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Safe radical azidonation using polystyrene supported diazidoiodate(I)

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Abstract—Aldehydes are converted to acyl azides and benzyl ethers to azido ethers by treatment with polymer supported iodine azide in MeCN at 83 °C. The reaction provides a safe and convenient alternative to the use of iodine azide in radical azidonations.

1. Introduction

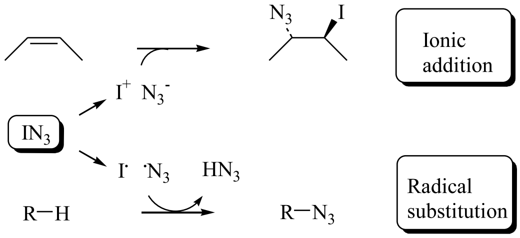
The azido group is a highly useful functionality in organic synthesis due to it ready conversion to amino groups and its photochemical or cycloaddition reactions.[1] Iodine azide is a very useful reagent for the introduction of the azido group. Besides the classical electrophilic reactions pioneered by Hassner,[2] that exploits the polarized character of IN_3 and allows addition of iodine and azide to double bonds, several radical azidonation reactions using iodine azide have recently been investigated by us.[3–5] In these reactions, homolysis of the weak I–N bond lead to radicals (Scheme 1) that cause azide substitution of active hydrogens. However, a considerable drawback with IN_3 as a reagent, is its potentially explosive nature, which inhibits its widespread use.

In 1999 Kirschning et al. described a stable electrophilic polymer-bound reagent that synthetically behaves like iodine azide (Scheme 1).[6] By reacting the polystyrene-bound iodide **1** with phenyliodonium diacetate in dichloromethane at room temperature and subsequently with trimethysilyl azide, the resin **3** was generated. They also obtained **3** by direct azido transfer after treatment of iodide **1** with (diazido)benzene (Scheme 2). The polymer **3** was shown to be unexplosive and a number of electrophilic IN_3 additions to alkenes could be performed simply by mixing **3** and the alkene.[6] It was presumed that the diazidoiodate ion was the active species in these reactions.

Being aware of the work from the Kirschning group we speculated whether the polymerically supported diazidoiodate could not only emulate ionic iodine azide, but also the radical reactions with which we have been focused. In the present work, we report the finding that the diazidoiodate(I) ion can indeed be used for radical azidonation, and hence that the Kirchning groups polymer **3** is a safe and efficient solid-phase reagent for radical azidonation reactions. The reactions provide a useful addition to the arsenal that can be carried out with solid supported reagents,[7] and used for parallel or solution-phase combinatorial chemistry.[8]

2. Results and discussion

Solution phase reactions. We first investigated whether the diazidoiodate ion could be employed in lieu of iodine azide in radical azidonation reactions in solution. For this purpose we prepared tetraethylammonium diazidoiodate(I) in situ in a similar manner to the solid-phase conversion of **2** to **3** (Scheme 2). Thus tetraethylammonium iodide was reacted with phenyliodonium diacetate to give tetraethylammonium diacetoxyiodate(I) (**4**, Scheme 3). Reaction of aldehyde **6** with 2.5 equiv of **4** and 2.8 equiv of $TMSN_3$ in MeCN at 83 °C gave the carbamoyl azide **7** in 76% yield, where IN_3



Scheme 1.

Keywords: Polymer supported reagent; Radical substitution; Solution phase combinatorial chemistry.

