Parallel synthesis of 1,2,3-triazole derivatives on a soluble polymeric support

Jun-Ke Wang[a,b*], Ying-Xiao Zong[a], Guo-Ren Yue[a], Hong-Gang, An[a] and Xi-Cun Wang[b]

[a]*Key Laboratory of Resources and Environment Chemistry of West China, Department of Chemistry, Hexi University, 734000, Zhangye, Gansu, P.R.China*

[b]*Department of Chemistry, Northwest Normal University, 730070, Lanzhou, Gansu, P.R.China*

The synthesis of 1,2,3-triazole derivatives on a modified soluble polymer, poly(ethylene glycol)(PEG), is described.

Keywords: synthesis, poly(ethylene glycol)(PEG), 1,2,3-triazole derivatives

Solid-phase synthesis can overcome limitations in the efficiency of classical chemical synthesis.[1-2] 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. In recent years, the research efforts, towards the liquid-phase combinatorial synthesis to generate libraries by use of soluble polymer support, has become more popular.[3] The macromolecular carrier used in the liquid-phase synthesis, is soluble in many organic solvents and has a strong tendency to precipitate in ether, hexane and *tert*-butyl methyl ether. After the reactions completing, the products remain covalently bonded to the support, and purification is generally carried out after precipitation simply by filtration and washing away the unwanted materials. Furthermore, this non-destructive method allows routine analytical methodologies (*e.g.* ^{1}H, ^{13}C NMR, IR, TLC) to monitor the reaction transformations and determine the structures of compounds attached to the polymer support.

1,2,3-triazole derivatives have indeed shown interesting biological properties, such as antiallergic,[4] antibacterial,[5] antiinflammatory,[6] anticonvulsant,[7] and muscarinic,[8] and anti-HIV activities.[9] The synthesis of 1,2,3-triazole derivatives from azides and various alkynes has been widely studied in solution phase.[10] However, there are few published reports on PEG support. In connection with our research on the PEG-supported liquid-phase synthesis,[11] we report herein the parallel synthesis of 1,2,3-triazole derivatives through a 1, 3-dipolar cycloaddition of azide with various alkynes on PEG support.

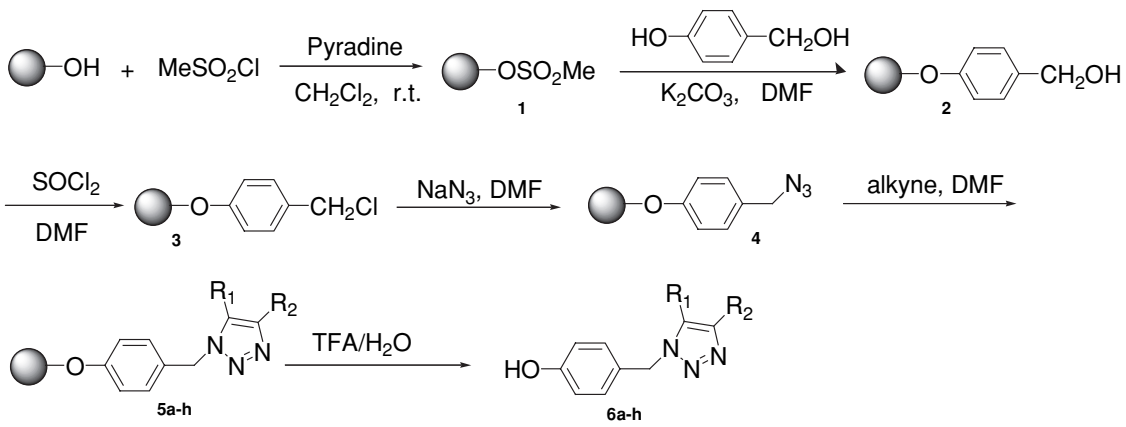
The synthetic route described in Scheme 1 is utilised for the synthesis of the representative library. PEG-6000 was modified with the commercially available methanesulfonyl chloride to afford the immobilised **1** in high yield. **1** reacted with *p*-hydroxybenzyl alcohol in the presence of potassium carbonate to give PEG-bound benzyl alcohol **2**. After refluxing with thionyl chloride, compound **2** was converted into corresponding PEG-bound benzyl chloride **3**. Compound **3** on treatment with sodium azide gave PEG-bound azide **4** as an intermediate, which reacted with various alkynes in DMF to afford PEG-bound 1,2,3-triazole derivatives **5**. Compound **1-4** and **5a–h** were purified by precipitation and washing with diethyl ether. The whole course of the reactions was monitored by TLC analysis (observation of disappearing alkynes) and estimated directly by ^{1}H NMR without detaching material from the support. **5a–h** efficiently cleaved from the support with TFA/H_2O to provide the desired compounds **6a–h** in 54–72% overall yield (Table 1).

