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α-Methoxy-α-trifluoromethylpropionic Acid (MTPr). A New Chiral Derivatizing Reagent for GC Separation of Enantiomeric Amino Acids

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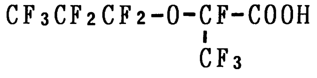
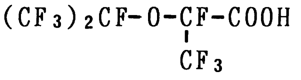
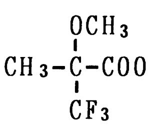
A title homochiral acid has been synthesized and shown to be an efficient chiral derivatizing reagent for capillary gas chromatographic separation of enantiomeric amino acids at considerably low column temperature.

Over the last two decades, various chiral derivatizing reagents have been developed for determination of enantiomeric purity and absolute configuration of optically active compounds by NMR and HPLC, among which the Mosher acid (MTPA, α-methoxy-α-trifluoromethylphenylacetic acid) has been most widely used.[1] However, those reagents which afford volatile diastereomers suitable for GC separation are only limited. The late Ishikawa and his co-workers have provided two such reagents, perfluoro-2-propoxypropionic acid (PPPA)[2a] and perfluoro-2-isopropoxypropionic acid (PIPA).[2b]

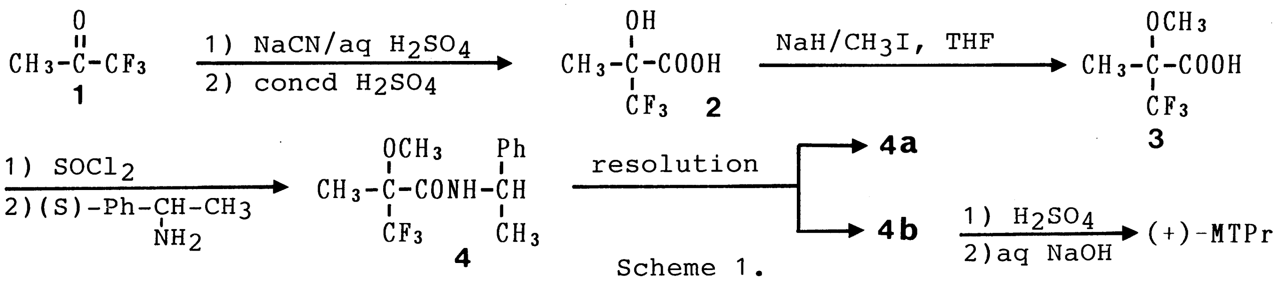

$CF_3CF_2CF_2\text{-}O\text{-}\underset{CF_3}{\underset{|}{C}}F\text{-}COOH$ (PPPA)


$(CF_3)_2CF\text{-}O\text{-}\underset{CF_3}{\underset{|}{C}}F\text{-}COOH$ (PIPA)


$CH_3\text{-}\overset{OCH_3}{\overset{|}{\underset{CF_3}{\underset{|}{C}}}}\text{-}COOH$ (MTPr)

Herein, we wish to report that homochiral α-methoxy-α-trifluoromethylpropionic acid (MTPr), which can readily be prepared in several tens of grams scale (Scheme 1), is an improved variant of these reagents for separation of optically active amino acids on capillary GC at considerably low column temperature.

α-Trifluoroacetone **1** was transformed into α-hydroxy-α-trifluoromethylpropionic acid **2** by the method of Darrall et al.,[3] and then treated with methyl



Scheme 1.

iodide and sodium hydride in THF to give (±)-MTPr **3**. Optical resolution of MTPr could be accomplished according to essentially the same method as used for the resolution of PIPA.[2b)] After conversion of **3** into the diastereomeric amides **4** with (*S*)-phenylethylamine, they were separated to each diastereomer (**4a**:$[\alpha]_D^{20}$ $-88.9°$(CHCl$_3$, *c* 0.97); mp 99.4−100 ℃, and **4b**:$[\alpha]_D^{20}$ $-43.8°$(CHCl$_3$, *c* 1.04); mp 40.5−41℃) by SiO$_2$ column chromatography (EtOAc-hexane (10/3)) or recrystallization from hexane. Treatment of **4b** with concd H_2SO_4 followed by alkaline hydrolysis afforded homochiral (+)-MTPr ($[\alpha]_D^{20}$ $+4.3°$(neat); bp 93 ℃/ 18 mmHg).

Eleven partially active amino acid methyl esters were quantitatively acylated to the diastereomeric pairs of the amides with excess acid chloride of (+)-MTPr in THF and triethylamine in the presence of DMAP. Figure 1 shows a chromatogram of the separation of valine derivatives. The results of separation are summarized in Table 1. All of the MTPr amides tested afforded excellent resolution (Rs) with complete base line separation. The amides from D-amino acids were eluted faster than those from L-isomers. These results indicate that MTPr is an excellent chiral derivatizing reagent for determination of enantiomeric purity and absolute configuration of amino acids by GC.

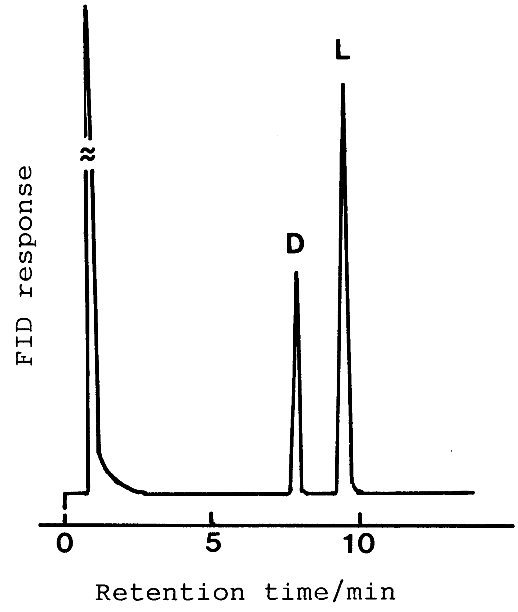


Fig. 1. Gas Chromatogram of (+)-MTPr Amides of Valine Methyl Ester.

Table 1. GC Separation of (+)-MTPr Amides of Amino Acid Methyl Esters[a)]

Substrate	Column temp/℃	k'[b)]	α[b)]	Rs[b)]
Ala-OMe	140	9.67	1.27	4.70
Val-OMe	140	10.59	1.23	5.00
Leu-OMe	140	16.13	1.28	6.84
Ile-OMe	140	15.06	1.23	4.29
Nle-OMe	140	20.94	1.24	8.43
Phe-OMe	200	13.85	1.10	2.76
Asp-(OMe)$_2$	170	20.66	1.13	2.94
Glu-(OMe)$_2$	170	37.86	1.15	4.28
Abu-OMe[c)]	140	11.09	1.25	5.48
$\mathrm{Ph(CH_2)_2\overset{NH_2}{C}HCOOMe}$	200	25.16	1.15	5.00
$\mathrm{Ph(CH_2)_3\overset{NH_2}{C}HCOOMe}$	200	32.46	1.12	4.00

a) Column:CBP20-W25-100(Shimadzu), Carrier gas:He at 0.5 kg/cm^2. b) k':Capacity factor of the more retained isomer, α:Separation factor, Rs:Resolution.
c) 2-Aminobutyric acid methyl ester.

References

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