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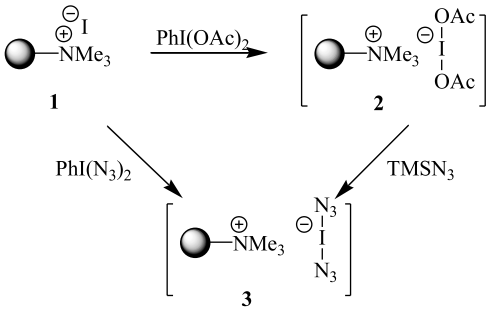
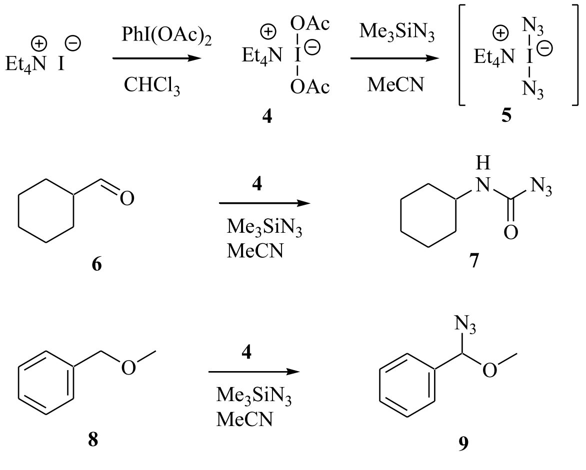


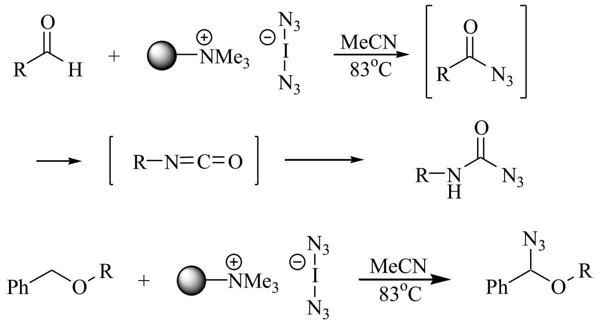
Scheme 2.

gives 89%.[4] This reaction occur by substitution of the aldehyde hydrogen atom with azide and subsequent Curtius rearrangement to an isocyanate that reacts with more azide (Schemes 3 and 4). Similarly the benzyl ether **8** was converted to azide **9** in 64% yield, where IN_3 gives the product in 93% yield.[2] It appears that the radical reactions in solution of **5** and IN_3 are essentially equivalent. Addition of a radical trap, *N-tert*-butyl-α-phenylnitrone, to the reaction of **8** prevented the formation of **9**, supporting a similarity of the reactions.

Solid phase reactions. We prepared the polymer **3** as described by Kirschning converting iodide **1** into diacetoxy-iodate **2** and hence diazidoiodate **3** (Scheme 2).[1] Two different sources of **1** was employed; the Amberlite IR-900 (Fluka) and a microreticular Amberlyst A-26 resin (Lancaster). Both resins essentially gave similar results. The resin **3** was reacted with aldehydes **6** and **10–13** and benzyl ethers **8**, **14** and **15** giving carbamoyl azides **7** and **16–20** and azidobenzyl ethers **9**, **21** and **22**, respectively (Scheme 4, Table 1). Typically the reaction was carried out by heating the substrate under reflux for 4 h with 4 equiv of **3** in MeCN. The yields were excellent for the aldehydes (87–96%), but somewhat lower (57–66%) for the benzyl ethers, than can be obtained with IN_3. The solid-phase reaction did not work satisfactorily with benzylidene acetals, presumably because the polymer contained an unavoidable amount of water as seen by IR. Thus acetal **17** gave the alcohol **26** in 96% yield; a product that can be obtained by hydrolysis of the intermediate benzoxonium ion. On the other hand reaction of the tertiary amine **18** was found to lead to fragmentation and the Schiff base **27**. Adding *N-tert*-butyl-α-phenylnitrone to the reaction of **6** with **3** inhibited formation of carbamoyl azide **9**. The reaction is accompanied by the formation of a brown colour, presumably iodine. Besides MeCN the solvents CH_2Cl_2, THF, MeOH, EtOH and *t*-BuOH were tried, but only *t*-BuOH gave satisfactory results, probably because it also has a high boiling point. In this solvent, a carbamoyl azide is still obtained from an aldehyde, and not the carbamate.



