Liquid-Phase Traceless Synthesis of 3,5-Disubstituted 1,2,4-Triazoles

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Abstract: A liquid-phase traceless route to 3,5-disubstituted-1,2,4-triazoles has been developed, which allows for the incorporation of two elements of diversity. The heterocycle was constructed upon PEG6000 (soluble polymer) modified by 4-hydroxy-2-methoxy-benzaldehyde, from which a traceless cleavage could be realized with TFA–CH_2Cl_2. This method provided a library of 3,5-disubstituted-1,2,4-triazoles with high yields and purity.

Key words: soluble polymer, 1,2,4-triazoles, Lawesson's reagent, cyclization reaction, traceless cleavage

Solid-phase synthesis along with high-throughput screening has emerged as a powerful tool for the discovery of novel drug candidates.[1] However, solid-phase synthesis suffers from various problems, such as the heterogeneous nature of the reaction condition, reduced rate of reactions, and mass transport of reagents.

Recently, organic synthesis of small molecular compounds on soluble polymers, i.e. liquid-phase chemistry, has been a focus of intense research activity.[2] In an effort to develop a method for the rapid parallel synthesis of chemical libraries, we have been exploring liquid-phase combinatorial synthesis (LPCS) by the use of soluble polymer support poly(ethylene glycol) to generate libraries.[3] 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.[4]

1,2,4-Triazole system has been known to be an important recognition element in biologically active molecules. This moiety was also found in potent agonist or antagonist receptor ligands.[5] 1,2,4-Triazole derivatives have been used as mimics[6] of the amide bond in attempts to increase bioavailability of the parent bioactive molecules. They have also been incorporated into peptides to surrogate *cis*-amide bonds.[7] Therefore, a practical method for accelerating synthesis of diverse collection of 1,2,4-triazoles would be of great value for drug discovery. The Yli-Kauhaluoma[8] group was the first to report the solid-phase synthesis of 1,2,4-triazoles by the reaction of münchnones with diethyl azodicarboxylate (DEAD) according to Huisgen's method.[9] We have successfully translated the solid-phase synthesis onto PEG support.[3d] Hitostuyanagi's group[10] has recently started from Boc-thionotripeptides and performed cyclization only with formic hydrazide to prepare 1,2,4-triazole derivatives. According to this method, Fehrentz's group reported solid-supported synthesis of 3,4,5-trisubstituted 1,2,4-triazoles with high purity.[11]

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. PEG-6000 was modified with the commercially available methanesulfonyl chloride to afford the immobilized **1** in quantitative yield.[3d] The PEG-bound **1** reacted with 4-hydroxy-2-methoxy-benzaldehyde (this linker may realize the cleavage of C–N bond[8,12]) in the presence of potassium carbonate at 60 °C for ten hours to give immobilized PEG-bound aldehyde **2**, which was converted to PEG-supported oxime **3** with hydroxylamine hydrochloride in the presence of pyridine. The resultant compound was reduced to PEG-supported benzylamine **4** with 1 M $LiAlH_4$ in THF.[13]

The first point of diversity of **4** is then incorporated by several arylacyl chlorides in CH_2Cl_2 in the presence of triethylamine to give polymer-supported **5**. The reaction proceeds well with various acyl chlorides without any unexpectedness. After reaction with Lawesson's reagent,[14] PEG-supported **5** was transformed to the corresponding thioamide **6**. This transformation is performed smoothly. The remaining step for completing the synthetic sequence involves a key cyclization of **7** with arylacyl hydrazide. This cyclization reaction proceeds smoothly in the presence of mercury(II) acetate in acetonitrile after standing 30 hours 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**–**7** were purified by precipitation and washing with diethyl ether. Whether the intermediates formed was estimated directly by ^1H NMR without detaching the material from the PEG support.

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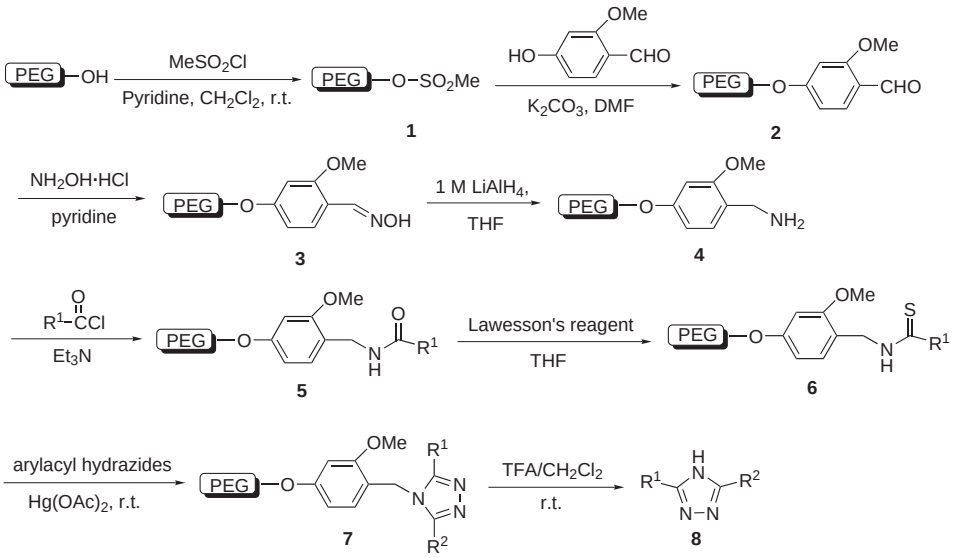

Scheme 1

Polymer-supported products **7** are subjected to a very efficient cleavage from the support with 30% TFA–CH_2Cl_2 at room temperature for about two hours to provide the desired compounds **8** in 75–90% overall yield for eight steps (Table 1). 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. As shown in Table 1, whether positions 3 and 5 of the target compounds are benzene rings or non-benzene rings, the expected compounds were obtained in good yield and good purity.

