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

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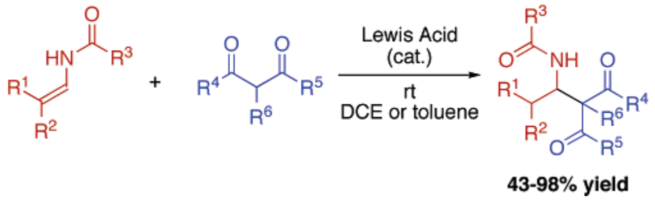
ABSTRACT

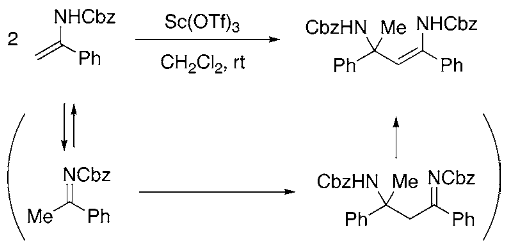


Novel Mannich-type reactions of 1,3-dicarbonyl compounds with enecarbamates have been developed. Stable and storable enecarbamates work as surrogates of aliphatic aldehyde-derived imines, which are known to be difficult to isolate and store.

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 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

Scheme 1. Self-Condensation of Enecarbamates



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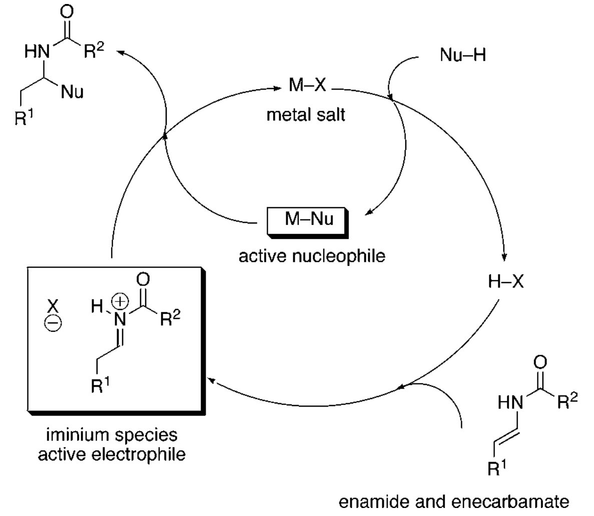
(1) (a) Kibayashi, C. *Chem. Pharm. Bull.* **2005**, *53*, 1375. (b) Joullié, M. M.; Richard, D. J. *Chem. Commun.* **2004**, 2011.

(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.

(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

Scheme 2. Proposed Catalytic Cycle

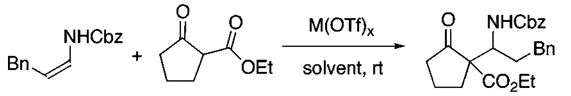


enamides and enecarbamates. We envisioned that the second enamides and enecarbamates might be replaced by other nucleophiles and that in that case enamides and enecarbamates might work as aliphatic imine surrogates. Herein we realize this idea, and would like to report the catalytic direct Mannich-type 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 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

Table 1. Screening of Metal Salts[a]

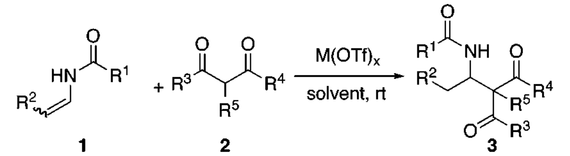


1a **2a** **3a**

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

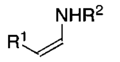
[a] Reaction conditions: a solution of **1a** (1.0 equiv) in the indicated solvent was added to a suspension of **2a** (1.5 equiv) and a metal salt (10 mol %) in the indicated solvent over 12 h at room temperature.

