# Rare Earth Triflate-Catalyzed Addition Reactions of Acylhydrazones with Silyl Enolates. A Facile Synthesis of Pyrazolone Derivatives

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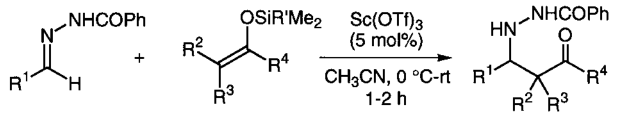
**Abstract:** In the presence of a catalytic amount of a rare earth triflate, benzoylhydrazones reacted with silyl enolates to afford the corresponding β-*N*'-benzoylhydrazino esters in high yields. The hydrazino esters thus obtained were readily converted to pyrazolone derivatives by treatment with a base. A three-component reaction between an aldehyde, an acylhydrazine, and a silyl enolate was also performed successfully.

In Lewis acid-mediated reactions of nitrogen-containing compounds, many Lewis acids are deactivated or sometimes decomposed by the nitrogen atoms of the starting materials or products, and even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by the nitrogen atoms.[1] It is desirable from a synthetic point of view that nitrogen-containing compounds are activated by Lewis acids catalytically. Recently, we have found that rare earth triflates are effective for the catalytic activation of nitrogen-containing compounds.[2] For example, rare earth triflates activate aldehydes containing nitrogen atoms or aldimines catalytically, and elegant carbon-carbon bond-forming reactions have been realized using these catalytic systems. The catalytic use of rare earth triflates is rationalized by the equilibrium of the Lewis acids-nitrogen atoms coordination. This is similar to the equilibrium of rare earth triflates-water coordination, which enables the Lewis acids to be stable in water without hydrolysis.[3] In the course of our investigations to explore the utility of rare earth triflates in synthesis, we further studied the activation of other useful nitrogen-containing compounds by rare earth triflates. In this paper, we describe the catalytic activation of acylhydrazones by rare earth triflates, which react with silyl enolates smoothly to afford β-*N*'-benzoylhydrazino ester derivatives.

We found that benzaldehyde benzoylhydrazone reacted with the silyl enolate[4] derived from methyl isobutyrate, in the presence of a catalytic amount of scandium triflate (Sc(OTf)$_3$). The reaction proceeded most efficiently in acetonitrile at -20 °C to afford the corresponding β-*N*'-benzoylhydrazino ester. Other benzoylhydrazones were then examined and the results are summarized in Table 1. Not only aromatic but also aliphatic, unsaturated aldehyde, and glyoxylate benzoylhydrazones worked well. In most cases, the reactions proceeded smoothly at 0 °C to rt for 1-2 h to afford the corresponding β-*N*'-benzoylhydrazino ester derivatives in high yields, although some yields were not optimized. As for silyl enolates, *t*-butyldimethylsilyl enolates reacted smoothly, and the silyl enolates derived from esters as well as thioesters also gave good results. It is noted that catalytic activation of the basic benzoylhydrazones has been achieved by using Sc(OTf)$_3$ as a Lewis acid catalyst, and that typical Lewis acids such as TiCl$_4$, SnCl$_4$, BF$_3$.OEt$_2$, etc. were not effective in this reaction (Table 2).

The β-*N*'-benzoylhydrazino esters obtained were readily converted to the pyrazolone derivatives.[5] Thus, treatment of the hydrazino ester derivatives with NaOMe in MeOH at 70 °C promoted the cyclization smoothly, and the corresponding pyrazolone derivatives were obtained in excellent yields (Scheme 1). Pyrazolone derivatives are a biologically interesting class of compounds,[5,6] and these reactions provide a useful route for the preparation of such derivatives.

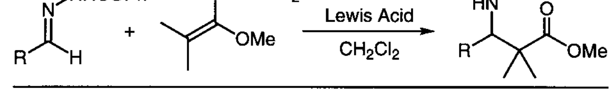
**Table 1.** Reactions of Acylhydrazones with Silyl Enolates



| R$^1$ | R$^2$ | R$^3$ | R$^4$ | R' | Yield/%[a] |
|---|---|---|---|---|---|
| Ph | Me | Me | OMe | Me | 81[b,c] (98) |
| PhCH=CH | Me | Me | OMe | Me | 63 (quant) |
| Ph(CH$_2$)$_2$ | Me | Me | OMe | Me | 98 |
| (CH$_3$)$_2$CHCH$_2$ | Me | Me | OMe | Me | 96 |
| (CH$_3$)$_2$CHCH$_2$ | Me | Me | OMe | $^t$Bu | quant |
| (CH$_3$)$_2$CHCH$_2$ | Me | Me | SEt | Me | 53 (78) |
| (CH$_3$)$_2$CHCH$_2$ | H | H | SEt | Me | 36 (75) |
| (CH$_3$)$_2$CHCH$_2$ | H | Me | OMe | $^t$Bu | 45[d] (76) |
| (CH$_3$)$_2$CHCH$_2$ | H | Me | SEt | $^t$Bu | 64[d] (82) |
| CO$_2$Et | Me | Me | OMe | $^t$Bu | 76 (90) |

[a] Isolated yield. Conversion yields are shown in parenthesis in some cases. [b] Containing a 2-benzoyl pyrazolidinone derivative (3%). The reaction was carried out at -20 °C for 6 h. [c] When Yb(OTf)$_3$ (5 mol%) was used, the product was obtained in a 54% yield (92% conversion) after 24 h. [d] Diastereomer ratio = ca. 1:1

