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A two-step method for the preparation of homochiral cathinones

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Abstract—A simple method for the preparation of homochiral ring-substituted 1-aryl-2-aminopropanones **2** ('cathinones') is described, involving initial Friedel–Crafts acylation of aromatics with (*S*)- or (*R*)-*N*-trifluoroacetylalanyl chloride, followed by acid hydrolysis of the intermediate trifluoroacetamido intermediates **1**, for which X-ray diffraction analysis confirmed the structures.

1. Introduction

Natural cathinones constitute a pharmacologically important family of compounds, related to the ephedrines and amphetamines and well recognized as CNS stimulants. The parent compound, 1-phenyl-2-aminopropanone, is responsible for the long known stimulant properties of khat (*Catha edulis* Forsk.), the use of which is widespread in Yemen and the Horn of Africa.[1,2] Its *N*-methylated derivative (*N*-methylcathinone, methcathinone, 'CAT'), has been known for some time as a drug of abuse in the former Soviet Union and is now classified as a Schedule I substance in the USA.[3]

The analogies between cathinone and amphetamine have suggested that cathinone derivatives with a given ring substitution pattern may behave similarly to the identically ring-substituted amphetamine derivatives. A comparison between 3,4-methylenedioxy- (MDA) and *N*-methyl-3,4-methylenedioxyamphetamine (MMDA) and their cathinone analogs partially confirmed these expectations. However, because of significant pharmacological differences between the studied compounds, it was concluded that new cathinone derivatives should require individual investigations in the future.[4] This justifies the interest in the preparation of novel ring-substituted cathinones for pharmacological studies, both as racemates and in enantiomerically pure forms. The interest in the latter may be illustrated by a recently reported method for the microscale separation of (±)-methcathinone.[5]

When larger amounts of pure, chiral derivatives are needed, the access to novel substituted cathinones should rely on simple and cheap synthetic methods. In connection with our interest in QSAR studies of these amines as MAO-A inhibitors,[6,7] we needed to compare some amphetamine derivatives which had exhibited significant IMAO activity with their cathinone analogs. The use of chiral alanine derivatives offered us the possibility of obtaining enantiomerically pure cathinones for pharmacological studies.[8–11] In the present report we describe a simple, two-step method for the preparation of chiral cathinones **2**, illustrated with four of these compounds (Scheme 1).

4-Methylthio-, 4-ethylthio- and 4-methoxyamphetamine are among the most potent MAO-A inhibitors described to date.[6] Furthermore, 4-methylthioamphetamine (MTA) is a potent, selective, non-neurotoxic serotonin releaser.[12,13] Therefore, the corresponding cathinone analogs were synthesized for the sake of comparison, and as possible intermediates en route to other β-funtionalized amphetamine derivatives. In view of the successful acylation of anisole using our method,

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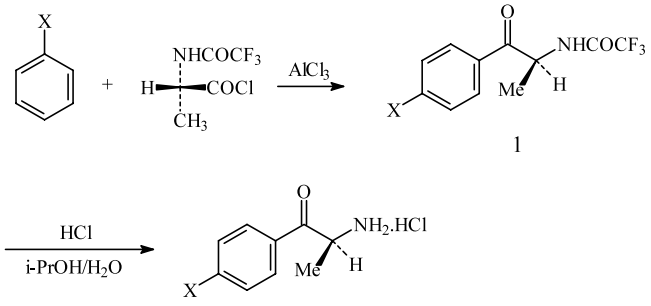

Scheme 1.

the series was extended to include toluene as a precursor.

Three intermediate *N*-protected cathinone trifluoroacetamides **1**, obtained by modifying the existing methodology of Friedel–Crafts acylation of aromatics with *N*-protected alanyl chlorides, had their structures confirmed by X-ray diffraction analysis.

