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A NEW CHIRAL ACID FOR THE RESOLUTION OF RACEMIC BASES : (S)-(-)-(2-PHENYLCARBAMOYLOXY)PROPIONIC ACID (CARBAMALACTIC ACID)

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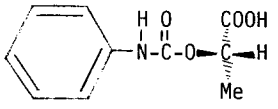
Summary : (S)-(-)-Carbamalactic acid is the phenylcarbamate derived from natural (S)-lactic acid. This new chiral reagent was efficiently used for the resolution of racemic bases such as α-methylbenzylamine, ephedrine and α-(1-naphthyl)ethylamine.

The choice of acidic resolving agents forming crystalline salts with racemic amines is more limited than that of basic resolving agents :[1] tartaric acid and some of its derivatives, as well as camphorsulfonic, mandelic and malic acids are amongst the most widely used commercial chiral acids.

As part of a program pertaining to the chemical valorization of by-products of dairy industry, we looked for new, potentially useful, and relatively cheap derivatives of natural (S)-lactic acid. We thus synthesized the phenylcarbamate 1 of natural (S)-lactic acid (which we propose calling carbamalactic acid), by treatment of ethyl (S)-lactate with phenylisocyanate, followed by saponification.[2] Surprisingly, despite their obviously simple structures, neither the chiral acid 1 nor its antipode seem to have been described in the literature. (S)-(-)-Carbamalactic acid 1 can be recrystallized from $CHCl_3$ as fine needles, m.p. 140-141°C, $[\alpha]_D^{20}$ -13±1° (c = 1, EtOH). Microcalorimetric measurements carried out by BRIENNE and COLLET[3] were in agreement with these data for an optically pure acid 1.[4]



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We successfully used the now commercially available chiral acid 1[5] for the resolution of various racemic amines. Thus the acid 1 was treated with 1 equ. of racemic amine in MeOH and 4 to 6 crops of salts were next isolated by gradual evaporation of the solvent. The salts having same rotations were pooled, recrystallized once from MeOH, and the corresponding amine was isolated in the usual way and purified by distillation. Resolution of (±)-α-methylbenzylamine using the acid 1 thus afforded the (R)-(+) base (71 % yield), $[\alpha]_D^{20}$ +40.7° (neat) and the (S)-(-) base (68 %), $[\alpha]_D^{20}$ - 40° (neat). Lit.[6] $[\alpha]_D^{25}$ ±39.1° (neat).

In the literature, (±)-α-methylbenzylamine was resolved using tartaric acid, hydroxymethylene camphor or (-)-di-O-isopropylidene-2-ketogulonic acid.[7] In the present case, (S)-(-)-carbamalactic acid appeared more advantageous than the afore-mentioned resolving acids, insofar as it gave either higher yields of both antipodes of the amine, or higher optical purities, and using a comparatively simpler experimental procedure.

Resolution of (±)ephedrine led to (+)-ephedrine hydrochloride (76 % yield), $[\alpha]_D^{20}$ +44° (c = 5, MeOH) and (-)-ephedrine-HCl (68 %), $[\alpha]_D^{20}$ -42°. Lit.[8] $[\alpha]_D^{20}$ ±38.5° (c = 4.6,MeOH).

In the literature, (±)-ephedrine was resolved using (+) and (-)-mandelic acids, D-arabonic acid, tartaric acid and (+)-binaphthyldiyl hydrogen phosphate.[9] The present results compare favourably with those reported in the literature.

The resolution of (±)-α(1-naphthyl) ethylamine by the same method gave the (R)-(+) base (87 %), $[\alpha]_D^{20}$ +58.5° (c = 2, MeOH) and the (S)-(-) base (70 %), $[\alpha]_D^{20}$ -53.2° . Lit.[10] $[\alpha]_D^{20}$ +59° and -61°. In the literature, (±)-α-(1-naphthyl) ethylamine was resolved with tartaric acid, L-menthyl hydrogenphthalate and di-O-isopropylidene-2-ketogulonic acid (no yields reported).[11]

The resolution of (±)-norephedrine, using the chiral acid 1 in isopropanol as a solvent, also gave good results.

Further work is in progress in our laboratory, in order to define more accurately the scope of (S)-(-)-carbamalactic acid 1 as a resolving acid.

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References and notes

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