Use of Acylhydrazones as Electrophiles in Mannich-Type Reactions, β -Lactam, Pyrazolidinone, and Pyrazolone Synthesis

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Abstract: In the presence of a catalytic amount of scandium triflate $[Sc(OTf)_3]$, 4-trifluoromethylbenzoylhydrazones reacted with silyl enolates to afford the corresponding adducts, β -N'-acylhydrazinocarbonyl compounds, in high yields. Reductive cleavage of the nitrogen-nitrogen bond of the hydrazino compounds was performed using Raney Ni under H₂ atmosphere, to give β -aminocarbonyl compounds. The two-step process is regarded as a novel Mannich-type reaction using acylhydrazones as electrophiles. Moreover, the hydrazino compounds were also successfully converted to β -lactam, pyrazolidinone, and pyrazolone derivatives.

Hydrazones are aldehyde and ketone equivalents as well as imines. Their stability is much higher than imines and actually hydrazones derived from aliphatic aldehydes are often crystalline and can be isolated and stored at room temperature. However, their reactivity as electrophiles is known to be low, and there have been much fewer reports on the reactions of hydrazones with nucleophiles than those of imines.^{1,2} We have recently found that benzoylhydrazones² reacted with silyl enolates to afford β -N'-benzoylhydrazinocarbonyl compounds, which were converted to pyrazolone derivatives.³ Although the reactions were catalyzed by rare earth triflates, lower yields were observed in some cases. In the course of our investigations to improve the yields, we have found that electron-defficient acylhydrazones were very reactive. In this paper, we report the use of a new acylhydrazone, 4trifluoromethylbenzoylhydrazone, as an electrophile in novel Mannichtype reactions. Facile syntheses of β -lactam, pyrazolone, and pyrazolidinone derivatives using these reactions are also described.

First we carefully examined the reactions of hydrazones with silyl enolates. While 3-phenylpropionaldehyde phenylhydrazone did not react with ketene silvl acetal **2b** ($R^2 = {}^tBu$) derived from methyl isobutyrate at all, 3-phenylpropionaldehyde acylhydrazones reacted with 2b in the presence of a catalytic amount of scandium triflate $[Sc(OTf)_3].^4$ Among the acylhydrazones tested. trifluoromethylbenzoylhydrazone (1a, $R^1 = CF_3$) gave the best yield (Table 1). It is noteworthy that the electronic effect of the benzoyl moieties influenced the yields dramatically. While hydrazones with electron-donating groups gave lower yields, higher yields were obtained using hydrazones with electron-withdrawing groups. As for Lewis acids, Sc(OTf)₃ gave an excellent yield,^{3,5,6} and much lower yields were obtained by using typical Lewis acids such as TiCl₄, SnCl₄, and BF₃·OEt₂.

Several examples of the reactions of 4trifluoromethylbenzoylhydrazones with silyl enolates are shown in Table 2. Hydrazones derived from aromatic, aliphatic, and α , β unsaturated aldehydes reacted with silyl enolates smoothly to afford the corresponding β -N'-acylhydrazinocarbonyl compounds in high yields. Lower yields obtained using benzoylhydrazones³ were much more improved (entries 6, 9, and 11). It is also noted that several aliphatic hydrazones, readily prepared from aliphatic aldehydes, reacted with silyl enolates smoothly to afford the corresponding adducts in high yields.⁷ All aliphatic acylhydrazones tested were crystalline and could be stored at room temperature. As for silyl enolates, the enolates derived



Table 1. Effect of R ¹ and Lewis Acids							
Entry	Lewis Acid	R ¹	R ²	Temp/°C	Yield/%		
1	Sc(OTf) ₃	н	^t Bu	-20	37		
2	Sc(OTf)3	MeO	⁷ Bu	-20	7		
з	Sc(OTf)3	NO ₂	^t Bu	-20	77		
4	Sc(OTf) ₃	CF ₃	[#] Bu	-20	88		
5	Sc(OTf)3	CF ₃	Me	-20	97 (75 ^{a,b}		
6	BF3•OEt2	CF ₃	Me	0	4 ^a		
7	TiCl ₄	CF_3	Me	0	13 ^a		
8	SnCl ₄	CF ₃	Me	0	46 ^a		

