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Soluble Polymer-Supported Synthesis of Pyrazoles via 1,3-Dipolar Cycloaddition Strategy

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Rapid parallel liquid-phase synthesis of pyrazoles has first been developed. The 1,3-dipolar cycloaddition between nitrilimines generated *in situ* and soluble polymer-supported alkynyl or alkenyl dipolarophiles in parallel one-pot fashion gave the corresponding PEG-supported regioisomeric pyrazoles or regiospecific pyrazolines. The latter was assuredly oxidated by DDQ to PEG-supported regiospecific pyrazoles. Cleavage from the support under mild conditions afforded pyrazoles in good yields and high purity.

Keywords pyrazole, 1,3-dipolar cycloaddition, soluble polymer, liquid-phase synthesis, combinatorial chemistry

Dipolar cycloaddition to alkenes and alkynes is a well-established and general method for the synthesis of both aromatic and non-aromatic five-membered ring heterocycles.[1] The 1,3-dipolar cycloaddition between nitrilimines and alkynyl or alkenyl dipolarophiles represents the choice method for the direct synthesis of variously substituted pyrazoles or their reduced forms pyrazolines. Substituted pyrazoles may display a wide range of biological diverse activities in the pharmaceutical and agrochemical industry. Due to these attractive activities, new methods for the regioselective synthesis of these compounds should be of interest. Although there have been many different synthetic strategies in the solid phase and in solution phase,[2] they usually lack the regioselectivity or the simplicity of the one-pot protocol from commercially available resource.

In recent years, the soluble polymer-supported synthesis of small heterocyclic molecules has been a subject of intense research activity,[3] since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry.[4] It profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without following the cleavage-and-check technique) and of solid-phase methods (use of excess reagents and easy isolation and purification of products). Moreover, owing to the homogeneity of liquid phase reactions, the reaction conditions can be readily shifted from solution phase systems without large changes, and the amount of the excessive reagents is less than that in solid phase reactions. Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising.[5] In connection with our research on the PEG-supported liquid phase synthesis,[6] herein we disclose our findings pertaining to [3+2] cycloaddition of nitrilimine generated *in situ* and polymer-supported propiolate or acrylate in parallel one-pot fashion. Commercially available cheap difunctional PEG 4000 was chosen as a soluble polymer support.

We designed two different routes to liquid-phase synthesis of pyrazoles using nitrilimines generated *in situ*: first, directing 1,3-dipolar cycloaddition of nitrilimines onto polymer-supported propiolate in one-pot fashion, or second, employing polymer-supported acrylate, which would afford the pyrazoles after an oxidation of the cycloadduct intermediates pyrazolines. The nitrilimines involved in these [3+2] approaches to polymer-supported pyrazoles and pyrazolines would be generated *in situ* from commercially available aldehydes and hydrazine hydrochlorides.

As shown in Scheme 1, the PEG 4000 linked propiolate **1** was prepared by reacting PEG 4000 with propynoic acid in anhydrous toluene under reflux for 24 h. The good conversion of terminal hydroxyl groups on PEG 4000 was determinated by ^{1}H NMR analysis. The liquid-phase direct synthesis of pyrazoles in one-pot fashion took place as follows: after combining aldehyde (1.0 mmol), hydrazine hydrochloride (1.0 mmol) and trioctylamine (TOA, 1.0 mmol) in toluene (8 mL) at room temperature for 30 min, *N*-bromosuccinimide (NBS, 1.0 mmol) was partly added at 0 ℃ and the mixture was stirred for 30 min at the same temperature. Then, PEG-supported propiolate **1** (0.25 mmol) and trioctylamine (1.0 mmol) were added in one portion, and the resulting mixture was stirred for 24 h at 100 ℃. Upon completion of the reaction, cold diethyl ether (30 mL) was slowly added to the reaction mixture to precipitate the PEG-bound regioisomeric pyrazole **4** and **4′**. The precipitate was then collected on a sintered glass

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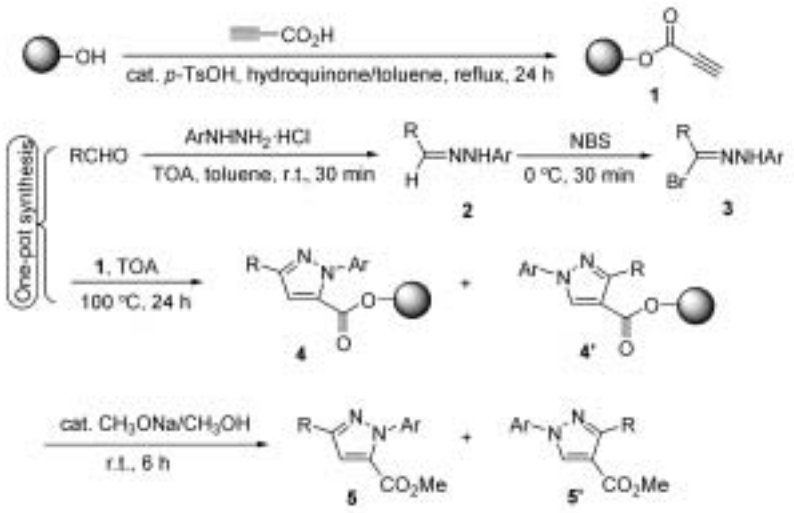
Scheme 1 Soluble polymer-supported synthesis of regioisomeric pyrazoles



