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RESEARCH ARTICLE

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Synthesis of 4-hydroxymethylbenzophenone by phase transfer catalytic method

Abstract An important organic intermediate 4-hydroxymethylbenzophenone was synthesized by halogenation and hydrolyzation with phase transfer catalytic method using 4-methylbenzophenone as raw material and the technological conditions of reactions were investigated as well. Experimental results show that *N*-bromosuccinimide (NBS) is a good reagent to give 4-bromomethylbenzophenone undergoing a radical reaction with 4-methylbenzophenone with the yield of about 70.7%; 4-bromomethylbenzophenone can be hydrolyzed under basic conditions in the presence of phase transfer catalyst triethylbenzylammonium chloride for 5 h to give 4-hydroxymethylbenzophenone with yield of 84.4%. After the crude product is recrystallized from tetrahydrofuran (THF), the final product is obtained with purity above 99% .The structure of the titled compound is determined by infrared spectrum(IR), proton nuclear magnetic resonance (HNMR), and mass spectrum (MS) and elemental analysis (EA).

Keywords phase transfer catalytic method, 4-hydroxymethylbenzophenone, mass spectrum, nuclear magnetic resonance

1 Introduction

Chemical, photochemical and chemical-photochemical crosslinking agents have been employed extensively to probe the structure and function of enzymes and receptor proteins. While many of the photo reactive reagents contain azido, diazo or diazirine groups as photophores, more recently, benzophenone photoprobes [1–8] have been extensively used to study nucleotide, receptor and enzyme binding sites; combined with a chemically reactive groups, the benzophenone-containing reagents have also been employed as crosslinkers to investigate intramolecular as well as protein–protein interactions [9–11]. The benzophenone photoprobe can be superior to other photoactivatable groups since the benzophenone group is chemically more stable, and the benzophenone is photoactivated at 350 nm～360 nm, avoiding protein-damaging shorter wavelengths. 4-Hydromethylbenzophenone is an important and very useful organic intermediate, from which a series of benzophenone derivatives can be synthesized. For example, Oatis and Knapp [12] synthesize a cleavable heterobiofunctional benzophenone protein crosslinker 4-benzophenonemethyl maleimidoacetate by treatment of 4-hydromethylbenzophenone with maleimidoacetyl chloride. But there are few reprots about the synthesis of 4-hydromethylbenzopheone domestically and abroad at present. With the aim of developing new and more efficient benzophenone photoprobes and crosslinkers, this paper describe the technology conditions to synthesize 4-hydromethylbenzopheone by phase catalytic method [13] using intermediate 4-bromothylbenzopheone [14, 15] obtained from halogenation of 4-methylbenzophenone.

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2 Materials and methods

2.1 General

Unless otherwise stated, all reagents used are commercially available. Solvent were purified and dried by the standard procedures. All reactions were monitored by thin layer chromatography (TLC) on Sikica Gel F-254 plates with detection under ultraviolet (UV). All evaporations were carried out under reduced pressure at 5 °C. Uncorrected

melting was determined on an XR-01 apparatus. Infrared (IR) spectra were recorded on an AVATAR-360-FT spectrophotometer with KBr plates. Purity was measured through P230 high performance liquid chromatography (HPLC). Mass spectra (MS) were measured with an HP 5988 instrument. All nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-400 (400 MHz) Fourier transform spectrometer, and chemical shifts were expressed in parts per million (δ) relative to tetramethylsilane (TMS, 0 ppm) or $CHCl_3$ as an internal reference (7.26 ppm for ^1H). Elemental analysis was recorded on a PE-2400 instrument.

4-Methylbenzophenone was supplied by Hunan HaiIi Chemical Industry Co., Ltd.

2.2 Synthetic route

4-Methylbenzophenone undergoing a two-step reaction can successfully obtain the titled compound 4-hydromethylbenzophenone as shown in Fig. 1.

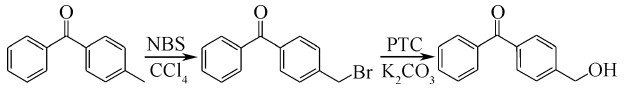


Fig.1 Synthetic route for 4-hydromenthylbenzophenone

2.3 Preparation of 4-bromomethylbenzophenone

A mixture of 4-methylbenzophenone (29.4 g, 0.15 mol), *N*-bromosuccinimide (NBS, 26.7 g, 0.15 mol), and benzoyl peroxide (0.7 g, 2.9 mmol) in CCl_4 (300 mL) was stirred at 85 ℃ for 3 h . The resulting mixture was cooled to room temperature and the white solid was removed by filtration. After the solvent was evaporated, the crude product was purified by recrystallization from CCl_4 to give 4-bromomethylbenzophenone (29.1g,70.7%),m.p.118°C～120°C.

