CSIRO PUBLISHING

Communication

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2006**, *59*, 921–924

Efficient Synthetic Method for β-Enamino Esters Catalyzed by $Yb(OTf)_3$ under Solvent-Free Conditions

Ravi Varala,[A,B] *Sreelatha Nuvula*,[A] *and Srinivas R. Adapa*[A]

[A] Indian Institute of Chemical Technology, Hyderabad 500007, India.
[B] Corresponding author. Email: rvarala_iict@yahoo.co.in

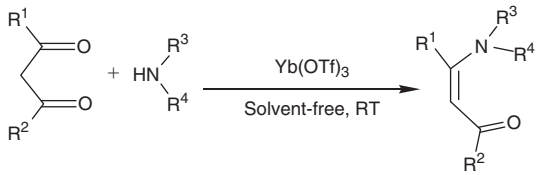
A wide range of β-enamino esters have been synthesized in moderate to excellent yields by reacting 1,3-dicarbonyl compounds with amines in the presence of catalytic amounts of $Yb(OTf)_3$ (2 mol%). The reaction proceeds smoothly at ambient temperature under solvent-free conditions. The catalyst can be recovered and reused.

Manuscript received: 8 July 2006.
Final version: 8 October 2006.

The development of facile synthetic methods leading to β-enamino compounds and their derivatives, without byproducts, is an active ongoing area of research in synthetic organic chemistry.[1] β-enamino esters are widely used as a versatile class of intermediates for the synthesis of therapeutic and biologically active analogues including taxol,[2] anticonvulsant,[3] anti-inflammatory[4] and antitumour agents,[5] as well as quinoline antibacterials and antimalarials.[6] Several methods have been reported for the preparation of β-enamino compounds.[7] The direct condensation of 1,3-dicarbonyl compounds with amines is the most simple approach.[8] A variety of catalysts such as $InBr_3$,[9] mineral acids,[10] I_2,[10a] *p*-TSA,[11] $BF_3{\cdot}Et_2O$,[12] $CeCl_3{\cdot}7H_2O$,[13] $NaAuCl_4$,[14] and $Zn(ClO_4){\cdot}6H_2O$[15] have been used to improve product yields. Nevertheless, most of the approaches currently available are associated with one or more disadvantages such as the use of either expensive or less easily available reagents, harsh reaction conditions, long reaction times, unsatisfactory yields, low selectivity, toxic solvents, cumbersome product isolation procedures, and requirement of excess of reagents. Because there is an emerging importance of these compounds as intermediates in organic synthesis, there is further scope for the development of convenient, environmentally benign, high-yielding approaches.

During the last decade, rare earth metal triflates have been found to be unique Lewis acids that are water-tolerant, recyclable catalysts and can effectively promote several carbon–carbon and carbon–heteroatom bond formation reactions.[16] Another promising synthetic approach to environmentally friendly chemistry is to either minimize or eliminate the use of harmful organic solvents. A paradigm shift from using solvents toward solvent-free reactions improves outcomes and simplifies organic synthesis.[17]

As a part of our ongoing studies to explore the utility of lanthanide triflates and other reagents, especially for the carbon–carbon and carbon–heteroatom bond formation reactions,[18] we present our results pertaining to the synthesis of β-enamino ketones and esters (Scheme 1).



Scheme 1.

Table 1. Screening of several Lewis acids for the condensation of aniline with ethyl acetoacetate under solvent-free conditions[A]

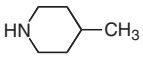
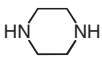
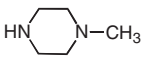
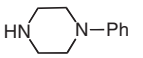
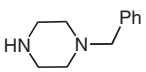
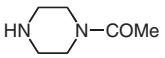
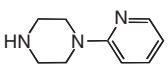
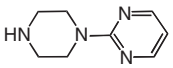
Entry	Catalyst	Time [h]	Yield [%][B]
1	None	48	36
2	$Nd(NO_3){\cdot}6H_2O$	12	75
3	$La(NO_3){\cdot}6H_2O$	8	86
4	$PrCl_3{\cdot}6H_2O$	15	84
5	$TbCl_3{\cdot}6H_2O$	6	78
6	$SmCl_3{\cdot}6H_2O$	14	89
7	CuI	4	67
8	CAN	24	60
9	$Yb(OTf)_3$	1	95
10	$Pd(acac)_2$	6	48
11	$VO(acac)_2$	3	82
12	$Ru(acac)_3$	5	65
13	$Co(acac)_3$	3.5	74
14	$PdCl_2$	12	78
15	$RuCl_3{\cdot}3H_2O$	4.5	92
16	$RhCl_3$	2	88

[A] Conditions: ethyl acetoacetate (1 mmol), aniline (1 mmol), reagent (2 mol%).
[B] Yields refer to isolated pure products after column chromatography.