2. Results and discussion

The Friedel–Crafts acylation of the aromatic substrates was carried out with (*S*)-*N*-trifluoroacetylalanyl chloride and $AlCl_3$. The alanyl derivative was prepared by a slight modification of a reported procedure.[11,12] The use of 1,1,3,3-tetramethylguanidine as base,[9,14] instead of triethylamine,[11] reduced the reaction time and led to the isolation of a cleaner crude product which, after washing with hexane, was sufficiently pure for all subsequent reactions. The acylation reaction proceeded reasonably well with toluene and anisole, following the procedure described in the literature.[8,9] However, for methyl- and ethylthiobenzene, the use of excess acid chloride and $AlCl_3$ led to a very low yield of the corresponding ketone. This could be considerably improved when equimolar amounts of the three components were made to react. This modification, which was also successful with toluene and anisole, was therefore adopted in all cases.

From the molecular pharmacological viewpoint it was of interest to establish the coplanarity of the aromatic ring and the carbonyl group, expected due to conjugation. Previous work had revealed the importance of electron-donation by ring substituents to the IMAO activity of phenethylamines.[7] However, good crystals of the salts of the cathinone analogs could not be obtained. On the other hand, trifluoroacetamides **1a–c** crystallized nicely, and were therefore subjected to X-ray diffraction. Relevant crystallographic data for all three structures are presented in Table 1, while Figures

Table 1. Relevant crystallographic data for compounds **1a–c**

	1a	**1b**	**1c**
Empirical formula	$C_{12}H_{12}F_3NO_2$	$C_{12}H_{12}F_3NO_3$	$C_{12}H_{12}F_3NO_2S$
Molecular weight	259.2	275.2	291.3
Density (g cm^{-3})	1.352	1.427	1.389
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
Z (formula units/cell)	4	4	4
Cell dimensions			
a (Å)	9.898(1)	4.987(2)	5.020(1)
b (Å)	13.956(2)	8.726(4)	9.095(2)
c (Å)	9.218(1)	29.45(1)	30.509(7)
Cell volume (Å^3)	1273.3(3)	1281.(1)	1393.1(5)
Reflections			
Collected	6127	5650	6712
Unique	2771	2753	3042
$I>2\sigma(I)$	1714	1288	1005
2θ Range (°)	5.04–56.10	2.76–55.90	4.68–55.92
R(F)			
All	0.087	0.142	0.183
$I>2\sigma(I)$	0.050	0.069	0.051
$wR(F^2)$			
All	0.126	0.221	0.099
$I>2\sigma(I)$	0.110	0.189	0.074
Goodness-of-fit, $S(F^2)$	1.012	0.964	0.841

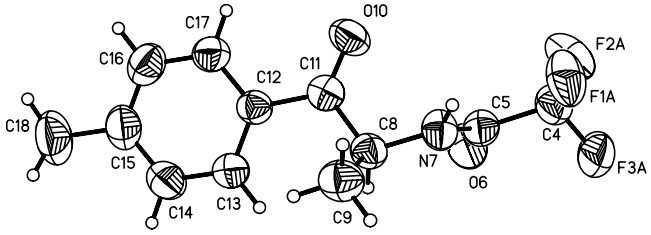

Figure 1. ORTEP projection of **1a**.

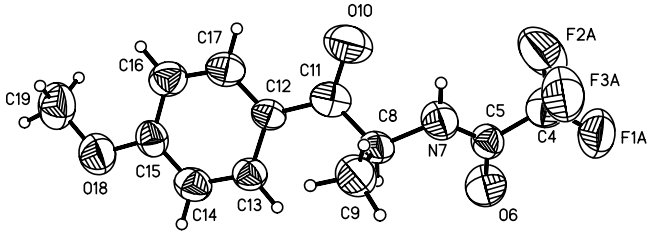

Figure 2. ORTEP projection of **1b**.

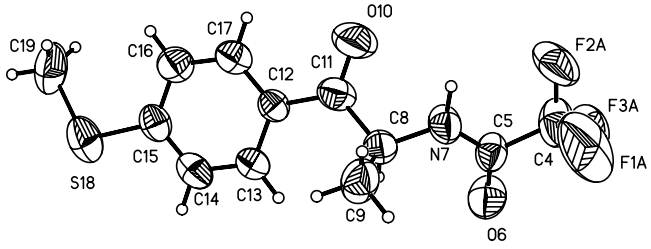

Figure 3. ORTEP projection of **1c**.