2.4 Preparation of 4-hydroxymethylbenzophenone

A mixture of 4-bromomethylbenzophenone (11.0 g, 40 mmol),K_2CO_3(15.2 g, 120 mmol) and benzyltriethylammonium chloride (1.0 g) in water (100 mL) was stirred at 100 °C for 5 h. The product was extracted into ethyl acetate (2×100 mL) and the organic extracts were dried over Na_2SO_4. After the solvent was removed by evaporation, the crude product was recrystallized from propanol to give 4-hydroxymethylbenzophenone (7.1 g, 84.4%), m.p. 98°C～100 °C (Ref. [12] 59 °C～61°C).

3 Structural characterization

Recrystallization from THF give the titled compound 4-hydromethylbenzophenone with melt point 98°C～100 °C higher, about 40°C than the reported value 59–61 °C in Ref. [12]. We think the possible reason is that 4-hydromethylbenzophenone in the literature [12] was obtained by liquid chromatography, which contains some solvent in it, so the melt point was lower. High liquid performance chromatography (HPLC) indicates the purity is above 99%.

4-Hydromethylbenzophenone is successfully characteri zed [16] by elemental analysis, infrared spectrum, mass spectrum and proton nuclear magnetic resonance. Elemental analysis: calcd. for $C_{14}H_{12}O_2$: C, 79.24, H, 5.66. Found: C, 79.53, H, 5.61. IR (cm^{-1}): 3,418 (ν_{O-H}), 1,647 ($\nu_{C=O}$), 1,607 (ν_{Ar-H}).

3.1 MS analysis

The mass spectrum of 4-bromomethylbenzophenone is shown in Fig. 2.

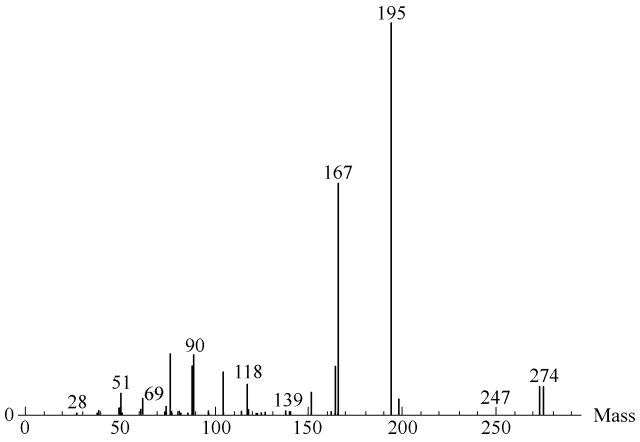


Fig.2 Mass spectrum of 4-bromomethylbenzophenone

The molecular ion of 4-bromomethylbenzophenone appears at *m*/*z* 274 and a ratio of M+2 (*m*/*z* 276) to M (*m*/*z* 274) peaks of approximately 1:1 indicates the presence of a single bromine atom in the compound because bromine in nature is 50.7% ^{79}Br and 49.3% ^{81}Br. The base peak at *m*/*z* 195 (M-79) corresponds to loss of a bromine radical from the molecular ion and loss of CO as a neutral molecule from this radical cation gives an ion of *m*/*z* 167. In addition, the peaks at *m*/*z* 105, 89, 77, 53 and 41 suggest the existence of benzophenone backbone. Assignment of characteristic peaks in mass spectrum of 4-bromomethylbenzophenone is shown in Table 1.

The mass spectrum of 4-hydromethylbenzophenone is shown in Fig. 3.

The molecular ion of 4-hydromethylbenzophenone appears at *m*/*z* 212. The peak at *m*/*z* 194 (M-18) corresponds to loss of water as a neutral molecule from the molecular ion. The peak at *m*/*z* 181 (M-31) corresponds to loss of hydromethyl from the molecular ion and loss of an oxygen atom from this radical cation gives an ion of *m*/*z* 165. The base peak at *m*/*z* 135 corresponds to loss of phenyl from the molecular ion. Similarly, the peaks at *m*/*z* 105, 89, 77 and 51

suggest the existence of benzophenone backbone. Assignment of characteristic peaks in mass spectrum of 4-hydromethylbenzophenone is shown in Table 2.

