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Polymer-Supported Acylhydrazones. Use in Sc(OTf)3-Catalyzed Mannich-Type Reactions Providing an Efficient Method for the Preparation of Diverse Pyrazolone Derivatives

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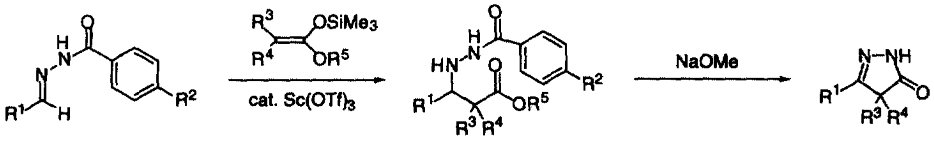
Abstract: *Polymer-supported acylhydrazones, prepared from polystyrene resin (1%-divinylbenzene), reacted with ketene silyl acetals in the presence of a catalytic amount of scandium triflate ($Sc(OTf)_3$), to afford the corresponding β-hydrazinoesters, which were cyclized and cleaved from the support simultaneously by treatment with a base to produce diverse pyrazolone derivatives.* © 1999 Elsevier Science Ltd. All rights reserved.

Solid-phase organic synthesis has been recognized as a powerful and rapid method for the preparation of large numbers of structurally distinct molecules.[1] Particularly in the past two or three years, a switch from known liquid-phase reactions to solid-phase reactions has been investigated intensively.[1] While a certain success has been made, low reactivity, low loading, and "trace" after cleavage from a polymer-support, etc. have been pointed out as problems of solid-phase reactions. In addition, it was also revealed that some known liquid-phase reactions are inappropriate when applied to solid-phase reactions, and in that case development of new liquid-phase reactions applicable to solid-phase reactions is required.[2]

In the course of our project to develop a method for the preparation of a pyrazolone and related compounds library, we developed an efficient liquid-phase reaction at an early stage.[3,4] It was found that acylhydrazones were activated by a catalytic amount of $Sc(OTf)_3$ to react with ketene silyl acetals to give the corresponding β-hydrazinoesters, which were cyclized under basic conditions to afford pyrazolones in high yields (Scheme 1). Benzoylhydrazones were tested to ensure that their benzene rings were connected to polymer supports in solid-phase reactions.



Scheme 1. Liquid-Phase Synthesis of Pyrazolones

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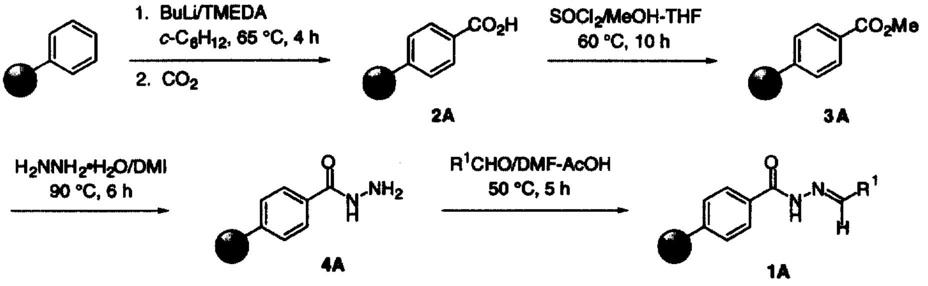
We planned to prepare polymer-supported hydrazone (**1A**) according to Scheme 2. Polystyrene resin (1%-divinylbenzene) was treated with BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at 65 °C for 4 h, and then was added to dry ice-THF to afford polymer-supported carboxylic acid **2A** (1.0-1.3 mmol/g).[5] The carboxylic acid was then methylated using $SOCl_2$ in MeOH-THF at 60 °C for 10 h to produce **3A** quantitatively. The methyl ester resin thus obtained was treated with hydrazine•hydrate in methanol (1/1) at 60 °C for 6 h to give the corresponding hydrazide resin (**4A**) in a 63% yield. The yield was improved when the reactions were carried out using 1,3-dimethyl-2-imidazolidinone (DMI) at 90 °C for 6 h (75%, hydrazine•hydrate in DMI (1/1); quantitative, hydrazine•hydrate in DMI (2/1)). The hydrazide resin thus prepared was then reacted with aldehydes in DMF-AcOH (20/1)[6] at 50 °C for 5 h to afford the corresponding hydrazones (**1A**). In the presence of 0.3 eq. of scandium triflate ($Sc(OTf)_3$), these hydrazones were then treated with the ketene silyl acetal derived from methyl isobutyrate (**5**) in dichloromethane at room temperature for 12 h. After the reactions, the resins were treated with sodium methoxide (NaOMe) in MeOH at 60 °C for 8 h to afford the corresponding pyrazolone derivatives. Several aldehydes were tested and the results are summarized in Table 1. While 3-phenylpropionaldehyde or heptanal reacted smoothly to afford the corresponding pyrazolones in high yields, lower yields were obtained in the reaction of benzaldehyde or 2-furylaldehyde.



