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MeOPEG-bounded azide cycloadditions to alkynyl dipolarophiles

Luisa Garanti and Giorgio Molteni*

Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, via Golgi 19, 20133 Milano, Italy Received 27 November 2002; revised 13 December 2002; accepted 16 December 2002

Abstract—The MeOPEG-supported azide 2 was reacted in the presence of a number of alkynyl dipolarophiles. The corresponding 1-MeOPEG-supported-1,2,3-triazoles were obtained in nearly quantitative yields. Acidic hydrolysis of the cycloadducts **5b** and **6b** caused the removal of the MeOPEG pendant giving 4-methoxycarbonyl-1,2,3-triazole **9** and 5-methoxycarbonyl-1,2,3-triazole **10**, respectively. © 2003 Elsevier Science Ltd. All rights reserved.

As it was disclosed from Huisgen's works,¹ the 1,3dipolar cycloaddition between organic azides and alkynyl dipolarophiles represent the choice method for the direct synthesis of variously substituted 1,2,3-triazoles.² The latter may display a wide range of biological activity as anti-HIV³ and anti-microbial⁴ agents as well as selective β_3 adrenergic receptor agonist.⁵ Due to these attractive activities, new methods for the regioselective synthesis of these compounds should be of interest. Within this context, it could be considered that the polymer-supported synthesis of small heterocyclic molecules is the subject of intense research activity,⁶ since it represents one of the most promising ways to generate small molecular libraires in the field of combinatorial chemistry.⁷

Recently, soluble polymers like poly(ethylene glicol) (PEG) and linear polystyrene (LPS)⁸ have gained popularity among organic chemists due to a number of advantageous features like the analytical simplicity, the high reactivity and the low price of the starting materials. Furthermore, the typical ease of the reaction work-up parallels one of the most appreciated features of solid-supported synthesis. The first example of 1,3-dipolar intermediate linked to the PEG was described recently by Janda and co-workers⁹ and is concerned with the generation of a supported nitrile oxide. Following this approach, we undertook the first study on the 1,3-dipolar cycloadditions between the soluble-polymer-supported azide $\mathbf{2}$ and a number of alkynyl dipolarophiles.

The monomethylether of poly(ethylene glycol) with a M_w of 5000 (MeOPEG) was devised as the suitable soluble support for our purposes. MeOPEG-supported azide 2 was obtained by treating MeOPEG-mesylate 1¹⁰ with sodium azide in anhydrous dimethylformamide (Scheme 1).

First, in order to demonstrate the feasibility of the soluble-polymer-supported azide cycloadditions, we heated **2** in dry toluene and in the presence of an excess of DMAD (10 mol. equiv.). 1-MeOPEG-supported-4,5-bismethoxycarbonyl-1,2,3-triazole **3** was obtained with 98% yield as a white solid by simple precipitation from the reaction crude with diethylether.¹¹ Structural assignements of **3** rely upon ¹H NMR analysis¹² and are fully consistent with those of similar 4,5-bismethoxycarbonyl-1,2,3-triazoles.¹³

Next, we reacted 2 with monosubstituted acetylenes 4 obtaining a mixture of the regioisomeric MeOPEG-supported cycloadducts 5 and 6 (Scheme 2).¹⁴ Products, yields and product ratio are summarised in Table 1.¹⁵ All cycloadditions were fully satisfactory in terms of





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^{*} Corresponding author. Tel.: +0039-02-50314141; fax: +0039-02-50314139; e-mail: giorgio.molteni@unimi.it



Scheme 2.

 Table 1. Cycloaddition between MeOPEG-supported azide

 2 and alkynyl dipolarophiles
 4

R	Product yield (%) $5+6$	Product ratio ^a	
		5:6	7:8
Ph	98	80:20	50:50
COOMe	98	83:17	82:18
CH ₂ Cl	96	70:30	66:34
CH ₂ Br	96	70:30	_
CH ₂ OH	95	57:43	_
CH ₂ CH ₂ OH	93	76:24	_

^a Determined from ¹H NMR.

product yield, while the ratio **5:6** was generally similar to that of **7:8** as it was reported previously¹⁶ for the reaction between *n*-pentylazide and the appropriate alkynyl dipolarophile (Fig. 1 and Table 1).

Finally, the removal of the MeOPEG pendant from the mixture of supported cycloadducts 5b+6b was accomplished in mild conditions (see Scheme 3) giving 4-methoxycarbonyl-1,2,3-triazole 9^{17} or 5-methoxycar-



Figure 1.



bonyl-1,2,3-triazole 10,¹ respectively, with 83% overall yield. In conclusion, the present study provides the first insight into the cycloaddition between the MeOPEG-supported azide 2 and a number of alkynyl dipolar-ophiles. Further developments are in progress.

Acknowledgements

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- 11. The yields of MeOPEG-bounded materials were determined by weight of pure compounds. The purity of MeOPEG-bounded compounds was determined by ¹H NMR analyses with pre-saturation of the MeOPEG methylene signals at 3.64 δ .
- 12. ¹H NMR data of **3** (CDCl₃): δ 3.28 (2H, t, *J*=7.0, CH₃OCH₂-), 3.33 (3H, s, CH₃OCH₂-), 3.80 (2H, t, *J*=7.0, -CH₂CH₂N<), 3.94 (6H, s, CH₃COO-), 4.81 (2H, t, *J*=7.0, -CH₂CH₂N<).
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- 14. For a typical run: A solution of 2 (5.00 g, 1.0 mmol) and 4 (10.0 mmol) in dry toluene (40 mL) was refluxed for 20 h. Diethyl ether (50 mL) was added, the white precipitate was collected by filtation off affording a mixture of the MeOPEG-supported cycloadducts 5+6 (see Table 1).
- The following data are selected from the ¹H NMR analyses of the mixtures 5+6 in CDCl₃ solutions. 5a: δ 7.97 (1H, s, C₅-H); 6a: δ 7.65 (1H, s, C₄-H); 5b: δ 8.30 (1H, s, C₅-H); 6b: δ 8.06 (1H, s, C₄-H); 5c: δ 7.79 (1H, s, C₅-H);

6c: δ 7.58 (1H, s, C₄- \underline{H}); **5d**: δ 7.84 (1H, s, C₅- \underline{H}); **6d**: δ 7.65 (1H, s, C₄- \underline{H}); **5e**: δ 7.78 (1H, s, C₅- \underline{H}); **6e**: δ 7.60 (1H, s, C₄- \underline{H}); **5f**: δ 7.62 (1H, s, C₅- \underline{H}); **6f**: δ 7.51 (1H, s, C₄- \underline{H}).

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