DIRECT ESTERIFICATION OF 2-METHOXY-2-PHENYL-3,3,3--TRIFLUOROPROPIONIC ACID: A REINVESTIGATION

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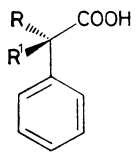
The direct esterification of enantiomeric 2-methoxy-2-phenyl-3,3,3-trifluoropropionic acids (MTPA) was reinvestigated. Preferential formation of one of the diastereoisomeric esters was avoided by using three equivalents of MTPA. Chromatographic behaviour of the obtained MTPA esters is discussed.

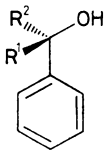
Our recent method[1] for direct esterification of enantiomeric 2-methoxy-2-phenyl--3,3,3-trifluoropropionic acids *Ia* and *Ib* (Mosher's acid, MTPA) represents a significant advance in the preparation of MTPA esters. The method consists in activation of MTPA by reaction with 2-chloro-1-methylpyridinium iodide (CMPI) in the presence of 4-dimethylaminopyridine (DMPA), followed by reaction with the alcohol. In contrast with the original method[2], our procedure does not require the not easily available chloride of MTPA and the isolation of products is very simple. Using our new method we found that the ratio of the corresponding diastereoisomeric MTPA esters (amides) did not correspond to the actual proportion of enantiomers in the studied mixture. For racemic alcohols the ratio of the diastereoisomers differed from the theoretical value 50 : 50. Naturally, this fact markedly distorted our results of enantiomeric purity determination which differed from the results obtained by other methods[3] (such as optical rotation or CD spectra). The same behaviour has also been found for the reaction of (*R*)-(+)-1-(1-naphthyl)ethylamine with racemic 2-phenylbutanoic acid[4] (using the same reagents for activation of the acid). The mentioned discrepancy is caused by incomplete reaction of the studied alcohol (amine) as observed by TLC of the reaction mixture. Under these conditions the reaction mixture is kinetically enriched in the faster arising diastereoisomer. Naturally, no enrichment can occur with pure enantiomers. In order to preserve the advantages of the described method[1] (short reaction time, mild reaction conditions) we tried to solve the problem by using an excess of MTPA.

As model compounds we chose various structural types of secondary alcohols: 1-phenylethanol (*II*) (benzylic type), cis-verbenol (*III*, *IV*) (allylic type), *trans*-2--(4-methoxybenzyl)-1-cyclohexanol (*V*) and its *cis*-isomer *VI* (sterically hindered

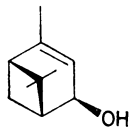
alcohols), and 2-octanol (aliphatic alcohol). The results are given in Table I. Under conditions of our original procedure[1] (alcohol: MTPA = 1 : 1) all the studied alcohols reacted with predominant formation of one of the diastereoisomers. Only with three equivalents of activated MTPA the alcohol reacted completely after 3 h at 40°C and no preference was observed (within the experimental error). With the



Ia, $R^1 = OCH_3$; $R^2 = CF_3$ (*R*)-(+)-MTPA
Ib, $R^1 = CF_3$; $R^2 = OCH_3$ (*S*)-(-)-MTPA



IIa, $R^1 = CH_3$; $R^2 = H$ (*R*)-(+)
IIb, $R^1 = H$; $R^2 = CH_3$ (*S*)-(-)



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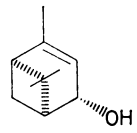

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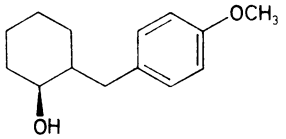
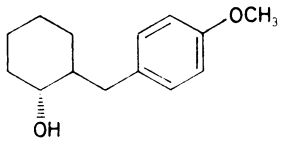


V



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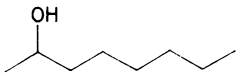
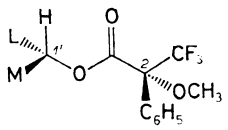


VII

less reactive alcohol *VII* even these conditions were not sufficient for complete conversion. The extent of the kinetic enrichment also depends on the alcohol structure: whereas for compounds *II* and *VI* the enrichment is high (22% e.e.), for alcohol *V* it is relatively low (6% e.e.). The absolute configuration of the MTPA esters followed from chromatographic comparison of esters, independently prepared from pure enantiomers (*IIa*, *IIb*, *III* and *IV*; see Table II), from the ^{19}F NMR spectra (*VII*) and from the literature data[5] (*V* and *VI*). The configuration of the predominating diastereoisomer (*VIII*) of the MTPA ester corresponded in all cases to that following from steric requirements of the acid and the alcohol (cf. preference in the Horeau's method[6]). In the series of our alcohols the absolute configuration of the predominating diastereoisomer *VIII* was *R,R'* or *S,S'*.



