(*R*)-[1-(1-Naphthyl)ethyl] Isothiocyanate and (*S*)-1-Phenylethyl Isothiocyanate. New Chirality Recognizing Reagents for the Determination of Enantiomeric Purity of Chiral Amines by NMR

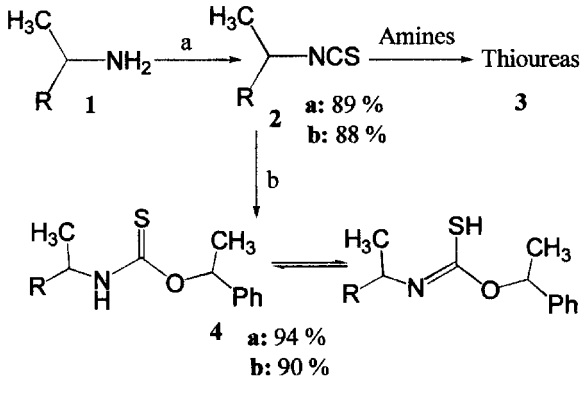
Dong Ju Jeon, Jung Soo Kim, Jung No Lee, Hyoung Rae Kim, and Eung K. Ryu*
Korea Research Institute of Chemical Technology, P. O. Box 107, Taejon 305-600, Korea

(Received September 22, 1999; CL-990771)

(*S*)-1-Phenylethyl isothiocyanate and (*R*)-[1-(1-naphthyl)ethyl] isothiocyanate which are easily formed and stable in aqueous conditions are utilized as new chirality recognizing reagents for the determination of enantiomeric purity of chiral amines by NMR.

Versatile reagents have been developed so far for the determination of the enantiomeric purity by NMR involving chiral derivatizing reagents making diastereomeric compounds, chiral solvents, and chiral lanthanide type shift reagents.[1] Most of the chiral derivatizing reagents making diastereomeric compounds have disadvantage in terms of storage and handling due to their sensitivity to the moisture. Chiral isocyanate reagents, (*R*)-1-naphthylethyl isocyanate[2] and α-methoxy-α-(trifluoromethyl)benzyl isocyanate,[3] were developed as chiral derivatizing and chromatographic separation reagents for the diastereomers. One advantage of these chiral derivatizing isocyanate reagents is directly to react in NMR tube by no removing hydrochloride being required and good reactivity especially to amines. However, isocyanates are usually sensitive to the moisture.

We here would like to report the development of (*S*)-1-phenylethyl isothiocyanate (**2a**) and (*R*)-1-naphthylethyl isothiocyanate (**2b**) as chiral derivatizing reagents, which are not only easily prepared but also stable to various protic solvents including water. They were prepared by the treatment of (*S*)-1-phenylethylamine (**1a**) and (*R*)-1-naphthylethylamine (**1b**) with thiophosgene without racemization,[4] respectively, which have good reactivities to the several primary or secondary amines to obtain the corresponding thioureas in nearly quantitative yields.

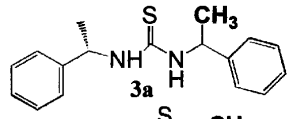
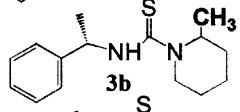
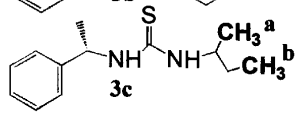
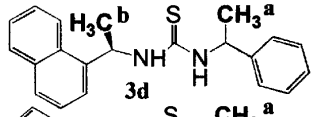
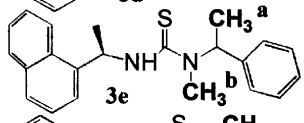
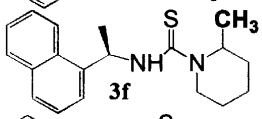
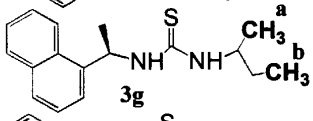
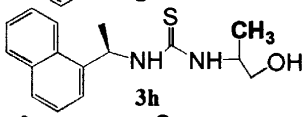
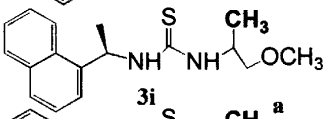
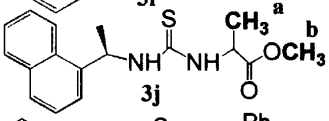
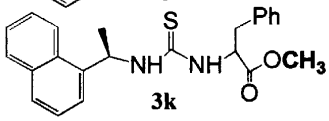


for **1**, **2**, **3**, and **4**, **a**: R= —Ph **b**: R=·····Naph

Reagents and conditions: a) $CSCl_2$, $NaHCO_3$, CH_2Cl_2 / H_2O, rt; b) 1-phenylethanol, $Bu_2Sn(OAc)_2$, toluene, reflux.

