Pergamon

Tetrahedron Letters, Vol. 38, No. 42, pp. 7317-7320, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01777-2

Lewis Acid Promoted Conjugate Addition of Vinylmagnesium Bromide to Chiral α,β-Unsaturated N-Acyl Oxazolidinones

Yinglin Han and Victor J. Hruby *

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

Abstract: Lewis acid promoted conjugated additions of vinylmagnesium bromide to chiral α,β-unsaturated N-acyl oxazolidinones are described. A series of enatiomerically pure β-branched 4-pentenoic acid derivatives have been synthesized with high diastereoselectivity. © 1997 Elsevier Science Ltd.

The conjugate addition of organometallic-Lewis acid reagents to α,β-unsaturated acyl compounds which contain a chiral auxiliary is a highly useful method in asymmetric organic synthesis.[1-4] Various products have been prepared with high diastereoselectivity via conjugated addition of organometallics to chiral oxazoline,[2] ester,[3] amide[4] or imide[5] derivatives. As part of our efforts to design and synthesize topographically constrained unusual β-branched amino acids,[6] we have developed an efficient procedure to prepare these important intermediates.[7] Using this methodology, the asymmetric Michael addition of various Grignard reagents to N-acyl oxazolidinones in the presence of CuBr•Me_2S complex was carried out with high stereoselectivities and yields.[7] However, in our initial attempts to synthesize β-branched glutamic acids, the conjugated addition of vinylmagnesium bromide to the Michael acceptor, (*2'E*)(*4R*)-cinnamoyl-4-phenyl-2-oxazolidinone did not work well using the previously developed reaction conditions.[7] Various Lewis acid systems have been developed to promote 1,4-addition of sterically highly crowded α,β-enones and unreactive α,β-unsaturated esters.[5a,8] Recently, excellent yields were obtained using the RCu-TMEDA-TMSCl or RCu-TMEDA-Bu_2BOTf systems for conjugated addition to a variety of α,β-enones and enoates.[5a,9] Unfortunately, however, the addition of vinylmagnesium bromide to (*2'E*)(*4R*)-cinnamoyl-4-phenyl-2-oxazolidinone still did not work well in the presence of 1.0 equivalent of the copper complex using the reported procedures, and the starting materials were recovered. Surprisingly we found that this reaction worked very well when promoted by TMEDA-TMSCl or TMEDA-Bu_2BOTf[10] without using a copper complex. We wish to report here a variety of Lewis acid-TMEDA

promoted Michael additions of vinylmagnesium bromide to chiral α,β-unsaturated imides to afford β-substituted N-acyloxazolidinones in high yields and optical purity (Table 1).

Scheme I

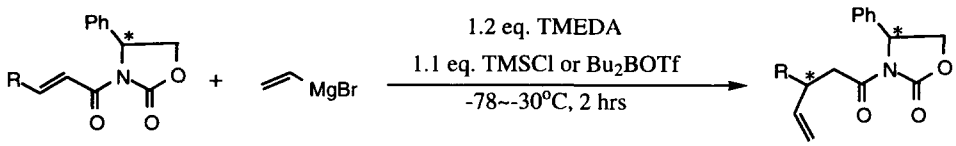
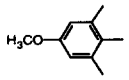
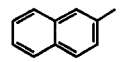


Table 1. Lewis acid-TMEDA promoted addition of vinylmagnesium bromide to N-acyloxazolidinones[a]

