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An Effective Green Procedure for the Synthesis of Phenacyl Derivatives Catalyzed by Silica-bound 3-{2-[Poly(ethylene glycol)]ethyl}-substituted 1-Methyl-1H-imidazol-3-ium Bromide as a Recyclable Phase Transfer Catalyst under Aqueous Media

N. Ayashi[a], M. Fallah-Mehrjardi[b,c] and A.R. Kiasat[a,*]

[a]*Chemistry Department, Collage of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran*

[b]*Chemistry Department, Payame Noor University, Tehran, 19395-4697, Iran*

[c]*Research Center of Environmental Chemistry, Payame Noor University, Ardakan, Yazd, Iran*

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The use of a recyclable phase transfer catalyst, SiO_2-PEG-ImBr, is demonstrated in a simple and highly efficient synthesis of phenacyl derivatives by nucleophilic substitution reaction of phenacyl halides with different anions in water. Advantages of this system are easy work-up, moderate to good yields, and recyclable catalyst. The catalyst can be recycled and reused several times with no loss of its efficiency.

Keywords: Phenacyl derivatives, Phenacyl halides, Phase transfer catalyst, Nucleophilic substitution, Silica supported

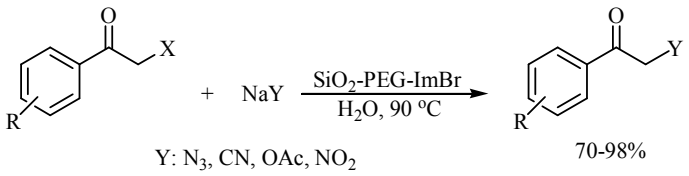
INTRODUCTION

Organic reactions in water, which avoid the use of harmful organic solvents, are nowadays of great interest, especially in relation to today's environmental concerns [1]. Unfortunately, the use of water as solvent is limited by the low solubility of most organic compounds in aqueous media. The use of phase transfer catalysts (PTCs) is one of the most important and effective strategies to overcome the limitations of water as solvent [2]. The fact that catalysts are in a distinct phase with respect to the reaction medium, accounts for a major advantage of the heterogeneous catalysts over the homogeneous ones as it makes the separation and reutilization of heterogeneous catalysts simple and cheap compared to the homogeneous catalysts [3]. Additionally, one of the major problems associated with the use of soluble catalysts lies in the recovery of the catalyst from the reaction medium. Immobilization of the catalyst on a polymeric matrix can provide a simple solution to this problem [4]. A further benefit is the ease of product isolation and purification.

*Corresponding author. E-mail: akiasat@scu.ac.ir

Being interested in the development of mild and convenient methodologies for the organic syntheses in aqueous media using recyclable catalysts, we have focused on the immobilization of polyethylene glycol derivatives on silica gel [5] and dowex resin [6]. In continuation of our work on the use of heterogeneous catalysts and phase transfer catalysts in organic syntheses [5-16], recently we introduced silica-bound 3-{2-[poly(ethylene glycol)]ethyl}-substituted 1-methyl-1H-imidazol-3-ium bromide, as phase transfer catalyst in the synthesis of β-hydroxynitriles [11] and 1,2-azidoalcohols [12]. We now wish to report here the synthetic applicability of this catalyst for the synthesis of phenacyl derivatives by the nucleophilic substitution reaction between phenacyl halides and different anions in water (Scheme 1).

The phenacyl derivatives are emerging as useful intermediates for various organic transformations. Phenacyl derivatives opened an important area of heterocyclic chemistry on account of the fact that many of them are subunits of natural products and pharmaceutical agents [17, 18]. Functional groups in these compounds can be readily converted to the other functional groups and a wide range of useful organic compounds are obtained [19]. Unfortunately,



Scheme 1. Phenacyl halides converted into their derivatives

the few synthetic methods available for the synthesis of phenacyl derivatives are tedious and need complex and environmentally high-impact reagents [20-24]. Consequently, the development of novel and efficient procedures under mild and more convenient conditions has attracted sustained interest in organic synthesis.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. Silica gel (Aldrich 70-270 mesh, 60 Å, Surface area > 500 m^2/G) was activated by treatment with HCl (5 N) for 6 h and dried in vacuum at 120 °C [25]. Polyethylene glycol (600) was heated at 80 °C under vacuum for 30 min before use to remove traces of moisture. Yields refer to isolated crude products. NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as internal standard. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel poly Gram SILG/UV 254 plates.

