Parallel Synthesis of Pyrazolines on Soluble Polymer Support

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Received 1 June 2003

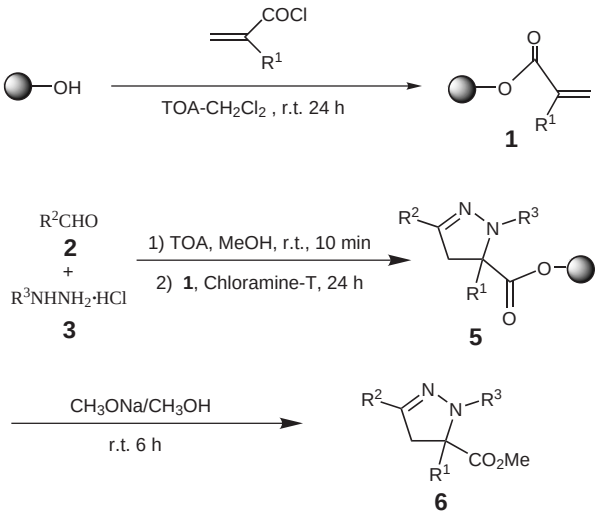
Abstract: An efficient and rapid parallel liquid-phase synthesis of pyrazolines has been developed. The one-pot three-components reaction of polyethylene glycol (PEG)-supported acrylate **1**, aldehyde **2** and aryl hydrazine **3** in the presence of chloramine-T in methanol gave the corresponding PEG-supported pyrazolines **5**. Cleavage from the support under mild conditions afforded pyrazolines **6** in good yields (69–91%) and high purities (91–100%).

Key words: pyrazolines, 1,3-dipolar cycloaddition, soluble polymer, liquid-phase synthesis, polyethylene glycol (PEG)

In recent years, the liquid-phase synthesis of small heterocyclic molecules has been a subject of intense research activity,[1] since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry.[2] 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). Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising.[3]

Substituted pyrazolines offer a high degree of structure diversity and have proven to be very important in medicinal chemistry.[4] Even though solution methods for their preparation via 1,3-dipolar cycloaddition are well studied,[5] there are very limited procedures available for the synthesis of this class of compounds on solid supports and soluble supports.[3d,6] In connection with our research on the PEG-supported liquid-phase synthesis,[7] herein we disclose our findings pertaining to [3+2] cycloaddition of in situ generated nitrile imine and polymer-supported acrylate. Commercially available difunctional PEG 4000 was chosen as soluble polymer support. Our efforts at obtaining a representative library of pyrazolines, which exploited three sites of chemical diversity, are presented below.

PEG-supported acryloyl esters **1** were easily obtained as illustrated in Scheme 1 and the conversion of terminal hydroxyl groups on PEG was determined by ^{1}H NMR analysis to be quantitative. Condensation of aldehydes **2** and aryl hydrazines **3** in methanol at room temperature for 10 minutes gave the hydrazones **4**. Then chloramine-T (CAT) and PEG-supported acryloyl esters **1** were added to the reaction mixture. The 1,3-dipolar cycloadditions of nitrile imines generated in situ with PEG-supported dipolarophile **1** provided the corresponding PEG-supported pyrazolines **5** in good yields. Quantitative conversion in the 1,3-dipolar cycloaddition reaction was verified by ^{1}H NMR analysis. The reactions carried out in the homogeneous phase at room temperature for 24 hours and the synthetic sequences performed in parallel one-pot fashion. Structural assignments of the cycloadducts rely upon ^{1}H NMR analysis. In particular, the proton on C_5 of the pyrazoline ring of **6d** resonates at δ = 4.85 ppm as a doublet of doublets, thus accounting for the depicted regiochemistry of the cycloaddition.



Scheme 1

The target compounds **6** were released from the PEG by treatment of the polymer bound products **5** with 0.1 N MeONa in methanol at room temperature. Normally, cleavage was completed after stirring in 0.1 N MeONa/MeOH for 6 hours.

A variety of hydrazones reacted well with the soluble polymer-supported acrylate under similar reaction conditions to afford the corresponding pyrazolines in good yields and high purities. The ready availability of aldehydes and hydrazines from commercial sources allows the preparation of large heterocyclic compound libraries. The proof of the structure of the pyrazolines was provided by ^{1}H NMR, ^{13}C NMR, GC-MS and HRMS spectra. In every case, only one isomer was obtained. Table 1 summarizes some of the initial results we have obtained by application of the above methodology.[8]

Synlett 2003, No. 10, Print: 05 08 2003.
Art Id.1437-2096,E;2003,0,10,1467,1468,ftx,en;U10103ST.pdf.