Each crude product is then analyzed by HPLC, which shows around 82–92% purity. Because 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 PEG-6000 as support. In each step of the reaction sequence, the immobilized intermediates were purified by simple precipitation and washing after the reactions were completed. Crude products are usually obtained in high purity and high yields just by simple work up. Furthermore, the desired compounds contain –NH, so if the diversity of molecule will be increased, some electrophilic reagent, such as halogenated hydrocarbon and acyl chloride, reacted with them to obtain 3,4,5-trisubstituted 1,2,4-triazoles. Synthesis and screening of combinatorial libraries based on pharmacophoric scaffolds may lead to the discovery of interesting biological activities.

The Typical Procedure – Preparation of PEG-Supported 1 and 2

According to the literature 3d, **1** and **2** were synthesized successfully without any unexpectedness. 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 (m, PEG–O–CH_2CH_2O). The polymer-supported **2** was characterized by IR analysis (1676 cm^{-1}) and 200 MHz ^{1}H NMR analysis in $CDCl_3$: δ = 3.66–3.87 (m, PEG), 4.20 (2 H, t, PEG–OCH_2CH_2OC=O), 6.42 (1 H, s), 6.47 (1 H, d,) 7.38 (1 H, d), 8.59 (1 H, s).

Preparation of PEG-Supported 3

PEG-supported **2** (1 mmol) was added into the mixture (30 mL) of pyridine and EtOH (1:10, v/v). Hydroxylamine hydrochloride (5 mmol) was added into the mixture stirred for 15 h at 50 °C followed by being cooled in an icebox. After 6 h, the system was filtred and washed in Et_2O to obtain PEG-supported **3**, which was 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 4

To a solution of PEG-supported oxime **3** (1 mmol) in THF (20 mL) was added 1 M $LiAlH_4$ in THF. The mixture was refluxed for 10 h, before the reaction mixture was cooled to 0 °C. Then, EtOH was added to quench the excess $LiAlH_4$, and then filtration was conducted. The resultant filtrate was condensed followed by the addition of Et_2O to give PEG-supported benzylamine **4**.

Preparation of PEG-Supported 6

Lawesson's reagent (3 mmol) was added to the PEG-supported **5** (1 mmol) in THF (20 mL) and place under stirring at 60 °C for 2 h. The solvent was removed under vacuum, and Et_2O (20 mL) was added to precipitate the solid that was the desired compound.

Preparation of PEG-Supported 7

A mixture of PEG-supported **6** (1 mmol) and arylacyl hydrazide (4 mmol) in MeCN (30 mL) was treated with (4 mmol) of Hg(OAc)2 for 30 h at r.t., and then it was filtered. The obtained filtrate was concentrated under vacuum and Et_2O was added to the solution to precipitate the PEG-supported triazoles **7**.

Preparation of the Desired Compounds 8

The PEG-supported 1,2,4-triazoles **7** was cleaved with 30% TFA–CH_2Cl_2 at r.t. for 2 h. Then, CH_2Cl_2 was removed, and H_2O was added into the residue to give the desired compounds, which were purified by chromatography on silica gel to obtain the analytical samples.

Table 1 Synthesis of 3,5-Disubstituted-1,2,4-triazoles **8** on the PEG

Entry	Compd	R^1	R^2	Yield (%)[a]	Purity (%)[b]
1	**8a**	C_6H_5	4-$CH_3C_6H_4$	82	90
2	**8b**	C_6H_5	4-ClC_6H_4	87	90
3	**8c**	C_6H_5	C_6H_5	85	88
4	**8d**	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	79	92
5	**8e**	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	90	87
6	**8f**	4-$CH_3OC_6H_4$	4-ClC_6H_4	80	89
7	**8g**	4-$CH_3OC_6H_4$	C_6H_5	88	88
8	**8h**	2-ClC_6H_4	4-$CH_3C_6H_4$	75	92
9	**8i**	2-ClC_6H_4	4-$CH_3OC_6H_4$	78	90
10	**8j**	2-ClC_6H_4	4-ClC_6H_4	80	86
11	**8k**	2-ClC_6H_4	C_6H_5	79	89
12	**8l**	2-ClC_6H_4	4-$NO_2C_6H_4$	80	90
13	**8m**	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	90	90
14	**8n**	4-$CH_3C_6H_4$	4-ClC_6H_4	84	86
15	**8o**	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	86	91
16	**8p**	CH_3	CH_3	80	96
17	**8q**	Benzyl	H	86	94

[a] Determined on weight of crude sample.
[b] Purity determined by HPLC analysis of crude products which show satisfactory IR, ^{1}H NMR and mass data.[15]

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(15) All the compounds were characterized and their structures were confirmed by spectrometric methods (^{1}H NMR, IR and MS) and elemental analysis.
For compound **8e**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.86 (6 H, s), 7.04–7.06 (4 H, m), 7.93–7.96 (4 H, m). IR: 1575, 1680, 2866, 3148 cm^{-1}. MS (EI): *m*/*z* = 281 [M$^+$]. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.39; H, 5.31; N, 14.90.
For compound **8i**: ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.86 (3 H, s), 7.03–7.08 (2 H, m), 7.44–7.52 (2 H, m), 7.57–7.79 (4 H, m). IR: 1570, 1694, 2891, 3133 cm^{-1}. MS (EI): *m*/*z* = 285 [M$^+$]. Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 63.17; H, 4.24; N, 14.68.