Scheme 3.



Scheme 4.

It was observed that when the polymer was heated to reflux in acetonitrile, a faint brown color was formed and a UV spectrum of the solution confirmed that IN_3 was present. Furthermore when the polymer was reacted with an excess of substrate and recovered, IR spectroscopy showed that the spent polymer was polymerically bound azide. Therefore the polymer probably functions by slow release of IN_3 from the polymer bound diazidoiodate(I) ion (Scheme 5). This explanation fits with the polymer bound reagent usually reacting slower than IN_3 in solution and also explains the very similar reaction profile of the polymer compared to IN_3.

$$I(N_3)_2^- \rightleftharpoons N_3^- + IN_3$$

Scheme 5.

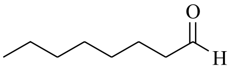
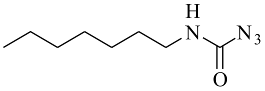
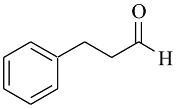
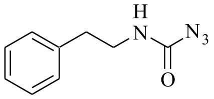
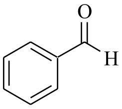
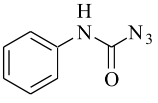
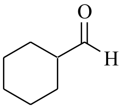
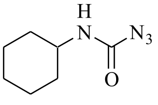
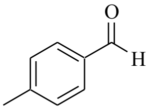
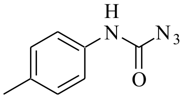
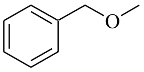
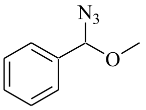
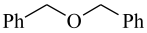
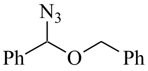
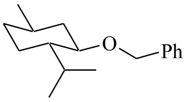
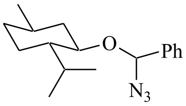
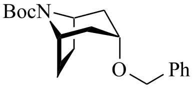
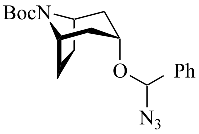
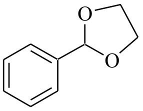
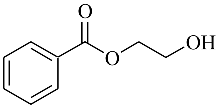
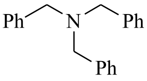
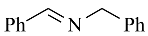
In conclusion, azidonation with polymer **3** is a convenient and safe alternative to the use of IN_3 in radical azidonations. It is also a useful reaction for parallel combinatorial synthesis since the requirements for purification are minimal when the reaction is carried out in this manner.

3. Experimental

3.1. General

Moisture sensitive reactions were carried out in flame-dried glassware under a N_2 atmosphere in solvents dried according to standard procedures. Commercially available compounds were used without further purification. Evaporation was carried out on a rotatory evaporator with the temperature kept below 40 °C. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC-plates (Merck, 60, F_{254}) were visualized by spraying with either A) phosphomolybdic acid hydrate (5% in EtOH), B) 2,4-dinitrophenylhydrazine (0.5% in 2 M HCl), or C) vanillin (3% in 1% H_2SO_4 in EtOH) and heating until

Table 1. Results of reaction of substrates with polymer 3 in MeCN at 83 °C

Substrate	Nr	Time (h)	Product	Nr	Yield[a] (%)
	**10**	4		**19**	95
	**11**	4		**20**	87
	**12**	4		**21**	87
	**6**	4		**7**	96
	**13**	4		**22**	96
	**8**	4		**9**	68[b]
	**14**	4		**23**	64
	**15**	4		**24**	60
	**16**	4		**25**	57
	**17**	4		**26**	96
	**18**	4		**27**	73

[a] Yields are after chromatography.

[b] Adjusted yield due to isolated starting material.

colored spots appeared. A is best for visualizing carbamoyl azides, while B is good for visualizing benzylic azides. NMR-spectra were recorded on a Varian Mercury 400 instrument. Mass spectra were run on a Micromass LC-TOF instrument.

