

An efficient method for synthesis of phenacyl derivatives under homogeneous phase transfer catalyst condition in aqueous media

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Abstract

In this letter, a mild and efficient procedure for synthesis of phenacyl derivatives under homogenous catalysis in the presence of tetrabutylammonium bromide in aqueous media is described. The nucleophilic substitution reactions were performed under ecofriendly conditions and gave the corresponding products in high yields and short reaction times.

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Keywords: Tetrabutylammonium bromide; Nucleophilic substitution; Synthesis of phenacyl derivatives

The phenacyl compounds are useful intermediates in organic synthesis and have attracted a great deal of interest [1,2]. Derivatives of α -keto compounds were opened an important area of heterocyclic chemistry on account of the fact that many of them are subunits of natural products and pharmaceutical agents. Azide and thiocyanate derivatives of α -keto compounds are useful intermediates in the synthesis of heterocyclic compounds such as pyrroles, oxazoles and thiazoles [3–5]. Due to their instability, α -iodo ketones have been scarcely used, except in some reactions like the Rap–Stoermer that has been reported for the synthesis of benzofurans [6]. Unfortunately, the few synthetic methods that available for synthesis of azide, thiocyanate, cyanide and iodide derivatives of α -keto compounds are tedious and need some complex and environmentally high-impact reagents [7]. Recently, because of the cost, availability, and compatibility across phases in biphasic organic-aqueous layer heterogeneous reaction systems with water as solvent, tetrabutylammonium bromide (TBAB) plays an important role as a homogeneous catalyst in various organic transformations [8–15]. On the basis of these drawbacks and in continuation of our ongoing effort to introduce novel catalysts for organic transformation [16,17], we decided to investigate the application of TBAB as a catalyst for synthesis of α -keto derivatives in water.

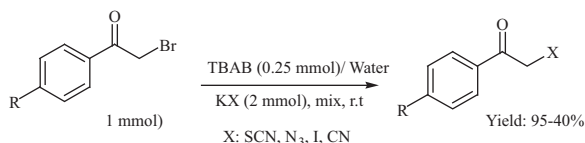
1. Experimental

All of the phenacyl derivatives were prepared by our procedure; their spectroscopic and physical data were compared with those of authentic samples. NMR spectra were recorded in CDCl₃ on a Bruker Advanced DPX

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Table 1

Results of the treatment of α -bromo acetophenone derivatives with various nucleophiles.

Entry	α -Bromo acetophenone derivatives	X	Time (min)	Yield ^{a,b} (%)
1a		N ₃	30	87
1b		SCN	40	92
1c		I	40	90
1d		CN	70	45 ^c
2a		N ₃	30	94
2b		SCN	25	95
2c		I	30	92
2d		CN	90	40 ^c
3a		N ₃	15	90
3b		SCN	30	93
3c		I	30	91
3d		CN	110	65 ^c
4a		N ₃	25	92
4b		SCN	35	93
4c		I	30	90
4d		CN	45	40 ^c

^a Products were identified by comparison of their physical and spectral data with those of authentic samples^b Isolated yields.^c The results according to GC analysis.

400 MHz instrument spectrometer using TMS as internal standard. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

To a mixture of sodium salt (2 mmol) and tetrabutylammonium bromide (TBAB) (0.25 mmol) in water (5.0 mL), α -bromoketone (1.0 mmol) was added and magnetically stirred for the time shown in Table 1. After completion of reaction, monitored by TLC (*n*-hexane:ethyl acetate; ratio = 5:1), the mixture extracted into ether (3 \times 5). The combined organic layer washed with cold water (3 \times 10), dried over CaCl₂ and then evaporated to dryness to give desired product. All of the reactions reported here were pure as judged by TLC, FTIR and NMR analysis of the crude reaction mixture. 1-(4-methoxyphenyl)-2-thiocyanatoethanone (entry **2b**): IR (neat): ν SCN (2157 cm⁻¹); ¹³C NMR (CDCl₃, 100 MHz): δ 42.9 (CH₂), 55.7 (CH₃O), 112.2 (SCN), 114.4 (m-C), 126.9 (C), 130.9 (O-C), 164.8 (p-C), 189.2 (CO); 2-iodo-1-(4-methoxyphenyl)ethanone (entry **2c**): IR (neat): ν C-I (615 cm⁻¹); ¹³C NMR (CDCl₃, 100 MHz): δ 1.72 (CH₂), 55.6 (CH₃O), 114.3 (m-C), 126.3 (C), 130.6 (O-C), 164.0 (p-C), 191.5 (CO); 2-azido-1-(4-bromophenyl)ethanone (entry **4a**): IR (neat): ν N₃ (2103 cm⁻¹); ¹³C NMR (CDCl₃, 100 MHz): δ 54.8 (CH₂), 129.4–133.0 (Ar-C), 192.3 (CO); 1-(4-bromophenyl)-2-thiocyanatoethanone (entry **4b**): IR (neat): ν SCN (2157 cm⁻¹); ¹³C NMR (CDCl₃, 100 MHz): δ 42.6 (CH₂), 111.5 (SCN), 129.8–132.6 (Ar-C), 189.8 (CO).

2. Results and discussion

In order to optimize the reaction condition and to evaluate catalytic activity of TBAB, 2-bromo-1-phenylethanone were used as a model compound and reacted with sodium thiocyanate in water at room temperature. According to thin-layer chromatographic analysis, the best results were obtained with the condensation of one mole of the phenacyl bromide with 2 mol of NaSCN using 0.25 mol of TBAB in water. The catalyst acted very efficiently and converted the entry to its corresponding 1-phenyl-2-thiocyanatoethanone in high isolated yield within

40 min. Table 1 shows the scope and limitations of these nucleophilic substitution reactions using several α -bromoacetophenone derivatives.

The formation of products can be easily detected by the characteristic ^{13}C absorption band of $-\text{SCN}$ group for phenacyl thiocyanate at ~ 112 and α -carbon in phenacyl azide and iodide that shift from ~ 30 in phenacyl bromide to ~ 54 and ~ 1.3 ppm, respectively. Although phenacyl thiocyanates, azides and iodides were obtained in high isolated yields, phenacyl cyanides could only be obtained in moderate yields; because the reaction system becomes pasty so hindering the completion of the reactions. These results are in agreement with the hard and soft acid and base principle (HSAB) and the data acquired by Sukata for alkyl halides [18].

To evaluate the efficiency of this method for the scaling up experiment, transformation of 1-(4-methoxyphenyl)-2-bromide was also performed on a 100 mmol scale. Gratifyingly, the substrate provided the corresponding phenacyl derivatives without appreciable decrease in the yields.

In conclusion, we have reported here the use of tetrabutylammonium bromide as an efficient catalyst in the synthesis of phenacyl derivatives in water. The reactions generated the corresponding products under mild conditions and with satisfactory yields.

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