Table 1 Characteristic peaks in mass spectrum of 4-bromomethylbenzophenone

m/z	Relative abundance (%)	Assignment
274	10.5	M^+
276	10.5	M^++2
195	100.0(base peak)	M^+-Br
167	66.7	M^+-(Br,CO)
118	8.7	p-$COC_6H_4CH_2^+$
105	12.3	$PhCO^+$
90	17.5	$C_7H_6^+$
77	15.8	$C_6H_5^+$
51	5.3	$C_4H_3^+$

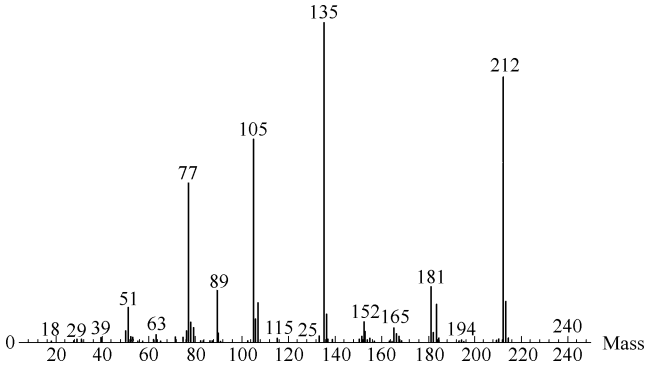


Fig.3 Mass spectrum of 4-hydromethylbenzophenone

Table 2 Characteristic peaks in mass spectrum of 4-hydromethylbenzophenone

m/z	Relative abundance (%)	Assignment
212	80.0	M^+
194	1.0	M^+-H_2O
181	18.0	M^+-CH_2OH
165	6.0	M^+-(CH_2OH, O)
152	7.6	M^+-(CH_2OH_2, O)
135	100.0(base peak)	$HOCH_2C_6H_4CO^+$
105	66.0	$PhCO^+$
89	14.0	$C_6H_4CH^+$
77	52.0	$C_6H_4^+$
51	12.0	$C_4H_3^+$

3.2 ^{1}H NMR of 4-hydromethylbenzophenone

^{1}H NMR of 4-hydromethylbenzophenone is shown in Fig.3. Analysis of the ^{1}H NMR of 4-hydromethylbenzophenone indicate that:

(a) The multiplet at δ7.772~7.798 corresponds to the four *ortho* hydrogens to the carbonyl in the two benzene rings. Similarly, multiplet at δ7.461~7.499 corresponds to the four *meta* hydrogens and multiplet at δ7.573~7.611 corresponds to the one *para* hydrogen in one of the two benzene rings. Because of the withdrawing effect of carbonyl, electron density of the *ortho* hydrogens is lower than the *meta* and *para* hydrogens, so the δ values of *ortho* hydrogens shift to downfield. According to resonace theory, electron density of the *meta* hydrogens is the highest, so its δ values shift to upfield. The signal splitting is more complicated due to the different chemical environment of the two benzene rings.

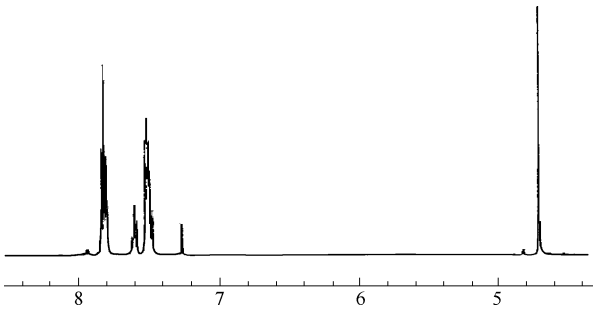


Fig.4 ^{1}H-NMR spectrum of 4-hydromethylbenzophenone

(b) The signal of hydrogens on the oxygen-bearing carbon appears as a singlet at δ4.793, which corresponds to a downfield shift of approximately 3.4 units compared with their normal position in alkanes.

(c) As well known, the chemical shift of the hydroxyl hydrogen is variable and depends on the purity of the sample, the concentration, the solvent, and the temperature. Signal of the hydroxyl hydrogen of 4-hydromethylbenzophenone is not seen in this spectrum.