^aDichloromethane was used as a solvent. ^b0 °C



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Table 2. Reactions of Acymydrazones with Silyr Enolates								
Entry	R ¹	R ²	R ³	R ⁴	Temp/°C	Yield/%		
1	Ph(CH ₂) ₂	Me	Ме	OMe	-20	97		
2	(CH ₃) ₂ CHCH ₂	Me	Me	OMe	rt	88		
3	CH ₃ (CH ₂) ₅	Ме	Me	OMe	0	95		
4	Ph	Ме	Me	OMe	rt	73		
5	CH₃CH=CH	Me	Me	OMe	0-rt	80		
6	PhCH=CH	Me	Me	OMe	rt	75 (63) ^d		
7	Ph(CH ₂) ₂	н	н	SEt	0	79		
8	CH ₃ (CH ₂) ₅	н	н	SEt	0	80		
9	(CH ₃) ₂ CHCH ₂	н	н	SEt	0-rt	68 (36) ^d		
10	c-C ₆ H ₁₁	н	н	SEt	0	68		
11	(CH ₃) ₂ CHCH ₂	Me	Me	SEt	0-rt	83 (53) ^d		
12	Ph(CH ₂) ₂	OBn	н	O ⁱ Pr	-78	90 ^{a,b}		
13	Ph(CH ₂) ₂	н	Me	OPh	-45-0	95 ^{a,c}		
14	Ph(CH ₂) ₂	н	н	Ph	rt	66		

^aPropionitrile was used as a solvent. ^b*Syn/anti* = 75/25. ^c*Syn/anti* = 64/36. ^dYield using benzoylhydrazone (Ref. 3)

from both esters and thioesters worked well. 1-Phenyl-1trimethylsiloxyethene (a ketone-derived silyl enolate) also reacted with an aliphatic acylhydrazone to afford the corresponding adduct in a good yield.

We then examined reductive cleavage of nitrogen-nitrogen bonds of the β -N'-acylhydrazinocarbonyl compounds. If the cleavage is successfully carried out, the two-step process can be regarded as a novel Mannich-type reaction. Namely, hydrazones, readily prepared from aldehydes and acylhydrazines, react with silyl enolates to give β -N'-acylhydrazinocarbonyl compounds, and reductive cleavage of nitrogen-nitrogen bonds gives β -aminocarbonyl compounds (Scheme 1).



Scheme 1. Mannich-Type Reactions Using Hydrazones

It is known that classical Mannich reactions often induce several side pathways under rather drastic conditions, and that the yields of the desired adducts are often low. Use of imines as starting materials have improved the yields,^{8,9} and among the reactions using imines, condensation with silyl enolates under the influence of a Lewis acid is the most promising.^{10,11} Although several efficient catalytic processes using imines have been reported,¹¹ a problem is instability of aliphatic imines containing α -protons, which are easily isomerized to enamine forms to induce self-condensation, etc.¹²

Reductive cleavage of the nitrogen-nitrogen bond of the hydrazino compound was successfully carried out using Raney Ni under H_2 atmosphere (Scheme 2).¹³ Thus, adduct **6a** was treated with a catalytic amount of Raney Ni (W-3) under H_2 (1 atm) at ambient temperature. After cleavage of the nitrogen-nitrogen bond, the resulting amine was protected as its *t*-butoxycarbonyl (Boc) group.



Scheme 2. Conversion to Aminoester Derivative

Finally, cyclization of β -N'-acylhydrazinocarbonyl compound **6a** to heterocycles was examined (Scheme 3). It was found that β -lactam **8**¹⁴ was obtained by treatment of **6a** with *n*-BuLi at -78 °C,¹⁵ while pyrazolone **9**³ was produced in the presence of NaOMe at room temperature (rt). Since isomerization from **8** to **9** was observed under these conditions (NaOMe), **8** and **9** were expected to be kinetic and thermodynamic products, respectively. Moreover, pyrazolidinone **10**¹⁶ was obtained in the presence of samarium diiodide $(SmI_2)^{17}$ in THF-MeOH at rt.



