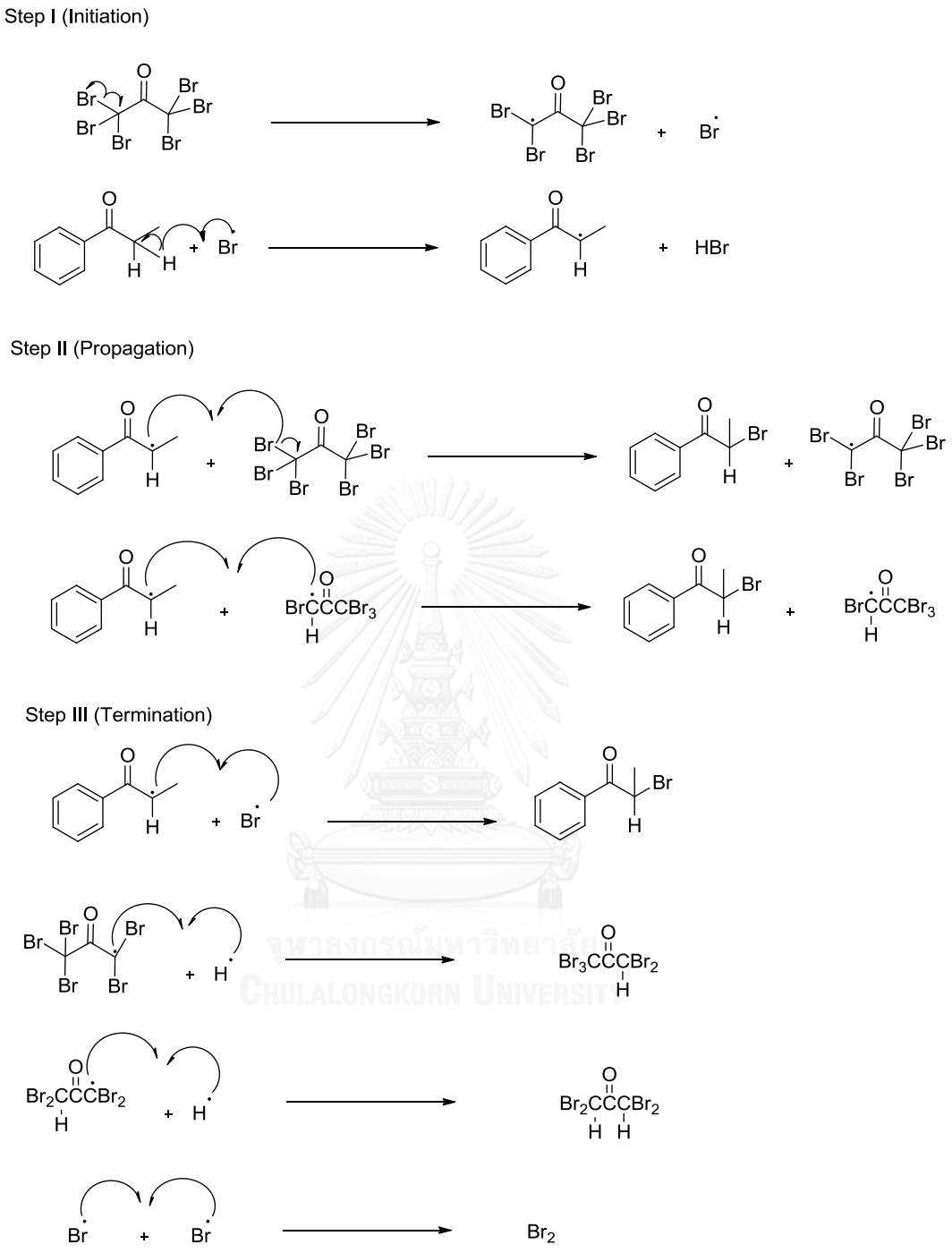
3.8 The Proposed Mechanistic Pathway for α-Bromination of Propiophenone Using HBA

The mechanistic pathway for the preparation of bromoketones from ketones using HBA has never been reported. It was believed that the reaction mechanism should take place *via* a radical process; the generation of radical was based on type of solvent [45, 46]. While HBA in a solid state is white, the solution of HBA in THF gave yellow color. It was assumed that HBA could generate Br• and subsequently two Br• combined to become Br_2, which normally was yellow-orange. To prove this

assumption, an experiment was conducted in which a radical scavenger, such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), was added to the general procedure to trap the Br• . DPPH has been shown to change color from violet to yellow when combined with a radical [45]. From this experiment, the color of the solution was changed from violet to yellow indicating that radicals in the reaction mixture were generated which were trapped by DPPH. Therefore, the first step of the mechanism was the homolytic cleavage of C-Br bond of HBA to generate Br•.