**Table 2.** Effect of Lewis Acids (R = (CH$_3$)$_2$CHCH$_2$)

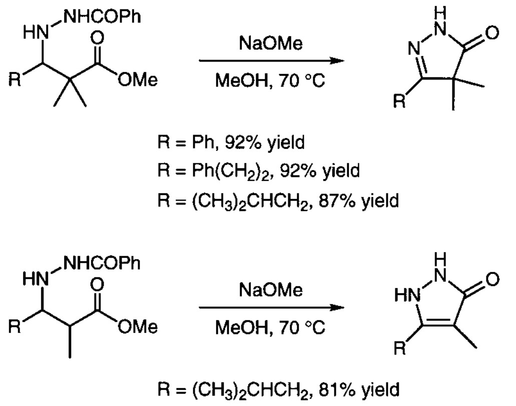


| Lewis Acid | Amount/mol% | Temp/°C | Time/h | Yield/% |
|---|---|---|---|---|
| Sc(OTf)$_3$ | 5 | rt | 1 | quant[a] |
| TiCl$_4$ | 100 | -20 to rt | 12 | trace[b] |
| SnCl$_4$ | 100 | -20 to rt | 12 | 10[c] |
| BF$_3$•OEt$_2$ | 100 | -20 to rt | 12 | 42[d] |

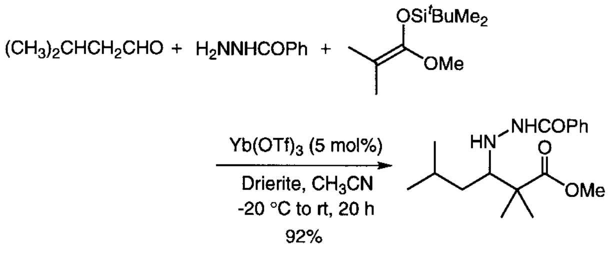
[a] Acetonitrile was used as a solvent. [b] The starting material was recovered in 83%. [c] 84%. [d] 52%

Finally, a three-component reaction of an aldehyde, a hydrazine, and a silyl enolate was examined, bearing in mind the application of these reactions to the synthesis of a pyrazolone library.[7,8] It was found that in the presence of a catalytic amount of ytterbium triflate (Yb(OTf)$_3$) and Drierite, benzaldehyde reacted with benzoylhydrazine and the *t*-butyldimethylsilyl enolate smoothly in acetonitrile at -20 °C to rt, to afford the desired β-*N*'-benzoylhydrazino ester in a 92% yield (Scheme 2).[9]

A typical experimental procedure is described for the reaction of isobutyroaldehyde benzoylhydrazone (**1**) with the trimethylsilyl enolate



**Scheme 1.** Conversion to Pyrazolone Derivatives



**Scheme 2.** A One-Pot Reaction Between an Aldehyde, an Acylhydrazine, and a Silyl Enolate

derived from methyl isobutyrate (**2**): To a mixture of $Sc(OTf)_3$ (9.8 mg, 0.02 mmol, 5 mol%) and **1** (82 mg, 0.4 mmol) in $CH_3CN$ (1.5 ml) were added **2** (105 mg, 0.6 mmol) in $CH_3CN$ (0.5 ml) at 0 °C. After the mixture was stirred for 1 h, aqueous sat. $NaHCO_3$ was added and the product was extracted with dichloromethane. After the organic layer was dried and evaporated, the crude product was chromatographed on silica gel to afford methyl 3-*N'*-benzoylhydrazino-2,2,5-trimethylhexanoate[10] (**3**, 118 mg, 96% yield). To a MeOH solution of **3** (31 mg, 0.10 mmol) was added NaOMe (16 mg, 0.30 mmol) at rt. The mixture was stirred for 2 h at 70 °C, and Amberlite IRC-76 resin was added to quench the reaction at 0 °C. After a usual work up, the desired pyrazolone (**4**)[11] was obtained in a 87% yield (15 mg).

In summary, rare earth triflate-catalyzed reactions of benzoylhydrazones with silyl enolates proceeded smoothly to afford the corresponding β-*N'*-benzoylhydrazino esters, which were readily converted to pyrazolone derivatives by treatment with a base in high yields. A three-component reaction between an aldehyde, an acylhydrazine, and a silyl enolate was also successfully carried out. These results have demonstrated the utility of rare earth triflates for the catalytic activation of nitrogen-containing compounds, which is generally difficult using typical Lewis acids. Further investigations along this line are now in progress in our laboratories.

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(9) When $Sc(OTf)_3$ was used under the same reaction conditions, the desired product was obtained in a 72% yield (97% conversion).

(10) **3**: Mp 84.3-84.5 °C (hexane-ethyl acetate). IR (KBr) 1728, 1640 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.91-0.96 (m, 6H), 1.11-1.35 (m, 8H), 1.97 (m, 1H), 3.27 (dd, 1H, $J$ = 2.1, 9.6 Hz), 3.57 (s, 3H), 4.90 (br s, 1H), 7.39-7.50 (m, 3H), 7.75 (d, 2H), 8.01 (br s, 1H).

(11) **4**: IR (KBr) 3208, 1699, 1602 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.99 (d, 6H, $J$ = 6.4 Hz), 1.22 (s, 6H), 2.13-2.17 (m, 3H); HRMS calcd for $C_9H_{16}ON_2$ ($M^+$) 168.1263, found 168.1265.