Journal of Fluorine Chemistry, 49 (1990) 67–73

Received October 31, 1989, accepted February 4, 1990

A FACILE METHOD FOR THE ASYMMETRIC SYNTHESIS OF ENANTIOMERICALLY PURE 1-(2-FLUOROPHENYL)-ETHYLAMINE [1]

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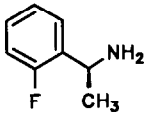
SUMMARY

A simple, two-step-procedure for the synthesis of optically active (*S*)-1-(2-fluorophenyl)-ethylamine (**1**) is described. Starting from commercially available 2-fluoro-acetophenone (**2**), imination with (*S*)-1-phenyl-ethylamine (**3**), followed by stereoselective hydrogenation over *Raney*-nickel gives the secondary amine **5a**. Subsequent regioselective hydrogenolytic cleavage of homogenous **5a** yields enantiomerically pure **1**.

INTRODUCTION

Optically active 1-phenyl-ethylamines are well known chiral building blocks, which have found widespread application as chiral auxiliaries in asymmetric synthesis [2]. They can be regarded as representatives of nearly ideally substituted stereogenic centers, bearing the amino-function and three greatly differentiated non-reactive ligands: the small hydrogen, the medium-sized methyl group and the relatively large phenyl substituent. This makes well understandable that the fields of application are multifold, including the use as (stoichiometric or catalytic) chiral auxiliaries in asymmetric synthesis, the direct incorporation into pharmaceutically active compounds [3] that bear such aryl-ethylamine subunits, the resolution of racemic mixtures [4], and the preparation of chiral phases for liquid chromatography [5].



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With respect to this broad utility of aryl-ethylamines, the preparation of ***nucleus-fluorinated*** 1-phenyl-ethylamines would be of special ***additional*** interest, since a combination of the de-

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scribed useful features of "ordinary" phenyl-ethylamines with the specific properties of fluorine might lead to very valuable novel reagents and auxiliaries. Thus, the fluorine substituent in **1** should help to monitor chiral interactions such as asymmetric inductions or racemate resolutions, e.g. by ^{19}F NMR spectroscopy. As chiral synthetic building blocks, *nucleus-fluorinated* aryl-ethylamines might help to incorporate fluorine into natural products (such as alkaloids) of pharmaceutical relevance [6], e.g. for metabolic studies.

Despite the great usefulness of substituted aryl-ethylamines, most of the synthetic pathways to these interesting molecules[+)] are hampered by severe limitations, e.g. multistep procedures, expensive chiral auxiliaries, or unsatisfactory asymmetric inductions. Consequently, there is an urgent demand for improved methods that allow an efficient synthesis of these important chiral compounds.

Recently, we have reported [12] an easy and reliable access to enantiomerically pure nucleus-oxygenated 1-phenyl-ethylamines by reductive amination of appropriately substituted acetophenones with optically active unsubstituted 1-phenyl-ethylamine, followed by regiospecific hydrogenolytic cleavage of the resulting bis-aryl-ethylamines. This two-step method is characterized not only by the high diastereoselectivities observed in the amination step, but also by the possibility of obtaining really enantiomerically pure 1-phenyl-ethylamines, by simple purification of the intermediate diastereoisomeric secondary amines, prior to the final cleavage step. Furthermore, with respect to the commercial availability of both (*R*)- and (*S*)-1-phenyl-ethylamine, this procedure allows to optionally synthesize aryl-ethylamines of any desired configuration. In this paper, we wish to describe the extension of this methodology to the stereoselective synthesis of enantiomerically pure 1-(2-fluoro-phenyl)-ethylamine (**1**) [13].

