Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 4983–4987

# 1,3-Dipolar cycloadditions of MeOPEG-bounded azides

Giorgio Molteni* and Paola Del Buttero

*Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via Golgi 19, 20133 Milano, Italy*

Received 20 December 2004; revised 25 February 2005; accepted 10 March 2005

Available online 7 April 2005

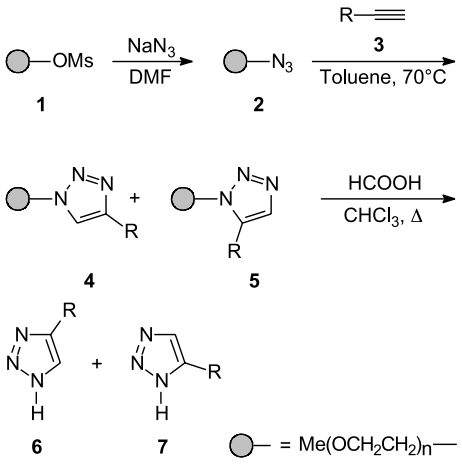
**Abstract**—1,3-Dipolar cycloadditions of MeOPEG-supported azide **2** with a variety of dipolarophiles have been studied. 1-MeOPEG-supported 1,2,3-triazoles **4** and **5**, 1,2,3,4-tetrazoles **12** and aziridine **14** were obtained in nearly quantitative yields. The removal of the MeOPEG moiety from the 1,2,3-triazole nucleus was achieved by acidic cleavage of the cycloadduct mixtures **4** and **5** giving 4- and 5-substituted-1,2,3-triazoles **6** and **7**.


## 1. Introduction

1,3-Dipolar cycloaddition between organic azides and a variety of unsaturated derivatives represent a versatile method for the direct synthesis of substituted azoles.[1] Recently, it have been recognised that 1,2,3-triazoles, which are formed via azide-acetylene cycloaddition[2] are the ideal representative of 'click chemistry'.[3] Furthermore, a number of examples are concerned with the synthesis of the 1,2,3,4-tetrazole ring by azide cycloaddition onto the cyano group.[4] Due to their biological activity as anti-HIV[5] and anti-microbial[6] agents, as well as selective $\beta_3$ adrenergic receptor agonist,[7] new methods for the regio- and/or stereoselective synthesis of both 1,2,3-triazoles and 1,2,3,4-tetrazoles should be highly valuable. In this context, the two following points should be considered: (i) the polymer-supported synthesis of small heterocyclic molecules is the subject of intense research activity,[8] since it represent one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry,[9] (ii) very few examples of cycloaddition reactions involving resin-bounded azides to acetylenes have been reported,[10,11] while no examples are available onto the ethylenic dipolarophile or the cyano group. In the above-mentioned papers, however, the azide was prepared using Merrifield's,[10a] polystyrene[10b] or Wang's[11] resin. These are insoluble in organic media. Recently, soluble polymers have gained popularity amongst organic chemists due to several advantageous features. Analytical simplicity, high reactivity and low costs of the starting materials actually compete with that of usual solution chemistry,[12] while the easy reaction work up is one of the major advantages of solid-supported synthesis. Thus, after having demonstrated the feasibility of poly(ethylene glycol)-supported azide (MeOPEG-supported azide) cycloadditions towards acetylenic dipolarophiles,[13] we present here a systematic study on the behaviour of these kind of azides towards acetylenes, ethylenes and the cyano group as dipolarophiles.

## 2. Results and discussion

First, of all, we devised the monomethylether of poly(ethylene glycol) with a $M_W$ of 5000 (MeOPEG) as the suitable soluble support. MeOPEG-supported azide **2** were easily obtained as previously reported[13] from MeOPEG-mesylate[14] (Scheme 1). Heating **2** in dry toluene in the presence of a large excess (10 mol equiv) of acetylenic




**a:** R = Ph, **b:** R = COOMe, **c:** $CH_2Cl$, **d:** $CH_2Br$, **e:** $CH_2OH$, **f:** $CH_2NH_2$

**Scheme 1.**

*Keywords*: Azides; 1,3-Dipolar cycloadditions; Azoles; Polymer-supported synthesis.
* Corresponding author. Tel.: +39 02 51314141; fax: +39 02 50314139; e-mail: giorgio.molteni@unimi.it