1–3 show the corresponding molecular diagrams. The three compounds were obtained as orthorhombic crystals in space group $P2_12_12_1$, with four formula units per cell, thus presenting a single enantiomer each.

Structures **1b** and **1c** are isostructural, while **1a** presents different cell parameters and a different packing arrangement. The molecules, however, do not differ significantly except for slight variations in the torsion angles around free rotation bonds (C5–N7, N7–C8, etc.). Even the H-bonding scheme is similar, with a single H-bond N7–H7–O6[$x-1,y,z$] which defines pseudo chains along the shortest crystallographic axis, a, with the molecular axis evolving normal to the chain direction. All three molecules are in a conformation in which the trifluoromethyl group is maximally separated from the aromatic moiety. The amide group is essentially flat, but the carbonyl oxygen lies a small distance out of the median plane of the aromatic ring. Thus, the dihedral angles O10–C11–C12–C17 are 18.2, 12.6 and 4.2° for **1a**–**c**, respectively. Conjugation between the keto group and the *para*-phenyl substituent is reflected in the O10–C11 carbonyl bond distance. It increases in the order 1.200 Å (**1a**, *p*-Me)<1.228 Å(**1c**, *p*-MeS)< 1.239 Å (**1b**, *p*-MeO), in parallel with the capacity of these groups to act as electron-donors to the ring. A measure of this capacity is provided by the corresponding σ_p^+ Hammett constants, that increase, in absolute values, in the same order, −0.3 (Me)<−0.6 (MeS)<−0.78 (MeO).

Attempts to hydrolyze the protected cathinones under basic conditions, as described in the literature for other trifluoroacetamides,[8,11] were unsuccessful, and the use of more rigorous conditions was avoided because of their likelihood to lead to racemization of the stereogenic center. We adapted with success for this reaction, with minor modifications, the acidic conditions described for the hydrolysis of *N*-formylcathinones.[13] Because of the low solubility of the amides **1** in aqueous HCl, an alcoholic cosolvent was added to the reaction mixture. 2-Propanol proved superior to methanol for this purpose. The reaction proceeded with complete retention of chirality, as confirmed by a comparison of the specific rotation of the isolated hydrochloride of (*S*)-2-amino-1-(*p*-methylphenyl)-1-propanone with the value reported in the literature.[15]

In order to confirm the general scope of the above method, and because of our specific interest in the MAO inhibitory activity of the corresponding enantiomeric cathinones and phenylisopropylamines,[6,7] we carried out the Friedel–Crafts acylation of methyl- and ethylthiobenzene with (*R*)-*N*-trifluoroacetylalanine chloride. These reactions, without further purification from ethyl trifluoroacetate and D-alanine, under conditions similar to those used for the (*S*)-alanyl derivatives, gave the corresponding (*R*)-2-trifluoroacetamido-1-(4-methylthiophenyl)-1-propanone and (*R*)-2-trifluoroacetamido-1-(4-ethylthiophenyl)-1-propanone in yields comparable to those of their enantiomers. The two amides exhibited $[\alpha]_D^{24}$ values of +29.0 and +28.6, respectively (cf. −28.5 and −28.7 for their respective enantiomers). These results, and the fact that the acid hydrolysis of the chiral amides **1** in 2-PrOH/HCl did not affect the chiral center, confirmed this as a general, two-step route for the preparation of chiral substituted cathinones.

3. Experimental

3.1. General

All reagents and solvents were commercially available and were used without any purification. L- and D-Alanine were purchased from Merck. Melting points were obtained with an Electrothermal apparatus and were not corrected. NMR spectra were recorded using a Bruker AMX 300 spectrometer at 300 (^{1}H) and 75 (^{13}C) MHz, employing tetramethylsilane as an internal standard. Chemical shifts are reported relative to TMS ($\delta = 0.00$) and coupling constants (J) are given in Hz. Optical rotation values were obtained with a Perkin–Elmer 241 polarimeter.