Screening of several available reagents allowed us to shortlist $Yb(OTf)_3$ for the enamination of ethyl acetoacetate (1 mmol) and aniline (1 mmol) as model substrates under solvent-free conditions at room temperature (Table 1).

10.1071/CH06239 0004-9425/06/120921

Table 2. Examination of functionalized amines with ethyl acetoacetate using $Yb(OTf)_3$ as catalyst

Entry	Catalyst	Time [h]	Yield [%][A]
1		6.0	68
2		4.5	85
3		3.0	65
4		4.0	88[B]
5		2.5	92
6		5.5	58
7		6.0	85
8		10	90
9		4.0	75
10		4.5	82

[A] Yields refer to isolated pure products.
[B] 2 equiv. EAA used.

As seen in Table 1, the condensation product was achieved in 95% yield in 1 h.

From Table 1, we can conclude that $Yb(OTf)_3$ (entry 9) was superior with respect to amount of catalyst, reaction times, and product yields. In the absence of catalyst, the model reaction was run and only 36% of the product could be isolated even with stirring for two days. Although reactions also proceeded with $RhCl_3$, $RuCl_3 \cdot 3H_2O$, and $La(NO_3)_3 \cdot 6H_2O$, long reaction times are typical to achieve comparable results to those obtained with $Yb(OTf)_3$. We noted that the optimum condition of 2 mol% $Yb(OTf)_3$ is sufficient to carry the reaction forward. The reaction is sluggish when carried out using even 0.2–0.5 equiv. of catalyst amounts. In addition, the catalyst can be almost quantitatively recovered by adopting the procedure of Curini et al.,[19] by the addition of 1 N NaOH to precipitate the catalyst as the corresponding hydroxide ($Yb(OH)_3$), filtration, and transformation into triflate salt. Recycled in this way, the catalyst could be reused several times without loss of activity. The enamination of aniline with ethyl acetoacetate as model substrate has been repeated a minimum of three times with yields of 93, 94, and 94%.

To evaluate the scope and limitations of this catalyst's application, various linear β-keto esters such as divergent acetoacetates were subjected to a range of primary, secondary, benzylic, and aromatic amines to give the corresponding β-enamino esters under standardized reaction parameters. Results are summarized in Tables 2 and 3. The reaction was clean and highly diastereoselective; in all reactions the products were obtained with the *Z*-geometry stabilized by intramolecular hydrogen bonding. Structures of the crude products were confirmed by ^1H NMR (δ_H 7.50–12.80 for NH). Further, the *Z*-geometry assignment was achieved by comparison of the reported chemical shifts of the vinylic protons of similar *Z*-enaminones.[9,20,21] Most probably the reaction proceeds through the activation of the carbonyl group of the acetyl part by complexation with Yb(III) ion followed by nucleophilic addition of amines to the carbonyl group, and subsequent enaminone formation by stable intramolecular hydrogen bonding (Scheme 2).

We then reacted aniline with different acetoacetates such as methyl acetoacetate (MAA), allyl acetoacetate (AAA), ethyl 4,4,4-trifluoro acetoacetate (TAA), phenyl acetoacetate (PAA), ethyl benzoyl acetoacetate (EBAA), and acetyl acetone (AA) to give their corresponding β-enamino products. The order of reactivity is: EAA > MAA (3.5 h, 92%) > PAA (4 h, 78%) > AAA (8 h, 70%) > AA (24 h, 7%) > EBAA (no reaction, 24 h) and TAA (no reaction, 24 h). When acetyl acetone was used with aliphatic amines, a carbinolamine derivative precipitate was formed.

