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A fast procedure for the preparation of vicinal azidoalcohols using polymer supported reagents

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Abstract—Several vicinal azidoalcohols were prepared in good to high yield and purity, starting from aryl α-haloketones, using reagents supported on a macroporous ion exchange resin. This is a fast and new approach to aryl azidoalcohols.

Solution-phase synthesis using solid-phase reagents or scavengers has been termed 'polymer-assisted solution-phase' synthesis, and the developments in this field have been subject of several reviews.[1] The interest in this field has caused a recent explosion in the number of scientific papers describing the development of novel support-bound reagents, catalysts and methods for purification. Supported reagents are reactive species, which are associated with a support material. The most important advantage in using a polymer supported reagent in an organic reaction is the simplification of reaction work-up, i.e. product separation and isolation. In the case of an insoluble polymeric reagent, filtration and repeated washing with suitable solvents can be generally used at the end of the reaction to isolate the product and therefore the need for complex chromatographic techniques can be avoided.[2] Monitoring the progress of the reactions is easy by applying TLC, NMR or LC/MS techniques. The use of an excess of reagent is also allowed without the need for additional purification steps.[3] Regeneration and reuse of the recovered polymer supported reagents are possible, thus providing an environmentally benign system.[4]

Organic azides are thermally and photochemically labile compounds but of considerable utility in the generation of other functionalities, for example, amines via reduction, imines via rearrangement, triazoles and other heterocycles via cycloaddition. It is precisely for the synthesis of such sensitive compounds that the use of polymeric reagents, for example, azide anion, supported on anion exchange resin (PS-azide) is ideally suited.[5]

Polymer supported borohydride exchange resin (PS-BER) was first reported in 1977 by Gibson and Baily[6] and differs from sodium borohydride in reactivity and stability in alcoholic solvents and acidic solution. It has been applied in solvent purification, generation of volatile metal hydrides and reduction of metal ions, some carbonyl compounds, acyl halides and unsaturated nitroalkenes.[7]

Our research interests concerned the preparation of chiral 1-aryl-2-azidoethanols through biotransformations of corresponding α-azidoketones.[8] These compounds are precursors of important biologically active natural compounds. We have been using conventional solution phase chemistry to prepare racemic vicinal azidoalcohols for kinetic enzymatic resolution.[9] In order to speed up the preparation of such compounds we devised an alternative procedure using polymer supported reagents (Scheme 1).

Polymer supported azide resin was found to be a highly effective reagent for the conversion of α-haloketones into α-azidoketones[10] (Table 1, product **2**). These compounds are most commonly prepared at low temperatures (5–10 °C) using polar aprotic solvents;

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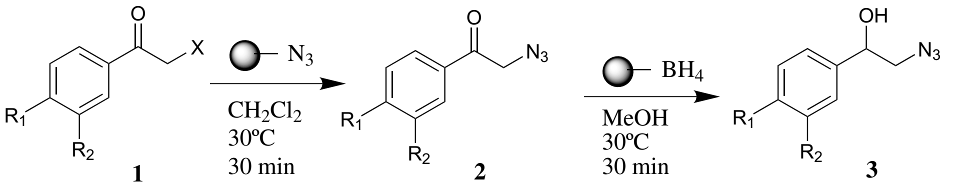

Scheme 1.

Table 1. α-Azidoketones and β-azidoalcohols prepared using polymer supported reagents

Entry	R_1	R_2	X	Yield/(%)[a]	
				2[b]	**3**[c]
1	H	H	Cl	95	90
2	F	H	Cl	90	88
3	Cl	H	Cl	92	87
4	Br	H	Cl	90	89
5	I	H	Cl	89	85
6	Cl	Cl	Cl	93	96
7	Me	H	Cl	91	88
8	MeO	H	Cl	92(79)[d]	93(89)[e]
9	NO_2	H	Br	68	80
10	H	NO_2	Br	75	78

[a] Crude yield. Purity was measured by ^1H NMR.

[b] Using PS-azide ion exchange resin.

[c] Using PS-BER.

[d] Yield after recrystallization from ethyl acetate/hexanes.

[e] Yield after column chromatography.

frequently, an additional step of product extraction is needed to obtain the desired α-azidoketone. Our results showed that using PS-azide exchange resin at room temperature and dichloromethane as solvent the α-azidoketones were prepared in very good yields. The reaction products can be obtained by simple filtration of the resin and evaporation of the solvent without further treatment.