3.2. Tetraethylammonium diacetoxyiodate(I) (4)

To a solution of tetraethylammonium iodide (4 g, 15.6 mmol) in dry chloroform (50 mL) was added iodosobenzene diacetate (5 g, 16 mmol) and the mixture was stirred at room temperature overnight. Then ethyl ether (60 mL) was added, and the reaction mixture was cooled to 0 °C, filtered and washed with cold dry ethyl ether (3× 20 mL). The light yellow product **4** was dried in vacuo and kept under nitrogen protected from light.

3.3. Procedure with 4 and Me_3SiN_3

3.3.1. Cyclohexylcarbamoyl azide (7). 0.94 g (2.5 mmol) of tetraethylammonium-salt **4** was dissolved in dry MeCN (4 mL) and 0.322 g (2.8 mmol, 0.367 mL) of Me_3SiN_3 and 0.112 g (1 mmol) cyclohexanecarbaldehyde were added, and the mixture heated to 83 °C for 2.5 h. The brown slurry was poured into 2 mL of water, and the mixture was extracted with dichloromethane (3×10 mL). The organic extracts were combined and washed with 10 mL of 5% sodium thiosulfate leaving a light yellow solution, which was dried over magnesium sulfate. Removal of the solvent under reduced pressure followed by column chromatography (EtOAc/pentane 1:10) afforded the cyclohexylcarbamoyl azide[5] (**7**, 0.127 g, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (bs, 1H), 3.56–3.46 (m, 1H), 1.88–182 (m, 2H), 1.66 –1.60 (m, 2H), 1.57–1.51 (m, 2H), 1.34–1.23 (m, 2H), 1.14–1.04 (m, 2H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C=O), 50.3 (C_1), 33.08 ($C_{2,6}$), 25.5 (C_4), 24.8 ($C_{3,5}$). IR (KBr, cm^{-1}): 1547.9(N–C=O), 1677.7 (strong C=O), 2140 (N_3), 3275.4 (NH). HRMS (ES): *m/z*: 191.0910 (calcd for $C_7H_{12}N_4ONa$ [M+Na$^+$]: 191.0908), mp=105.1 °C.

3.3.2. α-Azidobenzyl methylether (9). 0.94 g (2.5 mmol) of tetraethylammonium-salt **4** was dissolved in dry MeCN (4 mL) and 0.322 g (2.8 mmol, 0.367 mL) of Me_3SiN_3 and 0.122 g (1 mmol) of benzyl methyl ether were added, and the mixture heated to 83 °C for 2.5 h. The reaction was followed on TLC (pentane/CH_2Cl_2 3/1), and found complete after 2 h. The reaction mixture was poured into water (2 mL), and the mixture was extracted with dichloromethane (3×10 mL). The organic extracts were combined and washed with 10 mL of 5% sodium thiosulfate, brine, dried over magnesium sulfate and concentrated in vacuo to give the desired α-azido benzyl ether. Additional purification by flash chromatography (pentane/EtOAc gradient 1/0:10/1) provided the desired α-azido benzyl methylether[3] as a light yellow oil (**9**, 0.104 g, 64%). ^{1}H NMR: δ 7.22–7.38 (m, 5H), 5.24 (s, 1H), 3.43 (s, 3H).[3]

When this reaction was performed in presence of 0.26 equiv of *N*-*tert*-butyl-α-phenylnitrone no azidonation product was observed.

3.4. Synthesis of polymer 3

The untreated (Amberlyst A-26 iodide-resin from Lancaster was previously washed with dry CH_2Cl_2 and dried in vacuum) polymer-bound iodide **1** (1 equiv) was shaken at 1000 rpm with $PhI(OAc)_2$ (1.8 equiv) in dry CH_2Cl_2 (2.5 mL/mmol iodide) at room temperature under nitrogen overnight. During this time the reaction mixture was protected from light. The resulting light yellow resin **2** was filtered and washed with dry CH_2Cl_2 (5×25 mL/g resin) and dried in vacuum.

