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FULL-LENGTH PAPER

A simple and rapid protocol for the synthesis of phenacyl derivatives using macroporous polymer-supported reagents

Ali R. Kiasat · **Soheil Sayyahi**

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Abstract This article describes the use of Amberlite IRA-910 with different counter ions as excellent polymer-supported reagents in nucleophilic substitution reactions. The versatility of this protocol allowed the synthesis of a diversified library of phenacyl derivatives with high yields. The polymeric reagents can be reloaded several times with no loss of their efficiency.

Keywords Nucleophilic substitution · Macroporous resin · Polymer-supported reagent · Phenacyl derivative

Introduction

Since the pioneering study by Merrifield in the field of solid-phase chemistry [1], polymer-supported reagents have become state-of-the-art tools increasing interest as insoluble matrices in organic synthesis [2,3]. They offer advantages such as reaction monitoring as well as increased safety, especially when the non-supported reagents are toxic or hazardous as they can be easily removed from reaction media and recycled [4,5]. In addition, employing an excess amount of reagent is allowed without the need for additional purification steps [6].

Polymer-supported reagents have been and continue to be used successfully for the parallel synthesis of single compounds as well as the multi-step synthesis of different heterocyclic systems including complex natural products and pharmaceutical agents [7,20]. Although many polymer-supported reagents have been described for many transformations, there is still a need for new polymer-supported reagents to gain access to additional compounds classes [8–15].

In our continuing interest in the development of supported reagents and catalysts for organic transformation [16], we decided to investigate nucleophilic substitution reactions of α-bromo ketones using macroporous resins supported thiocyanate, azide, iodide, and cyanide for the synthesis of α-keto derivatives. Recently, this kind of matrix was used due to its low degree of swelling and excellent compatibility with a wide range of organic solvents as well as in aqueous and good mechanical stability [17,18]. The overall reactions are shown in Scheme 1.

The phenacyl compounds are useful intermediates in organic synthesis and have attracted a great deal of interest [19,20]. 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 [21–23]. Due to their instability, α-iodo ketones have been scarcely used, except in some reactions such as the Rap–Stoermer that has been reported for the synthesis of benzofurans [24]. Unfortunately, the few synthetic methods available for the synthesis of azide, thiocyanate, cyanide, and iodide derivatives of α-keto compounds are tedious and need complex and environmentally high-impact reagents [25].

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

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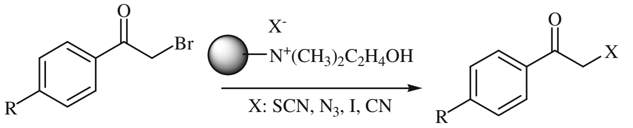
A. R. Kiasat (✉) · S. Sayyahi
Chemistry Department, College of Science, Shahid Chamran University, Ahvaz 61357-4-3169, Iran
e-mail: akiasat@scu.ac.ir



Scheme 1 Substitution reaction of α-bromo ketones using polymer-supported reagents

in $CDCl_3$ on a Bruker Advanced DPX 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.

Preparation of polymer-supported reagents

Amberlite IRA-910SCN, N_3, I, CN forms, which are not commercially available, were easily prepared from their corresponding chloride form via ion exchange using 10% NaSCN, NaN_3, NaI, and NaCN aqueous solutions, respectively. Ten grams of Amberlite IRA-910 chloride form (loading: 3.8 meq/g; mesh 16–50) were stirred for 6 h in the corresponding solution (100 mL), filtered-off, and washed several times with water and dried under vacuum at 50 °C before using.

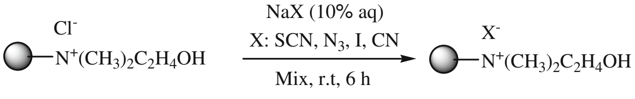
General experimental procedure α-bromo acetophenone derivatives with various polymeric reagents

To a mixture of Amberlite IRA-910 SCN, N_3, I, CN forms (1.0 g, loading: 1.8 meq/g) in acetonitrile (5.0 mL), α-bromo ketone (1.0 mmol) was added. The suspension was magnetically stirred under refluxing conditions for the time shown in Table 1. After complete consumption of α-bromo ketone as judged by TLC (*n*-hexane:ethyl acetate; ratio = 5:1), the resin was filtered and washed with acetonitrile (3 × 5 mL). The combined filtrates were dried over $CaCl_2$ and then evaporated to dryness to give desired product. The crude products were purified by either preparative TLC or flash chromatography.

1-(4-Methoxyphenyl)-2-thiocyanatoethanone (entry 2b): IR (neat): ν SCN$(2,157\,cm^{-1})$; ^{13}C NMR$(CDCl_3$, 100 MHz): δ 42.9 (CH_2), 55.7 (CH_3O), 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$(615\,cm^{-1})$; ^{13}C NMR$(CDCl_3$, 100 MHz): δ 1.72 (CH_2), 55.6 (CH_3O), 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 $N_3(2,103\,cm^{-1})$; ^{13}C NMR$(CDCl_3$, 100 MHz): δ 54.8 (CH_2), 129.4–133.0 (Ar–C), 192.3(CO).



