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Traceless liquid-phase synthesis of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles on polyethylene glycol (PEG)

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Abstract—A liquid-phase route to 3-alkylamino-4,5-disubstituted-1,2,4-triazoles has been developed, which permits the incorporation of three elements of diversity. The heterocycle was constructed upon PEG6000 (soluble polymer) modified by 4-hydroxy-2-methoxybenzaldehyde, from which a traceless cleavage could be realized with TFA/CH_2Cl_2. This method provided a library of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles with reasonable yields and excellent purity.

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.[1,2] 1,2,4-Triazole derivatives have been used as mimics[3,4] or isosteres[5] 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.[6]

Different approaches have been reported for the preparation of such heterocycles,[7] but the more explored strategy involves cyclization of an acylamidrazone intermediate at high temperature.[8] Synthesis of 1,2,4-triazoles on the solid phase has been reported.[9] However, the heterogeneous nature of this strategy might result in some problems, such as relatively low reactivity and selectivity, harsh reaction conditions, and extended reaction time, as well as the difficulty in characterizing the insoluble polymer-supported compounds.

Recently, liquid-phase synthesis on soluble polymer supports has increasingly become an attractive field.[10] This technique 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 reagents and easy isolation and purification of the products). Moreover, the soluble polymer-supported species allow using routine analytical methods (NMR, TLC or IR) to monitor the reaction process and to determine the structures of products attached to polymer support directly. Poly(ethylene glycol) (PEG) is one type of a polymer, which is soluble in many solvents, such as CH_2Cl_2, $CHCl_3$, THF, CH_3OH or H_2O at room temperature and can be precipitated from a solution by addition of diethyl ether, hexane, or *tert*-butyl methyl ether.[10a] Therefore, PEG can be considered as an ideal support for liquid-phase combinatorial synthesis in terms of its controllable solubility in different solvents. Hitostuyanagi's group[11] has recently started from Boc-thionotripeptides and performed cyclization only with formic hydrazide to prepare 1,2,4-triazole derivatives. This reaction is very attractive, owing to the mild reaction conditions used for the heterocycle formation, which contained the condensation of a thionotripeptide with an excess of formic hydrazide at room temperature in the presence of a thiophile metal salt such as mercury(II) acetate. In order to extend the synthetic scope and the functional group tolerance of this reaction, based on our previous research on the PEG-supported liquid-phase synthesis,[12] herein, we wish to explore this route for the traceless synthesis of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles

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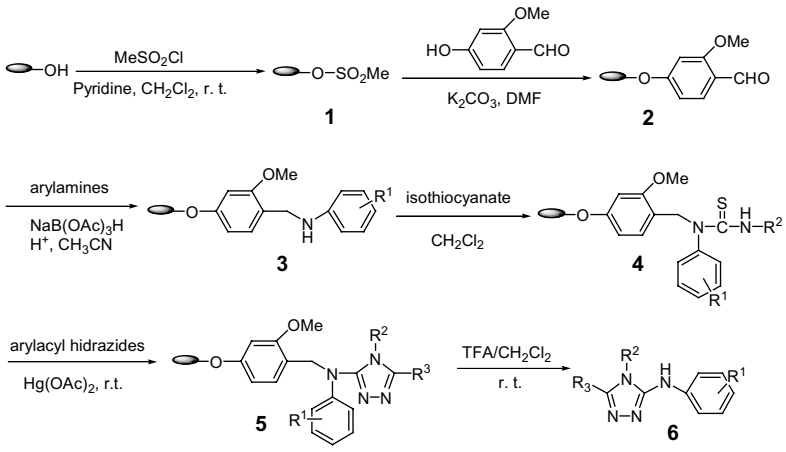

Scheme 1.

starting from PEG-supported thiourea and various benzoylhydrazines.

As described in Scheme 1, we prepared PEG-supported **2** following the procedure of the literature.[12d] After treating with an amine followed by sodium triacetoxyborohydride, the aldehyde **2** was converted into corresponding PEG-supported **3** which reacted with a variety of isothiocyanate to give PEG-supported thioureas **4** which was subjected to the condition (2 equiv of arylacyl hydrazine and 2 equiv of mercury(II) acetate in $CHCl_3$ for 48 h at rt) to obtain PEG-supported 1,2,4-triazoles **5**. In general, the progress of the formation of 1,2,4-triazole was routinely determined by IR and ^1H NMR spectroscopy (observing the disappearance of the peak of –NH–). Compounds **1**–**5** were purified by precipitation and washing with diethyl ether. The whole course of the reaction was estimated directly by ^1H NMR without detaching the material from the PEG support. PEG-supported **5** efficiently cleaved from the support with 10% TFA/CH_2Cl_2 at room temperature for about 2 h to provide the desired compounds **6a**–**j**.[13]

Using this procedure, a variety of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles were synthesized.[14] As reported in Table 1, the expected compounds were obtained in reasonable yield and excellent purity. However, when both positions 4 and 5 of the triazoles are benzene rings (entries 1 and 3), the reaction has not taken place. It is easy to understand, since two adjacent aryl groups may increase the steric hindrance. We attempted to prolong the reaction time to make it proceed, but the predicted results were not obtained. Therefore, we suppose that the steric hindrance is an important factor that influences the formation of **6a** and **6c**. In fact, we have initially examined various isothiocyanates to prepare this category. These experiments failed, and then our aim was transferred to non-aryl isothiocyanate.

