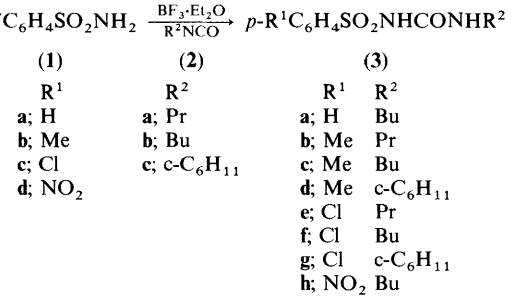
Lewis Acid Catalysed Preparation of some Carbamates and Sulphonylureas. Application to the Determination of Enantiomeric Purity of Chiral Alcohols

Hiroshi Irie,* Masataka Nishimura, and Morihiro Yoshida
Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan
Toshiro Ibuka
Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606 Japan

Lewis acids such as boron trifluoride–diethyl ether and aluminium chloride catalyze the reaction of alcohols and sulphonamides with isocyanates, affording carbamates and sulphonylureas, respectively, in acceptable yield. Applied to the formation of diastereoisomeric carbamates from chiral alcohols using Pirkle's reagents, [(*R*)- and (*S*)-1-(1-naphthyl)ethyl isocyanate (NPEI)], this technique provides a convenient method for determination of enantiomeric purity.

Recently one of us (T. I.) reported[1] a convenient method for the preparation of some carbamates by condensation of alcohols with isocyanates in the presence of the Lewis acid catalysts, aluminium chloride or boron trifluoride–diethyl ether. Bases such as dimethylaminoethanol,[2a] pyridine,[2b] triethylamine,[2b] lithium alkoxides,[2c] and tris(dimethylamino)-*N*-methylphosphine imide[2d] have previously been used to catalyse the reaction. The boron trifluoride–diethyl ether catalysed reaction of an alcohol with methyl isocyanate has been employed successfully for the synthesis of a natural product.[2e] As mentioned,[1] carbamate formation in the Lewis acid catalysed reaction is quite fast and is complete in a few minutes. We aimed at an application of these catalysts to the synthesis of sulphonylureas. We now report a facile method for sulphonylurea synthesis, and also a convenient method for determination of the enantiomeric purity of chiral alcohols using Pirkle's reagents, (*S*)- and (*R*)-1-(1-naphthyl)ethyl isocyanate [(*S*)- and (*R*)-NPEI].[3]

Treatment of toluene-*p*-sulphonamide (**1b**) with butyl isocyanate (**2b**) in ether in the presence of boron trifluoride–diethyl ether at room temperature for several hours gives tolbutamide (**3c**),[4]† an effective oral hypoglycemic drug, in good yield. The sulphonylurea has been prepared by a condensation of the same reagents under basic conditions using long reaction periods and higher temperatures (reflux).[5] Our results provide a new and milder method for preparation of this drug.[6,7] Other sulphonylureas obtained using the same reaction conditions are summarised in Table 1 and Scheme 1.



Scheme 1.

Next, we focused out attention on application of the facilitated carbamate formation reaction to the determination of the enantiomeric purity of chiral alcohols using (*R*)- and (*S*)-NPEI. Treatment of (L)-(*S*)- and (D)-(*R*)-methyl lactate with (*R*)-NPEI in dry benzene in the presence of boron trifluoride–diethyl ether at room temperature gives the diastereoisomeric [(L)-(*S*)]- and [(D)-(*R*)]-(*R*)-carbamates within 1 h and in good yields. The reaction is sufficiently fast and complete so that one need not be overly concerned that the ratio of the diastereoisomeric carbamates observed by ^{1}H n.m.r. spectrum does not correspond to the original enantiomeric purity of the alcohols being examined. Mosher's reagent has been used frequently for determination of the enantiomeric purity of chiral alcohols.[8] This method usually gives acceptable results although problems have been reported, either from inadequate enantiomeric purity of commercial samples of Mosher's acid or from kinetic fractionation in the formation of the diastereoisomeric esters. Moreover, Mosher's acid must be treated with thionyl chloride or oxalyl chloride before it can be used for acylation of the alcohol. Our carbamate method is convenient and allows easy preparation of a sample to be used for ^{1}H n.m.r. analysis of enantiomeric excess. Because ^{1}H n.m.r. spectra may be more 'cluttered' than ^{19}F spectra, the accuracy of the present method may, in some instances, be slightly inferior to that of Mosher's method.[8] The present method was tested with the commercially available chiral alcohols, methyl (*S*)- and (*R*)-lactate and (*R*)-and (*S*)-butan-2-ol. Results are summarised in Table 2. The enantiomeric purities indicated in Table 2 are