Scheme 1.

Table 1. Chemical shift differences of diastereomeric thioureas derived from (*S*)-1-phenylethyl and (*R*)-1-naphthylethyl isothiocyanate

Entry	Diastereomeric Thioureas	|δ(*R*, *R*) - δ(*R*, *S*)| (ppm) ^{1}H	^{13}C
1	 **3a**	0.148 [a]	0.463 [b]
2	 **3b**	0.036	0.107
3	 **3c**	**a**. 0.180 **b**. 0.279	**a**. 0.493 **b**. 0.531
4	 **3d**	**a**. 0.125 [c] **b**. 0.172 [d]	—— [e]
5	 **3e**	**a**. 0.038 **b**. 0.034	**a**. 0.303 **b**. 0.114
6	 **3f**	0.101	—— [f]
7	 **3g**	**a**. 0.215 **b**. 0.345	**a**. 0.348 **b**. 0.508
8	 **3h**	0.22	0.15
9	 **3i**	0.14	0.24
10	 **3j**	**a**. 0.103 **b**. 0.167	**a**. 0.151 **b**. 0.106
11	 **3k**	0.233	0.151

[a](*S*,*S*): 1.477, (*S*,*R*): 1.329; [b](*S*,*S*): 22.994, (*S*,*R*): 22.531; [c](*R*,*R*) :1.403, (*R*,*S*) :1.288; [d](*R*,*R*): 1.657, (*R*,*S*) :1.485; [e] Nonequivalence of two methyls was not observed; [f]indistinguishable by complex peaks.

These isothiocyanates could react effectively to amines in various nonpolar, polar, or protic solvents involving *n*-hexane, chloroform, methanol, DMSO, or water. Since the reaction proceeded smoothly at room temperature, addition of the isothiocyanate reagents to the amines in various NMR solvents directly provided the samples for the NMR analysis.

(*S*)-1-Phenylethyl isothiocyanate (**2a**) reacted either with (*R*)-, or (*S*)-1-phenylethylamine to give the corresponding optically pure thiourea derivatives (**3a**). As shown in Table 1, the thiourea derivative (*S*,*S*)-**3a** from the (*S*)-1-phenylethylamine shows a doublet at 1.477 ppm in ^{1}H NMR and the signal at 22.994 ppm in ^{13}C NMR pertaining to the methyl protons and the carbon, respectively, while in the (*S*,*R*)-**3a**, the corresponding doublet at 1.329 ppm in ^{1}H NMR and the signal at 22.531 ppm in ^{13}C NMR were observed. With other primary and secondary amines, the corresponding thioureas (**3b** and **3c**) obtained also quantitatively from the reaction of the phenylethyl isothiocyanate, and discernible nonequivalences of the two methyl protons between the diastereomers in **3b** and **3c** were found in both ^{1}H and ^{13}C NMR spectra. (*R*)-1-Naphthylethyl isothiocyanate was also proved to be a useful chiral derivatizing reagent with primary and secondary amine (Entry 4~11 in Table 1). The thiourea (*R*,*S*)-**3d** from the (*R*)-1-phenylethylamine showed two doublet at 1.403 and 1.657 ppm, pertaining to the methyl protons **a** and **b**, respectively, while in the (*R*,*S*)-**3d**, the corresponding doublet at 1.288 ppm in **a** and 1.485 ppm in **b** are observed in ^{1}H NMR.

Since it is generally known that the *Z*-configuration of the *Z*- and *E*-forms in a thioamide like an amide is more stable,[5] the *Z*-configuration in a thiourea is expected to be more favorable, therefore, two methyl proton's peaks of (*S*,*S*)-**3a** and the methyl protons **a** and **b** of (*R*,*R*)-**3d** should exist at the same side of the aromatic group. In this case ordinarily, two methyl proton's peaks of (*S*,*S*)-**3a** and the methyl protons **a** and **b** of (*R*,*R*)-**3d** should be observed at more upfield than those of (*S*,*R*)-**3a** and (*R*,*S*)-**3d** by the effect of diamagnetic anisotropy of the phenyl group at the same side.[6,7] However, two methyl proton's peaks of (*S*,*S*)-**3a** and the methyl protons **a** and **b** of (*R*,*R*)-**3d** were observed at more downfield than those of (*S*,*R*)-**3a** and (*R*,*S*)-**3d** in both ^{1}H and ^{13}C NMR. Further confirmation of these observation remains to solve in the future.