Preparation of Silica Chloride [26]

To the dried activated silica gel (20 g) was added dropwise freshly distilled $SOCl_2$ (45 ml) under nitrogen atmosphere and at room temperature. Evolution of copious amounts of HCl and SO_2 occurred instantaneously. After stirring for another 4 h, the excess unreacted thionyl chloride was distilled off and the resulting grayish silica chloride was flame dried, stored in air-tight container and used as such for the reactions.

Preparation of Polyethylene Glycol Monobromide, HO-PEG-Br [27]

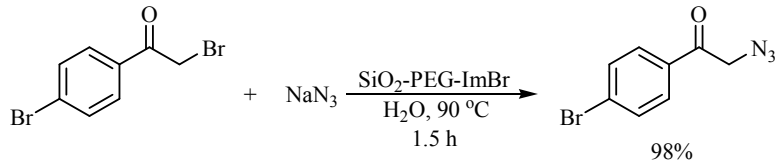
To a solution of polyethylene glycol 600 (30 g, 0.1 mol OH) and pyridine (7.9 g, 0.1 mol) in 500 ml of toluene, thionyl chloride (8 g, 0.07 mol) was slowly added with stirring over a period of half an hour. The mixture was then refluxed for about 6 h. After cooling and filtering off the pyridine hydrochloride salt, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and treated with activated alumina. The process was repeated twice. The CH_2Cl_2 solution was filtered and evaporated to dryness. The yield was 28 g (90%) of polyethylene glycol monochloride. Then, a mixture of HO-PEG-Cl (28 g, 45 mmol) and sodium bromide (15.5 g, 150 mmol) was heated in an oil bath at 120 °C overnight. After cooling, CH_2Cl_2 (20 ml) was added, the solution was filtered, and the solvent was removed to obtain polyethylene glycol monobromide (26 g, 87%).

Preparation of SiO_2-PEG-ImBr [12]

To a well-stirred silica chloride (11 g) in dry CH_2Cl_2 (40 ml) was added dropwise HO-PEG-Br (5 g) under nitrogen atmosphere and at room temperature. HCl was instantaneously evaluated. After stirring for another 3 h, the obtained SiO_2-PEG-Br was removed by filtration and the product was washed several times with acetone (3×20 mL) and dried. Then, a mixture of SiO_2-PEG-Br (14 g) and 1-methyl imidazole (8.2 g, 0.1 mol) was heated with stirring at 80 °C in an oil bath for 48 h. The inorganic-organic graft copolymer was washed with Et_2O (20 ml) and then with MeCN (20 ml) and dried.

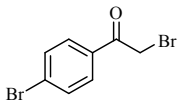
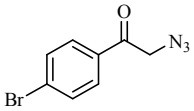
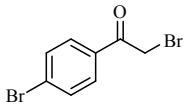
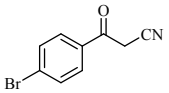
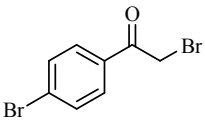
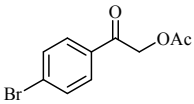
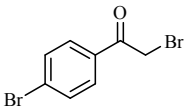
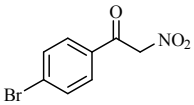
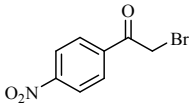
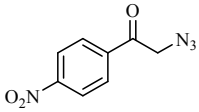
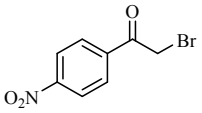
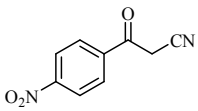
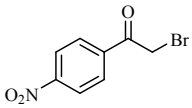
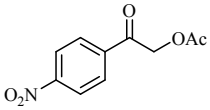
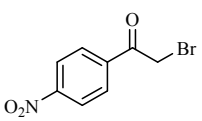
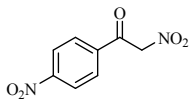
General Procedure for the Preparation of Phenacyl Derivatives in Water

To a mixture of the phenacyl halide (1 mmol) and NaY (Y: N_3, CN, OAc and NO_2) (2-7 mmol) in water (5 ml) was added SiO_2-PEG-ImBr (0.2 g). The mixture was stirred at 90 °C for the time shown in Table 1. Progress of the reaction was monitored by TLC using Hexane:EtOAc (5:1). After completion of the reaction, the catalyst was recovered for reuse by filtration and the product was extracted with



Scheme 2. Azidation of *p*-bromo phenacyl bromide in the presence of SiO_2-PEG-ImBr catalyst

Table 1. Synthesis of Phenacyl Derivatives from the Reaction of Phenacyl Halides with Azide, Cyanide, Acetate and Nitrite Anions Catalyzed by SiO_2-PEG-ImBr in Water at 90 °C