Table 1 One-Pot Liquid-Phase Synthesis of Pyrazolines

Compound	R^1	R^2	R^3	Yield (%)[a]	Purity (%)[b]
6a	H	*p*-$CH_3OC_6H_4$	Ph	70	89
6b	H	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	87	94
6c	H	*p*-$CH_3OC_6H_4$	*p*-FC_6H_4	84	92
6d	H	Ph	Ph	75	92
6e	H	Ph	*p*-$CH_3C_6H_4$	79	98
6f	H	Ph	*p*-FC_6H_4	88	91
6g	H	2-Furyl	Ph	84	94
6h	H	2-Furyl	*p*-$CH_3C_6H_4$	75	95
6i	H	2-Furyl	*p*-FC_6H_4	69	93
6j	CH_3	*p*-$CH_3OC_6H_4$	Ph	90	98
6k	CH_3	*p*-$CH_3OC_6H_4$	*p*-$CH_3C_6H_4$	85	97
6l	CH_3	*p*-$CH_3OC_6H_4$	*p*-FC_6H_4	81	98
6m	CH_3	Ph	Ph	91	100
6n	CH_3	Ph	*p*-$CH_3C_6H_4$	87	99
6o	CH_3	Ph	*p*-FC_6H_4	88	100
6p	CH_3	2-Furyl	Ph	80	96
6q	CH_3	2-Furyl	*p*-$CH_3C_6H_4$	83	95
6r	CH_3	2-Furyl	*p*-FC_6H_4	77	97

[a] Yields refer to product cleaved from PEG.
[b] Purities were determined by GC-MS analysis. GC purity was consistent with the purity determined by ^{1}H NMR.

In summary, we have demonstrated that liquid-phase methodology can be applied efficiently in parallel synthesis of pyrazoline library, which exploited three sites of chemical diversity. 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 washings, so they could be directly used in primary biological assays without further purification. The synthesis of large pyrazoline libraries is presently under investigation.

Acknowledgment

This work was financially supported by the National Natural Science Foundation of China (No. 20272051) as well as the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, P.R.C.

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(8) **Typical Procedure for Pyrazoline Synthesis:** After combining aldehyde (1.0 mmol), hydrazine hydrochloride (1.0 mmol) and trioctylamine (TOA, 1.0 mmol) in MeOH (8 mL) at r.t. for 10 min, PEG-supported acryloyl ester (0.25 mmol) and chloramine-T (1.0 mmol) were added and the mixture was stirred for 24 h under N_2. Upon completion of the reaction, cold Et_2O (30 mL) was added to the reaction mixture to precipitate the PEG-bound pyrazoline. The precipitate was then collected on a sintered glass funnel and thoroughly washed with Et_2O (10 mL × 3). PEG-bound pyrazoline was then dried under vacuum. Finally, the resulting PEG-bound pyrazoline was cleaved by 0.1 N MeONa in MeOH (5 mL) at r.t. for 6 h. Cold Et_2O (30 mL) was added to precipitate the detached PEG-OH. The polymer was filtered and the combined filtrate was flash passed through a short column to remove trace amount of PEG and MeONa. The solvent was removed to give the corresponding crude product. All compounds listed in Table 1 give satisfactory ^{1}H NMR, ^{13}C NMR, GC-MS and HRMS data. For compound **6p** is as follows: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.64 (s, 3 H), 3.24 (d, *J* = 16.7 Hz, 1 H), 3.65 (d, *J* = 16.7 Hz, 1 H), 3.76 (s, 3 H), 6.49 (s, 1 H), 6.60 (d, *J* = 3.4 Hz, 1 H), 6.90 (t, 1 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 7.24 (m, 2 H), 7.5 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 148.0, 143.7, 143.3, 137.9, 129.3, 120.6, 115.0, 111.9, 109.6, 68.9, 53.3, 48.1, 21.3. MS (EI): *m/z* = 284. HRMS calcd for $C_{16}H_{16}N_2O_3$ ($[M + H]^+$): 285.1161. Found: 285.1170.