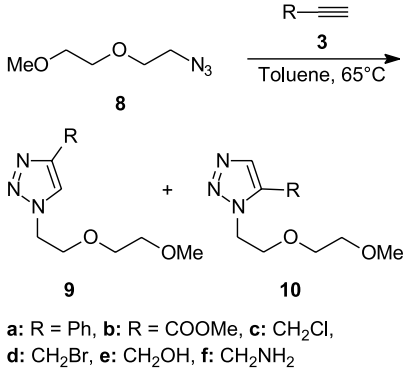
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.049

**Table 1**. Cycloaddition between MeOPEG-supported azide **2** and 1-(1-ethoxy-2-azido)-2-methoxyethane **8** with akynyl dipolarophiles **3**

| R | Product yield (%)[a] | | | Product ratio[b] | |
|---|---|---|---|---|---|
| | **4**+**5** | **9** | **10** | **4**: **5** | **9**: **10** |
| Ph | 98 | 58 | 16 | 80:20 | 50:50 |
| COOMe | 98 | 66 | 17 | 83:17 | 80:20 |
| $CH_2Cl$ | 96 | 49 | 26 | 70:30 | 65:35 |
| $CH_2Br$ | 96 | 46 | 25 | 70:30 | 65:35 |
| $CH_2OH$ | 95 | 34 | 28 | 57:43 | 55:45 |
| $CH_2NH_2$ | 97 | 30 | 24 | 55:45 | 55:45 |

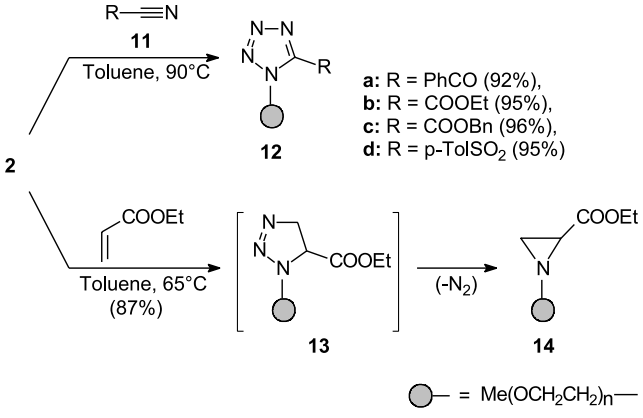
[a] Isolated yields.
[b] Determined by $^1$H NMR spectroscopy.

dipolarophile **3** gave the desired MeOPEG-supported-1,2,3-triazole cycloadducts **4** and **5**, as mixture of inseparable regioisomers. Product yields and ratios are summarised in Table 1. MeOPEG-supported-1,2,3-triazoles **4** and **5** were obtained as white solids, in near quantitative yields, simply by addition of diethyl ether to the crude reaction mixtures. Structural assignments of the MeOPEG-supported cycloadducts rely upon $^1$H NMR spectroscopic analysis and are fully consistent with those of 4- and 5-substituted-1,2,3-triazoles reported in the literature.[15] In particular, the proton on the $C_5$ of the 1,2,3-triazole ring of **4a-f** appears in the range $\delta$ 7.79–8.02, thus accounting for the depicted regiochemistry resulting from cycloaddition. As can be inferred from Scheme 1, the removal of the MeOPEG pendant from the mixture of supported cycloadducts **4**+**5** was accomplished under acidic conditions, affording 1-unsubstituted 1,2,3-triazoles **6** and **7** with 71–85% overall yield. Finally, the latter products were obtained as pure regioisomers through silica gel column chromatography. In order to ensure the effect of the MeOPEG moiety on regioselectivity, we submitted 1-(1-ethoxy-2-azido)-2-methoxyethane **8**[16] to a reaction with acetylenic dipolarophiles **3** (Scheme 2). The results summarised in Table 1 show that regioselectivity ratio of 1-methoxyethoxy ethyl-1,2,3-triazoles **9**: **10** are generally similar to that observed for MeOPEG-supported materials and reflect the usual balance of HOMO and LUMO-dipole control of azide cycloadditions.[17] The only exception to this behaviour arises with phenylacetylene **3a** and may be ascribed to steric repulsion between the phenyl ring of the dipolarophile and the MeOPEG residue in the formation of MeOPEG-supported-5-phenyl-1,2,3-triazole **7a**.