The β-azidoalcohols were prepared starting from α-azidoketones using polymer supported borohydride exchange resin[11] and the results are summarized in Table 1 (product **3**). In all instances the β-azidoalcohols were formed in high yield after a short reaction time. In the reaction conditions PS-BER was very selective, reducing only the ketone and leaving the azido and aromatic nitro functionalities intact.

In conclusion we have developed a new and efficient procedure for the preparation of α-azidoketones and β-azidoalcohols using polymer supported reagents. The advantages of the present method in terms of ease of manipulation, fast reaction rates and formation of cleaner products should make this protocol as a valuable alternative to the existing methods.

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10. General procedure for preparation of α-azidoketones: Polymer supported azide was prepared using a commercial macroporous ion exchange resin, Amberlite® IRA 900 as previously reported.[5a,e] In an Erlenmeyer flask the α-haloketone (2.7 mmol) was dissolved in 25 mL of dichloromethane and the azide resin (3.2 g) was added. The reaction was carried out on a Dubnoff bath at 30 °C. The progress of the reaction was followed by TLC. On completion of the reaction, the resin was filtered off and washed with dichloromethane. The solvent was removed under reduced pressure. α-Azidoketones were identified by comparison of their spectral data with those reported in the literature.[12] This material was sufficiently pure for use in the next step without further treatment. If desired, the α-azidoketone can be purified by recrystallization from hexanes/ethyl acetate. Compound **2**, entry 5, 2-azido-1-(4-iodophenyl)ethanone: Yellowish solid, mp 89–91 °C. IR (KBr): 2097, 1689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (s, 2H), 7.59–7.64 (dt, 2.1, 8.7 Hz, 2H), 7.86–7.90 (dt, 2.1, 8.7 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.6, 102.1, 129.0, 133.4, 138.2, 192.0 ppm. Entry 9, 2-azido-1-(4-nitrophenyl)ethanone: Brown solid, mp 79 °C dec. IR

(KBr): 2114, 1705, 1524, 1345 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.61 (s, 2H), 8.07–8.11 (dt, 2.1, 9.0 Hz, 2H), 8.34–8.38 (dt, 2.1, 9.0 Hz, 2H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ 55.1, 124.0, 128.9, 138.5, 150.7, 191.9 ppm. Entry 10, 2-azido-1-(3-nitrophenyl)ethanone: Orange solid, mp 52–54 °C. IR (KBr): 2115, 1694, 1530, 1357 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 4.63 (s, 2H), 7.75 (t, 8.1 Hz, 1H), 8.25–8.29 (ddd, 1.2, 1.8, 7.8 Hz, 1H), 8.48–8.51 (ddd, 1.2, 2.2, 8.1 Hz, 1H), 8.73 (t, 1.8 Hz, 1H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ 54.9, 122.7, 128.2, 130.2, 133.3, 135.3, 148.3, 191.3 ppm.

11. General procedure for preparation of β-azidoalcohols: Polymer supported borohydride was prepared using Amberlite® IRA 900 as previously described.[14] The β-azidoalcohol was prepared using the same procedure above described changing the azide resin for borohydride resin. It was used 2.23 mmol of α-azidoketone, 0.75 g of borohydride resin in 25 mL of methanol. The products were characterized by their spectral data, which were identical to those in the literature.[13] Compound **3**, entry 5, 2-azido-1-(4-iodophenyl)ethanol: Yellow oil. IR (neat): 3385, 2106 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.35 (br s, 1H), 3.42–3.44 (m, 2H), 4.81–4.85 (t, 6.0 Hz, 1H), 7.10–7.15 (dt, 2.1, 8.7 Hz, 2H), 7.68–7.73 (dt, 2.1,8.7 Hz, 2H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ 57.7, 72.6, 93.7 127.6 137.6 139.9 ppm. Entry 10, 2-azido-1-(3-nitrophenyl)ethanol: Yellow oil. IR (neat): 3434, 2105, 1526, 1348 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.62 (br s, 1H), 3.46–3.53 (dd, 7.3, 12.6 Hz, 1H), 3.53–3.58 (dd, 4.2, 12.6 Hz, 1H), 4.98–5.02 (dd, 4.2, 7.3 Hz, 1H), 7.57 (t, 8.1 Hz, 1H), 7.71–7.75 (m, 1H), 8.16–8.20 (ddd, 1.2, 2.1, 8.1 Hz, 1H), 8.26–8.28 (m, 1H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ 58.0, 72.5, 121.3, 123.4, 129.9, 132.3, 142.9 148.6 ppm.

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