VIII

TABLE I

Dependence of the ratio of diastereoisomeric MTPA esters on the reagent ratio

Alcohol[a]	MTPA	Method	Ratio of diastereoisomers[b]	Enantiomeric excess, %
II	*Ia*	a	61/39	22
II	*Ia*	b	59/41	18
II	*Ia*	c	52/48	4
II	*Ib*	a	59/41	18
II	*Ib*	b	58/42	17
II	*Ib*	c	51/49	2
II	*Ia*[c]	a	55/45	10
II	*Ia*[c]	b	50/50	0
III + *IV*[d]	*Ia*	a	53/47	6
III + *IV*[d]	*Ia*	b	45/55	10
III + *IV*[d]	*Ia*	c	44/56	12
III + *IV*[d]	*Ib*	a	53/47	6
III + *IV*[d]	*Ib*	b	43/57	8
III + *IV*[d]	*Ib*	c	43/57	14
III + *IV*[d]	*Ia*[c]	b	46/54[e]	8
V	*Ia*	a	53/47	6
V	*Ia*	b	52/48	4
V	*Ia*	c	50/50	0
VI	*Ib*	a	61/49	22
VI	*Ib*	b	60/40	20
VI	*Ib*	c	50/50	0
VII	*Ia*	a	59/41[f]	18
VII	*Ia*	b	57/43[f]	14
VII	*Ia*	c	54/46[f]	8

[a] Unless stated otherwise, racemic alcohol was used; [b] ratio *R,R*(*S,S*)/*R,S*(*S,R*), determined by HPLC (unless stated otherwise); [c] Mosher's method[2]; [d] in the tested mixture *III* : *IV* = 46 : 54; [e] ratio determined by ^{1}H NMR; [f] ratio determined by ^{19}F NMR.

The ratio of the diastereoisomeric MTPA esters was determined by HPLC on silica gel in light petroleum containing small amounts of ether (up to 5%). The accuracy of the determination (±0·6 rel%) is substantially higher than that achieved by ^{1}H and ^{19}F NMR spectroscopy (±5 rel%) The chromatographic behaviour of the MTPA esters is summarized in Table II. The best resolution was obtained with diastereoisomeric MTPA esters derived from alcohols *III* and *IV* (R_s = 5·70) whereas the esters of alcohol *VII* were not separated at all; in this case the ratio of diastereoisomers and the absolute configuration[7] were determined from the ^{19}F NMR spectra. From the chromatographic viewpoint it would be desirable to relate the structure with the retention properties Although this matter is not clear so far[8], some relations can be found. Thus, e g. for the best separated diastereoisomeric esters, the molecule of alcohol *III* (and its enantiomer *IV*) is rigid and the groups bonded to the chiral center are structurally different. On the other hand, alcohol *VII*, which forms unseparable esters, is flexible and the groups on the chiral center are not markedly different. However, both alcohols show a similar kinetic enrichment.

EXPERIMENTAL

The reaction course and product purity were followed by analytical thin-layer chromatography (TLC) on silica gel G according to Stahl, type 60 (Merck, Darmstadt). Column chromatography of the reaction mixtures was performed on Kieselgel M (0·05–0·1 mm, Herrmann, Köln, F.R.G.). IR spectra were recorded on a UR-20 spectrometer (Carl Zeiss, Jena, G.D.R.) in tetrachlorometha-

TABLE II
Chromatographic behaviour of MTPA esters

Alcohol	MTPA	HPLC conditions[a]	1. peak r_{t1}/k_1,	2. peak r_{t2}/k_2,	R_s[b]
II[c]	*Ia*	A	21·9/2·71	23·3/2·95	2·53
IIa	*Ia*	A	22·0/2·72	—	
IIb	*Ia*	A	—	23·5/2·97	
III + *IV*	*Ia*	B	12·9/2·39	15·0/2·94	5·70
III	*Ia*	B	—	14·8/2·90	
IV	*Ia*	B	12·6/2·35	—	
V[c]	*Ia*	C	29·9/11·0	32·1/11·9	2·19
VI[c]	*Ib*	C	40·6/15·2	42·7/16·1	1·54
VII[c]	*Ia*	B	19·7/4·18	19·7/4·18	0

[a] A: solvent system 1·25% of ether, 0·025% of ethanol in light petroleum; flow rate 0·4 ml min^{-1}, B: solvent system ad A, flow rate 0·6 ml min^{-1}, C: solvent system 5% of ether in light petroleum, flow rate 1 ml min^{-1}; [b] resolution $R_s = 2(r_{t1} - r_{t2})/(w_1 + w_2)$; w width of peaks; [c] racemic alcohol.