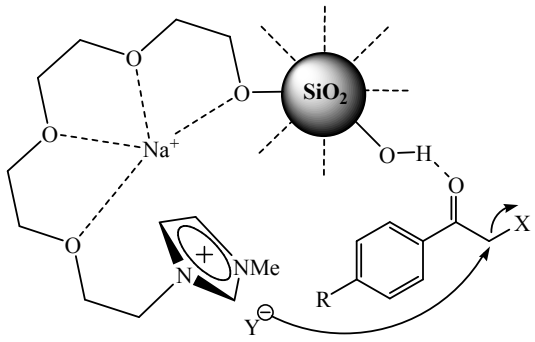
Entry	Substrate	Product	Substrate:nuclephile	Time (h)	Yields (%)[a]
1			1:3	1.5	98
2			1:3	1.5	90
3			1:7	2	70
4			1:7	2	72
5			1:2	1	85
6			1:2	0.5	75
7			1:6	1.5	90
8			1:6	1.5	70

[a]Yields refer to pure isolated products which were identified by the comparison of their m.p., TLC, IR and NMR spectral data with those of authentic samples.

Table 2. IR Absorption Frequencies and ^{13}C Signals of Phenacyl Derivatives Functional Groups

Functional group	IR (cm^{-1})	^{13}C NMR (ppm)
-CN	~2250	~115
-OAc	~1750	~170
$-N_3$	~2100	~54[a]
$-NO_2$	~1380 and ~1550	~85[a]

[a] ^{13}C NMR of α-carbon.



Scheme 3. Catalytic activity of SiO_2-PEG-ImBr

Et_2O (3 × 10 ml). The solvent was dried with $CaCl_2$ and evaporated under reduced pressure. The desired phenacyl derivatives were obtained in high isolated yields (70-98%).

Spectral Data for Respective Compounds

2-Azido-1-(4-bromophenyl)ethanone (entry 1). IR (neat) ν_{max} N_3 (cm^{-1}): 2104; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 53.9 (CH_2), 128.8-134.7 (Ar-C), 193.2 (CO).

2-(4-Bromophenyl)-2-oxoethyl acetate (entry 3). IR (neat) ν_{max} CO (cm^{-1}): 1747; ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 20.6 (CH_3), 64.9 (CH_2), 128.3-133.2 (Ar-C), 169.8 (CO_2), 194.4 (CO).

1-(4-Bromophenyl)-2-nitroethanone (entry 4). IR (neat) ν_{max} NO_2 (cm^{-1}): 1380 and 1551; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 85.3 (CH_2), 113.1 (Ar-C), 131.4-133.2 (Ar-C), 163.7 (Ar-C), 192.3 (CO).

3-(4-Nitrophenyl)-3-oxoprapanenitrile (entry 6). IR (neat) ν_{max} CN (cm^{-1}): 2253; ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 31.2 (CH_2), 117.8 (CN), 121.4-138.7 (Ar-C), 160.3 (Ar-C), 187.0 (CO).

RESULTS AND DISCUSSION

Based on previous reports on the use of silica-bound 3-{2-[poly(ethylene glycol)]ethyl}-substituted 1-methyl-1H-imidazol-3-ium bromide in organic syntheses under aqueous conditions [11,12], we first attempted the azidation of *p*-bromo phenacyl bromide using SiO_2-PEG-ImBr. The reaction resulted in the formation of the corresponding phenacyl azide in 98% yield after 1.5 h (Scheme 2). The reaction in the presence of SiO_2 was not accomplished even after a very long time, while, in the presence of PEG, SiO_2-PEG and ImBr, the reaction was done but was not completed after 3 h. Therefore, SiO_2-PEG-ImBr as a heterogeneous phase transfer catalyst was considered as the best catalyst in this transformation.

To study the scope of this approach, various phenacyl halides were subjected to nucleophilic substitution reaction

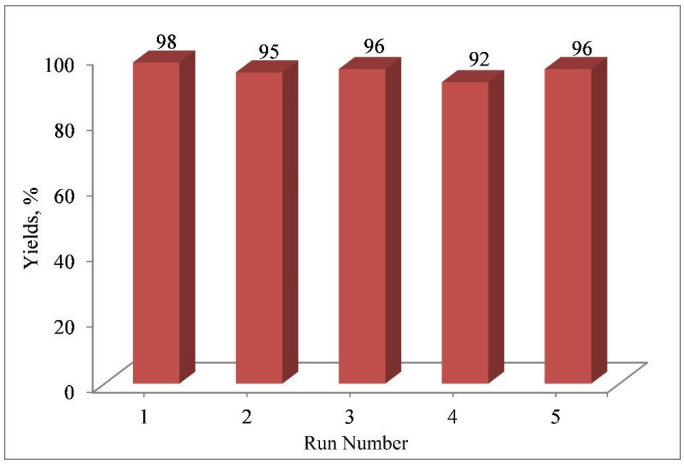


Fig. 1. The reusability of catalyst.