**Scheme 2.**

We have also developed the first example of cycloaddition between MeOPEG-supported azide **2** and a series of electron-poor (activated) nitriles **11** (Scheme 3). Clean cycloaddition reactions were performed by heating **2** in dry toluene in the presence of 20 mol equiv of the appropriate cyano dipolarophile, while the usual reaction workup gave MeOPEG-supported-1,2,3,4-tetrazoles **12** in near quantitative yields. Finally, the same protocol using ethyl acrylate gave the MeOPEG-supported-2-ethoxycarbonyl aziridine **14** (Scheme 3). Structural assignments of the latter product rely upon $^1$H NMR spectroscopic analysis, the data obtained agrees with that of the known 1-benzyl-2-ethoxycarbonyl aziridine.[18] The formation of the MeOPEG-supported aziridine **14** is not surprising since its formation follows the known thermal degradative behaviour of the initially-formed 4,5-dihydro-1,2,3-triazole cycloadduct **13**.[19]




**Scheme 3.**

## 3. Conclusions

The behaviour of MeOPEG-supported azide **2** towards a variety of acetylenes, ethylenes and the cyano group as dipolarophiles illustrates the advantages concerned with soluble polymer-supported synthesis. All cycloadditions were satisfactory in terms of product yields and easy workup procedures. The removal of the MeOPEG pendant was achieved onto 1,2,3-triazole derivatives **4** and **5**, giving 1-unsubstituted-1,2,3-triazoles **6** and **7**. As a concluding remark, the presence of the MeOPEG mojety had little or no influence on cycloaddition regioselectivity compared with that of non-polymeric azides.

## 4. Experimental

Melting points were measured with a Büchi apparatus in open capillary tubes and are uncorrected. IR Spectra were recorded with a Perkin–Elmer 1725X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. $^1$H NMR and $^{13}$C NMR Spectra were taken with a Bruker AC 300 or AMX 300 instruments in $CDCl_3$ solutions at room temperature unless otherwise stated. Chemical shifts are given as ppm from tetramethylsilane, *J* values are given in Hz.

Before use, all MeOPEG-bounded materials were melted at 90 °C at 1 mmHg for 1 h to remove moisture.

Compounds **6a**,[20] **6b**,[21] **6c**,[22] **6e**,[23] **6f**[24] and **7a**,[20] **7b**[25] are known in the literature. MeOPEG-azide **2**[12] and 1-(1-ethoxy-2-azido)-2-methoxyethane **8**[16] was synthesised according to literature procedures.

### 4.1. Yields and $^1$H NMR purity determination of MeOPEG-bounded compounds

The yields of MeOPEG-bounded materials were determined by weight of pure compounds. It was assumed that the average $M_W$ of MeOPEG monomethylether residue is 5000 Da, while the $M_W$ actually encompasses the range between 4500 and 5500 Da. The purity of MeOPEG-bounded compounds were determined by $^1$H NMR analyses with pre-saturation of the MeOPEG methylene signals at $\delta$ 3.64. In order to ensure complete relaxation of the proton nuclei and integration accuracy, we set relaxation delay (RD) to 6 s and aquisition time (AQ) to 4 s. The integrations of the PEG fragment $CH_3OCH_2$, which were found between $\delta$ 3.30 and 3.37, were used as internal standards with an estimated integration error of $\pm$4%.

**4.1.1. MeOPEG-supported 1,2,3-triazoles 4 and 5.** A solution of **2** (5.00 g, 1.0 mmol) and the appropriate alkynyl derivative **3** (10.0 mmol) in dry toluene (40 mL) was heated to 70 °C for 48 h. The solvent was partly removed under reduced pressure and $Et_2O$ (40 mL) was added. The white solid was collected by filtration affording a mixture of the MeOPEG-supported cycloadducts **4**+**5** (see Table 1 for yields and yield ratio).

The following data are selected from the $^1$H NMR analyses of the mixtures **5**+**6** in $CDCl_3$ solutions; signals due to the PEG fragment $CH_3OCH_2$ have been omitted.

**4a**: $\delta$ 4.53 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 7.20–7.40 (4H, m, aromatics), 7.97 (1H, s, $C_5$–*H*); **5a**: $\delta$ 4.47 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 7.20–7.40 (4H, aromatics), 7.65 (1H, s, $C_4$–*H*).

**4b**: $\delta$ 3.93 (3H, s, COO*$CH_3$*), 4.54 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 8.02 (1H, s, $C_5$–*H*); **5b**: $\delta$ 3.90 (3H, s, COO*$CH_3$*), 4.90 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 7.65 (1H, s, $C_4$–*H*).