funnel and thoroughly washed with diethyl ether (30 mL). PEG-bound pyrazole was then dried under vacuum and the good conversion of propiolate groups on PEG was determinated by ^{1}H NMR analysis. Finally, the resulting PEG-bound pyrazole was cleaved by using 0.1 N MeONa in anhydrous methanol (5 mL) at room temperature for 6 h to obtain regioisomeric pyrazoles **5** and **5′**.[7]

It can be noted that, as reported previously,[8] although a variety of nitrilimines generated *in situ* reacted well with the soluble polymer-supported propiolate under similar reaction conditions to afford the corresponding pyrazoles in good yields and high purity, cycloaddition regioselectivity was disappointing. Table 1 summarizes some of the initial results we have obtained by use of the above methodology. We felt that this was not suitable for pyrazole library we intended to prepare because expected changes in that ratio among different substrates would mask the true structure-activity relationships from the minor isomers. Therefore, soluble polymer-supported synthesis of regiospecific pyrazoles was further investigated using the second route.

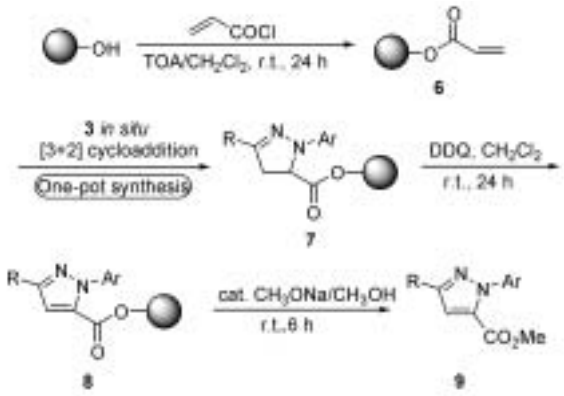
Table 1 Cycloaddition between PEG-supported propiolate and nitrilimines

Entry	R	Ar	Ratio[a]/% **5**∶**5′**	Yield[b]/% **5**+**5′**	Purity[a]/% **5**+**5′**
a	Ph	*p*-FC_6H_4	87∶13	93	>99
b	*p*-$CH_3C_6H_4$	*p*-FC_6H_4	80∶18	78	98
c	2-Furyl	*p*-FC_6H_4	79∶14	70	93
d	*n*-Propyl	*p*-FC_6H_4	74∶21	84	95

[a] Determined by GC-MS. [b] Determined based on weighing crude sample.

As shown in Scheme 2, the PEG-supported acrylate **6** was prepared by reacting PEG 4000 with acryloyl chloride at room temperature for 24 h. The good conversion of terminal hydroxyl groups on PEG 4000 was determined by ^{1}H NMR analysis. The liquid-phase synthesis of pyrazolines in one-pot fashion took place under similar reaction conditions for the synthesis of pyrazoles. But, attempts to cyclize **6** by refluxing it with nitrilimine generated *in situ* from **3a** in toluene in air gave the mixture of 5-substituted pyrazoline, 5- and 4-substituted pyrazoles and their ratio was 92∶3∶5 as indicated by GC-MS analysis after removal from the polymer. In these products, we did not observe the 4-substituted pyrazoline. It indicated that the 1,3-dipolar cycloaddition between nitrilimines and the PEG-supported acrylate was regiospecific,[9] and the PEG-supported 5-substituted pyrazoline was oxidated by air to isomeric products. Fortunately, when the reaction was carried out under nitrogen condition, only regiospecific 5-substituted pyrazoline was formed in high yield.

Scheme 2 Liquid phase synthesis of regiospecific pyrazoles



Oxidative aromatization of pyrazolines with some oxidants should provide an efficient method for the preparation of pyrazole derivatives. Actually, pyrazolines have been oxidized to the corresponding pyrazoles by several reagents such as lead tetraacetate, manganese dioxide, mercury oxide, potassium permanganate, silver

nitrate, and iodobenzene diacetate.[10] However, these methods either easily form isomeric mixtures or work up labouriously. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is a versatile reagent for the oxidation of alcohols and selected amino groups, and is very commonly used for aromatization of carbocycles and fused heterocycles. It was once reported that DDQ was also an efficient reagent for the oxidative aromatization of pyrazolines to produce pyrazoles.[11] Thus, we treated the PEG-supported pyrazolines **7** with 3.0 eq. DDQ in CH_2Cl_2 at room temperature for one day to obtain the desired PEG-supported regiospecific 5-substituted pyrazoles **8**. The good conversion was tracked by ^{1}H NMR analysis. 4,5-Dichloro-3,6-dihydroxy-phthalonitrile (DDP), the reduced product of DDQ and excessive DDQ were easily removed by simple precipitation and washings. Finally, the regiospecific 5-substituted pyrazoles **9** were removed from the support under mild conditions with good yields and high purity.[12] The results are presented in Table 2.

