PEG-Supported Synthesis of 3,5-Disubstituted 1,2,4-Triazoles

Jun-Ke Wang,* Ying-Xiao Zong, Guo-Ren Yue

Key Laboratory of Resources and Environment Chemistry of West China, Department of Chemistry, Hexi University, Zhangye 734000, P. R. China
Fax +86(936)8282045; E-mail: wangjk@hxu.edu.cn

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Abstract: 1,3-Dipolar cycloadditions between diethyl azodicarboxylate and the polymer-bound munchnones generated from the corresponding carboxylic acids provided a library of 3,5-disubstituted 1,2,4-triazoles in excellent yield and high purity.

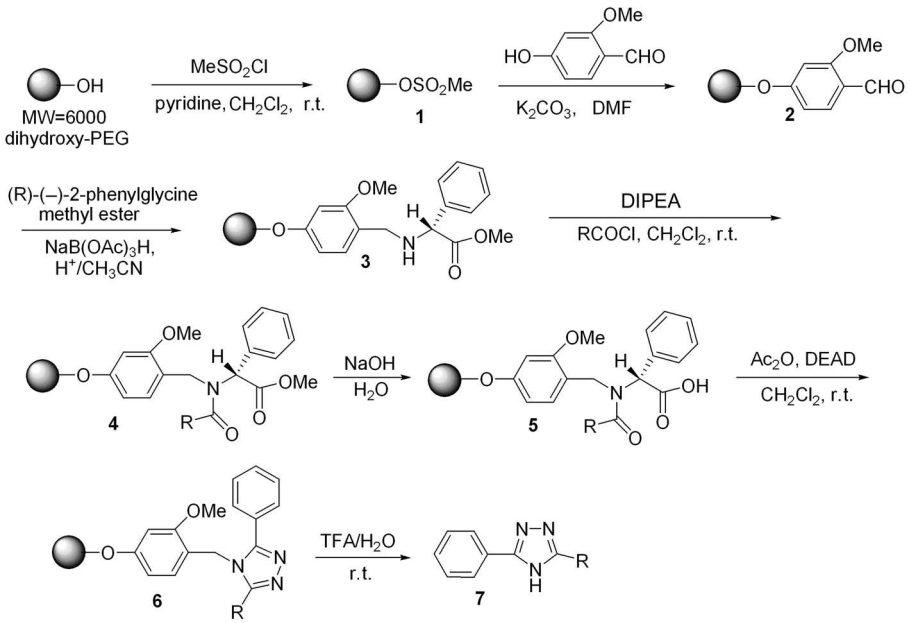
Key words: PEG-bound munchnones, diethyl azodicarboxylate, cycloadditions, 1,2,4–triazoles, parallel synthesis

Recently, organic synthesis of small molecular compounds on soluble polymers, i.e. liquid-phase chemistry, has been the focus of intense research activity.[1] It couples the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis without the cleavage-and-check procedure) with those of solid-phase chemistry (use of an excess amount of reagents, easy isolation, and purification of product). Among the various soluble polymers, polyethylene glycol (PEG) has increasingly become attractive as a solid support.[2]

Substituted 1,2,4-triazoles offer a high degree of structural diversity and possess a broad spectrum of biological activity,[3] therefore, they have become very important in medicinal chemistry. Solution method for their synthesis by the reaction of munchnones with diethyl azodicarboxylate (DEAD) was firstly reported by the Huisgen group.[4] In connection with our research on the PEG-supported liquid-phase synthesis,[5] we wish to report herein the parallel synthesis of 3,5-disubstituted-1,2,4-triazoles through a cycloaddition between diethyl azodicarboxylate and munchnones on PEG support.

As described in Scheme 1, the commercially available methanesulfonyl chloride was attached to the PEG6000 support by esterification of PEG with methanesulfonyl chloride in anhydrous CH_2Cl_2 at room temperature for 8 hours. The conversion of the terminal hydroxyl groups on PEG was determined by ^1H NMR analysis to be quantitative. The PEG-bound **1** reacted with 4-hydroxy-2-methoxybenzaldehyde in the presence of potassium carbonate at 60 °C for 10 hours to give immobilized PEG-bound aldehyde **2** in high yield. In general, the progress of both formation of sulfonic acid ester and the etherification was routinely determined by ^1H NMR spectroscopy.[6]

After treatment with (*R*)-(–)-2-phenylglycine methyl ester in the presence of sodium triacetoxyborohydride, the



Scheme 1

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aldehyde **2** was converted into corresponding PEG-bound amino acid ester **3**. Amino acid ester **3** was acylated with a variety of carboxylic acid chlorides and subjected to hydrolysis with 10% NaOH to yield the polymer-bound carboxylic acids **5**, which are precursors to the corresponding munchnones (Figure 1).