**4c**: $\delta$ 4.45 (2H, t, $J$=6.9 Hz, *$CH_2$*–N<), 4.67 (2H, s, *$CH_2$*Cl), 7.79 (1H, s, $C_5$–*H*); **5c**: $\delta$ 4.56 (2H, t, $J$=6.9 Hz, $CH_2$–N<), 4.74 (2H, s, *$CH_2$*Cl), 7.58 (1H, s, $C_4$–*H*).

**4d**: $\delta$ 4.53 (2H, t, $J$=6.9 Hz, *$CH_2$*–N<), 4.58 (2H, s, *$CH_2$*Br), 7.84 (1H, s, $C_5$–*H*); **5d**: $\delta$ 4.60 (2H, t, $J$=6.9 Hz, *$CH_2$*–N<), 4.67 (2H, s, *$CH_2$*Br), 7.65 (1H, s, $C_4$–*H*).

**4e**: $\delta$ 4.52 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 4.73 (2H, s, *$CH_2$*OH), 7.97 (1H, s, $C_5$–*H*); **5e**: $\delta$ 4.56 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 4.67 (2H, s, *$CH_2$*OH), 7.65 (1H, s, $C_4$–*H*).

**4f**: $\delta$ 4.28 (2H, t, $J$=7.4 Hz, *$CH_2$*$NH_2$), 4.50 (2H, t, $J$=6.9 Hz, *$CH_2$*–N<), 7.87 (1H, s, $C_5$–*H*); **5f**: $\delta$ 4.31 (2H, s, *$CH_2$*$NH_2$), 4.56 (2H, t, $J$=7.0 Hz, *$CH_2$*–N<), 7.56 (1H, s, $C_4$–*H*).

**4.1.2. MeOPEG-supported 1,2,3,4-tetrazoles 12.** A solution of **2** (5.00 g, 1.0 mmol) and the appropriate nitrile **11** (20.0 mmol) in dry toluene (40 mL) was heated to 90 °C for 48 h. The solvent was partly removed under reduced pressure and $Et_2O$ (40 mL) was added. The white solid was collected by filtration giving the MeOPEG-supported cycloadducts **12**.

**12a** (4.76 g, 92%). $\delta_H$ 3.25 (2H, t, $J$=7.0 Hz, $CH_3OCH_2$–), 3.34 (3H, s, *$CH_3$*$OCH_2$–), 4.54 (2H, t, $J$=7.0 Hz, –*$CH_2$*–N<), 7.50–7.75 (5H, aromatics).

**12b** (4.96 g, 95%). $\delta_H$ 1.46 (3H, t, $J$=6.6 Hz, *$CH_3$*–$CH_2OCO$), 3.25 (2H, t, $J$=7.0 Hz, $CH_3OCH_2$–), 3.34 (3H, s, *$CH_3$*$OCH_2$–), 4.26 (2H, q, $J$=6.6 Hz, $CH_3$–*$CH_2$*OCO), 4.56 (2H, t, $J$=7.0 Hz, –*$CH_2$*–N<).

**12c** (4.88 g, 96%). $\delta_H$ 3.25 (2H, t, $J$=7.0 Hz, $CH_3OCH_2$–), 3.34 (3H, s, *$CH_3$*$OCH_2$–), 4.35 (2H, s, Ph-*$CH_2$*OCO), 4.56 (2H, t, $J$=7.0 Hz, –$CH_2$–N<), 7.10–7.60 (5H, aromatics).

**12d** (4.99 g, 95%). $\delta_H$ 2.38 (3H, s, $CH_3$–$C_6H_4$), 3.25 (2H, t, $J$=7.0 Hz, $CH_3OCH_2$–), 3.34 (3H, s, *$CH_3$*$OCH_2$–), 4.58 (2H, t, $J$=7.0 Hz, –*$CH_2$*–N<), 7.50–8.00 (4H, aromatics).

