Three-Component Condensation of Meldrum's Acid with Aldehyde and Thiol Catalyzed by Polymer-Supported Reagent

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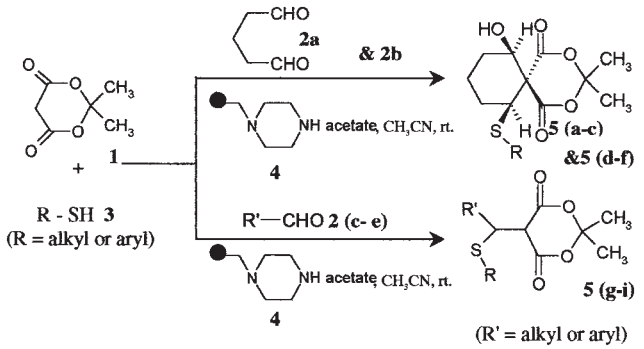
Piperazinomethyl polystyrene serves as an efficient and reusable catalyst in acetic acid (piperazinomethyl polystyrene acetate) for the three component condensation reaction of Meldrum's acid, aldehyde and a thiol which affords the corresponding spirocyclic derivatives in good yields and purity.

Owing to the perpetual demand of combinatorial methods of synthesis, in the discovery of potential therapeutic agents, there has been growing interest in solid-phase organic synthesis[1] (SPOS) for the preparation of small molecule libraries. Among the combinatorial methods of synthesis, parallel synthesis of single compounds plays an important role. To meet this challenge, multiple component condensations are more suitable for parallel synthesis because, large arrays of compounds with diverse substitution patterns can be prepared in single step, often in high yields under mild reaction conditions. There has thus been renewed interest in multiple condensation reactions catalyzed by polymer-supported reagents.[2] Thioalkylation of Meldrum's acid[3] with aldehydes in the presence of piperidinium acetate gives rise to spirocyclic compounds.[4] We, now wish to explore the synthetic scope of this reaction via a combinatorial approach to three-component coupling protocol applying a polymer-supported catalyst. Thus we report herein that Meldrum's acid undergoes three component condensation with aldehydes and thiols catalyzed by piperazinomethyl polystyrene acetate to afford a variety of spirocyclic derivatives (Scheme 1).

The polymer bound base that has been utilized in the three-component condensation is piperazinomethyl polystyrene.[5] This reaction was carried out using 1,5-and 1,4-dialdehydes **2a** and **2b** with Meldrum's acid **1** and variety of thiols **3(a–d)** in the presence of piperazinomethyl polystyrene acetate **4** in acetonitrile at room temperature for 6 h which furnished six membered **5(a–c)** and five membered **5(d–f)** spirocyclic products in (65–87%) yields. Similarly, the condensation was also carried out with mono-aldehydes **2(c–e)** to afford the corresponding products **5(g–i)** in (92–94%) yields within 3–4 h. The results are summerized in Table 1.



Scheme 1.

Table 1. Polymer-supported reagent catalyzed condensation[a] of Meldrum's acid with aldehyde and thiol

Entry	Aldehyde	Thiol	Product	Yield[b,c]/%
1	**2a**	**3a**	**5a**	75
2		**3b**	**5b**	78
3		**3c**	**5c**	87
4	**2b**	$HSCH_2COOCH_3$ **3d**	**5d**	65
5		**3a**	**5e**	81
6		**3b**	**5f**	83
7	**2c**	**3e**	**5g**	92
8	**2d**	**3f**	**5h**	94
9	**2e**	**3a**	**5i**	92

[a]All experiments were carried out at r.t for 3-6 h. [b]All new compounds exhibited correct ^{1}H NMR, ^{13}C NMR, IR, Mass spectra and chemical analyses. [c]Isolated yields.