3.2. X-Ray diffraction analysis

For each of the three structures a single crystal (0.50×0.30×0.30 mm for **1a**, 0.40×0.20×0.20 mm for **1b**, 0.40×0.25×0.20 mm for **1c**), was mounted on a glass fiber and a highly redundant data set collected at room temperature (T = 295 K), up to a 2θ max. of ca. 58°, with a Bruker AXS SMART APEX CCD diffractometer using monochromatic Mo Kα radiation, $\lambda = 0.71069$ Å. In all cases the structure resolution was achieved routinely by direct methods and difference Fourier analysis. The structures were refined by least-squares on F^2, with anisotropic displacement parameters for non-H atoms. The terminal CF_3 groups in all three structures presented rotational disorder around the C–C bond. This was accounted for by means of a split model consisting of two sets of fluorine atoms (A and B), which were allowed to rotate independently as a rigid body around the C–C axis, as well as to expand/contract. The model was found to be quite suitable as it left a very low residual electron density unaccounted for. H atoms bound to carbon were introduced at ideal positions and allowed to ride. H7, attached to N7 and taking part in H bonding, was refined with an isotropic displacement parameter. All calculations to solve the structures, refine the models proposed and obtain derived results were carried out with the computer programs SHELXS-97 and SHELXL-97,[16] and SHELXTL-PC.[17]

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 199457–199459. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.3. (*S*)-*N*-Trifluoroacetylalanine

1,1,3,3-Tetramethylguanidine (3.75 mL, 30 mmol) was added to a suspension of L-alanine (2.0 g, 22 mmol) in MeOH (11 mL). After 5 min, ethyl trifluoroacetate (3.3 mL, 28 mmol) was added and the reaction was stirred for 4 h at room temperature. The solvent was then removed by rotary evaporation and the residue dissolved in H_2O (35 ml) and acidified with concentrated HCl (4 mL). After stirring for 15 min, the mixture was extracted with EtOAc (2×30 mL) and the organic layers were combined and washed with brine (30 mL), dried over Na_2SO_4 and rotary evaporated to give a solid which was washed with *n*-hexane and dried to afford the crude amide, mp 62–64°C, lit.[12] mp 70–71°C, yield 3.5 g (86%), sufficiently pure for all subsequent uses. ^{1}H NMR ($CDCl_3$) δ 1.57 (d, 3H, $CHC\underline{H}_3$, $J=7.3$), 4.66 (m, 1H, $C\underline{H}CH_3$, 7.3), 7.22 (d, 1H, $N\underline{H}_3$, $J=6.8$), 10.00 (s, 1H, $COO\underline{H}$). ^{13}C NMR ($CDCl_3$) δ 17.2 ($CH\underline{C}H_3$), 48.4 ($\underline{C}HCH_3$), 109.7, 113.5, 117.3, 121.1 (quartet, $\underline{C}F_3CO$), 156.2, 156.7, 157.2, 157.7 (quartet, $CF_3\underline{C}O$), 176.1 ($\underline{C}OOH$).

3.4. General procedure for the preparation of (*S*)-2-trifluoroacetamido-1-aryl-1-propanones 1

To a stirred suspension of (*S*)-*N*-trifluoroacetylalanine (1 g, 5.4 mmol) in dry CH_2Cl_2 (20 mL), cooled to 0°C in an ice-water bath, was added oxalyl chloride (1.1 mL, 12.8 mmol) followed by pyridine (1 drop). The reaction mixture was allowed to warm gradually to room temperature and was then stirred further for 5 h. The solvent and excess oxalyl chloride were removed by rotary evaporation at 35°C to afford the crude acid chloride. To this chloride was then added with stirring a solution of the aromatic compound (5.4 mmol) in CH_2Cl_2 (5 mL), followed by $AlCl_3$ (0.72 g, 5.4 mmol) and the resulting mixture was allowed to react for 18 h. The reaction mixture was then cooled in an ice-water bath and slowly quenched with 1N HCl (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2×30 mL) and the organic layers were combined, dried over Na_2SO_4, and rotary evaporated to give the crude product, which was crystallized in hexane. In this way the following acetamides **1** were prepared:

3.4.1. (*S*)-2-Trifluoroacetamido-1-(4-methylphenyl)-1-propanone 1a. Prepared from 5.4 mmol of (*S*)-*N*-trifluoroacetylalanine and 7 mL of toluene, which also acted as solvent, instead of CH_2Cl_2, yield 43%, prisms, mp 77–78°C; $[\alpha]_D^{24}$ −48.7 (*c* 1.0 g/100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3H, $J=7.1$, $C\underline{H}_3CH$), 2.45 (s, 3H, $C\underline{H}_3Ar$), 5.46–5.56 (m, 1H, $C\underline{H}CH_3$), 7.34 (d, 2H, $J=8.0$, ArH-3,5), 7.67 (s, 1H, NH), 7.89 (d, 2H, $J=8.3$, ArH-2,6). ^{13}C NMR ($CDCl_3$) δ 19.8 ($\underline{C}H_3CH$), 22.2 ($\underline{C}H_3Ar$), 51.1 ($\underline{C}HCH_3$), 110.4, 114.2, 118.0, 121.8 ($\underline{C}F_3CO$), 129.4 (ArC-3,5), 130.2 (ArC-2,6), 130.8 (ArC-4), 146.2 (ArC-1), 156.6, 157.1 ($CF_3\underline{C}O$) and 196.9 (COCH).

3.4.2. (*S*)-2-Trifluoroacetamido-1-(4-methoxyphenyl)-1-propanone 1b. Yield 60%, prisms, mp 97–99°C; $[\alpha]_D^{24}$ −32.2 (*c* 1.03 g/100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3H, $J=6.9$, $C\underline{H}_3CH$), 3.91 (s, 3H, $C\underline{H}_3O$), 5.44–5.53 (m, 1H, $C\underline{H}CH_3$), 7.00 (d, 2H, $J=9.0$, ArH-3,5), 7.70 (d, 1H, $J=3.7$, $N\underline{H}$), 7.98 (d, 2H, $J=9.0$, ArH-2,6). ^{13}C NMR ($CDCl_3$) δ 19.6 ($\underline{C}H_3CH$), 50.5 ($\underline{C}H_3O$), 55.7 ($\underline{C}HCH_3$), 114.4 (ArC-3,5), 121.2 (ArC-4), 131.3 (ArC-2,6), 135.4 (ArC-4), 156.2, 156.7 ($CF_3\underline{C}O$), 164.7 (ArC-1) and 195.3 ($\underline{C}OCH$).

3.4.3. (*S*)-2-Trifluoroacetamido-1-(4-methylthiophenyl)-1-propanone 1c. Yield 40%, prisms, mp 129–130°C; $[\alpha]_D^{24}$ −28.5 (*c* 1.03 g/100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.52 (d, 3H, $J=7.1$, $C\underline{H}_3CH$), 2.55 (s, 3H, $C\underline{H}_3S$), 5.44–5.51 (m, 1H, $C\underline{H}CH_3$), 7.32 (d, 2H, $J=8.2$, ArH-3,5), 7.65 (d, 1H, $J=4.4$, $N\underline{H}$), 7.89 (d, 2H, $J=8.8$, ArH-2,6). ^{13}C NMR ($CDCl_3$) δ 14.60 ($\underline{C}H_3CH$), 19.52 ($\underline{C}H_3S$), 50.59 ($\underline{C}HCH_3$), 113.8, 117.6 ($\underline{C}F_3CO$), 125.1 (ArC-3,5), 128.9 (ArC-4), 129.2 (ArC-2,6), 148.4 (ArC-1), 156.2, 156.7 ($CF_3\underline{C}O$) and 195.8 (Ar$\underline{C}OCH$).

