Tetrahedron Letters, Vol.30, No.3, pp 317-320, 1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ENANTIOMERICALLY PURE OXYGENATED 1-PHENYLETHYLAMINES FROM SUBSTITUTED ACETOPHENONES: BY REDUCTIVE AMINATION AND REGIOSPECIFIC BENZYLIC CLEAVAGE[1]

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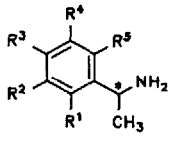
Abstract: An efficient method for the asymmetric synthesis of chiral, oxygenated 1-phenylethylamines (**1**) in essentially two steps is described. The substituted acetophenones **2** are reductively aminated with unsubstituted chiral 1-phenylethylamine ("PEA", **3**), *via* the corresponding imines **4**. These can directly be hydrogenated with high diastereoselectivities to the secondary amines **5**, which are obtained diastereomerically pure by simple recrystallization. The bis-benzylic amines **5** are cleaved astonishingly regioselectively by hydrogenolysis, leading to the desired primary amines **1**.

Substituted chiral 1-phenylethylamines deserve interest as enzyme inhibitors[2,3], as derivatizing agents for the analysis and/or resolution of enantiomeric mixtures[4], and as potentially improved reagents or catalysts in asymmetric synthesis[5]. Moreover, especially when bearing oxygen functions on the aromatic ring, 1-phenylethylamines are partial structures, and thus useful synthetic precursors[6], of important natural products, not only of simple 1-methyl-tetrahydroisoquinoline alkaloids[7], but also of more complex substances, such as naphthylisoquinoline alkaloids[8], tetrahydroprotoberberines[9], and certain antibiotics[10].



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Chiral primary 1-phenylethylamines [$\overset{*}{\text{Ar}}\text{CH}(\text{NH}_2)\text{CH}_3$] have been prepared *e.g.*

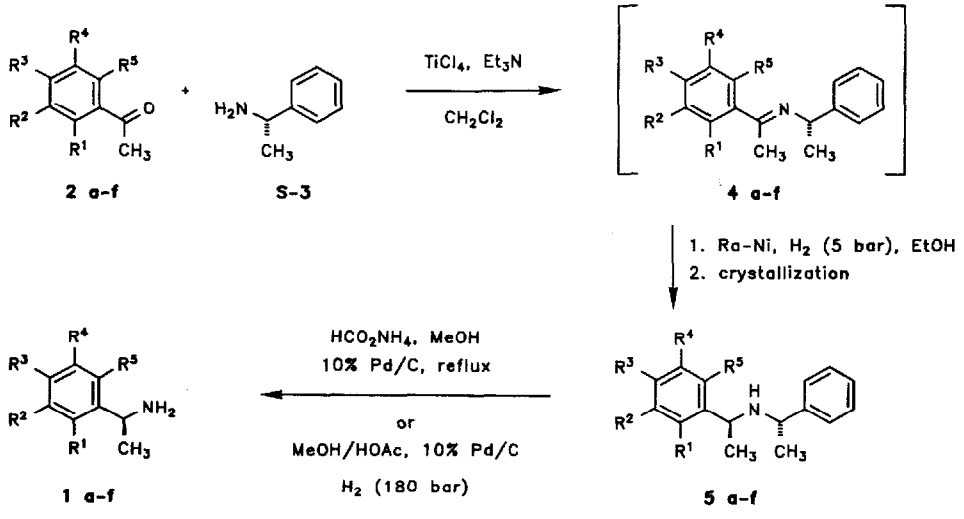
- by diastereoselective C-methylation of chirally modified benzaldimines[11] or hydrazones[12],
- by diastereoselective reduction of chirally modified acetophenone imines[13], as well as
- by enantioselective reduction of prochiral acetophenone imines[14] or oximes[15].

Most of these methods are hitherto hampered by the fact that the chiral auxiliary used is either not easily prepared or expensive, or available in only one configuration. And often, the enantiomeric excesses obtained are not at all satisfactory[13-15]. Practicable results have thus been achieved only for very few, simple examples, which moreover do not possess substitutents in the aromatic ring[16]. As a consequence, substituted chiral 1-phenylethylamines are normally still prepared by tedious enantiomer resolution of racemic material[17].

We now report the facile, high yield preparation of chiral phenylethylamines **1a-f**, with oxygen functions in the aromatic ring, by reductive amination of the corresponding acetophenones **2a-f**. The required chiral auxiliary, unsubstituted 1-phenylethylamine (**3**, "PEA"), is inexpensive as either enantiomer.