With 1-phenylethanol, (*S*)-1-phenylethyl isothiocyanate (**2a**) and (*R*)-1-naphthylethyl isothiocyanate (**2b**) failed to react under the basic conditions including triethylamine,[8] sodium hydride,[9] and potassium hydroxide, but under Lewis acid catalytic conditions such as dibutyltin diacetate and titanium(IV) ethoxide,[10] the corresponding thiourethanes were obtained in good yields. However, since these thiourethanes exist in two tautomeric forms at the usual NMR conditions,[11,12] we observed that these isothiocyanates could not be applicable as chiral derivatizing reagents to alcohols due to the complexity of the NMR peaks.

In summary, we have demonstrated that phenyl and naphthyl isothiocyanates, which can be readily obtained from commercially available amines by one step and are easy for handling due to their insensitivity to the moisture and thermal stability, are useful as new chirality recognizing reagents for the determination of enantiomeric purity of the chiral amines by NMR. Although the magnitude of the nonequivalence are insufficient in some cases, the splitting is generally large enough to determine enantiomeric purity of the versatile amines.

References and Notes

1 For a review, D. Parker, *Chem. Rev*., **91**, 1441 (1991).
2 W. H. Pirkle and J. R. Hauske, *J. Org. Chem*., **42**, 1839 (1977).
3 A. Nabeya and T. Endo, *J. Org. Chem*., **53**, 3358 (1988).
4 Typical Procedure: To a thiophosgene (5.7 g, 49 mmol) solution in a mixture of dichloromethane (50 ml) and water (30 ml) was added slowly (*S*)-1-methylbenzylamine (5 g, 41 mmol) solution in dichloromethane (10 ml) and then added sodium bicarbonate (4.2 g, 49 mmol). The reaction mixture was stirred at room temperature for 5h. The usual work up followed by column chromatography afforded (*S*)-1-phenylethyl isothiocyanate (6.0 g, 89%). Spectroscopic data of (*S*)-1-phenylethyl isothiocyanate (**2a**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44 – 7.26 (5H, m, Ar), 4.93 (1H, q, *J*=6.8 Hz), 1.68 (3H, d, *J*=6.8 Hz)); IR (NaCl): 2089 cm^{-1} ; MS (*m/z*): 163 (M^+); $[\alpha]_D^{25}$ +7.42 (c = 0.3, acetone); HRMS found 163.0454, calcd for C_9H_9NS 163.0456. (*R*)-1-Naphthylethyl isothiocyanate (**2b**): yield: 88 %; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.96 – 7.47 (7H, m, Ar), 5.71 (1H, q, *J*=6.8 Hz), 1.85 (3H, d, *J*=6.8 Hz); IR (KBr): 2127 cm^{-1}; MS (*m/z*): 213 (M^+); $[\alpha]_D^{25}$ –130.9 (c = 0.1, acetone); HRMS, found 213.0611, calcd for $C_{13}H_{11}NS$ 213.0611.
5 W. Walter and H. Huhnerfuss, *Tetrahedron Lett*., **22**, 2147 (1981).
6 S. D. Munari, G. Marazzi, A. Forgione, A. Longo, and P. Lombardi, *Tetrahedron Lett*., **21**, 2273 (1980).
7 S. K. Latypov, J. M. Seco, E. Quinoa, and R. Riguera, *J. Org. Chem*., **60**, 1538 (1995).
8 N. A. Nedolya, V. P. Zinoveva, V. I. Komel'Kova, and B. A. Trofimove, *Zh. Org. Khim.*, **30**, 1173 (1994). [CA, 121: 229961d]
9 M. Oba and K. Nishiyama, *Tetrahedron Lett*., **50**, 10193 (1994).
10 G. Purnima and S. Roy, *Indian J. Chem. Sec. B*., **33**, 291 (1994).
11 C. N. R. Rao and R. Venkataraghavan, *Tetrahedron*, **18**, 531 (1962).
12 W. H Pirkle, K. A. Simmons, and C. W. Boeder, *J. Org. Chem*., **44**, 4891 (1979).