Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2432–2434
Tetrahedron Letters

Cerium(IV) ammonium nitrate catalyzed synthesis of α-dehydro-β-amino esters

Moumita Paira, Samir Kumar Mandal, Subhas Chandra Roy *

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

Received 27 November 2007; revised 5 February 2008; accepted 10 February 2008
Available online 13 February 2008

Abstract

α-Dehydro-β-amino esters have been synthesized regioselectively from acetates of Baylis–Hillman adducts with amines in the presence of a catalytic amount of ceric ammonium nitrate (CAN) in good yield. The regioselectivity does not differ with respect to the polarity of the solvent.

Keywords: Baylis–Hillman adduct; Ceric ammonium nitrate; Amine; α-Dehydro-β-amino esters; Regioselective

α-Dehydro-β-amino esters are useful synthetic intermediates for indenoquinoline derivatives, nonproteinogenic β-amino acids as well as β-lactams, which facilitates the development of modern medicines.[1–4] Peptide derivatives of α-dehydro-β-amino acids exhibit intramolecular hydrogen bonding, which plays a significant role in biochemical molecular recognition and mimics a β-turn.[5–8] Similar to dehydro-α-amino acids, α-dehydro-β-amino acids can provide constraint after incorporation into a peptide molecule and thus renders a peptide more favorable to binding to its target.[9,10] It is noteworthy that the β-amino acid in a cytotoxic depsipeptide[11] namely, kulokekahilide-1 often requires synthesis when they are not available commercially. Thus, numerous methods have been developed for the construction of β-amino ketones, acids or esters such as, the reduction of an aziridine ring with SmI_2,[12] cobalt-catalyzed epoxide opening,[13] Michael addition of amide cuprate reagents,[14] Sharpless asymmetric aminohydroxylation of olefins,[15] $(ZnBF_4)_2$ mediated Mannich reaction,[16] ring opening of β-lactams,[17] nucleophilic substitution reactions,[18,19] Pd(0)-catalyzed amination[5] and rearrangement of carbamates (Table 1).[20] However, to our knowledge, only two methods[21,22] are reported in the literature using Baylis–Hillman adducts as precursors for the synthesis of β-amino esters, (i) DABCO-catalyzed allylic amination (40–79% yield), and (ii) thermal addition of amines to Baylis–Hillman adducts (67–78% yield). Although some of the reported procedures are quite elegant, many suffer from long reaction times, use of excess and costly reagents, low regioselectivity and low yields in some cases. So, methods for the synthesis of α-dehydro-β-amino esters are still desirable. Herein, we disclose a simple and facile method

Table 1
A comparison of different reported amination reactions

Ref.	Reagent used	Yield[a] (%)
5	$Pd(PPh_3)_4$	57–78[b]
12	SmI_2	78–98
13	Co(II) or Co(III)	32–69
14	Amide cuprate	29–88
15	$(DHQD)_2$–PHAL or $(DHQ)_2$–PHAL	48–78
16	$Zn(BF_4)_2$	48–98
17	No reagent	76–90
18	No reagent	47–91[b]
19	Et_3N	20–95[b]
20	CsF or DABCO or KF–AL_2O_3 or K_2CO_3	30–98

[a] Range of yields refers to products with different substrates.
[b] Mixture of SN2 and SN2′ products.

* Corresponding author. Tel.: +91 33 2473 4971; fax: +91 33 2473 2805.
E-mail address: ocscr@iacs.res.in (S. C. Roy).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.054

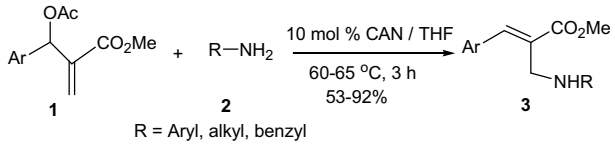
for the synthesis of α-dehydro-β-amino esters by the reaction of Baylis–Hillman acetates with various primary amines catalyzed by ceric ammonium nitrate (CAN).

Acetates of Baylis–Hillman adducts are of valuable synthetic intermediates for the synthesis of a number of complex molecules.[23] It is well documented in the literature[24–26] that CAN is a useful catalyst for C–C and C–N bond formation in synthetic organic chemistry. In continuation of our efforts[27–30] to develop novel methodologies for organic transformations using cheap and commercially available CAN as a catalyst, we report that CAN acts as an effective catalyst for the addition–elimination reaction to furnish β-amino esters from amines and Baylis–Hillman acetates.