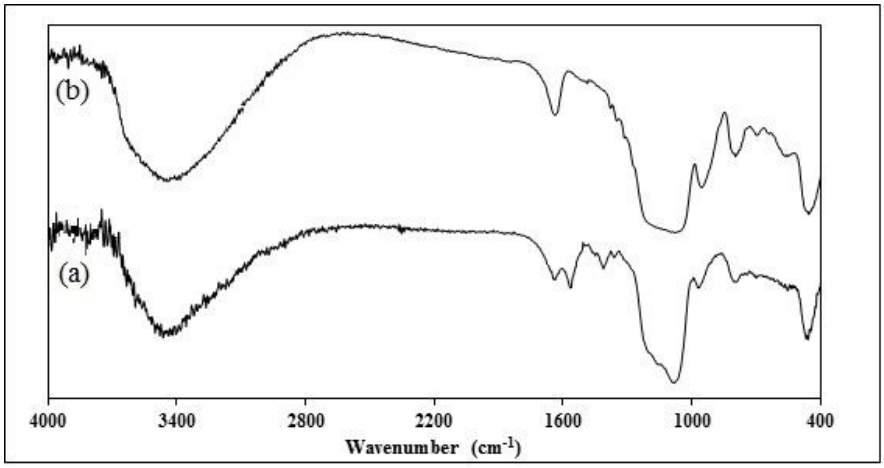


Fig. 2. FT-IR spectra of SiO_2-PEG-ImBr (a) fresh, and (b) after 5 runs recycle.

with different anions using catalytic amounts of SiO_2-PEG-ImBr to afford the corresponding phenacyl derivatives in yields ranging from 70-98% in an appropriate time (Table 1, Scheme 1). These reactions were completed in a time period of 0.5-2 h, whereas no reaction was observed in the absence of catalyst, even after a long reaction time.

The structure of all products was settled from their analytical and spectral (IR, ^{13}C NMR) data and by direct comparison with authentic samples. The IR absorption frequencies and the ^{13}C signals of functional groups in the isolated products are listed in Table 2.

In the absence of the catalyst, the reactions were very slow in water. The addition of SiO_2-PEG-ImBr significantly improved the reaction rates and yields. This is probably due to activation of the phenacyl halide by the hydrogen bonding between silanol hydroxy groups at the silica gel surface and the oxygen of carbonyl group in the phenacyl halide. In addition, polyethylene glycol units in PTC can encapsulate sodium cation, much like crown ethers, and this complex causes the nucleophiles to be activated. The 1-methylimidazol-3-ium units introduced ionic liquid property to the catalyst. Furthermore, the rate of reaction could be facilitated due to the presence of bromide to the nucleophile anion exchange (Scheme 3).

The reusability of the heterogeneous catalyst is of great importance from synthetic and economical points of view. While, the homogeneous polyethylene glycol (PEG) cannot be recovered even for one time, the PEG supported catalysts can be filtered and reused several times without significant loss of their activity. The reusability of SiO_2-PEG-ImBr, were investigated in the azidation reaction of *p*-bromo phenacyl bromide. At the end of each reaction, the catalyst was separated by simple filtration, washed with water and methanol and dried at 70 °C. The recycled catalyst was reused for a consecutive run under the same reaction conditions. The results showed that the catalyst preserves its catalytic activity for at least five consecutive runs (Fig. 1). The color of the catalyst remains unchanged even after the fifth cycle. Furthermore, the intensity and peak positions between the used and fresh catalyst in the FT-IR spectra after the reaction, indicated that structure of the catalyst has been remained the same as that of the fresh catalyst (Fig. 2).

CONCLUSIONS

In conclusion, the present study offers a better alternative to the existing methods for the synthesis of phenacyl derivatives using a recyclable phase transfer catalyst, SiO_2-PEG-ImBr, in water *via* nucleophilic substitution reaction. This method is mild and gave moderate to good yields of phenacyl azides, cyanides, acetates and nitrites. The important features of this procedure are mild reaction condition, easy work-up, high yield, green aspects such as avoiding hazardous organic solvents, toxic catalysts and waste, ease of recovery and reuse of the catalyst.

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