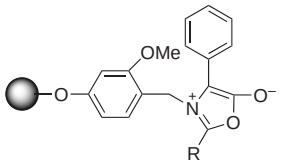

Figure 1

Table 1 Liquid-Phase Synthesis of 3,5-Disubstituted 1,2,4-Triazoles on PEG Support

Compd.	R	Yield (%)[a]	Purity (%)[b]
7a	C_6H_5	93	92
7b	2-$CH_3C_6H_4$	92	96
7c	3-$CH_3C_6H_4$	94	93
7d	3-$NO_2C_6H_4$	87	97
7e	4-$NO_2C_6H_4$	88	92
7f	4-$CH_3OC_6H_4$	94	98
7g	4-EtC_6H_4	90	96
7h	4-ClC_6H_4	89	96
7i	4-FC_6H_4	92	92
7j	4-IC_6H_4	88	95
7k	2-Naphthyl	95	95

[a] The yield is based on the PEG-6000.
[b] Purity is based on analysis by ^{1}H NMR and HPLC (UV detector at 280 nm) of crude products.

PEG-bound munchnones are key intermediates, which reacted with diethyl azodicarboxylate in CH_2Cl_2 to afford PEG-bound 3,5-disubstituted 1,2,4-triazoles **6**. Compounds **1**–**6** were purified by precipitation and washing with diethyl ether. The whole course of the reactions was monitored directly by ^{1}H NMR without detaching material from the PEG support. PEG-bound **6** was efficiently cleaved from the support by 25% TFA/H_2O at room temperature within one hour to provide the desired compounds **7**.[7]

A variety of 3,5-disubstituted 1,2,4-triazoles were synthesized using this procedure. As shown in Table 1, the yields are good to excellent (87–94%) and the purity is satisfactory (≥92%).

In order to extend the scope of the method, our research group is utilizing various amino acids to examine the synthesis of triazoles.

In conclusion, we have demonstrated a soluble polymer-supported methodology for the efficient parallel synthesis of 3,5-disubstituted 1,2,4-triazoles. Due to the homogeneity of the reactions on PEG support, products were obtained in good yields under mild conditions. All the reactions furnished the desired compound in high yield. Crude products are usually obtained in high purity and high yield just by simple precipitation and washing, allowing their direct use in primary biological assays without further purification.

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(6) The polymer-bound **1** was characterized by 200 MHz ^{1}H NMR analysis in $CDCl_3$: δ = 3.08 (3 H, s, CH_3SO_2), 3.52–3.74 (PEGO-CH_2CH_2O, m). The polymer-bound **2** was characterized by 200 MHz ^{1}H NMR analysis in $CDCl_3$: δ = 3.66–3.87 (PEG, m), 4.20 (t, 2 H, -PEGOCH_2CH_2OC=O), 6.42 (1 H, d), 6.47 (1 H, d,) 7.38 (1 H, d), 8.59 (1 H, s).

(7) All the compounds were characterized and their structures were confirmed by spectrometric methods (^{1}H NMR, ^{13}C NMR, MS) and elemental analysis. Compound **7f** is as follow: ^{1}H NMR (400MHz, CD_3OD): δ = 3.84 (3 H, s), 7.03–7.06 (2 H, dt, *J* = 2.4, 9 Hz), 7.47–7.50 (3 H, m), 7.96–7.99 (2 H, dt, *J* = 2.4, 9 Hz), 8.04–8.07 (2 H, m); ^{13}C NMR (CD_3OD): δ = 56.1, 115.5, 115.6, 127.8, 129.4, 129.4, 130.3, 130.6, 131.2, 131.4, 162.9; MS (EI): *m*/*z* = 251 (M^+); Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.52; H, 5.29; N, 16.64.