N-COUMARINYL-L-PROLINE, A NOVEL CHIRAL DERIVATIZING AGENT FOR ^{1}H NMR DETERMINATION OF ENANTIOMERIC PURITIES OF ALCOHOLS AND AMINES[1)]

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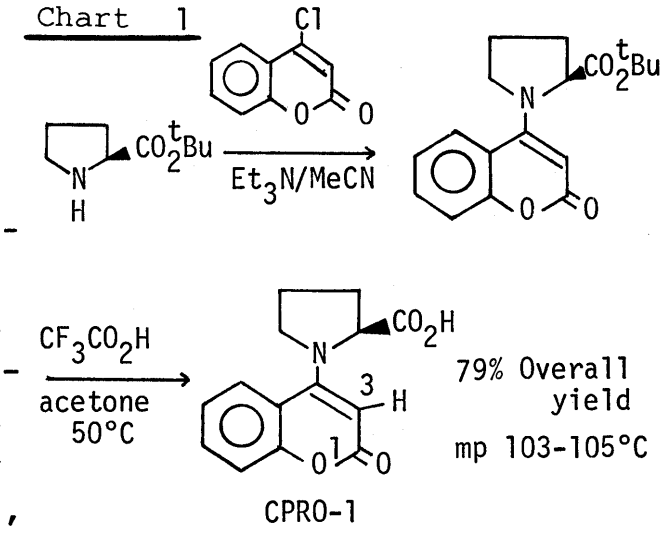
N-(Coumarin-4-yl)-L-proline[CPRO-1], readily prepared from commercially available Cbz-L-proline and 4-hydroxycoumarin, was proved to be an efficient and useful chiral derivatizing agent by ^{1}H NMR inspection of the resulting diastereomeric esters and amides.

KEY WORDS N-coumarinyl-L-proline; chiral derivatizing agent; ^{1}H NMR; enantiomeric purity; chiral alcohol; chiral amine

Recent revolution in the advance of methods for asymmetric synthesis has led to the vast new needs of chiral derivatizing agents (CDAs) in the determination of enantiomeric purity by using an NMR technique and various kinds of CDAs have been documented for this purpose.[2)] However, the new and better agents are always required because of several handicaps found in the CDAs reported thus far, such as the necessity to use less reactive,[3)] unstable,[4)] and/or inconvenient[5)] to handle agents, narrow range of applicability[6)] and to use essentially the multinuclear NMR probes like ^{19}F,[3,5)] ^{29}Si,[7)] ^{31}P,[4)] and ^{77}Se[8)] *which are not always available to most synthetic chemists.* As a continuation of our current programme on the coumarin chemistry, we here report an efficient synthesis of the novel optically pure N-(coumarin-4-yl)-L-proline,

Chart 1



CPRO-1

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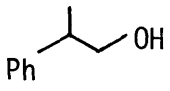
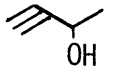
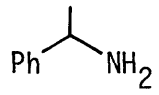
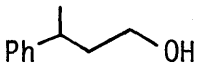
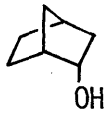
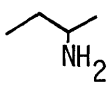
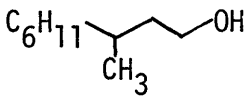
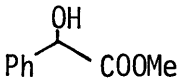
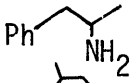
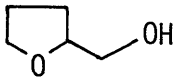
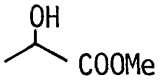
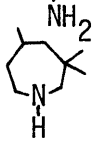
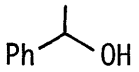
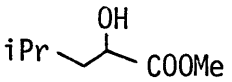
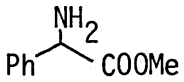
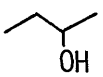
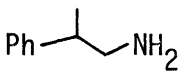
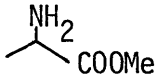
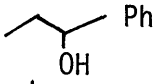
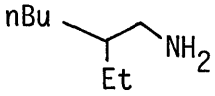
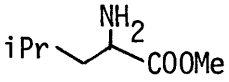
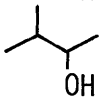
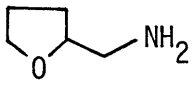
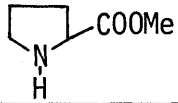
Table I. ^{1}H NMR Chemical Shift Difference, Δ_δ(in ppm) of Diastereomeric Esters and Amides with CPRO-1[a)]

Entry	Racemic substrate	Δ_δ	Entry	Racemic substrate	Δ_δ	Entry	Racemic substrate	Δ_δ
I		0.029	*9*		0.040	*I7*		0.023[b)]
2		0.013[b)]	*I0*		0.024[d)]	*I8*		0.004[b,e)]
3		0[c)]	*II*		0.127	*I9*		0.030
4		0.012[b)]	*I2*		0.107	*20*		0.029
5		0.015[b)]	*I3*		0.074	*2I*		0.015[b)]
6		0.016[b)]	*I4*		0.049	*22*		0.029
7		0.006[b,e)]	*I5*		0	*23*		0.035
8		0.029	*I6*		0.036	*24*		0.181

a) Measured in $CDCl_3$ on a JEOL FX-100 spectrometer unless otherwise specified. b) By JEOL GX-270($CDCl_3$). c) Nonequivalence(Δ_δ=0.025ppm, FX-100) observed in CH_3 resonance of the substrate, citronellol. d) Δ_δ=0ppm in Ref. 4a. e) No base-line resolution was observed.