Scheme 2. Synthesis of Polymer-Supported Hydrazone 1A

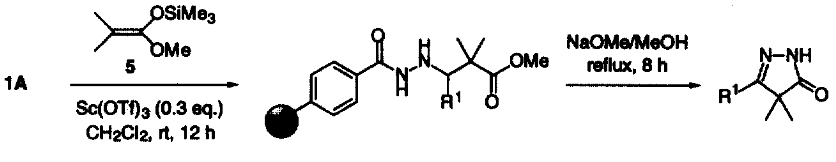
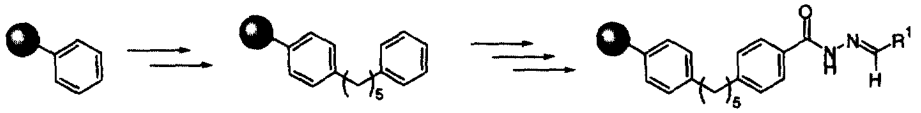


Table 1. Synthesis of Pyrazolones (1)

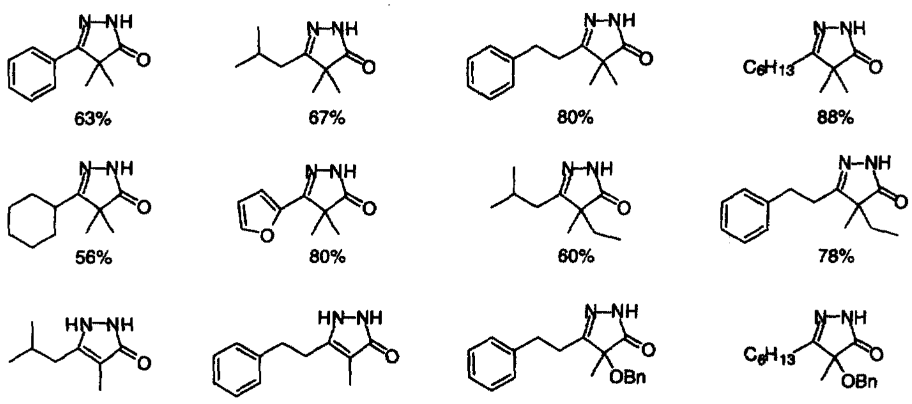
R^1	yield/%
Ph	38
$PhCH_2CH_2$	80
C_6H_{13}	88
2-furyl	44

To improve the lower yields, a carbon-spacer resin was used. Recently, we developed 5-(4'-chloromethylphenyl)pentylpolystyrene resin (CMPP resin),[7] and polymer-supported hydrazones having carbon-spacers (**1B**) were prepared on the basis of the CMPP resin (Scheme 3). In the presence of a catalytic amount of $Sc(OTf)_3$, **1B** were treated with ketene silyl acetals in dichloromethane for 12 h. After the reactions, the resulting resins were treated with sodium methoxide (NaOMe) in MeOH for 8 h under reflux to afford the corresponding pyrazolone derivatives. Several examples are shown in Scheme 4. In all cases, the desired pyrazolone derivatives were obtained in good yields. It is noted that the yields were much improved in the reactions of benzaldehyde or 2-furylaldehyde.



1B

Scheme 3. Synthesis of Polymer-Supported Hydrazone **1B**



Scheme 4. Synthesis of Pyrazolones (2). Use of **1B**

A typical experimental procedure is as follows. Polymer-supported acylhydrazone (**1B**, R = C_6H_{13}, 200 mg, 0.84 mmol/g), which was prepared from the corresponding polymer-supported acylhydrazine and heptanal, was combined with $Sc(OTf)_3$ (0.050 mmol) in dichloromethane (2 ml) at room temperature. To this mixture was added ketene silyl acetal **5** (0.84 mmol) in dichloromethane (1 ml), and the mixture was stirred for 12 h at the same temperature. Saturated aqueous sodium hydrogen carbonate was added to quench the reaction, and the resin was washed with dichloromethane, THF, water, THF, and ether successively, and finally dried under reduced pressure to afford the corresponding β-hydrazino ester resin. To the resin in methanol (2 ml) was added NaOMe (0.84 mmol), and the mixture was stirred for 8 h under reflux. Amberlite IRC-76 was then added, and the resin was filtered and washed with methanol. The filtrate was concentrated under reduced pressure and the crude product was purified by preparative TLC to afford the corresponding pyrazolone (88%).

In summary, polymer-supported acylhydrazones having carbon-spacers have been prepared. The hydrazones reacted with ketene silyl acetals using Sc(OTf)$_3$ as a catalyst, and treatment of the resulting adducts with NaOMe provided diverse pyrazolone derivatives.

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References and Notes

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