4 Results and discussion

4.1 Halogenation of 4-methylbenzophenone

Cl_2 , Br_2 and NXS (X=I,B,C) are commonly used in the halogenation reaction. Considering the high toxicity of Cl_2 and Br_2, this study only discusses the halogenation effects of 4-methylbenzophenone reacting with *N*-bromosuccini mide (NBS), *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) respectively, the results are as shown in Table 3.

Table 3 The effect of different NXS on halogenation reactions

NXS	Reaction time (h)	Yield (%)
NIS	1	68.9
NBS	3	70.7
NCS	10	21.4

It can be inferred from Table 3 that both NIS and NBS are good halogenation reagents to 4-methylbenzophenone in theory, but NIS is much more expensive than NBS, and yet its yield is not superior to NBS. So NBS is confirmed as the

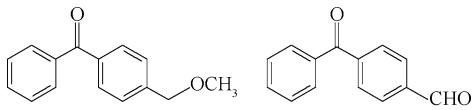
halogenation reagent in this reaction.

4.2 Synthetic technology conditions of 4-hydromethyl-benzophenone

It was found that the reaction mixture was a two-phase system when 4-bromomethylbenzophenone was hydrolyzed in K_2CO_3 solution because of its low solubility in water. This study has tried different organic solvents and phase transfer catalysts to improve the yield and decrease the reaction time.

4.2.1 Choosing the organic solvents

Four kinds of solvents such as THF, 1,4-diethylene dioxide, methanol and dimethyl sulfoxide (DMSO) were tried to hydrolyze compound 4-hydromethylbenzophenone (see Fig. 1). The result indicates that: (1) the solution of 4-hydromethylbenzophenone in THF or 1,4-diethylene dioxide cannot mix with water either, so it is still a two-phase reaction with low yield; (2) the solution of 4-hydromethylbenzophenone in methanol and DMSO can mix with K_2CO_3 solution very well, but there are many side-products generated. For example, when the organic solvent is methanol, the side-product is 4-methoxymethylbenzophenone (shown in Scheme 1), and when the solution is DMSO, the side-product is 4-benzoylbenzaldehyde (shown in Scheme 1). So it fails to find a good organic solvent that is suitable for the basic hydrolyzation of 4-hydromethylbenzophenone in our laboratory.



Scheme 1

4.2.2 Choosing the phase transfer catalysts

Polyethylene glycol 1000 (PEG-1000), cetyl trimethyl ammonium bromide (HTAB), nonyl phenol ethoxylate (10) mol (NPE-10), tetrabutyl ammonium tribromide (TBAB), dodecyldimethylbenzyl ammonium chloride (DDBAC) and benzyl triethyl ammonium chloride (BTEAC) were used in the hydrolyzation reaction, their catalytic effect are shown in Table 4. The result indicates that: (1) there are many side-products generated and still part of 4-hydromethylbenzophenone left in the presence of PEG-1000; (2) during these catalysts, BTEAC is the best. After the crude product is recrystallized from THF, the yield can get to 84.4%.

4.2.3 Purification of the crude product

HPLC indicates that there are still some side-products in the crude product. So ethyl acetate, isopropanol and THF are tried respectively to recrystallize the titled compound and the results are shown in Table 5 indicating that THF is a good solvent to recrystallize 4-hydromethylbenzophenone.

Table 4 The effect of different PTCs on hydrolyzation yield

PTC	Yield (%)
PEG-1000	40.6
HTAB	58.7
NPE-10	27.6
TBAB	60.7
DDBAC	76.3
BTEAC	84.4

Table 5 The effect of different solvents to recrystallize 4-hydromethylbenzophenone

Solvent	Yield (%)
Ethyl acetate	79.4%
isopropanol	73.5%
THF	84.4%

5 Conclusions

(a) Considering the reaction activity and price of NBS, NCS and NIS, NBS is a good free radical halogenation reagent. 4-Methylbenzophenone reacting with NBS with the mole ratio 1:1 in the presence of benzoyl peroxide and CCl_4 can give intermediate 4-bromomethylbenzophenone with 70.7% yield.

(b) 4-Hydromethylbenzophenone can be obtained by hydrolyzing 4-bromomethylbenzophenone for 5 h in the presence of K_2CO_3 and BTEBA, after the crude product is recrystallized from THF, the yield reaches 84.4% and purity above 99%.

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