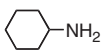
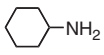
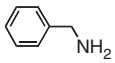
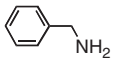
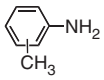
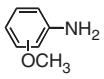
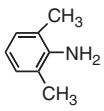
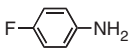
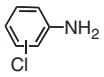
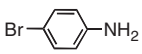
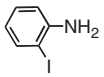
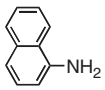
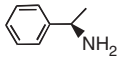
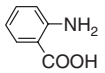
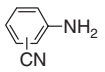
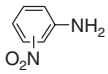
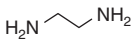
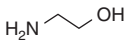
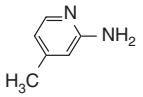
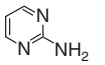
Next, we studied the enamination of electronically divergent functionalized piperazines, chosen in order to understand the substrate scope and tolerance of the present methodology using $Yb(OTf)_3$ as the catalyst. Results are summarized in Table 2. The yields are fair in almost all cases and the corresponding β-enamino esters and the new compounds are sufficiently characterized by IR, ^1H NMR, and mass spectral studies.

Several structurally and electronically divergent amines and various β-keto esters were also used for effective condensation to take place with some limitations. Results are shown in Table 3. The condensation of amines to linear β-keto esters depended on the steric and electronic properties of both participants. In general, aliphatic amines were found to be more reactive in term of times and product yields compared to the aromatic amines because of higher nucleophilicity (i.e. cyclohexyl amine, allyl amine, benzyl amine; entries 1–6, Table 3). Reactivities of the divergent anilines were found to depend on the electronic nature of the substituents. α-Naphthyl amine (entry 14, Table 3), on reacting with ethyl acetoacetate, gives the corresponding enamine product in excellent yield (4 h, 95%). The presence of an electron-withdrawing group on the benzene ring retarded the progress of reaction even when stirred for 2 days (entries 17, 18, and 19). Generally, *ortho*-substituted anilines require longer reaction times. Optically active (*R*)-(+)-α-methyl benzyl amine was converted into the corresponding β-enamino esters with complete retention (entry 15, Table 3).

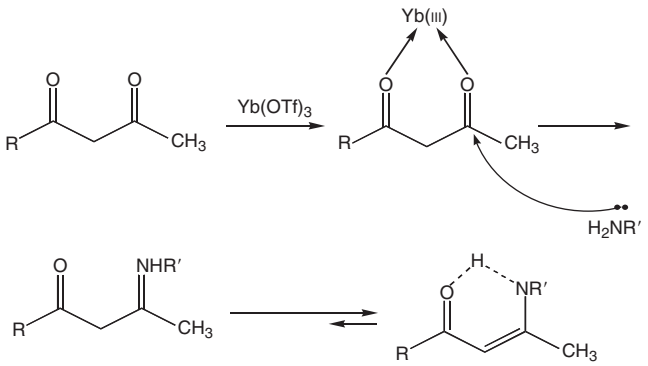
In the case of ethylene diamine (entry 21, Table 3) condensation with EAA, 2 equiv. of β-dicarbonyls were used and the product was formed with two enamino ester groups. Neither diphenylamine nor dimethyl amine (entry 20, Table 3) gave the expected products, even with stirring for 24 h.

In conclusion, we have successfully demonstrated the use of $Yb(OTf)_3$ as a highly efficient, selective and convenient Lewis acid catalyst for the preparation of pharmacologically relevant β-enamino compounds in moderate to excellent yields. The present protocol has several advantages: mild reaction conditions (room temperature), small quantity of

Table 3. Synthesis of β-enamino esters by condensation of β-keto ester 1 with amine 2 catalyzed by $Yb(OTf)_3$

Entry	R^1	R^2	Amine	Time [min]	Yield [%][A]
1	Me	OEt		30	92
2	Me	OMe		45	90
3	Me	OEt		60	86
4	Me	OMe		60	84
5	Me	OEt		30	94
6	Me	OMe		60	90
7	Me	OEt		*o*- 180	82
				p- 150	88
8	Me	OEt		*o*- 240	78
				p- 210	88
9	Me	OEt		1440	58
10	Me	OEt		600	82
11	Me	OEt		*o*- 480	78
				p- 330	93
12	Me	OEt		360	92
13	Me	OEt		270	90
14	Me	OEt		240	95
15	Me	OEt		360	92
16	Me	OEt		1440	48
17	Me	OEt		*o*- 2880	N.R.[B]
				p- 2880	N.R.
18	Me	OEt		*o*- 2880	N.R.
				p- 2880	N.R.
19	Me	OEt		*o*- 2880	N.R.
				p- 2880	N.R.
20	Me	OEt	Ph_2NH/Me_2NH	1440	N.R.
21	Me	OEt		60	78
22	Me	OEt		720	56
23	Me	OEt		960	28
24	Me	OEt		1200	12

[A] Yields refer to pure isolated products.
[B] No reaction.