When unsymmetrically substituted alkynes were used in 1,2,3-triazoles synthesis, either a mixture of two regioisomers or one main regioisomer with 4-hydroxybenzyl substituent at nitrogen was obtained. The regiochemistry of the cycloaddition reaction has been documented well, and the classical regiochemistry has been determined for several alkynes. The results were consistent with the results reported for

Table 1 PEG-supported liquid-phase synthesis of 1,2,3-triazoles (**6a–h**)

Compd.	R_1	R_2	Yield/%[a]	Purity/%[b]
6a	H	H	54	97
6b	H	Ph	72	94
6c	Ph	CHO	66	96
6d	Ph	CO_2Et	58	98
6e	CH_2OH	CH_2OH	68	98
6f	CO_2Me	CO_2Me	71	93
6g	H	CO_2Me	63	98
6h	H	CO_2Et	70	94

[a]The yield based on the PEG-6000.
[b]Purity determined by HPLC analysis of products.



Scheme 1

* Correspondent. E-mail:wangjk@hxu.edu.cn

benzylic azides[12] with ethyl propiolate, phenylacetylene, Methyl and ethyl propiolate reacted regioselectively and gave 4-substituted regioisomers **6g** and **6h** as main products. Phenylpropargyl aldehyde and ethyl phenylpropiolate gave 5-phenyl-substituted regioisomers **6c** and **6d** as the main isolated products.

In conclusion, we herein show soluble polymer supported methodology for the synthesis of 1,2,3-triazole derivatives. Due to the homogeneity of the reactions on PEG support, products were obtained in good yields under mild condition. All reactions involved here are highly efficient in giving the desired compound. 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.

Experimental

IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR spectrophotometer and ^{1}H NMR spectra on a Bruck AM-400 spectrometer using DMSO as solvent and Me_4Si as internal standard. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70eV). Elemental analyses were performed on a Vario El Elemental Analysis instrument. The product purity was determined using 1671-CHA HPLC (SHIMADZU, JAPAN) with UV-VIS detector. Melting points were determined with an electrothermal micromelting point apparatus and uncorrected.

General treatment of sodium azide.

Caution: Sodium azide is toxic and forms explosive compounds with heavy metals and dichloromethane. It also liberates toxic hydrazoic acid gas in acidic conditions.

Before disposal, the sodium azide waste was treated with an excess of a 20% solution of sodium nitrite, acidified with a 30% solution of sulfuric acid, and neutralised with a solution of sodium hydroxide.[13]

Preparation of **1**: To a solution of PEG-6000 (12.00 g, 2 mmol) and pyridine (20 mmol) in CH_2Cl_2 (80 ml), methanesulfonyl chloride (20 mmol) was added dropwise at 0°C and the reaction mixture was stirred for 12 h at r. t. The mixture was concentrated under reduced pressure until slightly viscous and purified by precipitation in Et_2O to give **1** (12.07 g, 98% yield based on PEG-6000). ^{1}H NMR ($CDCl_3$) δ: 3.00 (s, 3H, CH_3SO_2), 3.50–3.70 (m, PEGO-CH_2CH_2O).

Preparation of **2**: Na_2CO_3 (10 mmol) and *p*-hydroxybenzyl alcohol (10 mmol) were added to a solution of **1**(12.07 g) in DMF. The mixture was stirred for 10 h at 60°C, then distilled to remove DMF under vacuum until slightly viscous. The residue was dissolved in H_2O and further neutralised with dilute aqueous solution of hydrochloric acid until pH = 7. Then the whole mixture was extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried with $MgSO_4$, filtered and concentrated under vacuum until slightly viscous. Purification by precipitation in cold Et_2O gave **2** (11.57 g, 95% yield based on compound **1**). The purity of **2** was monitored by TLC (observing the disappearance of *p*-hydroxybenzyl alcohol by using ethyl acetate and petroleum ether (2:1) as eluent.)

Preparation of **3**: Four drops of DMF were added to a solution of **2** (11.57 g) in thionyl chloride. The mixture was refluxed for 6 h, then the excess amount of thionyl chloride was removed under vacuum to give **3** (11.17 g, 96% yield based on compound **2**).

Preparation of **4**: Polymer-bound **3** (11.17 g) was treated with sodium azide (0.65 g, 10 mmol) in DMF at 70 °C for 4 h. Then the solvent was removed, and the residue was dissolved in 60 ml of water, followed by extraction with CH_2Cl_2(3 × 10ml), and dried with $MgSO_4$. After the solution was concentrated into a third of its volume under reduced pressure, the appropriate volume of ether was added until the precipitation was completed. The precipitate was collected by filtration and washed with ether to obtain **4** (10.30 g, 92% yield based on compound **3**).

Preparation of **5**: An alkynes (2 mmol)was added into the solution of polymer-bound **4** (0.5 mmol) in DMF, the resulting mixture was reacted at about 80°C for 2–10 h. After cooling, anhydrous Et_2O (80 ml) was poured onto the mixture to precipitate the white solid, which was washed with Et_2O several times to obtain **5a–h** (80–92% yield based on compound **4**). The purity of **4** was monitored by TLC (observing the disappearance of alkyne by using EtOAc as eluent).