In conclusion, we demonstrated a method for the liquid-phase synthesis of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles. The successful synthesis for the target compounds on PEG support shows that this strategy may provide a useful tool for the synthesis of new scaffolds and may allow preparation of triazole libraries. Our

Table 1. Liquid-phase synthesis of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles on PEG support

Entry	Compound **6**	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]
1	**6a**	H	Ph	4-CH_3O-C_6H_4	0	—
2	**6b**	H	$PhCH_2$	4-NO_2-C_6H_4	56	87
3	**6c**	H	Ph	Ph	0	—
4	**6d**	H	$PhCH_2$	Ph	80	90
5	**6e**	H	$PhCH_2$	4-CH_3O-C_6H_4	87	92
6	**6f**	H	$PhCH_2$	4-CH_3-C_6H_4	86	86
7	**6g**	H	*n*-C_4H_9	Ph	78	83
8	**6h**	4-CH_3O	*n*-C_4H_9	4-CH_3-C_6H_4	81	86
9	**6i**	4-CH_3	*n*-C_4H_9	4-NO_2-C_6H_4	77	90
10	**6j**	4-CH_3	$PhCH_2$	Ph	89	80
11	**6k**	4-CH_3	$PhCH_2$	4-CH_3O-C_6H_4	96	88
12	**6h**	4-CH_3	$PhCH_2$	4-Br-C_6H_4	89	81
13	**6i**	4-CH_3	$PhCH_2$	2-Naphthyl	84	89
14	**6j**	4-CH_3O	$PhCH_2$	CH_3	92	93

[a] The crude yield based on the PEG-6000.
[b] Purity based on HPLC analysis of crude products before purification.

ongoing efforts for the synthesis of other reactions starting from intermediate **4** will be reported elsewhere.

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13. The typical procedure: Preparation of PEG-supported **1** and **2**: According to the literature,[12d] **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 (3H, s, CH_3SO_2), 3.52–3.74 (m, PEG-O-CH_2CH_2O). The polymer-bound **2** was characterized by 200 MHz ^{1}H NMR analysis in $CDCl_3$: 3.66–3.87 (m, PEG), 4.20 (2H, t, –PEGOCH_2CH_2OC═O), 6.42 (1H, s), 6.47 (1H, d,) 7.38 (1H, d), 8.59 (1H, s). Preparation of PEG-supported **3**: PEG-supported **2** (1 mmol) was added into the mixture of HOAc (two drops) and CH_3CN (20 mL), and a kind of amine (5 mmol) was added into the solution and subsequently treated with 1.06 g (5 mmol) of sodium triacetoxyborohydride. The reaction mixture was stirred for 8 h at room temperature. Et_2O was added to the corresponding solution to precipitate the PEG-supported **3**. After drying in vacuum, the solid was stored to be used in the next step of the synthesis. Preparation of PEG-supported **4**: A solution of an appropriate isothiocyanate (4 mmol) in CH_2Cl_2 (20 mL) was added to PEG-supported **3** (1 mmol) and stirred at room temperature for 6 h. Et_2O was added to the corresponding solution to offer the PEG-supported **4**. Preparation of PEG-supported **5**: A mixture of PEG-supported **4** (1 mmol) and arylacyl hydrazide (4 mmol) in CH_3CN (30 mL) was treated with (4 mmol) of $Hg(OAc)_2$ for 36 h at room temperature, 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. Preparation of the desired compounds **6**: The PEG-supported 1,2,4-triazoles **5** was cleaved with 10% TFA/CH_2Cl_2 at room temperature for 2 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 analytical samples.
14. All the compounds were characterized and their structures were confirmed by spectrometric methods (^{1}H NMR, MS) and elemental analysis. For compound **6e** is as follows: ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.48 (2H, m, Ar); 7.22–7.09 (7H, m, Ar); 6.90 (2H, m, Ar); 6.74 (1H, m, Ar); 6.54 (2H, m, Ar); 5.06 (2H, s, CH_2); 4.12 (1H, s, NH); 3.78 (3H, s, CH_3). MS (EI, *m/z*) 356 (M^+). Calcd for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.20; H, 5.56; N, 15.80.