Scheme 3. Conversion to β-Lactam, Pyrazolone, and Pyrazolidinone

A typical experimental procedure is described for the reaction of isovaleraldehyde 4-trifluoromethylbenzoylhydrazone (4a, R^1 = $(CH_3)_2CHCH_2$ with ketene silvl acetal **2a** (R² = Me). To a solution of Sc(OTf)₃ (4.9 mg, 0.01 mmol) and 4a (54.2 mg, 0.2 mmol) in acetonitrile (1.2 ml) was added a solution of 2a (52.6 mg, 0.3 mmol) in acetonitrile (0.4 ml) at room temperature. After stirring for 4 h at the same temperature, the reaction was quenched with saturated aqueous NaHCO3 solution, and the aqueous layer was extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give methyl 2,2,5-trimethyl-3-[N'-(p-trifluoromethylbenzoyl)hydrazino]hexanate (6a, 65.9 mg, 88%) as white crystals. To a solution of 6a (33.0 mg, 0.09 mmol) in ethanol (2.0 ml) was added a catalytic amount of Raney Ni (W-3). After stirring under H2 at 1 atm for 24 h, a solution of di-t-butoxydicarbonate (76.9 mg, 0.4 mmol) in ethanol (1.0 ml) was added under argon and the solution was stirred for 15 h at room temperature. Raney Ni was then filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane) to give 7 (18.0 mg, 71 %) as a colorless oil.

In summary, 4-trifluoromethylbenzoylhydrazones reacted with silyl enolates, in the presence of a catalytic amount of scandium triflate $(Sc(OTf)_3)$, to afford the corresponding adducts, β -*N'*-acylhydrazinocarbonyl compounds, which were readily converted to β -aminocarbonyl compounds in high yields. It is noted that aliphatic hydrazones, which are mostly crystalline and can be stored at room temperature, reacted smoothly, and that these reactions may supersede Mannich-type reactions using imines. Moreover, the hydrazino compounds were also successfully converted to β -lactam, pyrazolone, and pyrazolidinone derivatives. Further studies to use acylhydrazones as electrophiles in synthetic reactions are now in progress in our laboratories.

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- 14. **8:** IR (neat) 1765, 1685, 1325 cm⁻¹; ¹H NMR (CDCl₃) δ 0.93 (dd, 6H, *J* = 6.4, 8.4 Hz), 1.26 (s, 3H), 1.42-1.51 (m, 1H), 1.49 (s, 3H), 1.56-1.72 (m, 2H), 3.92 (t, 1H, *J* = 6.6 Hz), 7.54 (d, 2H, *J* = 8.3 Hz), 7.75 (d, 2H, *J* = 8.1 Hz), 9.81 (s, 1H); ¹³C NMR (CDCl₃) δ 17.1, 22.46, 22.51, 23.1, 25.8, 37.9, 50.6, 67.6, 125.50, 125.55, 125.60, 125.65, 127.6, 133.7, 150.7, 164.3, 176.5.
- 15. The structure was confirmed by X-ray analysis of the corresponding N-benzoyl derivative.
- 16. **10:** Mp 114-115 °C. IR (neat) 1717 cm⁻¹; ¹H NMR (CDCl₃) δ 0.93 (d, 3H, *J* = 6.6 Hz), 0.96 (d, 3H, *J* = 6.6 Hz), 0.99 (s, 3H), 1.11 (s, 3H), 1.23-1.37 (m, 2H), 1.68-1.82 (m, 1H), 3.29 (dd, 1H, *J* = 4.6, 9.0 Hz), 3.72 (br, 1H), 8.09 (brs, 1H); ¹³C NMR (CDCl₃) δ 16.5, 21.3, 22.1, 23.5, 25.1, 36.8, 42.5, 66.9, 182.4; HRMS calcd for C₉H₁₈N₂O (M+) 170.1419, found 170.1423.
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