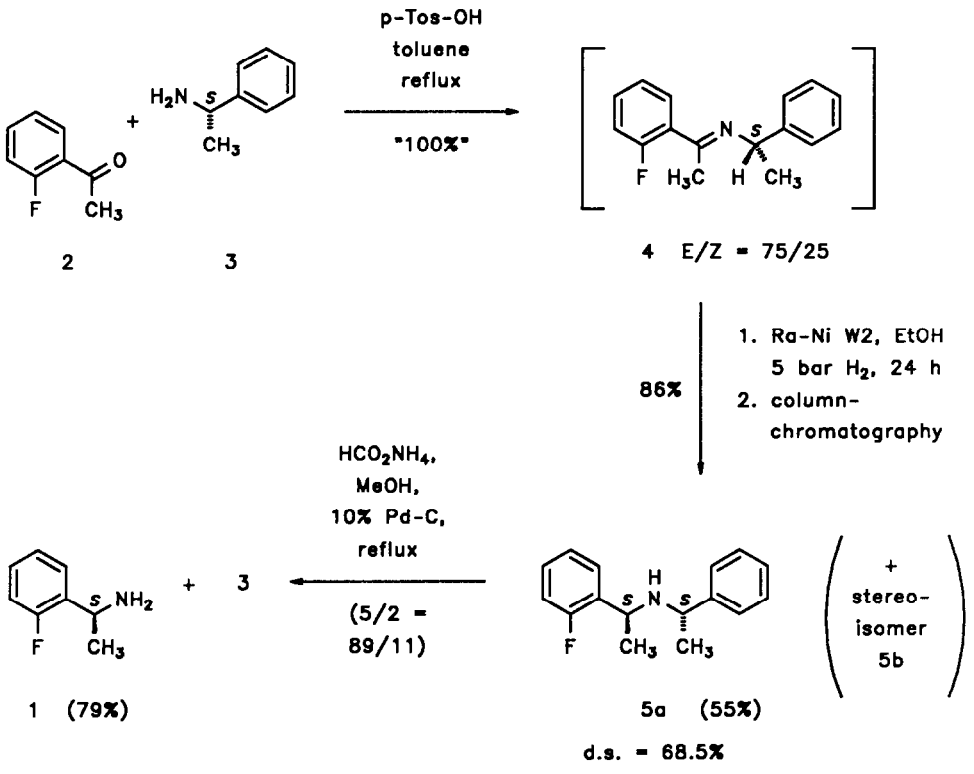
RESULTS AND DISCUSSION

For our attempt to enlarge this useful principle to the asymmetric synthesis of halogenated aryl-ethylamines, we had to face three main problems:

- an imaginable possible lack of stereoselectivity in the reductive amination step,
- a probable loss of halogen under the hydrogenation conditions [14], and, finally
- a possible lack of regioselectivity in the ultimate cleavage of the bis-aryl-ethylamine **5**. Still worse, due to the electronegative character of the fluorine, even a preferential cleavage of the wrong benzylic C-N-bond, which would destroy the new chiral center, could not be excluded.

[+)] Hitherto known syntheses of optically active phenyl-ethylamines are mostly based on diastereoselective *C*-alkylations [7] or reductions [8] of chirally modified imino derivatives (internal asymmetric induction) or on enantioselective reductions of prochiral acetophenone imines [9] or oximes [10] (external asymmetric induction). Recently, nucleus-chlorinated chiral 1-phenyl-ethylamines were prepared by chemical transformation of optically active unsubstituted 1-phenyl-ethylamine [11].

Nonetheless, we have tried this strategy, starting from 2-fluoro acetophenone (**2**). Our results are summarized in the reaction scheme. Condensation of commercially available 1-(2-fluorophenyl)-ethan-1-one (**2**) with (*S*)-1-phenyl-ethylamine (**3**) is brought about under standard conditions (p-toluene sulfonic acid, toluene, reflux under *Dean-Stark*-trap) yielding the imine **4** as a mixture of E/Z isomers (ratio 75/25, ^{1}H NMR). To avoid hydrolytic decomposition back to the starting materials, the imine **4** is immediately hydrogenated over *Raney*-nickel [15] (5 bar H_2), thus leading to a mixture of the diastereoisomeric secondary amines **5a** and **5b** (ratio 68.5 : 31.5, ^{1}H-NMR) in 86 % yield. Separation of **5a/5b** is achieved by repeated recrystallization of the corresponding hydrobromides, or, more conveniently, by column-chromatography of the free bases on deactivated silica gel. To our surprise, the subsequent hydrogenolytic cleavage of the purified, stereochemically uniform diastereoisomer **5a** by transfer hydrogenolysis [16] with ammonium formate and Pd-C (10%) could be performed highly regioselectively, to give the desired 1-(2-fluorophenyl)-ethylamine **1**, along with a small amount of **3** (ratio 89 : 11, ^{1}H-NMR). The mixture was separated by column-chromatography, and pure **1** was obtained in 79% yield.