Preparation of **6**: Polymer-bound **5a–h** were treated with TFA–H_2O (9: 1) for 1.5 h at room temperature to give solid crude **6**. Washing the solid with warmed water and drying it under vacuum to afford pure **6a–h**(>75% yield based on compound **5**). The analytic samples can be obtained by column chromatography. The analytical data for compound **6a–h** are given below:

4-(1,2,3-Triazol-1-ylmethyl)phenol (**6a**): M.p. 179–180°C (lit. 173–176 °C[12]). ^{1}H NMR (400 MHz, DMSO-d_6): 9.50 (s, 1H), 8.09 (s, 1H), 7.71 (s, 1H), 7.16 (d, *J* = 8 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.46 (s, 2H). IR δ (cm^{-1}): 1520, 1270, 1241, 1117, 780. MS: *m/z* 175(M$^+$). Calcd for $C_9H_9N_3O$: C 61.70, H 5.18, N 23.99. Found: C 61.80, H 5.10, N 24.00.

4-(4-Phenyl-1,2,3-triazol-1-ylmethyl)phenol (**6b**): M.p. 220–221°C (lit. 215–218 °C[6]). ^{1}H NMR (400 MHz, DMSO-d_6): 9.55 (s, 1H), 8.56 (s, 1H), 7.83 (d, *J* =7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 2H). IR δ (cm^{-1}): 3142, 1520, 1245, 1089, 765. MS: *m/z* 251(M$^+$). 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 16.55.

1-(4-Hydroxybenzyl)-5-phenyl-1H-1,2,3-triazole-4-carbaldehyde (**6c**): M.p. 136–137 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.91(s, 1H), 9.51 (s, 1H), 7.59–7.49 (m, 5H), 6.80 (d, *J* = 8.5Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.47 (s, 2H). IR δ (cm^{-1}): 3155, 1710, 1517, 1273, 840. MS: *m/z* 279(M$^+$). Calcd for $C_{16}H_{13}N_3O_2$: C 68.81, H 4.69, N 15.04. Found C 68.66, H 4.78, N 15.00.

Ethyl 1-(4-hydroxybenzyl)-5-phenyl-1H-1,2,3-triazole-4-carboxylate (**6d**): M.p.147–148 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.49 (s,1H), 7.55–7.47 (m, 3H), 7.38–7.36 (m, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.62 (d, *J* = 8.5 Hz, 2H), 5.36 (s, 2H), 4.13 (q, *J* = 7 Hz, 2H), 1.09 (t, *J* = 7 Hz, 3H). IR δ (cm^{-1}): 1723, 1519, 1250, 1197, 1061. MS: *m/z* 323(M$^+$). Calcd for $C_{18}H_{17}N_3O_3$: C 66.86, H 5.30, N 13.00. Found: C 66.70, H 5.41, N 13.20.

4-[4,5-Bis(hydroxymethyl)-1,2,3-triazol-1-ylmethyl]-phenol (**6e**): M.p. 155–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.48 (s, 1H), 7.11 (d, *J* =8 Hz, 2H), 6.72 (d, *J* =8.5 Hz, 2H), 5.44 (s, 2H), 5.40 (t, *J* =5.5 Hz, 1H), 5.02 (t, *J* =5.5 Hz, 1H), 4.54 (d, *J* =5Hz, 2H), 4.49 (d, *J* =5.5 Hz, 2H). IR δ (cm^{-1}): 3237, 1522, 1235, 1030, 1006. MS: *m/z* 235(M$^+$). Calcd for $C_{11}H_{13}N_3O_3$: C 56.16, H 5.57, N 17.86. Found: C 55.99, H 5.60, N 17.15.

Dimethyl 1-(4-hydroxybenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate (**6f**): M.p. 161–162 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.58 (s, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* =8.5 Hz, 2H), 5.65 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H). IR δ (cm^{-1}): 1734, 1468, 1355, 1249, 1069. MS: *m/z* 291(M$^+$). Calcd for $C_{13}H_{13}N_3O_5$: C 53.61, H 4.50, N 14.43. Found: C 54.50, H 4.43, N 14.57.

Methyl 1-(4-hydroxybenzyl)-1H-1,2,3-triazole-4-carboxylate (**6g**): M.p.175–176°C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.56 (s, 1H), 8.80 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* =8.5 Hz, 2H), 5.51 (s, 2H), 3.81 (s, 3H). IR δ (cm^{-1}): 3130, 1730, 1523, 1234, 1063. MS: *m/z* 233(M$^+$). Calcd for $C_{11}H_{11}N_3O_3$: C 56.65, H 4.75, N 18.02. Found: C 56.77, H 4.52, N 17.89.

Ethyl 1-(4-hydroxybenzyl)-1H-1,2,3-triazole-4-carboxylate (**6h**): M.p. 155–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 9.57 (s, 1H), 8.78(s, 1H), 7.21 (d, *J* =8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H),5.50 (s, 2H), 4.28 (q, *J* =7 Hz, 2H), 1.28 (t, *J* =7 Hz, 3H). IR δ (cm^{-1}): 3136, 1729, 1520, 1235, 1060. MS: *m/z* 247(M$^+$). Calcd for $C_{12}H_{13}N_3O_3$: C 58.29, H 5.30, N 16.99. Found: C 58.33, H 5.15, N 16.76.

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