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A novel traceless route to synthesize 3,5-disubstituted-1,2,4-triazoles on PEG6000

Xi-Cun Wang,[a,*] Jun-Ke Wang,[a,b] Yu-Xia Da,[a] Zheng-Jun Quan[a] and Ying-Xiao Zong[b]

[a] *Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, PR China*

[b] *Key Laboratory of Resources and Environment, Chemistry of West China, Department of Chemistry, Hexi University, Zhangye 734000, PR China*

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Abstract—A novel traceless route to 3,5-disubstituted-1,2,4-triazoles has been described, which allows the incorporation of two elements of diversity. This method provided a library of 3,5-disubstituted-1,2,4-triazoles with high yields and purity.

The 1,2,4-triazole system has been known to be an important heterocycle in biologically active molecules. This five-numbered ring was also found in potent agonist or antagonist receptor ligands.[1] Furthermore, 1,2,4-triazole derivatives have been used as mimics[2] of the amide bond in order to increase bioavailability of the parent bioactive molecules. They have also been incorporated into peptides to surrogate *cis* amide bonds.[3] Therefore, a practical method for accelerated synthesis of diverse collection of 1,2,4-triazoles would be of great value for drug discovery. Solid-phase synthesis of 1,2,4-triazoles was reported.[4,5] However, solid-phase synthesis suffers from various problems, such as the heterogeneous nature of the reaction condition, reduced rate of reactions, and hindered mass transport of reagents.

Recently, liquid-phase synthesis has been a focus of intense research activity.[6] In an effort to develop a method for the rapid parallel synthesis of chemical libraries, we have been exploring liquid-phase combinatorial synthesis by the use of soluble polymer support-poly(ethylene glycol) to generate libraries.[7] Unlike an insoluble matrix, the soluble polymer support (PEG) 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 excessive regents and easy isolation and purification of product). Among the various soluble polymers, polyethylene glycol (PEG) has increasingly become an attractive support.[8]

Hitostuyanagi's group[9] has started from Boc-thionotripeptides and performed cyclization only with formic hydrazide to prepare 3,5-disubstituted 1,2,4-triazole derivatives. As part of our continuing effort to adapt heterocyclic methods to a high-throughput synthesis format, we report here our preliminary study in soluble polymer-supported synthesis of 3,5-disubstituted-1,2,4-triazoles. The synthetic route to the targeted molecule is outlined in Scheme 1. The PEG-bound aldehyde **1** was synthesized as described previously[7d] and subsequently converted to PEG-supported oxime **2** with hydroxylamine hydrochloride in the presence of pyridine. The resultant compound was reduced to PEG-supported benzylamine **3** with 1 M $LiAlH_4$ in THF.[10] The first point of diversity of **3** is then incorporated by various substituted benzoylchlorides in CH_2Cl_2 in presence of triethylamine to give polymer-bound **4**. The reaction proceeds well with various acyl chlorides without any unexpectedness. By reaction with Lawesson's reagent,[11] PEG-supported **4** was smoothly transformed to the corresponding thioamides **5**. The remaining key step for completing the synthetic sequence involves cyclization of **6** with aryloxyacetic acid hydrazides. This cyclization reaction proceeds smoothly in the presence of mercury(II) acetate in acetonitrile after standing for 30 h

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Keywords: PEG; 1,2,4-Triazoles; Lawesson's reagent; Cyclization reaction; Traceless cleavage.

[*] Corresponding author. Tel./fax: +86 93 6828 4286; e-mail: wangxc@nwnu.edu.cn

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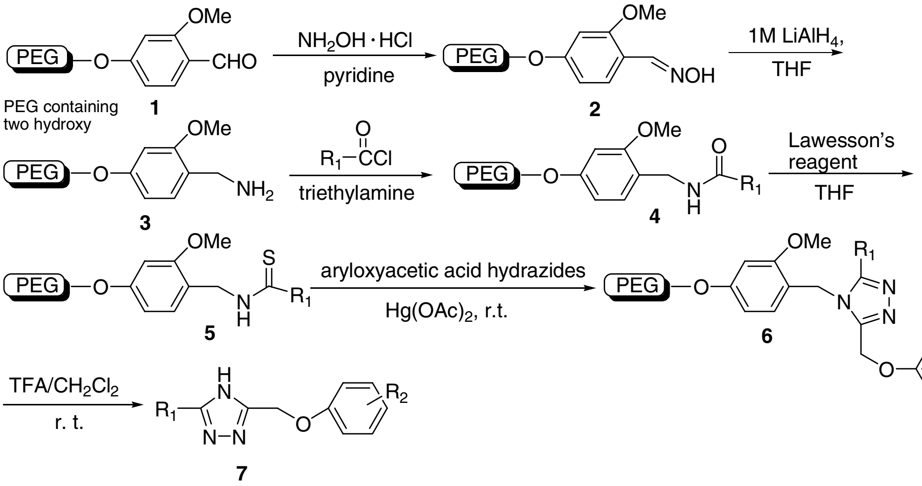

Scheme 1.