CPRO-1, and evidence its usefulness as a chiral derivatizing agent for enantiomeric alcohols and amines *by employing the most widely used ^{1}H NMR*.

Condensation of t-butyl L-prolinate made from commercial Cbz-L-proline with 4-chlorocoumarin obtained by $POCl_3$-chlorination of commercial 4-hydroxycoumarin, followed by a CF_3COOH-treatment gave the fine crystalline CPRO-1 in high yield(Chart 1). Diastereotopic nonequivalence(Δ_δ ppm) of the specific *sharp-singlet* proton(~5.5 ppm) at coumarin C-3 of CPRO-1 is routinely verified as in Table I[9)] except that the proton signals of the compounds appear in this region. During derivatization, neither racemization nor kinetic resolution[10)] was observed by allowing CPRO-1 to react with the enantiopure compounds in Table I, showing not any presence of diastereomer, and

with racemic substrates listed in Table I, always giving a 50:50 ratio of diastereomers by NMR integration. The major drawback to using CPRO-1 was, however, insufficient reactivity toward the tertiary alcohol like linalool.

Noteworthy are the following. 1) An irksome optical resolution is not definitely required for CPRO-1. 2) CPRO-1 is crystalline and stable: no change after a 3-year storage at room temperature. 3) Despite some exceptions, base-line resolution was generally ascertained. 4) CPRO-1 appears quite good for the bifunctional compounds (entries 11-13 & 22-24) due to the greatest Δ_δ values(0.181 ppm) with methyl prolinate acquired. Work is under way in this field.

REFERENCES AND NOTES

1) Partial financial support from the Japan Research Foundation for Optically Active Compounds is very grateful.
2) S.Yamaguchi,"Asymmetric Synthesis," ed. by J.D.Morisson, Academic Press, New York(1983), Vol.1, pp.125-152; D.Parker, Chem. Rev., 91, 1441(1991).
3) J.A.Dale and H.S.Mosher, J. Am. Chem. Soc., 95, 512(1973) and references cited therein. CDAs' low reactivities often, but not always, resulted in the kinetic resolution(ref.10), a disadvantage for the exact e.e. determination. MTPA reacted, for instance, with racemic methyl leucinate under the similar reaction conditions in ref.9 to give at most a 50% yield of the expected amide. MTPA gave none(Δ_δ=0ppm), in contrast to a nonequivalence(Δ_δ=0.019ppm) found in 2-octanol ester with CPRO-1. Besides, a quartet-like broad OMe signal in MTPA, presumably because of a long-range coupling with a CF_3 group often discourages an NMR examination.
4) a) R.C.Anderson and M.J.Shapiro, J. Org. Chem., 49, 1304(1984);b) A.Alexakis, S.Mutti, J.F.Normant, and P.Mangeney, Tetrahedron Asymmetry, 1, 437(1990).
5) Y.Takeuchi, N.Itoh, T.Satoh, T.Koizumi, and K.Yamaguchi, J. Org. Chem., 58, 1812(1993). Use of CFPA as a CDA can not help causing some extent of hesitation owing to an oily compound.
6) D.Terunuma, M.Kato, M.Kamei, H.Uchida, and H.Nohira, Chem. Lett., 1985, 13.
7) T.H.Chan, Q.-J.Peng, D.Wang, and J.A.Guo, J. Chem. Soc., Chem. Commun., 1987, 325.
8) L.A.Silks,III, R.B.Dunlap, and J.D.Odom, J. Am. Chem. Soc., 112, 4979(1990).
9) Typical procedure: A solution of CPRO-1(50 mg, 0.19 mmol) and 1,1'-carbonyldiimidazole(34 mg, 0.21 mmol) in fresh dry tetrahydrofuran(THF, 3 ml) was first stirred at room temperature for 1h under argon and then to this was added racemic methyl leucinate(23 mg, 0.16 mmol: entry 23) in fresh dry THF (1 ml) via a syringe. After the whole was stirred at the same temperature for further 3h, THF was evaporated followed by a proton NMR inspection of the resultant(Table 1) with a JEOL FX-100 or GX-270 spectrometer. A full detail including a comparison of CPRO-1 with other CDAs will be presented elsewhere.
10) J.S.Dutcher, J.G.MacMillan, and C.H.Heathcock, J. Org. Chem., 41, 2663(1976); A.Svatos, I.Valterova, D.Saman, and J.Vrkoc, Collect. Czech. Chem. Commun., 55, 485(1990).

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