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A CONVENIENT LEWIS ACID CATALYZED PREPARATION OF CARBAMATES FROM SECONDARY ALCOHOLS AND ISOCYANATES

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The Lewis acids have been found to be highly effective catalysts for the carbamate formation from secondary alcohols and isocyanates.

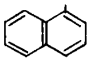
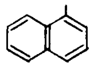
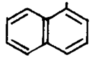
KEYWORDS —— Lewis acid; secondary alcohol; isocyanate; carbamate; γ-carbamoyloxy-α,β-enoate

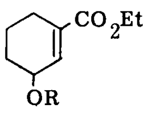
Protecting groups are indispensable devices to prevent reactivity at the hydroxy group during synthesis, since alcohols are susceptible to oxidation and substitution involving the hydroxy group during the synthesis.1) In the reaction and synthesis of organic compounds, hydroxy groups are often protected as their carbamates.2) Furthermore, carbamates are usually well crystalized compounds suitable for characterization,3) isolation,4) and resolution5) of many organic compounds. There have been many reports on the use of basic catalysts such as pyridine and triethylamine for isocyanate-alcohol reaction,6) but it has been reported only recently that this reaction is effectively catalyzed by organotin,7a) lithium alkoxide,7a) and tris(dimethylamino)-N-methylphosphinoimine.7b) However, in the conventional method of treating an isocyanate with an alcohol with or without a basic catalyst, it is difficult to form carbamates from some secondary alcohols and isocyanates, as shown in Table I (Entries 1, 3, 12, and 17).

Our interest in carbamates stems from their usefulness as synthetic precursors to naturally occuring compounds.2,7b,8,9) Many reports have shown that bases are effective catalysts for carbamate formation,6,7) but Lewis acids have been neglected as catalysts for the isocyante-alcohol reaction.10) We now report that Lewis acids, such as boron trifluoride etherate ($BF_3.Et_2O$) and aluminum trichloride ($AlCl_3$), promote the reaction of secondary alcohols with isocyanates in analytically and synthetically useful ways.11,12)

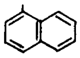
Table I details representative results of a current study of the effects of Lewis acids ($BF_3.Et_2O$ and $AlCl_3$) on the carbamate formation. A representative experimental procedure is as follows: To a solution of the alcohol (3) (100 mg, 1.0 mmol) in 3 ml of ether, phenyl isocyanate (240 mg, 2.0 mmol) is added, followed by $AlCl_3$ (133 mg, 1.0 mmol in 1 ml of ether) at 25°C with stirring. The mixture is stirred until TLC (silica gel, $CHCl_3$:hexane = 1:3) indicates complete consumption of the starting material (15 min). To the mixture is added 5% aq. $NaHCO_3$ (2 ml), and the mixture is vigorously stirred for 30 min. Extraction of the mixture with $CHCl_3$ and the usual workup followed by silica gel column chromatography yields the carbamate (14) (201 mg, mp 84°C (hexane), 91% yield).

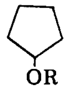
Table I. Lewis Acid Catalyzed Reaction of Secondary Alcohols with Isocyanates