The prepared resin **2** was treated with Me_3SiN_3 (2.6 equiv with respect to **1**) in dry CH_2Cl_2 (4 mL/mmol) and shaked at 1000 rpm under nitrogen overnight. The yellow resin was filtered and washed with dry CH_2Cl_2 (5×25 mL/g resin) and dried under vacuum. The calculated loading (from weight increase) was up to 2.1 mmol reagent per g resin for the Lancaster resin and up to 2.5 mmol reagent per g resin in the Fluka case. The resin was stored in a desiccator at room temperature.

3.5. Azidonation of compounds with resin 3, general procedure

To a suspension of resin **3** (5 equiv with respect to substrate) in dry MeCN (4 mL/g resin) was added 1 equiv of aldehyde, and the reaction mixture was heated to 83 °C. The reaction was followed on TLC (pentane/ CH_2Cl_2 1/1), and the time for a complete reaction was normally between 2 and 4 hours. The resin was filtered and washed with dry CH_2Cl_2. The resulting organic layer was washed with a solution of 5% sodium thiosulfate, dried over magnesium sulfate and concentrated under reduced pressure to give the crude azide. Additional purification by flash chromatography (pentane/ ethyl acetate 10/1) provided the desired compound in the yield given in Table 1.

3.5.1. Heptyl carbamoylazide (19).[5] A colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.28 (bs, 1H), 3.2 (q, 2H, J=8.0 Hz), 1.52–1.44 (m, 2H), 1.29 –1.21 (m, 8H), 0.84 (t, 3H, J=7.2 Hz).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6 (C=O), 41.3 (C_1), 31.8 (C_5), 29.6 (C_2), 29.05 (C_4), 26.8 (C_3), 22.7 (C_6), 14.1 (C_7). IR (KBr, cm^{-1}): 1702 (C=O), 2139.7 (N_3), 2858/2929 (C–H sp^3), 3331.8 (NH).

3.5.2. 2-Phenylethyl carbamoylazide (20).[5] White crystals. Mp=85.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.25–7.10 (m, 5H), 4.99 (bs, 1H), 3.42 (q, 2H, J=6.7 Hz), 2.75 (t, 2H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4 (C=O), 137.1 (Ar C_1), 127.6 (Ar $C_{3,4,5}$), 125.6 (Ar $C_{2,6}$), 41.1 (CH$_2$–NH), 34.5 (CH$_2$). IR (KBr, cm^{-1}): 1543 (N–C=O), 1671.8 (strong C=O), 2141.9 (N_3), 2930.2 (C–H sp^3), 3029 (C–H sp^2) 3280.3 (NH).

3.5.3. Phenyl carbamoylazide (21).[5] White crystals. Mp=107.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.4 (m, 3H), 7.1 (m, 2H), 7 (bs, 1H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5 (C=O), 137.1 (Ar C_1), 129.3 (Ar $C_{3,5}$), 124.9 (Ar C_4), 119.7 (Ar $C_{2,6}$). IR (KBr, cm^{-1}): 1554 (N–C=O), 1688.6 (strong C=O), 2147.4 (N_3), 3325.6 (NH).

3.5.4. 4-Methylphenyl carbamoylazide (22).[5] Light yellow crystals. Mp=130.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.2 (d, 2H, J=8.0 Hz), 7 (d, 2H, J=8.0 Hz), 6.7 (bs, 1H), 2.2 (s, 3H).[5] ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.2 (C=O), 134.6 (Ar C_1), 129.8 (Ar $C_{3,4,5}$), 119.6 (Ar $C_{2,6}$), 21.03 (CH$_3$).[5] IR (KBr, cm^{-1}): 3276 (NH), 2143, (medium, N_3), 1682 (strong, C=O), 1538 (N–C=O).[5]