Entry	R	4-	Lewis acid	Copper complex	Yield (%)[b]	mp (°C)[c]	$[\alpha]_D^{20}$	de (%)[d]
1	CH_3	R	TMSCl	-	83	89-90	-57.37 (c = 1.12)	>90%
2	CH_3	S	TMSCl	-	78	89-90	+59.73 (c=0.44)	>90%
3	$(CH_3)_2CH$	R	TMSCl	-	82	97-98	-53.21 (c=1.01)	>90%
4	$(CH_3)_2CH$		TMSCl	-	84	101-102	+52.42 (c=1.03)	>90%
5	$CH_3OCH_2CH_2$	R	TMSCl	-	-[e]	-	-	-
6	$CH_3OCH_2CH_2$	R	-	1.0 eq. CuBr•Me_2S	-[f]	-	-	-
7	C_6H_5	R	Bu_2BOT_f	-	86	-	+1.6 (c=1.03)	>95%
8	C_6H_5	R	-	0.2 eq. CuBr•Me_2S	-[g]	-	-	-
9	C_6H_5	R	-	1.0 eq. CuBr•Me_2S	-[g]	-	-	-
10	C_6H_5	R	TMSCl	0.2 eq. CuI•TMEDA	42[h]	-	-	-
11	C_6H_5	R	TMSCl	1.0 eq. CuI•TMEDA	-[e]	-	-	-
12[i]	C_6H_5	R	TMSCl	-	87[j]	130-131	+1.7 (c=1.12)	>95%
13	C_6H_5	S	TMSCl	-	84	126-127	-2.2 (c=1.03)	>95%
14	m-$CH_3OC_6H_4$	R	TMSCl	-	78	114-116	+3.7 (c=1.02)	>95%
15		R	TMSCl	-	87	139-141	+6.28 (c=1.08)	>95%
16		R	TMSCl	-	89	155-156	-3.40 (c=1.03)	>95%

[a]All reactions were carried out on a 2-mmol scale except for reaction 15 (Table 1) which was run on a 1-mmol scale. [b] The yield was calculated from the weight of product after column chromatography purification. All new compounds were fully caracterized by NMR, MS and IR. [c] Uncorrected. [d] de>90% means it was very hard to determine the exact % and de>95% means we did not find any diastereoisomers from ^{1}H-NMR. [e] Starting material was recovered. [f] A highly polar compound was formed. [g] Gave a complicated mixture. [h] Starting material also was recovered. [i] Reaction was carried out on a 100 mmol scale. [j] After crystallization from EtOAc/Hexane, colorless needles.

Table 1 summarizes the results of TMSCl or Bu_2BOTf-activated addition of vinylmagnesium bromide to N-acyloxazolidinones, in comparision with the CuBr•Me_2S or CuI•TMEDA complex mediated addition reactions. The 1,2-addition product was the major pathway when using 1.0 eqivalent of CuBr•Me_2S complex (runs 8 & 9) and the starting material was recovered when using the CuI•TMEDA complex (run 11). Even with 0.2 equivalents of CuI•TMEDA complex, the reaction was not completed in 12 hours. Without using the copper complex, both Lewis acids exibited good reactivities and led to almost complete conversion of all starting materials within 6 hours except in reaction 5 in which the starting material was recovered. A highly constrained substrate (reaction 15) went very well within 8 hours.

In summary, we have developed a vinylmagnesium bromide-Lewis acid system for the rapid, highly diastereoselective 1,4-addition to chiral imides. These reaction conditions are currently under investigation for other Grignard reagents. Finally, these β-branched 4-pentenoic acid derivatives can be easily converted into corresponding novel β-branched glutamic acids and derivatives using chemistry previously elaborated in our laboratory.[7]

General Procedures: Vinylmagnesium bromide (1M in THF[10], 2.1 mL, 2.1 mmol) was placed in a 25 mL two necked flask and cooled to -78°C. Then TMEDA (1M in THF, 2.4 mL, 2.4 mmol) was added by syringe followed by TMSCl (1M in THF, 2.2 mL, 2.2 mmol) or Bu_2BOTf (1M in Et_2O, 2.2 mL, 2.2 mmol). The resulting mixture was stirred for a few minutes and then the N-acyloxazolidinone in THF (10 mL) was added dropwise followed by stirring at -78 to -30°C for 6-8 hours. Then saturated ammonium chloride (5 mL) was added, and the mixture was warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were dried and the solvents removed by rotary evaporation. The products were purified by flash column chromatography (EtOAc:Hexane, v/v, 40:60).