Scheme 2.

catalyst, operational and experimental simplicity, environmentally benign solvent-free protocol, and easily recoverable and reusable catalyst for applicability in large scale synthesis. We believe that this $Yb(OTf)_3$ catalyzed methodology will be a valid contribution to existing processes in the field of synthesis of β-enamino compounds.

Experimental

Typical Procedure for Preparation of β-Enamino Esters

Mixtures of β-keto ester (1 mmol), amine (1 mmol), and $Yb(OTf)_3$ (0.02 mmol) were stirred at ambient temperature for appropriate times (Tables 2 and 3). After completion of the reaction, 1 N NaOH (2 mL) was added, the white precipitate filtered, and the resulting solution extracted with Et_2O (2×2 mL). The organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated and subjected to column chromatography to afford the desired product. Most of the products are known in the literature and all new compounds were characterized by IR, ^1H NMR spectroscopy, and mass spectrometry.

Ethyl 3-Piperidino-2-butenoate

Table 2, Entry 1: ν_{max}/cm^{-1} 1658, 1605. δ_H (300 MHz, $CDCl_3$) 1.24 (t, *J* 6.94, 3H), 1.56–1.62 (m, 6H), 2.40 (s, 3H), 3.24–3.29 (m, 4H), 4.21 (q, *J* 6.94, 2H), 4.70 (s, 1H). *m*/*z* (EI) 197 (M^+).

Ethyl 3-Morpholino-2-butenoate

Table 2, Entry 3: ν_{max}/cm^{-1} 1656, 1606. δ_H (300 MHz, $CDCl_3$) 1.19 (t, *J* 7.53, 3H), 2.33 (s, 3H), 3.14 (t, *J* 5.28, 4H), 3.66 (t, *J* 4.53, 4H)-, 4.02 (q, *J* 6.79, 2H), 4.69 (s, 1H). *m*/*z* (EI) 199 (M^+).

Ethyl 3,4-(3-Ethoxy-1-methyl-3-oxo-1-propenyl) Piperazino-2-butenoate

Table 2, Entry 4: ν_{max}/cm^{-1} 1652, 1607. δ_H (300 MHz, $CDCl_3$) 1.24 (t, *J* 6.79, 6H), 2.41 (s, 6H), 3.22–3.45 (m, 8H), 4.05 (q, *J* 6.79, 4H), 4.70 (s, 2H). *m*/*z* (EI) 311 ($M^+ + H$).

Ethyl 3-(4-Benzylpiperidino)-2-butenoate

Table 2, Entry 7: ν_{max}/cm^{-1} 1658, 1604. δ_H (300 MHz, $CDCl_3$) 1.24 (t, *J* 7.55, 3H), 2.38 (s, 3H), 2.42–2.45 (m, 4H), 3.23–3.26 (m, 4H), 3.49 (s, 2H), 4.05 (q, *J* 6.79, 2H), 4.71 (s, 1H), 7.21–7.27 (m, 5H). *m*/*z* (EI) 288 (M^+).

Ethyl 3-[4-(2-Pyrimidinyl)piperazino]-2-butenoate

Table 2, Entry 10: ν_{max}/cm^{-1} 1660, 1607. δ_H (300 MHz, $CDCl_3$) 1.25 (t, *J* 7.03, 3H), 2.46 (s, 3H), 3.37 (t, *J* 5.47, 4H), 3.86 (t, *J* 5.47, 4H), 4.08 (q, *J* 7.03, 2H), 4.77 (s, 1H), 6.48–6.53 (m, 1H), 8.27–8.29 (d, *J* 4.68, 2H). *m*/*z* (EI) 276 (M^+).