Table 2. Catalytic Reactions of Enecarbamates **1** with 1,3-Dicarbonyl Compounds **2**[a]

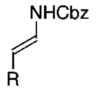


1 **2** **3**

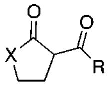
entry	1	2	3	M(OTf)$_x$	solvent	yield (%)[b]
1	**1a**	**2a**	**3a**	$Cu(OTf)_2$	DCE	89
2	**1b**	**2a**	**3b**	$Cu(OTf)_2$	DCE	97
3	**1c**	**2a**	**3c**	$Cu(OTf)_2$	DCE	69
4	**1a**	**2b**	**3d**	$Cu(OTf)_2$	DCE	78
5	**1a**	**2c**	**3e**	$Sc(OTf)_3$	Tol	72
6	**1b**	**2c**	**3f**	$Cu(OTf)_2$	DCE	91
7	**1c**	**2c**	**3g**	$Cu(OTf)_2$	DCE	61
8	**1a**	**2d**	**3h**	$Sc(OTf)_3$	Tol	79
9	**1b**	**2d**	**3i**	$Cu(OTf)_2$	DCE	72
10	**1c**	**2d**	**3j**	$Sc(OTf)_3$	DCE	68
11	**1d**	**2d**	**3k**	$Cu(OTf)_2$	DCE	71
12	**1e**	**2d**	**3j**	$Cu(OTf)_2$	DCE	49
13	**1a**	**2e**	**3l**	$Cu(OTf)_2$	DCE	76
14	**1b**	**2e**	**3m**	$Cu(OTf)_2$	DCE	61
15	**1c**	**2e**	**3n**	$Sc(OTf)_3$	DCE	67
16	**1a**	**2f**	**3o**	$Cu(OTf)_2$	DCE	96
17	**1b**	**2f**	**3p**	$Cu(OTf)_2$	DCE	77
18	**1a**	**2g**	**3q**	$Cu(OTf)_2$	DCE	98
19	**1b**	**2g**	**3r**	$Cu(OTf)_2$	DCE	86
20	**1d**	**2g**	**3s**	$Cu(OTf)_2$	DCE	80
21	**1a**	**2h**	**3t**	$Sc(OTf)_3$	Tol	61
22	**1a**	**2i**	**3u**	$Cu(OTf)_2$	DCE	71
23	**1a**	**2j**	**3v**	$Cu(OTf)_2$	DCE	64
24	**1b**	**2j**	**3w**	$Cu(OTf)_2$	DCE	74
25	**1a**	**2k**	**3x**	$Cu(OTf)_2$	DCE	61
26	**1a**	**2l**	**3y**	$Cu(OTf)_2$	DCE	55
27	**1a**	**2m**	**3z**	$Cu(OTf)_2$	DCE	43



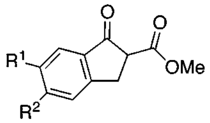
1a: R^1 = Bn, R^2 = Cbz
1b: R^1 = Bn, R^2 = Boc
1c: R^1 = *i*-Pr, R^2 = Cbz



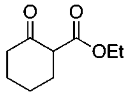
1d: R = Ph
1e: R = *i*-Pr



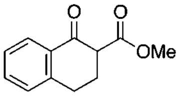
2a: X = CH_2, R = OEt
2b: X = O, R = Me
2c: X = NBn, R = Me



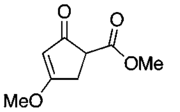
2d: R^1 = H, R^2 = H
2e: R^1 = H, R^2 = OMe
2f: R^1 = H, R^2 = Cl
2g: R^1 = Me, R^2 = H



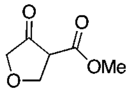
2h



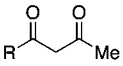
2i



2j



2k



2l: R = Me
2m: R = 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).

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(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 1,3-diketones smoothly to afford the corresponding adducts in high yields. In general, $Cu(OTf)_2$ gave high yields, whereas $Sc(OTf)_3$ 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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(5) (a) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679. (b) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed*. **2004**, *43*, 3258. (c) Matsubara, R.; Vital, P.; Nakamura, Y.; Kiyohara, H.; Kobayashi, S. *Tetrahedron* **2004**, *60*, 9769. (d) Fossey, J. S.; Matsubara, R.; Vital, P.; Kobayashi, S. *Org. Biomol. Chem.* **2005**, *3*, 2910. (e) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814.

(6) CuF_2, CuOAc, and $CoCl_2$ promoted isomerization of enecarbamates. Isomerization and further self-condensation occurred when $BiCl_3$, $Nd(OTf)_3$, $Ce(OTf)_3{\cdot}H_2O$, $Zn(OTf)_2$, and $AgSbF_6$ 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 1,3-dicarbonyl 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.