3.4.4. (*S*)-2-Trifluoroacetamido-1-(4-ethylthiophenyl)-1-propanone 1d. Yield 27%, prisms, mp 104–106°C; $[\alpha]_D^{22}$ −28.7 (*c* 1.02 g/100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, $J=7.7$, $CH_3\underline{C}H_2S$), 1.52 (d, 3H, $J=7.1$, $C\underline{H}_3CH$), 3.05 (q, 2H, $J=7.1$, $CH_3C\underline{H}_2S$), 5.47 (m, 1H, $C\underline{H}CH_3$), 7.33 (d, 2H, $J=8.8$, ArH-3,5), 7.63 (d, 1H, $J=4.9$, $N\underline{H}$), 7.87 (d, 2H, $J=8.2$, Ar-2,6). ^{13}C NMR ($CDCl_3$) δ 13.8 ($\underline{C}H_3CH$), 19.5 ($\underline{C}H_3CH_2S$), 25.8 ($CH_3\underline{C}H_2S$), 50.6 ($\underline{C}HCH_3$), 113.8, 117.6 ($\underline{C}F_3CO$), 126.1 (ArC-3,5), 129.1 (ArC-4), 129.2 (ArC-2,6), 147.4 (ArC-1), 156.2, 156.7 ($CF_3\underline{C}O$) and 195.8 (Ar$\underline{C}OCH$).

3.4.5. (*R*)-2-Trifluoroacetamido-1-(4-methylthiophenyl)-1-propanone. Prepared in the same way as compound **1c**, yield 45%, prisms, mp 131–132°C; $[\alpha]_D^{24}$ +29.0 (*c* 1.03 g/100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, $J=7.1$, $C\underline{H}_3CH$), 2.55 (s, 3H, $C\underline{H}_3S$), 5.45–5.52 (m, 1H, $C\underline{H}CH_3$), 7.31 (d, 2H, $J=8.2$, ArH-3,5), 7.66 (d, 1H, $J=4.4$, $N\underline{H}$), 7.89 (d, 2H, $J=8.8$, ArH-2,6). ^{13}C NMR ($CDCl_3$) δ 14.6 ($\underline{C}H_3CH$), 19.5 ($\underline{C}H_3S$), 50.6 ($\underline{C}HCH_3$), 113.8, 117.6 ($\underline{C}F_3CO$), 125.1 (ArC-3,5), 128.9 (ArC-4), 129.2 (ArC-2,6), 148.4 (ArC-1), 156.2, 156.7 ($CF_3\underline{C}O$) and 195.8 (Ar$\underline{C}OCH$).

3.4.6. (*R*)-2-Trifluoroacetamido-1-(4-ethylthiophenyl)-1-propanone. Prepared in the same way as compound **1d**, yield 25%, prisms, mp 105–107°C; $[\alpha]_D^{24}$ +28.6 (*c* 1.03 g/100 mL, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, $J=7.7$, $CH_3\underline{C}H_2S$), 1.51 (d, 3H, $J=7.1$, $C\underline{H}_3CH$), 3.06 (q, 2H, $J=7.1$, $CH_3C\underline{H}_2S$), 5.47 (m, 1H, $C\underline{H}CH_3$), 7.33 (d, 2H, $J=8.8$, ArH-3,5), 7.64 (d, 1H, $J=4.9$, $N\underline{H}$), 7.87 (d, 2H, $J=8.2$, Ar-2,6). ^{13}C NMR ($CDCl_3$) δ 13.8 ($\underline{C}H_3CH$), 19.5 ($\underline{C}H_3CH_2S$), 25.8 ($CH_3\underline{C}H_2S$), 50.6 ($\underline{C}HCH_3$), 113.8, 117.6 ($\underline{C}F_3CO$), 126.1 (ArC-3,5), 129.1 (ArC-4), 129.2 (ArC-2,6), 147.4 (ArC-1), 156.2, 156.7 ($CF_3\underline{C}O$) and 195.8 (Ar$\underline{C}OCH$).