The proposed mechanism is shown in Scheme 3.1. In the initial step, homolysis of HBA to from Br• was initiated. A bromine atom had an unpaired electron and acted as a free radical. In the propagation, Br• induced the cleavage of **α**-proton $COC\underline{H}_2CH_3$ into $COC•HCH_3$ which then reacted with HBA resulting in the desired product plus another $•CBr_2COCBr_3$. This radical would then go on to take part in another propagation reaction of the bromination reaction.

In the last step, various reactions between possible pairs of radicals allowed the formation of $COCHBrCH_3$, $Br_3CCOCHBr_2$, $Br_2CHCOCHBr$ and Br_2.



Scheme 3.1 The proposed mechanistic pathway for **α**-bromination of ketones using HBA

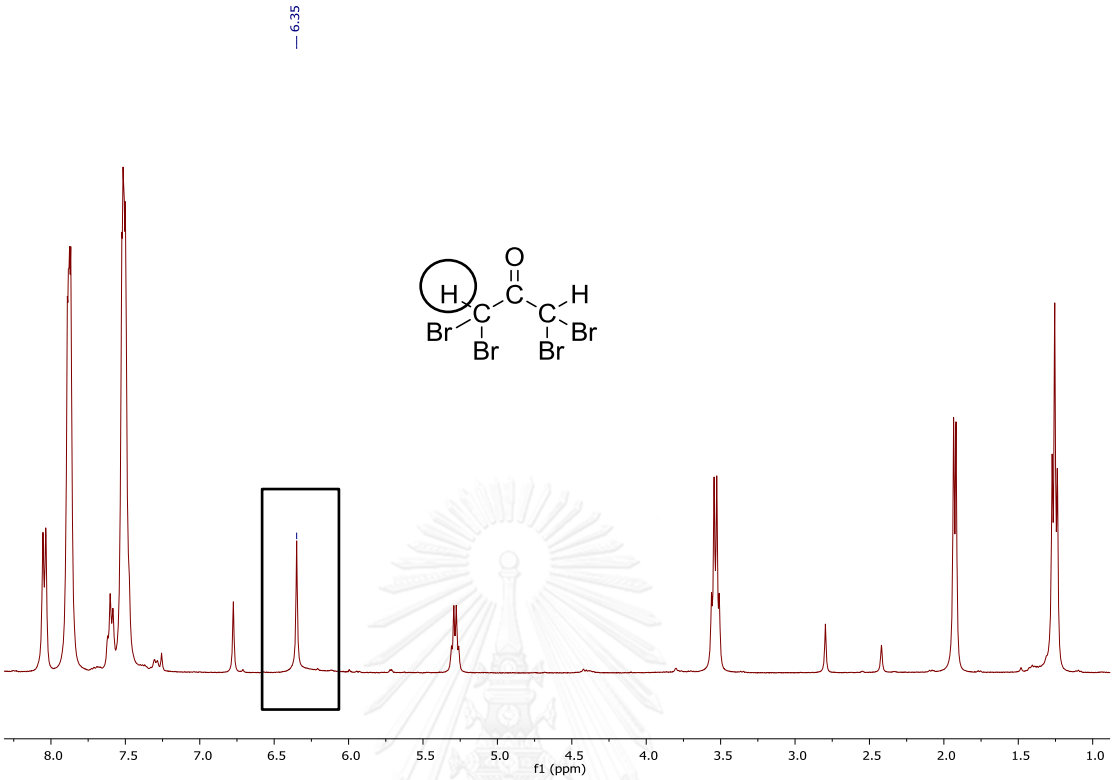


Figure 3.10 The ^{1}H NMR spectrum of the crude reaction mixture of propiophenone (**1**) using HBA (from entry 1, Table 3.10)

According to Figure 3.10, the singlet peak at δ_H 6.35 ppm was assigned to the signal of $Br_2C\underline{H}CO\underline{C}H\underline{H}Br_2$ [45, 46], which was by-product from the reaction.