**4.1.3. MeOPEG-supported 2-ethoxycarbonylaziridine 14.** A solution of **2** (5.00 g, 1.0 mmol) and ethyl acrylate (2.00 g, 20.0 mmol) in dry toluene (40 mL) was heated to 70 °C for 16 h. The solvent was partly removed under reduced pressure and $Et_2O$ (40 mL) was added. The white solid was collected by filtration giving the MeOPEG-supported aziridine **14** (4.45 g, 87%) $\delta$ 1.24 (3H, t, $J$=7.1 Hz, *$CH_3$*$CH_2O$–), 1.51 (1H, dd, $J$=3.3, 1.3 Hz, –*H*CH–), 2.07 (1H, dd, $J$=6.7, 3.3 Hz, –*H*CCOOEt), 2.23 (1H, dd, $J$=6.7, 1.3 Hz, –HC*H*–), 3.30 (3H, s, *$CH_3$*$OCH_2$–), 3.35 (2H, t, $J$=7.0 Hz, $CH_3OCH_2$–), 4.11 (2H, q, $J$=7.1 Hz, $CH_3$*$CH_2$*O–).

**4.1.4. 1-*H*-1,2,3-Triazoles 6 and 7.** A solution of **4**+**5** (7.50 g) in chloroform (4.5 mL) and 95% formic acid (4.5 mL) was stirred at room temperature for 1 h, and then refluxed for 6 h. $Et_2O$ (40 mL) was added and the white solid was filtered off. The solvent was partly evaporated under reduced pressure, chloroform (20 mL) was added and the mixture was washed firstly with water (2×10 mL), then with 5% aqueous sodium hydrogencarbonate (2×10 mL). The organic layer was dried over sodium sulfate, the solvent was evaporated and the residue was chromatographed on a silica gel column with ethyl acetate/dichloromethane 4:1 affording 1-*H*-1,2,3-triazoles **6** and **7**.

**6a** (0.11 g, 42%).

**6b** (0.13 g, 68%).

**6c** (89 mg, 52%).

**6d** (0.12 g, 52%) as white solid mp 64 °C (from diisopropyl ether). $^1$H NMR (DMSO-$d_6$) $\delta$ 3.64 (2H, s), 8.37 (1H, s), 11.12 (1H, br s); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.4 (t), 127.85 (d), 128.50 (s); MS *m/z* (EI) 162 ($M^+$). Anal. Calcd for $C_3H_4BrN_3$: C, 22.24; H, 2.49; N, 25.94%. Found: C, 22.29; H, 2.54; N, 26.04.

**6e** (68 mg, 47%).

**6f** (55 mg, 39%).

**7a** (0.11 g, 42%).

**7b** (27 mg, 17%).

**7c** (48 mg, 28%) as white solid mp 57 °C (from diisopropyl ether). $^1$H NMR (DMSO-$d_6$) $\delta$ 3.76 (2H, s), 7.89 (1H, s), 11.05 (1H, br s); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 43.74 (t), 126.15 (s), 129.13 (d); MS *m/z* (EI) 117 ($M^+$). Anal. Calcd for $C_3H_4ClN_3$: C, 30.66; H, 3.43; N, 35.75%. Found: C, 30.61; H, 3.47; N, 35.82.

**7d** (66 mg, 28%) as yellow thick oil. $^1$H NMR (DMSO-$d_6$) $\delta$ 3.66 (2H, s), 7.83 (1H, s), 11.15 (1H, br s); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 37.9 (t), 126.00 (s), 128.88 (d); MS *m/z* (EI) 162 ($M^+$). Anal. Calcd for $C_3H_4BrN_3$: C, 22.24; H, 2.49; N, 25.94%. Found: C, 22.21; H, 2.54; N, 25.93.

**7e** (56 mg, 38%) as colourless thick oil. IR (nujol) 3385 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.80 (1H, br s), 3.90 (2H, s), 7.90 (1H, s), 10.90 (1H, br s); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 54.74 (t), 125.90 (s), 128.76 (d); MS *m/z* (EI) 99 ($M^+$). Anal. Calcd for $C_3H_5N_3O$: C, 36.36; H, 5.09; N, 42.41%. Found: C, 36.40; H, 5.12; N, 42.47.

**7f** (45 mg, 32%) as colourless thick oil. IR (nujol) 3280, 3160 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.24 (2H, br s), 3.16 (2H, s), 7.81 (1H, s), 10.86 (1H, br s); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 46.26 (t), 126.16 (s), 129.10 (d); MS *m/z* (EI) 98 ($M^+$). Anal. Calcd for $C_3H_6N_4$: C, 36.73; H, 6.16; N, 57.11%. Found: C, 36.78; H, 6.20; N, 57.17.