Table 1. Synthesis of 3,5-disubstituted-1,2,4-triazoles **7** on the PEG

Entry	Compounds	R$_1$	R$_2$	Yield (%)[a]	Purity (%)[b]
1	**8a**	C_6H_5	4-CH_3	90	87
2	**8b**	C_6H_5	4-Cl	94	88
3	**8c**	C_6H_5	H	85	90
4	**8d**	C_6H_5	4-CH_3	79	96
5	**8e**	C_6H_5	4-Br	85	83
6	**8f**	2-ClC_6H_4	4-CH_3	80	86
7	**8g**	2-ClC_6H_4	4-Cl	88	81
8	**8h**	2-ClC_6H_4	H	89	94
9	**8i**	2-ClC_6H_4	4-CH_3	77	83
10	**8j**	2-ClC_6H_4	4-Br	81	84
11	**8k**	2-ClC_6H_4	4-NO_2	79	95
12	**8l**	4-$CH_3C_6H_4$	4-NO_2	76	94
13	**8m**	4-$CH_3C_6H_4$	4-CH_3	90	85
14	**8n**	4-$CH_3C_6H_4$	4-Cl	88	94

[a] Determined by weight of crude sample.

[b] Purity determined by HPLC analysis of crude products, which show satisfactory IR, ^{1}H NMR, and mass data.[12]

at room temperature. In general, the progress of the formation of 1,2,4-triazole was routinely determined by IR spectroscopy (observing the disappearance of the peak of –NH–). Compounds **1**–**6** were purified by precipitation and washing with diethyl ether. The whole course of the reaction was estimated directly by ^{1}H NMR without detaching the material from the PEG support. Polymer-supported products **6** are subjected to a very efficient cleavage from the support with 30% TFA/CH_2Cl_2 at room temperature for about 2 h to provide the desired compounds **7** in 76–94% overall yield for eight steps (Table 1).

The following experimental procedure is representative for all synthesized compounds. Preparation of PEG-supported **1**: According to the literature,[7d] **1** was characterized by IR analysis (1676 cm^{-1}) and 200 MHz ^{1}H NMR analysis in $CDCl_3$: 3.66–3.87 (m, PEG), 4.20 (2H, t, PEG–$OCH_2C\mathit{H}_2OC{=}O$), 6.42 (1H, s), 6.47 (1H, d), 7.38 (1H, d), 8.59 (1H, s). Preparation of PEG-supported **2**: PEG-supported **1** (1 mmol) was added to a mixture (30 mL) of pyridine and ethanol (1:10, v/v). Hydroxylamine hydrochloride (5 mmol) was added and the mixture was stirred for 15 h at 50 °C followed by cooling in an icebox. After 6 h, the system was filtrated and washed in Et_2O to obtain PEG-supported **2**, which could be stored to be used in the next step of the synthesis. IR indicates complete disappearance of the carbonyl peak at 1676 cm^{-1}. Preparation of PEG-supported **3**: To a solution of PEG-supported oxime **2** (1 mmol) in THF (20 mL) was added 1 M lithium aluminum hydride in THF. The mixture was refluxed for 10 h, before the reaction mixture was cooled to 0 °C. EtOH was added to quench the excess lithium aluminum hydride, and then filtration was conducted. The resultant filtrate was condensed followed by the addition of Et_2O to give PEG-supported benzylamine **3**. Preparation of PEG-supported **4**: A solution of triethylamine (3 mmol) in CH_2Cl_2 (10 mL) was slowly (within 20 min) added to the mixture of PEG-supported **3** (1 mmol) and a kind of substituted benzoylchloride (3 mmol) and stirred for 4 h. After the solvent was removed under vacuum, Et_2O (20 mL) was added to precipitate the solid, which was directly used as the material for the next step. Preparation of PEG-supported **5**: Lawesson's reagent (3 mmol) was added to the PEG-supported **4** (1 mmol) in THF (20 mL) and heated under stirring at 60 °C for 2 h. The solvent was removed under vacuum, and Et_2O (20 mL) was added to precipitate the desired compound as solid. The preparation of the PEG-supported **6** is as follows: A mixture of PEG-supported **5** (1 mmol) and phenoxyacetic acid hydrazides (4 mmol) in CH_3CN (30 mL) was treated with (4 mmol) of $Hg(OAc)_2$ for 30 h at room temperature, and then filtered. The filtrate was concentrated under vacuum to remove the solvent and EtOH (20 mL) was added. After cooling for 8 h, the precipitate was filtered off, followed by washing with Et_2O (10 mL × 2) to obtain the PEG-supported triazoles **6**. Preparation of the desired compounds **7**: The PEG-supported 1,2,4-triazoles **7** was cleaved with 30% TFA/CH_2Cl_2 at room temperature for 3 h. CH_2Cl_2 was removed, and water was added into the residue to give the desired compounds, which were purified by chromatography on silica gel to obtain the analytically pure samples. By employing the desired reaction sequence, a validated library containing a diverse set of compounds is synthesized. The structures, yields, and purities obtained for representative sets of compounds are summarized in Table 1. Each crude product has been analyzed by HPLC, which shows around 82–92% purity. Since compound libraries are usually not purified before biological screening, crude products of high purity obtained from our liquid-phase protocol are especially valuable.

In conclusion, we have successfully developed an expedient synthesis sequence for effective preparation of the 3,5-disubstituted 1,2,4-triazoles using PEG6000 as support. All reactions involved here are highly efficient in giving the desired compounds at room temperature. Crude products are usually obtained in high purity and high yield just by simple precipitation and washing, providing their direct use in primary biological assays without further purification.

Acknowledgments

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References and notes

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12. All final compounds were characterized by spectrometric methods (^{1}H NMR and MS) and elemental analysis. For compound **8e** is as follows: ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.52$–7.56 (5H, m), 7.24–7.38 (4H, m), 5.40 (2H, s) MS = (EI, *m/z*) 285 (M^+). Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 63.00; H, 4.30; N, 14.66.