Enecarbamates as Imine Surrogates: Nucleophilic Addition of 1,3-Dicarbonyl Compounds to Enecarbamates

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ABSTRACT

Novel Mannich-type reactions of 1,3-dicarbonyl compounds with enecarbamates have been developed. Stable and storable enecarbamates work as surrogates of aliphatic aldehyde-derived imines, which are known to be difficult to isolate and store.

Nucleophilic addition to imines provides a facile synthetic route to nitrogen-containing compounds, many of which are of biological and chemical importance.¹ Although there have been many reports of addition reactions involving imines so far,² most of these have employed imines such as those derived from aromatic aldehydes or ethyl glyoxylate. In addition, imines bearing hydrogens at the α position are known to isomerize readily to the corresponding enamines and to be difficult to isolate and purify.³

Enamides and enecarbamates are stable under air and easy to handle, and they have often been used as substrates in

(3) To overcome this problem, a synthetic equivalent has been used. For an example, see: (a) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405. (b) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (c) Ha, H.-J.; Ahn, Y.-G. *Synth. Commun.* **1995**, *25*, 969. (d) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetrahedron* **1991**, *47*, 2683.

10.1021/ol0620186 CCC: \$33.50 © 2006 American Chemical Society Published on Web 09/21/2006 catalytic asymmetric hydrogenation ractions.⁴ Recently we have reported that enamides and enecarbamates can be used as nucleophiles and that they react with several electrophiles in the presence of Lewis acids.⁵ During these investigations, we found that enamides and enecarbamates dimerize on treatment with a strong Brønsted or Lewis acid such as TfOH, Sc(OTf)₃, or Cu(OTf)₂ (Scheme 1).⁶ These results



indicate that enamides and enecarbamates isomerize to the corresponding imines under acidic conditions and that imines so formed are activated by acids to react with the second

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^{(1) (}a) Kibayashi, C. Chem. Pharm. Bull. 2005, 53, 1375. (b) Joullié, M. M.; Richard, D. J. Chem. Commun. 2004, 2011.

⁽²⁾ Reviews: (a) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 923–961. (b) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (c) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.



enamides and enecarbamates. We envisioned that the second enamides and enecarbamates might be replaced by other nucleophiles and that in that case enamides and enecarbamates might work as aliphatic imine surrogates. Herein we realize this idea, and would like to report the catalytic direct Mannich-type reactions of 1,3-dicarbonyl compounds with enecarbamates catalyzed by Cu(OTf)₂ or Sc(OTf)₃.

To prevent enamides and enecarbamates from dimerizing under acidic conditions, it is necessary to use nucleophiles that are more reactive than enamindes and enecarbamates themselves. In general, however, most reactive nucleophiles such as metal-carbon nucleophiles are unstable under Brønsted acidic conditions. A strategy to overcome this problem is shown in Scheme 2. Nucleophiles would be activated by a metal salt to form a Brønsted acid,⁷ which could isomerize enamides and enecarbamates to iminium

Table 1. Screening of Metal Salts ^a									
l Bn 1a	NHCbz + O O O O O O O O O O O O O O O O O O O	M(OTf) _x	O NHCbz Bn CO ₂ Et 3a						
entry	$M(OTf)_x$	solvent	yield (%)						
1	$Cu(OTf)_2$	DCE	89						
2	$Cu(OTf)_2$	Tol	73						
3	$Sc(OTf)_3$	DCE	73						
4	Sc(OTf) ₃	Tol	49						
5	$Sn(OTf)_2$	DCE	71						
6	$Sn(OTf)_2$	Tol	55						
7	Yb(OTf) ₃	DCE	6						
8	Bi(OTf) ₃	DCE	56						
9	$Zn(OTf)_2$	DCE	0						
10	CuOTf	DCE	0						

^{*a*} Reaction conditions: a solution of **1a** (1.0 equiv) in the indicated solvent was added to a suspension of **2a** (1.5 equiv) and a metal salt (10 mol %) in the indicated solvent over 12 h at room temperature.

Table 2. Catalytic Reactions of Enecarbamates 1 with 1,3-Dicarbonyl Compounds 2^a