3.5. General procedure for the preparation of (*S*)-2-amino-1-aryl-1-propanone hydrochlorides 2

A modification of the reported procedure for the hydrolysis of *N*-formylcathinones[15] was employed, with the use of 2-propanol as solvent. The (*S*)-2-trifluoroacetamido-1-aryl-1-propanone derivatives **1** (0.7 mmol) were dissolved in 2-propanol (16 mL) and concentrated HCl (12 mL). The resulting solutions were then stirred at 40°C for 12 h. Elimination of the solvent by rotary evaporation, followed by addition of diethyl ether (15 mL) and 2-propanol (0.5 mL) precipitated the hydrochloride salts **2**. In this way the following cathinone hydrochlorides were prepared:

3.5.1. (*S*)-2-Amino-1-(4-methylphenyl)-1-propanone hydrochloride 2a. Yield 55%, prisms, mp 192–193°C; $[\alpha]_D^{22}$ −32.0 (*c* 1.06 g/100 mL, MeOH). Analysis, calculated for $C_{10}H_{14}NOCl{\cdot}0.5H_2O$: C, 57.57; H, 7.19%; found: C, 57.20; H, 6.86%. ^{1}H NMR (D_2O) δ 1.48 (d, 3H, $J=7.3$, $CHC\underline{H}_3$), 2.32 (s, 3H, $C\underline{H}_3Ar$), 5.05 (q, 1H, $J=7.3$, $C\underline{H}CH_3$), 7.34 (d, 2H, $J=8.4$, ArH-3,5), 7.80 (d, 2H, $J=8.3$, ArH-2,6). ^{13}C NMR (D_2O) δ 19.70 ($CH\underline{C}H_3$), 23.86 ($\underline{C}H_3Ar$), 54.67 ($\underline{C}HCH_3$), 131.9 (ArC-3,5), 132.5 (ArC-1), 132.8 (ArC-2,6), 150.0 (ArC-4) and 200.5 (Ar$\underline{C}$OCH).

3.5.2. (*S*)-2-Amino-1-(4-methoxyphenyl)-1-propanone hydrochloride 2b. Yield 43%, prisms, mp 198°C; $[\alpha]_D^{23}$ −32.1 (*c* 1.01 g/100 mL, MeOH). Analysis, calculated for $C_{10}H_{14}NO_2Cl$: C, 55.70; H, 6.50%; found: C, 55.33; H, 6.39%. ^{1}H NMR (DMSO-d_6) δ 1.46 (d, 3H, $J=7.1$, $CHC\underline{H}_3$), 3.91 (s, 3H, $C\underline{H}_3O$), 5.09 (broad multiplet, 1H, $C\underline{H}CH_3$), 7.15 (d, 2H, $J=8.9$, ArH-3,5), 8.08 (d, 2H, 8.9, ArH-2,6), 8.50 (broad singlet, 3H, $N\underline{H}_3$). ^{13}C NMR (DMSO-d_6) δ 17.77 ($CH\underline{C}H_3$), 50.77 ($\underline{C}HCH_3$), 56.10 ($\underline{C}H_3O$), 114.8 (ArC-3,5), 125.9 (ArC-1), 131.6 (ArC-2,6), 164.5 (ArC-4) and 195.2 (Ar$\underline{C}$OCH).

3.5.3. (*S*)-2-Amino-1-(4-methylthiophenyl)-1-propanone hydrochloride 2c. Yield 42%, prisms, mp 194–195°C; $[\alpha]_D^{22}$ −30.4 (*c* 0.98 g/100 mL, MeOH). Analysis, calculated for $C_{10}H_{14}NOSCl{\cdot}0.5H_2O$: C, 49.89; H, 6.24; N, 5.82%; found: C, 49.35; H, 5.89; N, 5.90%. ^{1}H NMR (DMSO-d_6) δ 1.43 (d, 3H, $J=7.1$, $CHC\underline{H}_3$), 2.56 (s, 3H, $C\underline{H}_3S$), 5.07 (q, 1H, $J=7.1$, $C\underline{H}CH_3$), 7.42 (d, 2H, $J=8.4$, ArH-3,5), 7.98 (d, 2H, 8.4, ArH-2,6), 8.58 (broad singlet, 3H, $N\underline{H}_3$). ^{13}C NMR (DMSO-d_6) δ 14.14 ($CH\underline{C}H_3$), 17.50 ($\underline{C}H_3S$), 50.82 ($\underline{C}HCH_3$), 125.4 (ArC-3,5), 129.1 (ArC-1), 129.5 (ArC-2,6), 147.7 (ArC-4) and 195.7 (Ar$\underline{C}$OCH).

