NEW CRYSTALLINE *N*-(COUMARIN-4-YL)-L-PYROGLUTAMIC ACID. THE FIRST SYNTHESIS AND APPLICATION TO ^{1}H NMR OPTICAL PURITY DETERMINATION OF ALCOHOLS AND AMINES[1,2]

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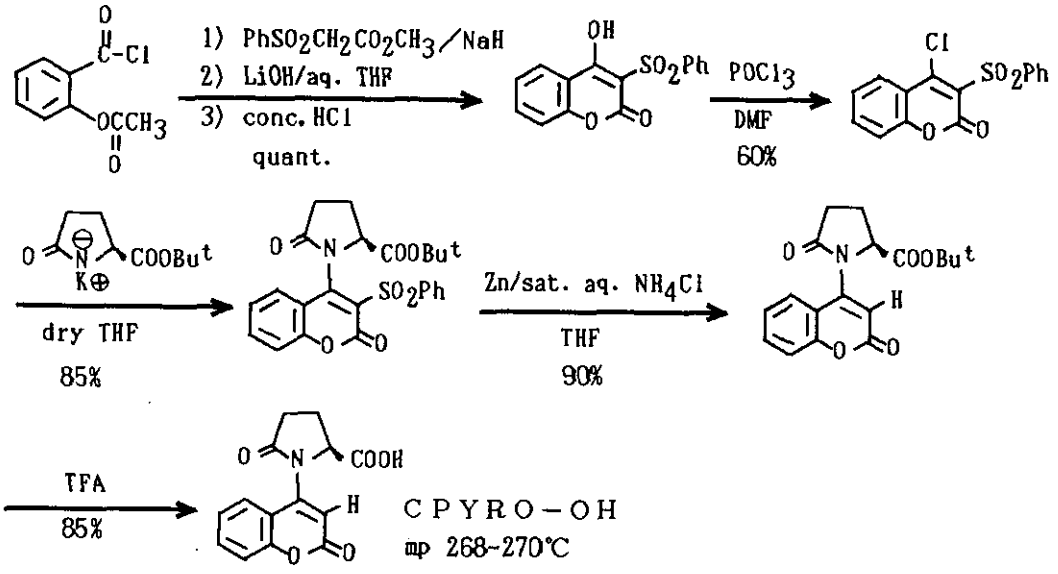
Abstract- *Condensation of* 3-phenylsulfonyl-4-chlorocoumarin with *tert*-butyl L-pyroglutamate potassium salt followed by desulfonylation and ester-cleavage yielded the novel crystalline N-(coumarin-4-yl)-L-pyroglutamic acid[CPYRO-OH], which being evidenced to be a versatile and reliable ^{1}H nmr optical purity determination agent for chiral alcohols and amines.

With the recent explosive progress in the diverse protocols for asymmetric synthesis, the design and development of new chiral derivatizing agents(CDAs) for an accurate, reliable, and convenient ^{1}H NMR enantiomeric excess(e.e.) determination remain a constant need despite a number of methods, e.g., polarimeter, GLC, and HPLC.[3] During our studies on the coumarin chemistry,[4] we frequently experienced that, in addition to remarkable solidity enhancement by coumarin nuclei, a sharp singlet proton signal of coumarin C-3 always appears at quite lower fields, 6.0-7.0 ppm,[5] than OMe protons(a quartet) in Mosher's acid,[6] the most well-known CDA, which makes attractive in the ^{1}H NMR e.e. determination due to the lesser overlap disturbance by other protons present in the substrate. Thus, it appears to us that the coumarin-containing amino acid might prove to be a promising candidate as a chiral derivatizing agent for ^{1}H NMR e.e. determination for chiral alcohols and amines. Our envisagement was realized and we report here our preliminary results.

In contrast to the preparation of 4-piperidinocoumarin from piperidine and 4-chlorocoumarin by Zagorevskii[7] and of 4-pyrrolidinocoumarin from pyrrolidine and 4-hydroxycoumarin by Badran,[8] attempts to condense pyroglutamic acid and its esters with both coumarins above have all failed to produce any desired coumarino-amino acid. However, according to the literature[9a] and our own results,[9b] an electron-withdrawing group at the C-3 position of 4-chlorocoumarin makes the condensation proceed extremely easily and considering ^{1}H NMR e.e. determination of coumarino-amino acids, a selection of sulfonyl group replaceable