Scheme.

The enantiomeric excess (e.e.) was determined according to literature procedures [17] by GC-analysis of the *Mosher*-type derivative, which proved **1** to be enantiomerically pure (e.e. = 98%), thus even exceeding the optical purity of the used chiral auxiliary **3** (e.e. = 95%).

For an elucidation of the configuration at the newly formed stereogenic center, the primary amine **1** was transformed into a thermodynamically induced diastereomeric mixture of 2,4-dinitrosulfenyl sulfonamides [18] [ratio 75 : 25 (^{1}H NMR)], with a positive sign of optical rotation [$[\alpha]_D^{25}$ = + 162.4 (c = 0.26, CH_2Cl_2)], from which the configuration at the α-C-atom is assigned to be *S*.

In conclusion, with regard to the commercial availability of both (*S*) *and* (*R*)-**3** as chiral auxiliaries, the presented reaction sequence allows the preparation of 1-(2-fluorophenyl)-ethylamine (**1**), in either configuration from cheap achiral precursors, by simple synthetic procedures.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are corrected. IR-spectra were recorded on a Perkin-Elmer 1420 spectrometer. ^{1}H NMR and ^{13}C NMR-spectra were measured on Bruker WM 300 and AC 250 spectrometers using TMS as internal standard. Mass spectra were obtained on a Varian MAT CH-7. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The microanalyses were performed by the Microanalytical Laboratory of the University of Würzburg. Deactivated silica gel was obtained by treatment of silica gel (0.063-0.200 mm, Merck) with 10% conc. ammonia and subsequent conditioning.

(α*S*,1'*S*)-*N*-(1-Phenylethyl)-2-fluoro-α-methyl-phenylmethylamine-hydrobromide (**5a** · HBr)

A solution of 2.00 g (14.5 mmol) commercially available (Fluka) 1-(2-fluorophenyl)-ethan-1-one (**2**), 1.76 g (14.5 mmol) (*S*)-1-phenyl-ethylamine [(*S*)-**3**] and a catalytical amount of p-toluene sulfonic acid in 80 ml toluene is refluxed under a *Dean-Stark*-trap, until conversion is complete [*Note*: Due to the unsatisfactory chromatographic properties of the imine **4**, TLC-monitoring of the reaction is performed by reduction ($NaBH_4$, methanol) of an analytical amount of the reaction mixture and subsequent analysis]. The toluene is distilled off *in vacuo*, the residue is dissolved in dry ethanol and transferred into a nitrogen-flushed hydrogenation vessel. After addition of 0.5 g ethanol-washed *Raney*-nickel W2 (Janssen) hydrogenation is carried out in a Parr-shaker under a hydrogen pressure of 5 bar at room temperature. After 24 h, the catalyst is filtered off and the filtrate evaporated *in vacuo*. Column-chromatography of the residue on deactivated silica gel, using ether/petroleum ether (1:1) as eluent, yields the pure diastereoisomer **5a** (1.92 g, 55%) as free base. Treatment with aqueous hydrobromic acid gives the hydrobromide of **5a**, which crystallizes in beautiful rhombs from dichloromethane/petroleum ether.

m.p. 218 ^{O}C (subl.).

IR (KBr): ν = 2910, 2800 cm^{-1} (C-H), 2470 (NH_2^+), 1610, 1580 (C=C), 1440, 1375 (C-H), 1220 (C-F), 750, 695 (Ar-H).

^{1}H NMR (free base, 300 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.64 Hz, 3 H, CH_3 at α-C or H_3C-CH-Ph), 1.32 (d, J = 6.61 Hz, 3 H, CH_3 at α-C or H_3C-CH-Ph), 1.64 (br s, 1 H, NH), 3.53 (q, J = 6.64 Hz, 1 H, α-H o. H_3C-C*H*-Ph), 3.77 (q, J = 6.79 Hz, 1 H, α-H or H_3C-C*H*-Ph), 7.00 (ddd, J = 10.76 Hz, J' = 8.06 Hz, J'' = 1.13 Hz, 1 H, 3-H), 7.11 (ddd, J = 7.38 Hz, J' = 7.37 Hz, J'' = 1.28 Hz, 1 H, 5-H), 7.18 - 7.32 (m, 7 H, 4-H, 6-H and Ph-H).