Thus, in a preliminary study,[31] benzyl amine was reacted with acetate **1a** in THF at 60–65 °C for 3 h using a catalytic amount of CAN (10 mol %) to give amino ester **3a** (Scheme 1, Table 2).

Thus, a series of amines were treated with various Baylis–Hillman acetates and the results are summarized in Table 2.

The stereochemistry of the products was established by comparing the signal of the vinylic proton in ^{1}H NMR spectra with the literature values.[2,5] The appearance of the vinylic proton of the *E*-isomer in the range of δ 7.63–7.94 and that of the *Z*-isomer in the range of δ 6.56–6.70 depending on the substrates used is in good agreement with the reported values. It was observed that the reaction in

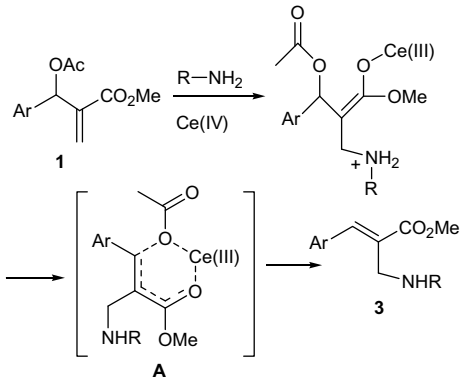


Scheme 1. Synthesis of β-amino esters.

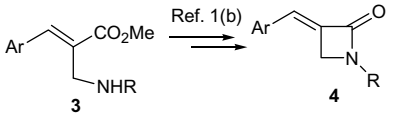
Table 2
CAN catalyzed synthesis of α-dehydro-β-amino esters

Entry	Ar	R	Yield of **3**[a] (%)	*E*/*Z* ratio[b]
a	Ph	Ph	84	100:0
b	Ph	Bn	85	92:8
c	Ph	4-MeC_6H_4	92	100:0
d	Ph	4-MeOC_6H_4	89	100:0
e	Ph	3-Cl-4-MeC_6H_3	78	94:6
f	Ph	α-Naphthyl	73	91:9
g	Ph	Me	57	78:22
h	Ph	*n*-C_8H_{17}	72	86:14
i	Ph	*n*-$C_{16}H_{33}$	55	85:15
j	Ph	Cyclo-C_6H_{11}	65	98:2
k	4-MeC_6H_4	4-MeC_6H_4	95	100:0
l	4-MeC_6H_4	3-O_2NC_6H_4	79	89:11
m	4-MeC_6H_4	Bn	87	88:12
n	4-MeC_6H_4	Me	53	80:20
o	4-ClC_6H_4	Ph	90	100:0
p	4-ClC_6H_4	Bn	91	96:4
q	4-ClC_6H_4	*n*-C_8H_{17}	74	83:17

[a] Yield refers to pure isolated yield.
[b] Isomeric ratio was determined from ^{1}H NMR spectra of the crude reaction mixture.



Scheme 2. Proposed mechanism for the formation of the *E*-isomer predominantly.



Scheme 3. Conversion of amino esters to β-lactams.

methanol or in THF resulted in the best yield compared to other solvents. 4-Chloro-substituted aromatic moieties in the Baylis–Hillman acetates enhanced the yield of the products with aromatic amines (Table 2, entries o and p). Aliphatic amines also underwent smooth amination under similar reaction conditions resulting in moderate to good yields of the amino esters. Aromatic amines required a little more reaction time compared to aliphatic amines, which may be due to the lower reactivity of aromatic amines. It was clear from the results that aromatic amines and benzyl amine gave relatively better yields than aliphatic amines and also showed higher *E*-selectivity. All products were characterized by NMR, IR and HRMS studies and were compared with those of the reported data.

Amines undergo Michael type addition followed by β-acetoxy elimination in the presence of CAN. The *E*-selectivity can be explained by the formation of the chelated intermediate (**A**) with cerium(IV) and the carbomethoxy group (Scheme 2).

Some of the amino esters **3** have already been proved[2] as versatile precursors for the synthesis of biologically active β-turn inducers and β-lactams **4** (Scheme 3).

In conclusion, we have developed an efficient and regioselective method for the synthesis of α-dehydro-β-amino esters in a stereoselective manner from Baylis–Hillman acetates and various primary amines catalyzed by ceric ammonium nitrate.