Table 2 Liquid-phase synthesis of pyrazoles

Entry	R	Ar	Yield [a]/%	Purity [b]/%
a	Ph	*p*-FC_6H_4	93	97
b	*p*-ClC_6H_4	*p*-FC_6H_4	88	92
c	*p*-$CH_3OC_6H_4$	*p*-FC_6H_4	90	93
d	Ph	*p*-$CH_3C_6H_4$	87	96
e	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	85	97
f	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	83	95
g	Ph	*p*-ClC_6H_4	90	97
h	*p*-ClC_6H_4	*p*-ClC_6H_4	81	97
i	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	81	98

[a] Determined based on weighing crude sample. [b] Determined by GC-MS.

In summary, we have found versatile and efficient parallel liquid-phase regiospecific synthesis of pyrazoles. DDQ was used as good oxidant for the synthesis of pyrazoles on soluble polymer. All reactions involved here are homogenous and highly efficient in giving the desired compounds under mild conditions. Crude products are usually obtained in good yields and high purity just by simple precipitation and washings. These procedures provide ready access to the large library of pyrazoles from commercially available starting materials.

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7 ^{1}H NMR **5a** ($CDCl_3$, 500 MHz) δ: 3.83 (s, 3H), 7.18 (t, J=8.4 Hz, 2H), 7.32 (s, 1H), 7.36 (t, J=7.2 Hz, 1H), 7.43 (t, J=8.7 Hz, 2H), 7.46—7.49 (m, 2H), 7.86 (d, J=7.3 Hz, 2H). ^{1}H NMR **5a′** ($CDCl_3$, 500 MHz) δ: 3.82 (s, 3H), 7.19 (t, J=8.5 Hz, 2H), 7.43—7.46 (m, 3H), 7.73—7.76 (m, 2H), 7.85 (d, J=6.5 Hz, 2H), 8.45 (s, 1H).

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12 Typical procedure for synthesis of pyrazole **9a**: after com-

bining 1 mmol of benzaldehyde, 1 mmol of 4-fluorophenylhydrazine hydrochloride and 1 mmol of trioctylamine in 8 mL of toluene at room temperature for 30 min under N_2, 1 mmol of *N*-bromosuccinimide was partly added at 0 ℃ and the mixture was stirred for 30 min at the same temperature. Then, 0.25 mmol of PEG-supported acrylate **6** and 1 mmol of trioctylamine were added in one portion, and the mixture was stirred for 24 h at 100 ℃. Upon completion of the reaction, 30 mL of cold diethyl ether was slowly added to the reaction mixture to precipitate the PEG-bound pyrazoline **7a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ : 3.50—3.80 (m, pyrazoline cyclic-4-H and PEG backbone), 4.33 (t, J=5 Hz, 2H, PEG-O-CH_2OCO), 4.80 (dd, J =6.9, 12.7 Hz, 1H), 6.98 (t, J=6.8 Hz, 2H), 7.07—7.10 (m, 2H), 7.35—7.41 (m, 3H), 7.70 (d, J=7.3 Hz, 2H). 0.75 mmol of DDQ was added to **7a** in 5 mL of CH_2Cl_2 under N_2 and the mixture was stirred at room temperature for 24 h. Upon completion of the reaction, 40 mL of cold diethyl ether was slowly added to the reaction mixture to precipitate the PEG-bound pyrazole **8a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.50—3.80 (m, PEG backbone, OCH_2CH_2O), 4.37 (t, J=5 Hz, 2H, PEG-*O*-CH_2OCO), 7.17 (t, J=8.4 Hz, 2H), 7.32—7.36 (m, 2H), 7.43 (t, J=8.7 Hz, 2H), 7.46—7.49 (m, 2H), 7.86 (d, J=7.3 Hz, 2H). **8a** was treated with 0.1 N MeONa in anhydrous methanol (5 mL) at room temperature. After 6 h of reaction, the detached PEG-OH was precipitated by adding cold diethyl ether (30 mL). The polymer was filtered, and the combined filtrate was flash passed through a short column to remove a trace amount of PEG and MeONa. The final compound was dried to offer the corresponding crude product **9a**. Spectral data of representative compound **9a** are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.83 (s, 3H), 7.18 (t, J=8.4 Hz, 2H), 7.32 (s, 1H), 7.36 (t, J=7.2 Hz, 1H), 7.43 (t, J=8.7 Hz, 2H), 7.46—7.49 (m, 2H), 7.86 (d, J =7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.4, 109.8, 115.7, 115.9, 126.0, 128.2, 128.3, 128.8, 129.0, 132.2, 134.5, 136.6, 151.9, 159.7, 163.8; EIMS (*m/z*): 296; HRMS calcd for $C_{17}H_{14}FN_2O_2$ ($[M+H]^+$) 297.0961, found 297.0965.

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