Table 1. Phenylsulphonylureas prepared by using Lewis acid (boron trifluoride–diethyl ether) catalysis

Compounds	Yields[a] (%)	M.p. (°C) (lit.)
(**3a**)	72	131—132 (131—133)[5]
(**3b**)	68	147—149 (149—151)[5]
(**3c**)	66	124—129 (127—129)[5]
(**3d**)	40	168—170 (167—169)[5]
(**3e**)	67	123—124 (127—128)[6]
(**3f**)	62	116—118 (115—116)[6]
(**3g**)	35	150—153 (158—159)[7]
(**3h**)	40	165—168 (169—170)[8]

[a] Isolation yield after purification.

† 1-Butyl-3-(*p*-tolylsulphonyl)urea.

Table 2. Determination of the enantiomeric purity of chiral alcohols using (*R*)- and (*S*)-NPEI

Substrate	NPEI	Configurations of products (lactate)-(NPEI) or (butanol)-(NPEI)	^{1}H n.m.r. signals	Optical purity of alcohols (%)
(*S*)-Methyl lactate	*S*	(*S*)-(*S*)	3.778[a]	98.3
(*S*)-Methyl lactate	*R*	(*S*)-(*R*)	3.712[a]	98.3
(*R*)-Methyl lactate	*S*	(*R*)-(*S*)	3.710[a]	97.9
(*R*)-Methyl lactate	*R*	(*R*)-(*R*)	3.779[a]	97.9
(*S*)-Butan-2-ol	*R*	(*S*)-(*R*)	0.779[b]	90.6
			1.219[c]	
(*R*)-Butan-2-ol	*R*	(*R*)-(*R*)	0.827[b]	92.1
			1.147[c]	

[a] Chemical shift of OCH_3 signal. [b] Chemical shift of CH_3CH_2 signal. [c] Chemical shift of CH_3CHO signal.

calculated on the assumption that the enantiomeric purities of the (*R*)- and (*S*)-NPEI used were 99%. The ^{1}H n.m.r. spectra of the carbamates from (*R*)- and (*S*)-butan-2-ol are temperature dependent in $CDCl_3$. However, the signals of both the primary and secondary methyl groups of the two diastereoisomers are clearly distinguishable in [$^2H_5$]pyridine at room temperature. These findings suggested that ^{1}H n.m.r. determination of enantiomeric purity of chiral alcohols in these carbamates may be widely possible through appropriate choice of solvents and signals.

Experimental

M.p.s were recorded with a Yanagimoto micro m.p. apparatus and are uncorrected. ^{1}H N.m.r. spectra were determined with JEOL-FX90 and JNM-GX450 spectrometers in $CDCl_3$ and [$^2H_5$]-pyridine using tetramethylsilane as an internal standard. Column chromatography and thin layer chromatography were performed with Merck silica gel (7734) and Merck thin layer plates (5715 and 5719), respectively. All compounds purchased from commercial sources were used without further purification before use and all solvents were purified by distillation in the usual manner.

General Procedure for the Preparation of Phenylsulphonylureas.—A solution of toluene-*p*-sulphonamide (**1b**) (171 mg, 1 mmol), butyl isocyanate (**2b**) (198 mg, 2 mmol), and boron trifluoride–diethyl ether (280 mg) in ether (10 ml) was stirred at room temperature for 2 h, and diluted with ether (10 ml). The ethereal solution was washed with aqueous sodium carbonate. The aqueous portion was acidified with conc. HCl and extracted with ethyl acetate which was then washed with brine and dried over sodium sulphate. Removal of the solvent under reduced pressure left a residue (190 mg) which crystallised from chloroform–hexane to give pure tolbutamide (**3c**), m.p. 125—127 °C. All the sulphonylureas cited in this report were prepared in the same manner. Acetonitrile was available as a solvent for the reaction.