Ethyl 3-(Cyclohexylamino)-2-butenoate

Table 3, Entry 1: ν_{max}/cm^{-1} 1655, 1607. δ_H (300 MHz, $CDCl_3$) 1.24 (t, *J* 7.1, 3H), 1.89 (m, 10H), 1.93 (s, 3H), 3.29–3.34 (m, 1H), 4.08 (q, *J* 7.1, 2H), 4.39 (s, 1H), 8.66 (br s, 1H, NH). *m*/*z* (EI) 211 (M^+).

Ethyl 3-(Benzylamino)-2-butenoate

Table 3, Entry 3: ν_{max}/cm^{-1} 1654, 1605. δ_H (300 MHz, $CDCl_3$) 1.25 (t, *J* 7.1, 3H), 1.89 (s, 3H), 4.11 (q, *J* 7.1, 2H), 4.42 (d, *J* 6.4, 2H), 4.56 (s, 1H), 7.22–7.39 (m, 5H), 8.95 (br s, 1H, NH). *m*/*z* (EI) 219 (M^+).

Ethyl 3-(Allylamino)-2-butenoate

Table 3, Entry 5: ν_{max}/cm^{-1} 1649, 1605. δ_H (300 MHz, $CDCl_3$) 1.24 (t, *J* 7.1, 3H), 1.89 (s, 3H), 3.83 (m, 2H), 4.07 (q, *J* 7.1, 2H), 4.47 (s, 1H), 5.15 (d, *J* 10.4, 1H), 5.20 (d, *J* 17.2, 1H), 5.81–5.90 (m, 1H), 8.67 (br s, 1H). *m*/*z* (EI) 169 (M^+).

Ethyl 3-(1-Naphthylamino)-2-butenoate

Table 3, Entry 14: ν_{max}/cm^{-1} 1652, 1607. δ_H (300 MHz, $CDCl_3$) 1.33 (t, *J* 7.55, 3H), 1.87 (s, 3H), 4.19 (q, *J* 7.55, 2H), 4.75 (s, 1H), 6.69–6.75 (m, 1H), 7.35–7.87 (m, 6H), 10.58 (br s, 1H, NH). *m*/*z* (EI) 255 (M^+).

Ethyl 3-{[2-(3-Ethoxy-1-methyl-3-oxo-1-propenyl)-aminoethyl]amino}-2-butenoate

Table 3, Entry 21: ν_{max}/cm^{-1} 1648, 1609. δ_H (300 MHz, $CDCl_3$) 1.24 (t, *J* 7.1, 6H), 1.93 (s, 6H), 3.34–3.37 (m, 4H), 4.07 (q, *J* 7.1, 4H), 4.48 (s, 2H), 8.59 (br s, 2H). *m*/*z* (EI) 284 (M^+).

Ethyl 3-[(2-Hydroxyethyl)amino]-2-butenoate

Table 3, Entry 22: ν_{max}/cm^{-1} 3360, 1650, 1607. δ_H (300 MHz, $CDCl_3$) 1.25 (t, *J* 7.03, 3H), 1.91 (s, 3H), 3.32 (q, *J* 5.47, 2H), 3.67 (t, *J* 5.47, 2H), 4.01 (q, *J* 7.03, 2H), 4.38 (s, 1H), 8.55 (br s, 2H). *m*/*z* (EI) 173 (M^+).

Acknowledgments

R.V. thanks DIICT, Dr J. S. Yadav, and Council of Scientific Industrial Research (CSIR, India) for financial support. IICT communication number 060527.