Acknowledgements

We sincerely thank DST, New Delhi, for financial support. M.P. and S.K.M. thank CSIR, New Delhi, for awarding the fellowships.

References and notes

1. Baldwin, J. E.; Moloney, M. G.; North, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 833.
2. Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213.
3. Gardner, B.; Nakanishi, H.; Kahn, M. *Tetrahedron* **1993**, *49*, 3433.
4. Chen, A.; Nelson, A.; Tanikkul, N.; Thomas, E. J. *Tetrahedron Lett.* **2001**, *42*, 1251.
5. Rajesh, S.; Banerji, B.; Iqbal, J. *J. Org. Chem.* **2002**, *67*, 7852.
6. Ball, J. B.; Hughes, R. A.; Alewood, P. L.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467 and references cited therein.
7. Curran, T. P.; Chandler, N. M.; Kennedy, R. J.; Keaney, M. T. *Tetrahedron Lett.* **1996**, *37*, 1933.
8. Feng, Y.; Pattarawarapan, M.; Wang, Z.; Burgess, K. *Org. Lett.* **1999**, *1*, 121.
9. Stammer, C. H. In *Chemistry and Biochemistry of Amino Acids, Peptides and Protein*; Weinstein, B., Ed.; Marcel Dekker: New York, 1982; Vol. IV, p 3.
10. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159.
11. Kimura, J.; Takada, Y.; Inayoshi, T.; Nakao, Y.; Goetz, G.; Yoshida, W. Y.; Scheuer, P. J. *J. Org. Chem.* **2002**, *67*, 1760.
12. Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660.
13. Bhatia, B.; Jain, S.; De, A.; Bagchi, I.; Iqbal, J. *Tetrahedron Lett.* **1996**, *37*, 7311.
14. Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427.
15. Li, G.; Chang, H-T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451.
16. Ranu, B. C.; Samanta, S.; Guchhait, S. K. *Tetrahedron* **2002**, *58*, 983.
17. Palomo, C.; Aizpurua, J. M.; Ganbao, I.; Maneiero, E.; Odriozola, B. J. *J. Chem. Soc., Chem. Commun.* **1994**, 1505.
18. Cromwell, N. H.; Leung, H.-K. *J. Org. Chem.* **1976**, *41*, 3241.
19. Chen, H.-Y.; Patkar, L. N.; Ueng, S.-H.; Lin, C.-C.; Lee, A. S.-Y. *Synlett* **2005**, 2035.
20. Foucaud, A.; Guemmout, F. E. *Bull. Soc. Chim. Fr.* **1989**, 403.
21. Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173.
22. Lee, C. G.; Lee, K. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409.
23. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811 and references cited therein.
24. Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett* **2003**, 156.
25. Duan, Z.; Xuan, X.; Li, T.; Yang, C.; Wu, Y. *Tetrahedron Lett.* **2006**, *47*, 5433.
26. Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862 and references cited therein.
27. Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Synlett* **2001**, 226.
28. Roy, S. C.; Guin, C.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 9253.
29. Roy, S. C.; Banerjee, B. *Synlett* **2002**, 1677.
30. Banerjee, B.; Mandal, S. K.; Roy, S. C. *Chem. Lett.* **2006**, *35*, 16.
31. *Typical procedure:* To a stirred solution of **1a** (234 mg, 1.0 mmol) and aniline (121 mg, 1.3 mmol) in THF under N_2, ceric ammonium nitrate (55 mg, 0.1 mmol) was added at 65 °C. After completion of the reaction (monitored by TLC), the volatiles were removed under reduced pressure and the residue obtained was extracted with ether (2×50 mL). The combined ether extract was washed successively with water (20 mL) and brine (20 mL) and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel to yield the pure α-dehydro-β-amino ester **3a** (224 mg, 84%) as a viscous oil. IR (neat): 3392, 1712, 1600, 1506, 1230, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.87 (s, 3H), 4.18 (s, 2H), 6.58 (d, $J = 7.7$ Hz, 2H), 6.77 (t, $J = 7.2$ Hz, 1H), 7.18 (t, $J = 7.7$ Hz, 2H), 7.42–7.48 (m, 5H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 41.0, 52.2, 113.5 (2C), 117.9, 128.8 (2C), 129.2 (2C), 129.3 (2C), 129.6 (2C), 134.8, 143.0, 147.8, 168.2; HRMS calcd for $C_{17}H_{17}NO_2Na$ 290.1157 $[M+Na]^+$, found 290.1152.