Carbamoylation of (L)-(S)-*Methyl Lactate with* (S)-NPEI.—A solution of (L)-(*S*)-methyl lactate (360 mg), (*S*)-NPEI. (690 mg) and boron trifluoride–diethyl ether (750 mg) in benzene (20 ml) was stirred at room temperature for 1 h. The solution was washed with 3% aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water and dried over sodium sulphate. Removal of the solvent gave a residue which was submitted to short column chromatography on silica gel using hexane–ethyl acetate (4:1) as eluant. Elution wih the same solvent gave the (L)-(*S*)-lactate-(*S*)-NPEI carbamate in 98% yield, m.p. 101—102 °C (Found: C, 67.7; H, 6.4; N, 4.5. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%).

The other three diastereoisomers were prepared in the same way in more than 85% yields: (L)-(*S*)-lactate-(*R*)-NPEI carbamate, m.p. 62—63 °C (Found: C 67.8; H, 6.4; N, 4.6%). (D)-(*R*)-lactate-(*S*)-NPEI carbamate, m.p. 63—65 °C (Found: C, 67.7; H, 6.1; N, 4.6%). (D)-(*R*)-lactate-(*R*)-NPEI carbamate, m.p. 101—102 °C (Found: C, 67.9; H, 6.4; N, 4.5%). (*R*)- and (*S*)-butan-2-ol and (*R*)-NPEI gave the (*R*)-butanol-(*R*)-NPEI carbamate and (*S*)-butanol-(*R*)-NPEI carbamate in 98 and 95% yields, respectively. The former, m.p. 84—85 °C (Found: C, 75.3; H, 7.8; N, 5.2. $C_{17}H_{21}NO_2$ requires C, 75.4; H, 7.8; N, 5.2%). The latter, m.p. 77—78 °C (Found: C, 75.4; H, 7.6; N, 5.2%).

Acknowledgements

This work was supported in part by a Grant-in-Aid for scientific research from the Ministry of Education, Science, and Culture of Japan.

References

1 T. Ibuka, G.-N. Chu, T. Aoyagi, K. Kitada, T. Tsukida, and F. Yoneda, *Chem. Pharm. Bull.*, 1985, **33**, 451.
2 (*a*) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, 1979, **44**, 2169; (*b*) W. R. Roush and M. A. Adam, *ibid.*, 1985, **50**, 3752; F. M. Hauser, R. P. Rhee, and S. R. Ellenberger, *ibid.*, 1984, **49**, 2236; (*c*) W. J. Bailey and J. R. Griffith, *ibid.*, 1978, **43**, 2690 and references cited therein; (*d*) R. Kuhlmeyer, R. Schwesinger, and H. Prinzbach, *Tetrahedron Lett.*, 1987, **25**, 3429; (*e*) D. A. Evans, E. B. Sjogren, A. E. Weber, and R. E. Conn, *ibid.*, **28**, 39.
3 W. H. Pirkle and M. S. Hoekstra, *J. Org. Chem.*, 1974, **39**, 3904.
4 D. R. Cassady, C. Ainsworth, N. R. Easton, M. Livezey, N. V. Sigal, Jr., and E. Van Heyningen, *J. Org. Chem.*, 1985, **50**, 923.
5 S. Onisi, *J. Pharm. Soc. Jpn.*, 1959, **79**, 559.
6 F. J. Marshall and M. V. Sigal, Jr., *J. Org. Chem.*, 1958, **23**, 27.
7 H. T. Nagasawa, W. E. Smith, C.-H. Kwon, and D. J. W. Goon, *J. Org. Chem.*, 1985, **50**, 4993.
8 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

Received 3*rd October* 1988; *Paper* 8/03923B