MS (EI, 70 eV): *m/z* (%) = 243 (0.6) [M^+ - HBr], 228 (83) [243 - CH_3], 124 (76) [228 - C_8H_8], 123 (81) [243 - $C_8H_{10}N$], 106 (100) [C_7H_8N], 105 (96) [C_8H_9], 103 (64) [123 - HF].

$[\alpha]_D^{25}$ = - 45.6 (c = 0.50, methanol).

elemental analysis for	calc.:	C 59.27	H 5.91	N 4.32.
$C_{16}H_{18}FN$·HBr (324.24)	found:	C 59.23	H 6.11	N 4.36.

(*S*)-2-Fluoro-α-methyl-phenylmethylamine-hydrobromide (**1** · HBr)

A mixture of 500 mg (2.05 mmol) of the secondary amine **5a** (free base), 518 mg (8.22 mmol) ammonium formate and 50 mg 10% Pd-C in 50 ml methanol is refluxed for 30 min and cooled down. The catalyst is filtered off, the evaporated residue is chromatographed on deactivated silica gel with dichloromethane/methanol (100:2) as eluent, giving the free base **1** (225 mg, 79%) as oil. Treatment with aqueous hydrobromic acid yields the hydrobromide of **1**, in colourless needles, after recrystallization from ethyl acetate/petroleum ether.

m.p. 141 ^{O}C.

IR (KBr): ν = 3000 cm^{-1} (NH_3^+), 2890 (C-H), 1610 (NH_3^+), 1600, 1580 (C=C), 1443, 1370 (C-H), 1240 (C-F).

^{1}H NMR (250 MHz, $CDCl_3$/[D_5]pyridine 95 : 5): δ = 1.78 (d, J = 6.88 Hz, 3 H, CH_3 at α-C), 4.86 (q, J = 6.86 Hz, 1 H, α-H), 6.99 (ddd, J = 10.35 Hz, J' = 8.20 Hz, J'' = 1.31 Hz, 1 H, 3-H), 7.14 (td, J = 7.56 Hz, J' = 1.27 Hz, 1 H, 5-H), 7.26 (tdd, J = 7.74 Hz, J' = 5.44 Hz, J'' = 1.78 Hz, 1 H, 4-H), 7.75 (td, J = 7.60 Hz, J' = 1.76 Hz, 1 H, 6-H), 8.91 (br s, 3 H, NH_3).

^{13}C-NMR (62.5 MHz, $CDCl_3$): δ = 20.15 (q, CH_3 at α-C), 45.42 (d, α-C), 115.77 (dd, $^2J_{C,F}$ = 21.6 Hz, 3-C), 125.01 (dd, $^4J_{C,F}$ = 2.5 Hz, 5-C), 125.36 (ds, $^2J_{C,F}$ = 13.2 Hz, 1-C), 128.28 (dd, $^4J_{C,F}$ = 3.1 Hz, 6-C), 130.52 (dd, $^3J_{C,F}$ = 8.4 Hz, 4-C), 159.75 (ds, $^1J_{C,F}$ = 246 Hz, 2-C).

MS (EI, 70 eV): *m/z* (%) = 139 (0.4) [M^+ - HBr], 124 (100) [139 - CH_3], 122 (4) [139 - NH_3], 97 (18) [$C_6H_6F^+$].

$[\alpha]_D^{25}$ = - 2.1 (*c* = 1.50, methanol).

elemental analysis for	calc.:	C 43.66	H 5.04	N 6.36.
$C_8H_{10}FN \cdot HBr$ (220.08)	found.:	C 43.66	H 5.20	N 6.46.

ACKNOWLEDGEMENTS

We thank the BASF AG, Ludwigshafen, F.R.G., for a generous gift of 3. Financial support by the Fonds der Chemischen Industrie and skillful technical assistance by L. Kinzinger is gratefully acknowledged. J.-P. G. thanks for a graduate research fellowship of the University of Münster.

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