3.5.5. α-Azidobenzyl benzyl ether (23). A light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.34–7. 51 (m, 10H, Ar), 5.529 (s, 1H, Ar-CH–N_3), 4.93 (d, 1H$_a$, J=11.6 Hz, Ar-CH_2), 4.73 (d, 1H$_b$, J=11.6 Hz, Ar-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.9 (1 C, Ar C$_1$), 129.3–126.3 (11C,Ar),91.5(Ar-CH–N_3),70.4(Ar-CH$_2$).IR(KBr, cm^{-1}): ν=1495, 1587 (Ar), 2105 (–N_3), 2874 (C–H sp^3), 3033/3065 (C–H sp^2). GS–MS: 211 (–N_2). HR-MS: 262.0950 (calcd for $C_{14}H_{13}N_3O$+Na$^+$: 262.0956).

3.5.6. Azidobenzyl (−)-menthyl ether (24).[9] A light yellow oil. ^{1}H NMR (200 MHz; $CDCl_3$): δ 0.79 (d, 3H, J=6.3 Hz), 0.98 (d, 6H, J=6.9 Hz), 1.0 (m, 2H), 1.2 (m, 1H), 1.4 (m, 2H), 1.65 (m, 2H), 2.1 (m, 1H), 2.2 (m, 1H), 3.65 (dt, 1H), 5.45 (s, 1H), 7.4 (m, 5H).[9]

3.5.7. 3-(Azido-phenyl-methoxy)-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (25).[10] A clear colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.36 (5H, m, Ar-H), 5.39 (1H, s, O–C$H$$N_3$-Ar), 4.19 (2H, br. s, H-1,5), 4.13 (1H, t, $J=4{,}4$ Hz, H-3), 2.22–1.78 (8H, m, 2H-2,4,6,7), 1.46 (9H, s, $(CH_3)_3$, Boc). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6 ($C{=}O$, Boc), 137.5 (C(Ar)), 129.3; 129.2; 128.9 (CH(Ar)), 91.5 (O–CHN$_3$-Ar), 79.4 ($C(CH_3)_3$, Boc), 72.4 (C_3), 53.1/52.3 ($C_{1,5}$), 37.2/36.4 ($C_{2,4}$), 35.3/34.4 ($C_{6,7}$), 28.7/28.0 ($(CH_3)_3C$, Boc).[10] IR (film, cm^{-1}): $\nu=3444$, 2978 (C–H sp^3), 2103 (N_3), 1694, 1652, 1548 cm^{-1}.[10]

3.5.8. 2-Hydroxyethyl benzoate (26).[11] Colourless oil. ^{1}H NMR ($CDCl_3$): $\delta=8.1$ (m, 2H, Ar; H_2, H_6), 7.5 (m, 1H, Ar; H_4), 7.4 (m, 1H, Ar; H_3, H_5), 4.4 (t, 2H, CH_2), 3.9 (t, 2H, CH_2) and 2.8 (bs, 1H, OH).[11]

3.5.9. Benzylidene benzyl amine (27).[12] Ligth yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.42$ (s, 1H, $=NH$), 7.81 (m, 2H, Ar; H_2, H_6), 7.45–7.22 (m, 9H, Ar; $H_{2\text{–}5}$, $H'_{2\text{–}6}$), 4.85 (s, 1H, –Ar-CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 162.1 ($C{=}N$–), 139.4 (Ar C_1), 136.3 (Ar C'_1), 130.8 (Ar C_4), 128.7–128.1 (8 C, Ar $C_{2,3,5,6}$, $C_{2',3',5',6'}$), 127.1 (Ar-$C_4{'}$), 65.2 (Ar-CH_2). IR (KBr, cm^{-1}): $\nu=1580$ (Ar), 1643 (–H$C{=}N$–), 2840/2872 (C–H sp^3), 3027/3085 (C–H sp^2). HR-MS: 196.1130 (calcd for $C_{14}H_{13}N+H^+$: 196.1126).

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