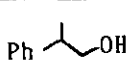
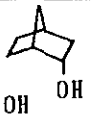
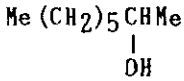
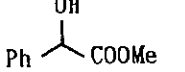
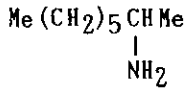
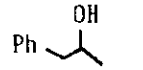
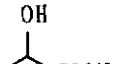
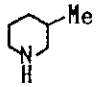
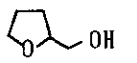
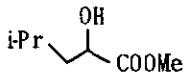
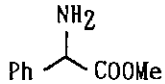
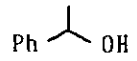
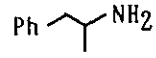
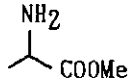
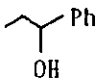
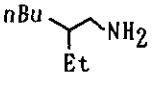
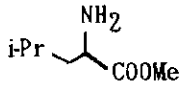
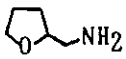
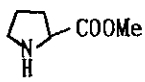
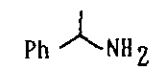
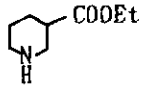
Scheme 1



by hydrogen is essential. As seen in Scheme 1, following the preparation of 3-phenylsulfonyl-4-hydroxycoumarin from aspirin chloride and methyl phenylsulfonylacetate *via* a modification of the Anschütz method,[10] condensation of 3-phenylsulfonyl-4-chlorocoumarin with *tert*-butyl L-pyroglutamate potassium salt gave an 85% yield of the desired *tert*-butyl *N*-(3-phenylsulfonylcoumarin-4-yl)-L-pyroglutamate. Removal of phenylsulfonyl group by Zinc dust and saturated aq. ammonium chloride followed by ester-cleavage with CF_3COOH furnished the new optically pure *N*-(coumarin-4-yl)-L-pyroglutamic acid[CPYRO-OH] in high yield. Results of the observed diastereotopic nonequivalence($\Delta\delta_{ppm}$) of the typical sharp singlet proton(~6.3 ppm) at coumarin C-3 of CPYRO-OH are shown in Table 1, wherein appearance of other proton signals in many organic compounds except for the active methylenic and the non-substituted vinylic compounds etc. is rarely scarce. Either racemization or kinetic discrimination was not induced throughout derivatization, as depicted in Table 2, by comparing the known enantiomeric ratios(%e.e.) of the weighed compositions of the two representative enantiopure methyl mandelates and methyl leucinates with diastereomeric ratios(%d.e.) from the ^1H NMR integration of their resultant ester and amide derived by CPYRO-OH.[11]

The following remarkable observations are noteworthy. 1) An irksome optical resolution is not absolutely required. 2) A sharp-singlet proton always used for the analysis originated from CPYRO-OH, which being independent of the spectroscopic properties of the substrate. 3) CPYRO-OH is a stable crystalline solid: it showed no change after a two-year storage without any precaution. 4) Generally, base-line resolution was ascertained for racemic substrates in Table 1. 5) In some racemic substrates like entries 1, 4, 15, 19, and 24,

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

Entry	Racemic substrate	Δ_δ	Entry	Racemic substrate	Δ_δ	Entry	Racemic substrate	Δ_δ
1		0.017	9		0.008[b, c)]	17		0.017
2		0.010	10		0.089	18		0.029
3		0.020	11		0.034	19		0.019
4		0.006[b, c)]	12		0.069	20		0.054
5		0.034	13		0.068	21		0.034
6		0.040	14		0.005[b, c)]	22		0.044
7		0.007[b, c)]	15		0.031	23		0.049
8		0.024	16		0.029	24		0.128

a) Measured in $CDCl_3$ on a *JEOL FX-100 spectrometer unless otherwise specified.*
b) By JEOL GX-270($CDCl_3$).
c) No base-line resolution was observed.

chiral recognition did perform efficiently wherein the chiral center is 9 atoms distant from the observed nucleus. 6) Quite congested secondary alcohol like 2,2-dimethyl-1-phenyl-1-propanol and tertiary alcohols, unfortunately, either do not react with CPYRO-OH or do so in extremely low yield.

Further investigations, in order to accomplish the wider applicability, are on going in our laboratory.

REFERENCES AND NOTES

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Table 2 Comparison of Optical Purity Determination by Optical Rotation and ^1H NMR Integration(100 MHz)

	(R)-and(S)-Composition by weight	%e.e.[a)]	Diastereomeric ratio of CPYRO-OH ester and amide by ^1H NMR	%d.e.
Methyl mandelate	50:50	1.2	50.5:49.5	1.0
	80:20	58.7	79.5:20.5	59.0
	95: 5	90.3	95.8: 4.2	91.6
Methyl leucinate	50:50	0	50.8:49.2	1.6
	70:30	40.5	69.5:30.5	39.0
	90:10	81.9	89.6:10.4	79.2

a) Determined by specific rotation, $[\alpha]_D^{20}$ (c=1,CH_2Cl_2).

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11. Besides, derivatization of CPYRO-OH with several other racemic substrates in Table 1 was inspected by NMR integration to yield, at any time, an almost 50:50 mixture of diastereomers. Typical procedure: A solution of 0.42 mmol of CPYRO-OH and 0.46 mmol of 1,1'-carbonyldiimidazole in dry CH_2Cl_2(28 mL) and dry DMSO(0.8 mL) was first stirred at rt for 1 h under dry argon and then to this was added a solution of 0.4 mmol of racemic substrate in dry CH_2Cl_2(7 mL) and dry DMSO(0.2 mL). After stirring for 3-20 h, a reaction mixture was washed successively with water, saturated aq. $NaHCO_3$ and brine followed by drying($MgSO_4$) and evaporation to give crude diastereomeric esters and amides which were submitted to ^1H NMR inspection.

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