ne, wavenumbers are given in cm^{-1}. Mass spectra were measured on a ZAB EQ (VG, Great Britain) instrument at 70 eV. ^1H NMR spectra were taken on a Varian XL-200 spectrometer (FT mode, 200 MHz) in deuterochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. Proton-decoupled ^{19}F NMR spectra were measured on a Bruker AM 400 instrument (376 MHz) using trifluoroacetic acid as an external standard. All parameters were obtained by first order analysis. HPLC analyses were performed on an HP 1090 (Hewlett–Packard) instrument combined with HP-85B computer, detection with a UV detector (DAD) at 220 nm, integration on a DPU eight-channel integrator. The separation was performed on a series of two 150 × 3·2 (i.d.) mm columns, packed with Separon SGX, particle size 5 μm (Tessek). The mobile phases and flow rates are specified in Table II. The employed dichloromethane was freed from ethanol (as stabilizer) by passing through a column of pre-heated silica gel (5 g) and of alumina (5 g). A middle fraction (10 ml) was taken (from 30 ml of the solvent). The reactions were performed in vials equipped with septum (Applied Science, Deerfield, U.S.A.).

General Procedure for Preparation of MTPA Esters

Weighed amounts of 4-dimethylaminopyridine and 2-chloro-1-methylpyridinium iodide were placed into the reaction vial, stirred with dichloromethane and cooled with ice. A solution of MTPA and the alcohol in dichloromethane (for their ratio see Table III) was introduced through the septum, the mixture was briefly stirred and heated to 40°C for 3 h. After removal from the bath, the dichloromethane was evaporated in a stream of nitrogen and the residue was diluted with light petroleum (in the case of more polar MTPA esters with a mixture of light petroleum and ether of suitable polarity). The mixture was stirred, transferred in a Pasteur pipette on a column of silica gel (1–2 g) and eluted with an appropriate solvent. According to this general scheme the reactions were performed on a 0·03–0·1 mmol scale.

Spectral data of the (*R*)-(+)-MTPA esters of alcohols *III*, *IV*, *V* and *VI* have already been published by us[1,5].

(*R*)-(+)-MTPA *ester of* (*R*)-(+)-1-*phenylethanol* (*IIa*): ^1H NMR spectrum: 1·58 d, 3 H (CH_3, J = 6·7); 3·47 q, 1 H (OCH_3, ^5J(H, F) = 1·3); 6·09 q, 1 H (CH, J = 6·7); 7·23–7·47 m, 10 H arom. H). IR spectrum: 1 756 (C=O); 1 270 (CF_3); 1 129 (OCH_3); 701 (Ar). Mass spetrum,. *m/z*: 189; 105 (base peak); 77.

TABLE III

Ratios of the reagents for MTPA esters preparations

Method	Alcohol[a]	MTPA	DMAP	CMPI
a	1	1·0	2·3	1·2
b	1	1·5	3·5	1·8
c	1	3·0	6·9	3·6

[a] Amounts of the alcohol ranged from 0·03 to 0·1 mmol and volume of dichloromethane from 0·3 to 1·0 ml.

(*S*)-(−)-MTPA *ester of* (*S*)-(−)-1-*phenylethanol* (*IIb*): ^{1}H NMR: 1·64 d, 3 H (CH_3, J = 6·7) 3·55 q, 3 H, (OCH_3, ^5J(H, F) = 1·3); 6·13 q, 1 H (CH, J = 6·7); 7·23–7·47 m, 10 H (Arom. H).

(*R*)-(+)-MTPA *esters of racemic* 2-*octanol* (*VII*): ^{1}H NMR spectrum: (*R*, 2′*R*)-diastereoisomer: 0·79 t, 3 H (CH_3, J = 6·8); 1·18 d, 3 H (CH_3, J = 6·2); 1·05–1·27 m, 10 H (5 × CH_2); 3·55 q, 3 H (OCH_3, ^5J(H, F) = 1·3); 5·14 m, 1 H (CH); 7·28–7·50 m, 5 H (arom. H); (*R*, 2′*S*)-diastereoisomer: 0·81 t, 3 H (CH_3, J = 6·8); 1·26 d, 3 H (CH_3, J = 6·2); 1·05–1·27 m, 10 H (5 × CH_2); 3·57 q, 3 H (OCH_3, ^5J(H, F) = 1·3); 5·14 m, 1 H (CH); 7·28–7·50 m, 5 H (arom. H). ^{19}F NMR spectrum: (*R*, 2′*R*) −71·9 s, 3 F (CF_3); (*R*, 2′*S*) −72·0 s, 3 F (CF_3).

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