Scheme 2 Preparation of polymer-supported reagents

1-(4-Bromophenyl)-2-thiocyanatoethanone (entry 4b): IR (neat): ν SCN$(2,157\,cm^{-1})$; ^{13}C NMR$(CDCl_3$, 100 MHz): δ 42.6 (CH_2), 111.5(SCN), 129.8–132.6 (Ar–C), 189.8(CO).

Results and discussion

The polymer-supported azide, iodide, thiocyanide, and cyanide were easily prepared by exchange of the anion of Amberlite IRA-910 Cl^- form by using aqueous solutions (10%) of NaN_3, NaI, NaSCN, or NaCN (Scheme 2).

We used 2-bromo-1-phenylethanone as a model compound and reacted with macroporous resin supported thiocyanate, P^+ SCN^-, in different solvent. Thin-layer chromatographic analysis showed that the polymeric reagent acted very efficiently in refluxing CH_3CN and 1.0 g of the P^+ SCN^- is enough to convert the entry to its corresponding 1-phenyl-2-thiocyanatoethanone in high isolated yield within 1 h. Table 1 shows the scope and limitations of these nucleophilic substitution reactions using several α-bromo acetophenone derivatives.

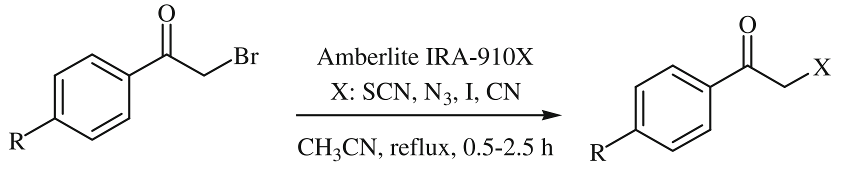
The formation of products can be easily detected by the characteristic ^{13}C signal of the –SCN group for phenacyl thiocyanate at ~112 ppm and α-carbon in phenacyl azide and iodide that shift from ~30 ppm in phenacyl bromide to ~54 ppm and ~1.3 ppm, respectively. Although phenacyl thiocyanates, azides, and iodides were obtained in high isolated yields, phenacyl cyanides could only be obtained in moderate yields. These results are in agreement with the hard and soft acid and base principle (HSAB) and the data acquired by Sukata for alkyl halides [26].

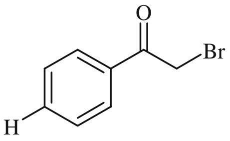
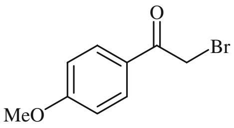
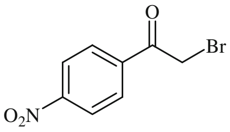
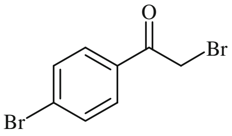
The nature of the substituent on the phenyl ring has a significant influence on the reaction rate. While α-bromo acetophenone derivatives with electron withdrawing groups react faster, derivatives with electron-donating groups require longer reaction times.

It is also worth mentioning that resin do not suffer from extensive mechanical degradation after operating and can be load again by reagents. In order to demonstrate the reusability of the reagent, thiocyanation of 2-bromo-1-phenylethanone with P^+ SCN^- was chosen as a model. After reaction completion, the polymeric reagent was washed with distilled water and then loaded again with aqueous NaSCN solution. This process repeated thrice and no appreciable yield decrease was observed (Table 2).

In conclusion, we report straight forward and reliable method for the preparation and use of Amberlite IRA-910

Table 1 Results of the treatment of α-bromo acetophenone derivatives with various polymeric reagents



Entry	α-Bromo acetophenone derivatives	X	Time (h)	Yield[a,b] (%)
1a		N_3	1.15	85
1b		SCN	1.0	90
1c		I	1.0	90
1d		CN	2.5	55[c]
2a		N_3	1.15	95
2b		SCN	1.5	95
2c		I	1.5	92
2d		CN	2.5	40[c]
3a		N_3	0.15	91
3b		SCN	0.5	94
3c		I	0.5	90
3d		CN	1.45	60[c]
4a		N_3	0.5	90
4b		SCN	0.5	92
4c		I	0.5	90
4d		CN	2.0	45[c]

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples [20,24,27]

[b] Isolated yields

[c] The results according to GC analysis

Table 2 Reusability of the reagent after reloading

Entry	Number of loading	Yield[a] (%)
1	1	90
2	2	87
3	3	85

[a] All reaction are carried out under similar condition

SCN, N_3, I, and CN resins as efficient heterogeneous reagents for the generation of thiocyanates, azides, iodo, and nitrile derivatives via nucleophilic substitution reactions.

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