Highly stereoselective reductive aminations with PEA (**3**), using Raney nickel as a hydrogenation catalyst, have so far been described predominantly for the synthesis of amphetamines[18,19], as well as of cycloalkylamines[20,21]. For the reductive amination of acetophenones[22], an additional problem had to be envisaged and solved: the required regioselective cleavage of the intermediate unsymmetrical bis-benzylamines **5**.

Our procedure is summarized in Scheme 1. Formation of the imines **4** from **2** and **3** can very neatly be brought about using $TiCl_4$ as a Lewis acid and dehydration agent[23]. The imines **4a-f** do not need to be isolated, but can be reacted further without workup, thus simultaneously minimizing the risk of hydrolysis back to the starting materials. Hydrogenation (5 bar H_2, Raney nickel) of the crude imines **4** affords the secondary amines **5** in good chemical



1,2,4,5	R^1	R^2	R^3	R^4	R^5
a	OMe	H	H	H	OMe
b	H	OMe	OMe	OMe	H
c	OMe	OMe	OMe	H	H
d	$-OCH_2O-$		OMe	H	H
e	O^{i}Prop	OMe	OMe	H	H
f	OH	OMe	OMe	H	H

Scheme 1.

yields and high diastereoselectivities (ds) (^{1}H-NMR, see Table 1), which can still be upgraded to "100%" in favour of the main (S,S)-diastereomers **5a-f**[24], by simple recrystallization of their hydrobromides or hydroperchlorates.

compound	ds (%)[a]	yield (%)[b]	m.p. (°C)	$[\alpha]_D^{25}$ (MeOH)
5a·HBr	94	75	188	-24.7° (c = 1.0)
5b·HBr	92	73	243	-33.5° (c = 1.0)
5c·HBr	96	77	165	-64.3° (c = 0.5)
5d·HBr	95	83	203	-46.0° (c = 1.0)
5e·HBr	97	74	207	-44.0° (c = 1.0)
5f·$HClO_4$	95	77	59	-60.4° (c = 0.5)

Table 1. a) Determined by ^{1}H-NMR. b) Yield of isolated, diastereomerically pure product.

Subsequent hydrogenolytic cleavage of the bis-phenylethylamines **5** either by hydrogenation over Pd/C under high H_2 pressure or, more easily, by transfer hydrogenolysis[25] with ammonium formiate and Pd/C, occurs next to the less substituted aromate, exclusively. Thus, all the oxygenated amines investigated (**5a-f**) were regiospecifically debenzylated, to afford the desired primary amines **1a-f**[24] in excellent yields (see Table 2), no PEA (**3**) itself being detectable as a cleavage product. The denoted stereochemistry of the generated chiral centers of **1** is supported to be S by chiroptical[26] as well as chemical[27] methods.

compound	ee (%)[a]	yield (%)[b]	m.p. (°C)	$[\alpha]_D^{25}$ (MeOH)	config.[c]
1a·HBr	97	93	191	+4.3° (c = 1.0)	S
1b·HBr	95	98	228	-9.8° (c = 0.5)	S
1c·HBr	97	95 (96)	163	+1.1° (c = 1.0)	S
1d·HBr	97	98 (94)	207	+2.2° (c = 0.5)	S
1e·HBr	97	95	197	+2.9° (c = 1.0)	S
1f·HBr	86	93	104	+18.4° (c = 1.0)	S

Table 2. a) Measured enantiomeric excesses[28]; in comparison with the chiral auxiliary S-PEA (**S-3**) used (ee 95%), some of the optical yields formally exceed 100%, due to enantiomer enrichment during recrystallization. b) Obtained by transfer hydrogenolysis, yields in brackets are given for high pressure hydrogenolysis. c) When using PEA (**3**) in its S-form. All dinitrosulfenyl sulfonamides (cp. ref. 26) of **1** showed a positive sign of rotation.

In conclusion, combined with the good availability of both S- and R-PEA, the reductive amination of substituted acetophenones **2** bearing oxygen substituents proves to be a simple and reliable method for the preparation of a broad spectrum of enantiomerically pure[28] 1-phenylethylamines **1** of any desired configuration. Work to evaluate the synthetic and analytic utility of such primary amines **1**, is in progress.

ACKNOWLEDGEMENTS: We are indebted to Dipl.-Chem. J.R. Jansen for fruitful discussions. Furthermore, one of us (J.-P. G.) thanks the Ministry of Research of Nordrhein-Westfalen for a fellowship according to the Graduiertenförderungsgesetz. In addition, financial support from the Fonds der Chemischen Industrie is gratefully acknowledged.

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(Received in Germany 7 November 1988)