**4.1.5. Dipolar cycloaddition between 1-(1-ethoxy-2-azido)-2-methoxyethane 8 and acetylenes 3.** A solution of **8** (0.36 g, 2.5 mmol) and the appropriate alkynyl derivative **3** (10.0 mmol) in dry toluene (25 mL) was heated to 65 °C for 48 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with ethyl acetate/hexane 2:1 affording 1,2,3-triazoles **9** and **10**.

**9a** (0.36 g, 58%) as colourless thick oil. $^1$H NMR $\delta$ 3.38–3.75 (8H, m), 3.80 (3H, s), 7.0–7.3 (5H, m), 8.07 (1H, s); MS *m/z* (EI) 247 ($M^+$). Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.30; N, 16.99%. Found: C, 63.19; H, 6.27; N, 17.05.

**9b** (0.38 g, 66%) as pale yellow thick oil. $^1$H NMR $\delta$ 3.30–3.70 (8H, m), 3.78 (3H, s), 3.93 (3H, s), 8.11 (1H, s); MS *m/z* (EI) 229 ($M^+$). Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33%). Found: C, 47.11; H, 6.64; N, 18.38.

**9c** (0.27 g, 49%) as colourless thick oil. $^1$H NMR $\delta$ 3.35–3.70 (10H, m), 3.76 (3H, s), 8.04 (1H, s); MS *m/z* (EI) 219 ($M^+$). Anal. Calcd for $C_8H_{14}ClN_3O_2$: C, 43.74; H, 6.42; N, 19.13%). Found: C, 43.79; H, 6.38; N, 19.18.

**9d** (0.30 g, 46%) as pale yellow thick oil. $^1$H NMR $\delta$ 3.40–3.80 (10H, m), 3.92 (3H, s), 7.96 (1H, s); MS *m/z* (EI) 264 ($M^+$). Anal. Calcd for $C_8H_{14}BrN_3O_2$: C, 36.38; H, 5.34; N, 15.91%. Found: C, 36.43; H, 5.38; N, 15.98.

**9e** (0.17 g, 34%) as colourless thick oil. $^1$H NMR $\delta$ 2.90 (1H, br s), 3.44–3.80 (10H, m), 3.90 (3H, s), 8.11 (1H, s); MS *m/z* (EI) 201 ($M^+$). Anal. Calcd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88%. Found: C, 47.71; H, 7.47; N, 20.95.

**9f** (0.15 g, 30%) as colourless thick oil. $^1$H NMR $\delta$ 3.12–3.85 (12H, m), 3.94 (3H, s), 7.91 (1H, s); MS *m/z* (EI) 200 ($M^+$). Anal. Calcd for $C_8H_{16}N_4O_2$: C, 47.99; H, 8.05; N, 27.98%. Found: C, 48.03; H, 8.09; N, 28.04.

**10a** (0.10 g, 16%) as colourless thick oil. $^1$H NMR $\delta$ 3.40–3.80 (8H, m), 3.82 (3H, s), 7.0–7.3 (5H, m), 7.69 (1H, s); MS *m/z* (EI) 247 ($M^+$). Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.30; N, 16.99%. Found: C, 63.11; H, 6.25; N, 16.93.

**10b** (95 mg, 17%) as pale yellow thick oil. $^1$H NMR $\delta$ 3.30–3.75 (8H, m), 3.78 (3H, s), 3.95 (3H, s), 7.65 (1H, s); MS *m/z* (EI) 229 ($M^+$). Anal. Calcd for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33%. Found: C, 47.20; H, 6.65; N, 18.40.

**10c** (0.14 g, 26%) as colourless thick oil. $^1$H NMR $\delta$ 3.35–3.78 (10H, m), 3.88 (3H, s), 7.51 (1H, s); MS *m/z* (EI) 219 ($M^+$). Anal. Calcd for $C_8H_{14}ClN_3O_2$: C, 43.74; H, 6.42; N, 19.13%. Found: C, 43.79; H, 6.38; N, 19.18.

**10d** (0.16 g, 25%) as pale yellow thick oil. $^1$H NMR $\delta$ 3.40–3.80 (10H, m), 3.90 (3H, s), 7.58 (1H, s); MS *m/z* (EI) 264 ($M^+$). Anal. Calcd for $C_8H_{14}BrN_3O_2$: C, 36.38; H, 5.34; N, 15.91%. Found: C, 36.42; H, 5.31; N, 15.86.