References

[1] (a) Z. Rappoport, *The Chemistry of Enamines, Part 1* **1994** (John Wiley: New York, NY).
(b) C. M. Kascheres, *J. Braz. Chem. Soc.* **2003**, *41*, 945.
[2] J. P. Michael, C. B. Koning, G. D. Hosken, T. V. Stanbury, *Tetrahedron* **2001**, *57*, 9635. doi:10.1016/S0040-4020(01)00964-4
[3] M. Azzaro, S. Geribaldi, B. Videau, *Synthesis* **1981**, 880. doi:10.1055/S-1981-29629
[4] G. Dannhardt, A. Bauer, U. Nowe, *J. Prakt. Chem.* **1998**, *340*, 256. doi:10.1002/PRAC.19983400309
[5] D. L. Boger, T. Ishizaki, J. R. J. Wysocki, S. A. Munk, P. A. Kitos, O. Suntornwat, *J. Am. Chem. Soc.* **1989**, *111*, 6461. doi:10.1021/JA00198A089
[6] Y. F. Wang, T. Izawa, S. Kobayashi, M. Ohno, *J. Am. Chem. Soc.* **1982**, *104*, 6465. doi:10.1021/JA00387A060
[7] (a) N. Jiang, Z. Qu, J. Wang, *Org. Lett.* **2001**, *3*, 2989. doi:10.1021/OL016324P
(b) S. Fustero, B. Pina, E. Salavert, A. Navarro, C. R. Arellano, A. Simon, *J. Org. Chem.* **2002**, *67*, 4667 doi:10.1021/JO025621K
(c) A. R. Katritzky, Y. Fang, A. Donkor, J. Xu, *Synthesis* **2000**, 2029. doi:10.1055/S-2000-8723
(d) G. Cimarelli, G. Palmieri, E. Volpini, *Tetrahedron Lett.* **2004**, 45, 6629. doi:10.1016/J.TETLET.2004.07.027
[8] (a) P. G. Baraldi, D. Simoni, S. Manfredini, *Synthesis* **1983**, 902. doi:10.1055/S-1983-30557
(b) T. Potesil, *J. Chromatogr.* **1984**, *312*, 387. doi:10.1016/S0021-9673(01)92790-6
(c) E. J. Cone, R. H. Garner, A. W. Hayes, *J. Org. Chem.* **1972**, *37*, 4436. doi:10.1021/JO00799A615
[9] Z.-H. Zhang, L. Yin, Y.-M. Wang, *Adv. Synth. Catal.* **2006**, *348*, 184. doi:10.1002/ADSC.200505268
[10] (a) C. R. Hauser, G. A. Reynolds, *J. Am. Chem. Soc.* **1948**, *70*, 2402. doi:10.1021/JA01187A025
(b) D. F. Martin, G. A. Janusonis, B. B. Martin, *J. Am. Chem. Soc.* **1961**, *83*, 73. doi:10.1021/JA01462A015
[11] A. D. Yapi, M. Mustofa, A. Valentin, O. Chavignon, J.-C. Teulade, M. Mallie, J.-P. Chapat, Y. Blache, *Chem. Pharm. Bull.* **2000**, *48*, 1886.
[12] B. Stefane, S. Polanc, *Synlett* **2004**, 698. doi:10.1055/S-2003-817787
[13] M. M. Khodaei, A. R. Khosropour, M. Kookhazadeh, *Synlett* **2004**, 1980. doi:10.1055/S-2004-830879
[14] A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, *Green Chem.* **2003**, *5*, 64. doi:10.1039/B210165C
[15] G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, P. Melchiorre, L. Sambri, *Synlett* **2004**, 239. doi:10.1055/S-2003-44974
[16] S. Kobayashi, M. Sugiura, H. Kitagawa, W. L. Lam, *Chem. Rev.* **2002**, *102*, 2227. doi:10.1021/CR010289I
[17] For reviews on solvent-free organic synthesis, see: G. W. V. Cave, C. L. Raston, J. L. Scott, *Chem. Commun.* **2001**, 2159, and references therein. doi:10.1039/B106677N
[18] (a) R. Varala, N. Sreelatha, S. R. Adapa, *Synlett* **2006**, 1009. doi:10.1055/S-2006-939066
(b) R. Varala, E. Ramu, N. Sreelatha, S. R. Adapa, *Tetrahedron Lett.* **2006**, *47*, 877. doi:10.1016/J.TETLET.2005.12.005
(c) R. Varala, N. Sreelatha, S. R. Adapa, *Synlett* **2006**, 1549, and references therein. doi:10.1055/S-2006-941588
(d) R. Varala, N. Sreelatha, S. R. Adapa, *J. Org. Chem.* **2006**, *71*, 8283. doi:10.1021/JO0612473
[19] M. Curini, F. Epifano, S. Genovese, M. C. Marcotullio, O. Rosati, *Org. Lett.* **2005**, 1331. doi:10.1021/OL050125E
[20] F. C. Pennington, W. D. Kehret, *J. Org. Chem.* **1967**, *32*, 2034. doi:10.1021/JO01281A092
[21] C. Kashima, H. Aoyama, Y. Yamamoto, T. Nishi, K. Yamada, *J. Chem. Soc., Perkin Trans. 2* **1975**, 665. doi:10.1039/P29750000665