The mechanism involves, the trapping of intermediate

dehydration product of the condensation of dialdehydes with Meldrum's acid by thiols. These derivatives are precursors for cyclic equilibrium/transfer alkylation cross-link [ETAC] chemistry.[6] This type of condensation can be applicable to chemical modification and tethering of probes to carbohydrate containing biological and macromolecular materials. Our own interest in these structures arise from their potential as unique alkylating bioprobes.

In conclusion, piperazinomehtyl polystyrene was found to be an efficient polymer bound reagent in three component condensation and represents an advantageous version of the same process in solution. It is due to its quantitative recovery with higher yields and purity achieving the major goals of green chemistry and can be reused several times without any loss of its activity.

Typical reaction procedure for dialdehyde condensation is as follows: a mixture of glutaraldehyde **2a** 2.5 M aqueous solution (1.5 ml, 3.65 mmol), Meldrum's acid **1** (0.5 g, 3.47 mmol), thiophenol **3a** (0.4 ml, 3.56 mmol) and piperazinomethyl polystyrene acetate **4** (0.174 g of resin bound base (loading value of piperazine species on PS matrix 1.5 mmol/g) in acetic acid), are stirred in 5 ml of acetonitrile at room temperature for 6 h. Then 5 ml of 5% aqueous citric acid solution was added and the reaction mixture was cooled to 5 °. The solid obtained was filtered, washed successively with water, DCM and dried.The resin bound base (0.174 g) separates out and thus quantitatively recovered. The filtrate containing the compound in DCM was dried on anhydrous sodium sulphate and evaporated to afford isopropylidene-*cis*-2-hydroxy-6-phenylthiocyclohexane-1,1-di-carboxylate **5a** (0.88 g, 75% yield). Recrystallization from CH_2Cl_2/hexane m.p. 152–154 °C.

Typical reaction procedure for monoaldehyde condensation is as follows: To a mixture of cooled solution of benzaldehyde **2c** (0.74 ml, 7.29 mmol), Meldrum's acid **1** (1.0 g, 6.94 mmol), and thiophenol **3a** (0.75 ml, 7.29 mmol) in 10 ml of acetonitrile, was added piparazinomethyl polystyrene acetate **4** (0.347 g of resin bound base in acetic acid) and the reaction mixture was stirred at room temperature for 4 h. Then 10 ml of 5% citric acid solution was added and the reaction mixture was cooled to 5 °. The solid obtained was filtered, washed successively with water, ethyl acetate and dried. The resin bound base (0.347 g) separates out and thus quantitatively recovered. The filtrate containing the compound in ethyl acetate was dried on anhydrous sodium sulphate and evaporated to furnish isopropylidene2-(phenylthio)ethane-1,1-dicarboxylate **5i** (2.18 g, 92% yield). Recrystallization from AcOEt/hexane m.p. 98–99 °C.

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7 Data for **5a:** IR (KBr)ν_{max}: 3445, 1764, 1718 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.45–7.25(m, 5H); 4.18 (dd, $J = 4.8$, 11.8, 1H); 3.50 (dd, $J = 4.4$, 12.8, 1H); 2.46(br, s, 1H); 2.28–2.01(m, 2H); 1.96–1.86(m, 3H); 1.85(s, 3H); 1.81(s, 3H); 1.42–1.28(m, 1H). ^{13}C-NMR ($CDCl_3$): 170.2; 164.3; 133.2; 133.1; 129.1; 128.2; 107.1; 60.4; 76.3; 53.1; 29.8; 29.6; 29.0; 28.9; 22.8. Mass: $m/z = 336(M^+)$. Anal. Calcd for $C_{17}H_{20}O_5S$: C, 60.70; H, 5.99; S, 9.53; Found C, 60.78; H, 6.05; S, 9.50%.

8 Data for **5i:** IR (KBr)ν_{max}: 1788, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 7.62–7.22(m, 10H); 5.20 (d, $J = 2.7$, 1H); 4.12 (d, $J = 2.7$, 1H); 1.68(s, 3H); 1.42(s, 3H); Mass: $m/z = 342(M^+)$.

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