**10e** (0.14 g, 28%) as colourless thick oil. $^1$H NMR $\delta$ 2.80 (1H, br s), 3.40–3.85 (10H, m), 3.90 (3H, s), 7.61 (1H, s); MS *m/z* (EI) 201 ($M^+$). Anal. Calcd for $C_8H_{15}N_3O_3$: C, 47.75; H, 7.51; N, 20.88%. Found: C, 47.80; H, 7.52; N, 20.94.

**10f** (0.12 g, 24%) as colourless thick oil. $^1$H NMR $\delta$ 3.10–3.85 (12H, m), 3.90 (3H, s), 7. 95 (1H, s); MS *m/z* (EI) 200 ($M^+$). Anal. Calcd for $C_8H_{16}N_4O_2$: C, 47.99; H, 8.05; N, 27.98%. Found: C, 48.01; H, 8.03; N, 27.94

## Acknowledgements

Thanks are due to MURST and CNR for financial support. We thank the NMR specialist Dr. Lara De Benassuti,

University of Milan, for $^1$H NMR analyses of the MeOPEG-supported materials. G. M. is grateful to Professor Luisa Garanti for valuable suggestions and comments.

## References and notes


1. (a) Sharp, J. T. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Product Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; Chapter 4, pp 473–538. (b) Lwowsky, W. In Padwa, A., Ed.; 1,3-Dipolar Cycloaddition Chemistry; Wiley-Interscience: New York, 1984; Vol. 1, Chapter 4, pp 621–627.
2. (a) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897. (b) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225. (c) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (d) Wang, Z.-X.; Qin, H.-L. *Chem. Commun.* **2003**, 2450. (e) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525.
3. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
4. (a) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2001**, *3*, 4091. (b) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110. (c) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2113.
5. (a) Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De, C.; Perno, C.; Karlsson, A.; Balzarin, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185. (b) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camarasa, M. J. *Antivir. Chem. Chemoter.* **1998**, *9*, 481.
6. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
7. Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wywratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111.
8. (a) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 17. (b) Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217. (c) Ellmann, J. A. *Chem. Rev.* **1996**, *96*, 555. (d) Krcnák, V.; Holladay, M. W. *Chem. Rev.* **2002**, 102.
9. Nefzi, A.; Otresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449.
10. (a) Löber, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett.* **2003**, *5*, 1753. (b) Löber, S.; Gmeiner, P. *Tetrahedron* **2004**, *60*, 8699.
11. Blass, B. E.; Coburn, K. R.; Faulkner, A. L.; Seibel, W. L.; Srivastava, A. *Tetrahedron Lett.* **2003**, *44*, 2153.
12. (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (b) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.
13. Garanti, L.; Molteni, G. *Tetrahedron Lett.* **2003**, *44*, 1133.
14. Benaglia, M.; Ciniquini, M.; Cozzi, F. *Tetrahedron Lett.* **1999**, *40*, 2019.
15. Zalkow, L. H.; Hill, R. H. *Tetrahedron* **1975**, *31*, 831.
16. Neumayer, D. A.; Belot, J. A.; Feezel, R. L.; Reedy, C.; Stern, C. L.; Marks, T. J.; Liable-Sands, L. M.; Rheingold, A. L. *Inorg. Chem.* **1998**, *37*, 5625.
17. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
18. Pierre, J. L.; Baret, P.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1971**, 3619.
19. (a) Bourgois, J.; Bourgois, M.; Texier, F. *Bull. Soc. Chim. Fr.* **1978**, 485. (b) Schultz, A. G. In Curran, D. P., Ed.; Advances in Cycloadditions; JAI: London, 1988; Vol. 1, p 53.
20. Trifonov, R. E.; Ostrovskii, V. A. *Croat. Chem. Acta* **1999**, *72*, 953.
21. Woerner, F. P.; Reimlinger, H. *Chem. Ber.* **1970**, *103*, 1908.
22. Szekeres, H. J.; Atack, J. R.; Chambers, M. S.; Cook, S. M.; Macaulay, A. J.; Pillai, G. V.; MacLeod, A. M. *Biorg. Med. Chem. Lett.* **2004**, *14*, 2871.
23. Banert, K. *Chem. Ber.* **1989**, *122*, 1963.
24. Banert, K. *Chem. Ber.* **1989**, *122*, 911.
25. Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014.