CHAPTER IV
CONCLUSION

The new synthetic method for **α-**bromoketones using HBA under mild conditions with short reaction time has been developed. Propiophenone was used as a model substrate for optimizing the conditions. Various parameters affecting the reaction were examined. The optimized conditions were treating propiophenone with HBA with the ratio of substrate to HBA as 1:1 in THF at RT for 5 min under UV (254 nm) irradiation. 2-Bromopropiophenone was obtained in high yield. The regioselectivity study was conducted using 2-hexanone and disclosed that the selectivity of reaction could be controlled by solvent.

In addition, another new protocol for **α**-bromination of certain ketones with HBA could be achieved by conducting in refluxing THF instead of using UV-irradiation. The scale-up of **α**-bromination of propiophenone into 2-bromopropio-phenone was also attempted with success.

Proposal for the Further Work

This methodology utilizing HBA should be applied with other carbonyl compounds such as amide and aldehyde under UV irradiation or reflux temperature. The regio-, chemo- and stereoselectivity studies of the system should be further investigated in order to comprehend the insight of this reaction.

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APPENDIX

Calculation method of % yield of product

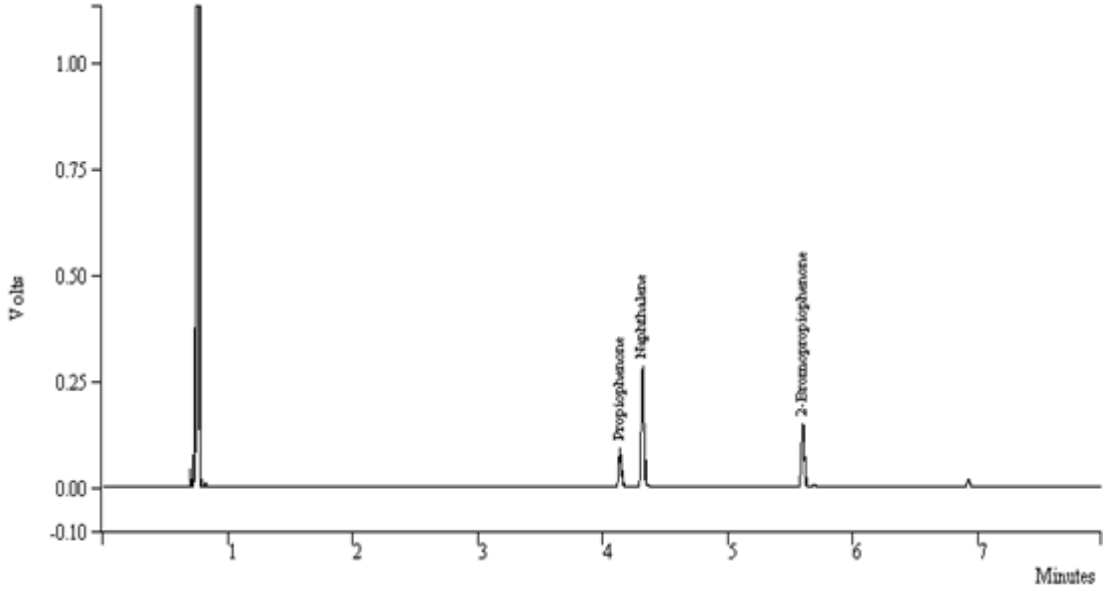

Figure 3.1 Chromatogram of the crude mixture for bromination of propiophenone (1)

By SGE-BP21 column

$$\frac{\text{Area of Internal standard}}{\text{Area of Sample}} \times \frac{\text{Mol. Of Sample}}{\text{Mol. Of Internal standard}} = \text{IRF}$$

$$\frac{\text{Actual mole of product}}{\text{Expect mole of product}} \times 100 = \%\text{yield}$$

By ^{1}H NMR

$$\%\text{yield} = \frac{\text{(integration of product)}}{\text{(integration of internal std)}} \times \frac{\text{(amount H of internal std)}}{\text{(amount H of product)}} \times 100$$

VITA

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