Acknowledgments: The authors wish to acknowledge the financial support of grants from NIDA, DA 06284 and the U.S. Public Health Service, DK 21085, and Mr. Jun Lin for NMR determinations.

References

1. (a) Tomioka, K.; Koga, K. in "*Asymmetric Synthesis*," Ed., Morrison, J. D., Academic Press, **1983**, *Vol 2*, 201-224. (b) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G. *Helv. Chim. Acta.* **1978**, *70*, 2201-2214. (c) Burner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865-1866.
2. (a) Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.* **1975**, *97*, 6266-6267. (b) Meyers, A. I.; Shipman,

M. *J. Org. Chem.* **1991**, *56*, 7098-7012.

3. (a) Fang, C.; Ogawa, T.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry* **1991**, *2*, 389-398. (b) Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 910-916.
4. (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett* . **1981**, 913-916. (b) Touet, J.; Baudouin, S.; Bown, E. *Tetrahedron: Asymmetry* **1992**, *3*, 587-590.
5. (a) Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron Lett.* **1997**, *38*, 1821-1824. (b) Melnyk, O.; Stephan, E.; Pourcelot, C.; Cresson, P. *Tetrahedron* **1992**, *48*, 841-850. (c) Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369-372.
6. (a) Hruby, V. J. *Biopolymers* **1993**, 1073-1082. (b) Hruby, V.J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249-262.
7. (a) Kazmierski, W.M.; Hruby, V.J. *Tetrahedron Lett.* **1991**, *32*, 5769-5772. (b) Boteju, L.W.; Wegner, K.; Hruby, V.J. *Tetrahedron Lett.* **1992**, *33*, 7491-7494. (c) Dharanipragada, R.; VanHulle, K.; Bannister, A.; Bear, S.; Kennedy, L.; Hruby, V. J. *Tetrahedron* **1992**, *48*, 4733-4748. (d) Nicolas, E.; Russell, K.C.; Hruby, V.J. *J. Org. Chem.* **1993**, *58*, 766-770. (e) Nicolas, E.; Russell, K.C.; Knollenberg, J.; Hruby, V.J. *J. Org. Chem.* **1993**, *58*, 7565 -7571. (f) Jiao, D.; Russell, K.C.; Hruby, V.J. *Tetrahedron* **1993**, *49*, 3511- 3520. (g) Li, G.; Jarosinski, M.A.; Hruby, V.J. *Tetrahedron Lett.*, **1993**, *34*, 2561-2564. (h) Li, G.; Patel, D.; Hruby, V.J. *Tetrahedron Lett.* **1994**, *35*, 2301-2304. (i) Li, G.; Patel, D.; Hruby, V.J. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3057-3059. (j) Qian, X.; Russell, K. C.; Boteju, L.W.; Hruby, V. J. *Tetrahedron* **1995**, *51*, 1033-1054. (k) Liao, S.; Hruby, V.J. *Tetrahedron. Lett.* **1996**, *37*, 1563-1566. (l) Liao, S.; Han, Y.; Qiu, W.; Bruck, M.; Hruby, V. J. *Tetrahedron Lett.* **1996**, *37*, 7917-7920.
8. (a) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240-3241. (b) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119-126. (c) Yamamoto, Y. *Angewandte Chemie*, **1986**, *25*, 947. (d) Smith, A. B., III.; Jerris, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 194. (e) Ibuka, T.; Minakate, H. *Synth. Comm.* **1980**, *10*, 119. (f) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.
9. (a) Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Steenkamp, J. A.; Ferreira, D. *Tetrahedron Lett.* **1992**, *33*, 2383. (b) Van Heerden, P. S.; Bezuidenhoudt, B. C. B.; Ferreira, D. *Tetrahedron* **1996**, *52*, 12313.
10. TMEDA: N,N,N′,N′-Tetramethylethylenediamine; Bu_2BOT_f: Dibutylboron triflate; TMSCl: Trimethylsilyl chloride; THF: Tetrahydrofuran.

(*Received in USA* 23 *July* 1997; *revised* 19 *August* 1997; *accepted* 20 *August* 1997)