Substrate	Entry	Isocyanate	Catalyst	Reaction condition	Product
(1)	1	Ph-NCO (3 eq)	——	Benzene, r.t., 30 min	(11): Trace
(1)	2	Ph-NCO (3 eq)	$BF_3.Et_2O$ (1 eq)	Benzene, r.t., 30 min	(11): 97%
(1)	3	NCO (1.2 eq) 	pyridine (0.1 eq)	Benzene, reflux., 10 h	(12): Trace
(1)	4	NCO (2 eq) 	$BF_3.Et_2O$ (1.6 eq)	Benzene, r.t., 10 h	(12): 98%
(2)	5	Ph-NCO (2 eq)	$BF_3.Et_2O$ (1 eq)	Benzene, r.t., 15 min	(13): 86%
(3)	6	Ph-NCO (2 eq)	$AlCl_3$ (1 eq)	Ether, r.t., 15 min	(14): 91%
(4)	7	Ph-NCO (2 eq)	$AlCl_3$ (0.3 eq)	Ether, r.t., 2 h	(15): 90%
(5)	8	Ph-NCO (3 eq)	——	Benzene, r.t., 144 h	(16): 90%
(5)	9	Ph-NCO (3 eq)	$BF_3.Et_2O$ (1 eq)	Benzene, r.t., 15 min	(16): 96%
(5)	10	Ph-NCO (3 eq)	$AlCl_3$ (1 eq)	Ether, r.t., 10 min	(16): 95%
(6)	11	Ph-NCO (2 eq)	$AlCl_3$ (1 eq)	Ether, r.t., 1 h	(17): 98%
(7)	12	Me-NCO (3 eq)	——	Benzene, r.t., 20 h	(18): Trace
(7)	13	Me-NCO (3 eq)	$BF_3.Et_2O$ (1 eq)	Benzene, r.t., 20 h	(18): 82%
(7)	14	Ph-NCO (2 eq)	$BF_3.Et_2O$ (1.5 eq)	Toluene, r.t., 8 h	(19): 99%
(8)	15	Ph-NCO (1.3 eq)	$BF_3.Et_2O$ (1.5 eq)	Benzene, 50°C, 1 h	(20): 93%
(9)	16	Ph-NCO (2 eq)	$BF_3.Et_2O$ (4 eq)	Benzene, r.t., 2 h	(21): 95%
(9)	17	Ph-NCO (2 eq)	——	Benzene, r.t., 40 h	(21): Trace
(10)	18	NCO (1.2 eq) 	$BF_3.Et_2O$ (1.7 eq)	Toluene, r.t., 24 h	(22): 92%

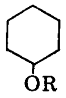


(1) R=H
(11) R=CONHPh
(12) R=CONH

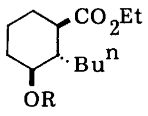




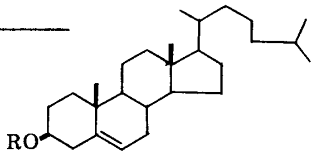
(2) R=H
(13) R=CONHPh



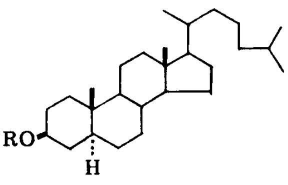
(3) R=H
(14) R=CONHPh



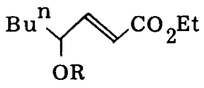
(4) R=H
(15) R=CONHPh



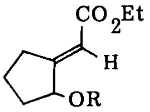
(5) R=H
(16) R=CONHPh



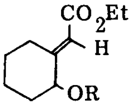
(6) R=H
(17) R=CONHPh



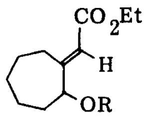
(7) R=H
(18) R=CONHMe
(19) R=CONHPh



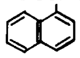
(8) R=H
(20) R=CONHPh



(9) R=H
(21) R=CONHPh



(10) R=H
(22) R=CONH



Lewis acid catalyzed reactions were cleaner and faster. Though the reaction proceeds efficiently at room temperature in the presence of Lewis acid, refluxing the mixture dramatically accelerates the reaction to complete the process within a reasonable period.

Although the yields of carbamates are not necessarily optimal, it is apparent from the preliminary data shown in Table I that the Lewis acid catalyzed method offers an unusually facile method of preparing carbamates.$^{13)}$

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11) For Lewis acid catalyzed organometallic reactions, see: M. J. Eis, J. E. Wrobel, and B. Ganem, *J. Am. Chem. Soc.*, 106, 3693 (1984); M. Yamaguchi and I. Hirao, *Tetrahedron Lett.*, 24, 391 (1983); M. Wada, Y. Sakurai, and K. Akiba, *Tetrahedron Lett.*, 25, 1079 (1984); Y. Yamamoto, S. Yamamoto, H. Yatagai, and K. Maruyama, *J. Org. Chem.*, 47, 119 (1982); T. Ibuka and E. Tabushi, *J. Chem. Soc., Chem. Commun.*, 1982, 703; T. Ibuka, H. Minakata, Y. Mitsui, K. Kinoshita, Y. Kawami, and N. Kimura, *Tetrahedron Lett.*, 21, 4073 (1980).
12) All compounds were characterized by spectroscopic and analytical or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.
13) The $TiCl_4$ catalyzed reaction of the alcohol (7) with MeNCO gave an oily unidentified product in 51% yield after silica gel column chromatography.

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