				0		
		C L		M(OTf) _x	R ¹	NH Q
⊢ B ² . ∠	IN R'	+ R ³		solvent, rt	→ R ²	R ⁴
- N	1		R° D		($D_{\mathbf{a}}^{\mathbf{H}^{3}}$
entrv	1	2	3	M(OTf),	solvent	vield (%) ^b
1	1a 1b	2a 2a	3a 3b	Cu(OTf) ₂	DCE	89
3	1c	2a 2a	30 30	Cu(OTf) ₂ Cu(OTf) ₂	DCE	97 69
4 5	1a 1a	2b 2c	3d 3e	Cu(OTf) ₂ Sc(OTf) ₂	DCE	78 72
6	1b	2c	3f	Cu(OTf) ₂	DCE	91
7 8	1c 1a	2c 2d	3g 3h	Cu(OTf) ₂ Sc(OTf) ₂	DCE Tol	61 79
9	1b	2d	3i	Cu(OTf) ₂	DCE	72
11	1d	2d 2d	3j 3k	$Cu(OTf)_2$	DCE	68 71
12 13	1e 1a	2d	3j 31	Cu(OTf) ₂	DCE	49 76
14	1b	2e 2e	3m	$Cu(OTf)_2$	DCE	61
15 16	1c 1a	2e 2f	3n 3o	Sc(OTf) ₃ Cu(OTf) ₂	DCE DCE	67 96
17	1b	2f	3p	Cu(OTf) ₂	DCE	77
18	1a 1b	2g 2g	3q 3r	$Cu(OTf)_2$ $Cu(OTf)_2$	DCE	98 86
20 21	1d 19	2ġ	3s 2+	Cu(OTf) ₂	DCE	80 61
22	1a	2i	3u	$Cu(OTf)_2$	DCE	71
23 24	1a 1b	2j 2i	3v 3w	Cu(OTf) ₂ Cu(OTf) ₂	DCE DCF	64 74
25	1a	2k	3x	Cu(OTf) ₂	DCE	61
26 27	1a 1a	21 2m	3y 3z	$Cu(OTf)_2$ $Cu(OTf)_2$	DCE	55 43
	NHB ²		йнс	Cbz	0 II	0
R1					x	Щ_
1	2		Ŕ			
1a: R' = 1b: R ¹ =	= Bn, R ² = = Bn, R ² =	: Cbz : Boc	1d: R = F 1e: R = <i>i</i> -	Ph 2a -Pr 21a	a: X = CH ₂ D: X = O, F	, R = OEt R = Me
1c: R ¹ =	<i>i</i> -Pr, R ²	= Cbz		20	:: X = NBr	n, R = Me
	0	o	0	0	ć	
R ¹	\checkmark	L				Ľ ľ
		Office				Olivie
R ²			Ý	2h	\sim	2i
2d: R' 2e: B ¹	= H, R ² =	= H - OMe				
2f: R ¹	= H, R ² =	CI				
2g: R ¹	= Me, R ²	= H				
	0 0		0	0	ö	ö
5		OMe		Ĭ	R	Me
Mac	<i>ل</i> ـــــر	0.110	\/	`OMe	31. D	- Mo
WeU	2j		2	2k	21: R 2m: F	l = Ph

^{*a*} Reaction conditions: a solution of **1a** (1.0 equiv) in the indicated solvent was added to a suspension of **2a** (1.5 equiv) and a metal salt (10 mol %) in the indicated solvent over 12 h at room temperature. ^{*b*} In most cases, diastereoselectivity is within a range of 1:1 and 1:2 except with **3d** and **3e** (single diastereomer), **3g** (4:1), and **3t** (9:1).

species. Iminium species would be reactive enough to undergo nucleophilic additions by activated metal-containing species to afford the desired adducts along with regeneration of the metal salt.

On the basis of this scheme, we examined the reaction of enecarbamates $1a^8$ with β -ketoester 2a.⁹ Several metal salts

⁽⁴⁾ Gridnev, I. D.; Imamoto, T. Acc. Chem. Res. 2004, 37, 633 and references therein.

and solvents were screened, and the results are summarized in Table 1. Of the metal salts used, $Cu(OTf)_2$ and $Sc(OTf)_3$ were revealed to be the most promising catalysts, 10 mol % of each metal salt affording the desired Mannich-type product in 89% and 73% yield, respectively. 1,2-Dichloroethane (DCE) and toluene (Tol) were found to be appropriate solvents. The reaction at 0 °C gave a yield lower than that of the reaction at room temperature. In all cases, slow addition of enecarbamate **1a** was conducted over 12 h, rapid mixing of all substrates directly giving a lower yield due to fast dimerization of the enecarbamate.

Having established optimal conditions, we then studied substrate scope of the reaction (Table 2). Enecarbamates reacted with various β -ketoesters, β -ketoamide, and 1,3diketones smoothly to afford the corresponding adducts in high yields. In general, Cu(OTf)₂ gave high yields, whereas

(6) CuF₂, CuOAc, and CoCl₂ promoted isomerization of enecarbamates. Isomerization and further self-condensation occurred when BiCl₃, Nd(OTf)₃, Ce(OTf)₃•H₂O, Zn(OTf)₂, and AgSbF₆ were employed. Isomerization can be suppressed by using appropriate ligands. For example, fast isomerization and dimerization of enecarbamate occurred when we used Cu(OTf)₂, whereas no isomerization was observed when a complex prepared from Cu(OTf)₂ and diphenylethylenediamine ligand was employed.

(7) A similar reaction mechanism was reported in palladium enolate chemistry. Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941 and references therein.

(8) Mecozzi, T.; Petrini, M. Synlett 2000, 73 and references therein.

(9) Recent examples of direct Mannich-type reactions using 1,3dicarbonyl compounds. (a) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, 8, 2003. (b) Tillman, A. L.; Ye, J. X.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (c) Terada, M.; Sorimachi, K.; Uraguchi, D. *Synlett* **2006**, 133. Sc(OTf)₃ provided better results in some other cases. Interestingly, a difference of reactivity between (*E*)- and (*Z*)enecarbamates was observed (entry 10 vs 12). (*Z*)-Enecarbamate is more reactive than (*E*)-enecarbamate, which is rationalized by considering the higher free energy of (*Z*)enecarbamate at ground state (due to steric repulsion), leading to easy isomerization to reactive iminium species. It is noted that the Boc protecting group (enecarbamate **1b**) is tolerant in this reaction.

In summary, we have developed novel Mannich-type reactions of 1,3-dicarbonyl compounds with enecarbamates. Lewis acids such as $Cu(OTf)_2$ and $Sc(OTf)_3$ promoted this reaction to provide the adducts in good yields. The proposed mechanism involves coordination of the metal salt first to the 1,3-dicarbonyl compound to generate a metal enolate and a strong Brønsted acid, which converts an enecarbamate to the corresponding labile iminium species. This reaction constitues a formal addition of 1,3-dicarbonyl compounds to aliphatic aldehyde-derived imines, which are generally unstable and difficult to isolate. Further investigations into an asymmetric version of the developed reaction, as well as application to the synthesis of biologically active compounds, are in progress.

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Supporting Information Available: Experimental details for the reported reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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