3.5.4. (*S*)-2-Amino-1-(4-ethylthiophenyl)-1-propanone hydrochloride 2d. Yield 50%, prisms, mp 197–198°C; $[\alpha]_D^{24}$ −22.9 (*c* 1.03 g/100 mL, MeOH). Analysis, calculated for $C_{11}H_{16}NOSCl$: N, 5.70%; found: N, 5.83%. ^{1}H NMR (DMSO-d_6) δ 1.30 (t, 3H, $J=7.3$, $C\underline{H}_3CH_2S$), 1.43 (d, 3H, $J=7.1$, $CHC\underline{H}_3$), 3.12 (q, 2H, $J=7.3$, $CH_3C\underline{H}_2S$), 5.07 (d, 1H, $J=5.2$, $C\underline{H}CH_3$), 7.44 (d, 2H, $J=8.5$, ArH-3,5), 7.98 (d, 2H, $J=8.5$, ArH-2,6), 8.52 (broad singlet, 3H, $N\underline{H}_3$). ^{13}C NMR (DMSO-d_6) δ 14.61 ($CH\underline{C}H_3$), 18.10 ($\underline{C}H_3CH_2S$), 25.53 ($CH_3\underline{C}H_2S$), 51.44 ($\underline{C}HCH_3$), 126.8 (ArC-3,5), 129.9 (ArC-1), 130.2 (ArC-2,6), 147.0 (ArC-4) and 196.3 (Ar$\underline{C}$OCH).

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References

1. Connor, J. D.; Makonnen, E.; Rostom, A. *J. Pharm. Pharmacol.* **2000**, *52*, 107–110.
2. Connor, J. D.; Rostom, A.; Makonnen, E. *J. Ethnopharmacol.* **2002**, *81*, 65–71.
3. Young, R.; Glennon, R. A. *Psychopharmacol.* **1998**, *140*, 250–256.
4. Dal Cason, T. A.; Young, R.; Glennon, R. A. *Pharmacol. Biochem. Behav.* **1997**, *58*, 1109–1116.
5. Wallenborg, S. R.; Lurie, I. S.; Arnold, D. W.; Bailey, C. G. *Electrophoresis* **2000**, *21*, 3257–3263.
6. Scorza, M. C.; Carrau, C.; Silveira, R.; Zapata-Torres, G.; Cassels, B. K.; Reyes-Parada, M. *Biochem. Pharmacol.* **1997**, *54*, 1361.
7. Vallejos, G.; Rezende, M. C.; Cassels, B. K. *J. Comp.-Aided Mol. Design* **2002**, *16*, 95–103.
8. Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laicos, G. D.; Vishwanath, V. M. *J. Org. Chem.* **1984**, *49*, 4107–4111.
9. Nordlander, J. E.; Njoroge, F. G.; Payne, M. J.; Warman, D. *J. Org. Chem.* **1985**, *50*, 3481–3484.
10. Itoh, O.; Honnami, T.; Amano, A.; Murata, K.; Koichi, Y.; Sugita, T. *J. Org. Chem.* **1992**, *57*, 7334–7338.
11. Chambers, J. J.; Kurrasch-Orbaugh, D. M.; Parker, M. A.; Nichols, D. E. *J. Med. Chem.* **2001**, *44*, 1003–1010.
12. Huang, X.; Marona-Lewicka, D.; Nichols, D. E. *Eur. J. Pharmacol.* **1992**, *229*, 3.
13. Scorza, M. C.; Silveira, R.; Nichols, D.; Reyes-Parada, M. *Neuropharmacol.* **1999**, *38*, 1055.
14. Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805–2807.
15. Berrang, B. D.; Lewin, A. H.; Carroll, F. I. *J. Org. Chem.* **1982**, *47*, 2643–2647.
16. Sheldrick, G. M. SHELXS-97 and SHELXL-97: Programs for Structure Resolution and Refinement (1997) Univ. of Göttingen, Germany.
17. Sheldrick G. M. SHELXTL-PC. Version 5.0 (1994). Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, USA.