Tetrahedron Letters, Vol.32, No.49, pp 7175-7178, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A General Enantioselective Synthesis of α-Arylethylamines

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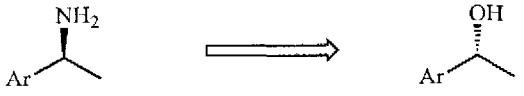
Key Words: acetophenones; enantioselective reduction; Mitsunobu reaction; α-arylethylamines.

Abstract: Optically active α-arylethylamines were prepared starting from acetophenones in ≥95%ee and ≥70% overall yield using oxazaborolidine catalyzed enantioselective reduction followed by the displacement of the hydroxy group by an azide group with clean inversion under Mitsunobu reaction conditions.

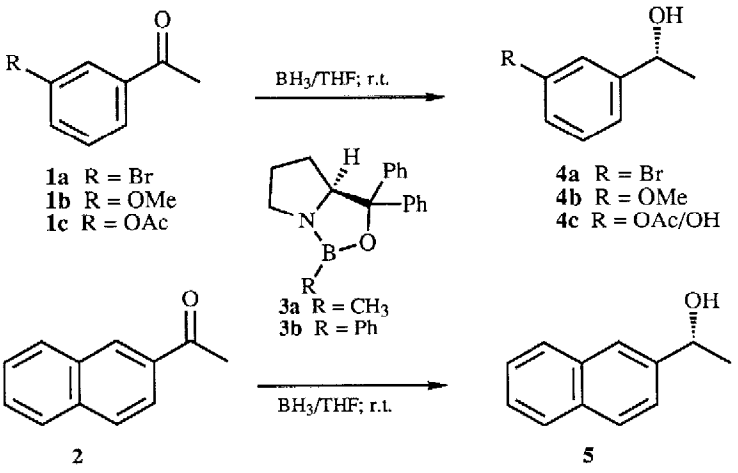
The use of enantiopure α-arylethylamines as intermediates in pharmacologically active compounds[1] prompted our interest in finding a general and an efficient method for their synthesis. Most of the reported methods involve either laborious resolution of amines or asymmetric reduction of imines or chirally modified imines with poor asymmetric induction.[2] Recent methods involving diastereoselective C-alkylation of chiral oxazolidines[3] or tetrahydro-1,3-oxazines[4] and diastereoselective reduction of Schiffs bases derived from acetophenones and chiral α-arylethylamines[2] use stoichiometric amounts of unrecoverable "chiral auxiliaries" thus making them inefficient. In the present work, we envisioned[5] the synthesis of α-arylethylamines using



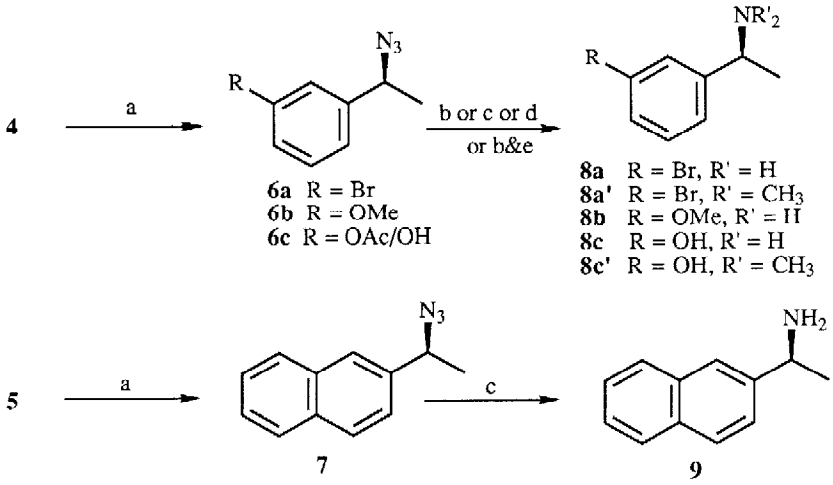
Scheme

the intermediacy of α-arylethanols (Scheme) which are easily accesible in both *R* and *S* forms from acetophenones by Corey's oxazaborolidine-catalyzed enantioselective reduction.[6]

The alcohols **4a-4c** and **5** that were used in the present study were made in high optical purities from the corresponding acetophenones using 0.1 equiv of *R*-oxazaborolidine **3a** as the catalyst and 0.8 equiv of BH_3 as the reducing agent in dry THF following the literature procedure.[6] The products were isolated in >90% yield and >95% *ee* (Table). There is room for further improvement of the optical yield by changing the substituent on boron in oxazaborolidine **3** from methyl to phenyl group.[7,8]



Next, the displacement of the hydroxy group with a nitrogen functionality with clean inversion was achieved under Mitsunobu reaction conditions,[9] by adding a solution of diethyl azodicarboxylate to a



a) $P\emptyset_3$, HN_3, $\emptyset CH_3$, DEAD; 0° C to r.t.; b) $P\emptyset_3$, THF, 2N HCl, r.t.; c) Pd/C, H_2, CF_3COOH; d) Raney Ni, HCHO, CF_3COOH, H_2, 60 psi, r.t.; e) 37% aq HCHO, HCOOH, reflux.

mixture of triphenylphosphine, α-arylethanol and HN_3 at 0° C; by standard work up, the corresponding azide[10] was isolated in quanitative yield.

Finally, the conversion of azides to the respective amines was achieved by one of the following methods. Treatment of the azide **6a** with triphenylphosphine in THF/2N HCl at room temperature[12] followed by the

Table

Comp. No.	$[\alpha]_D$ [a]	*ee* [b] (%)	Comp. No.	$[\alpha]_D$ [a]	Comp. No.	$[\alpha]_D$ [a]	*ee* [c] (%)	yield [d] %
4a	+29	96	**6a**	+42	**8a**	−16.7	95	85
4b	+35	97	**6b**	+99.4	**8b**	−19.7	97	93
4c	e	e	**6c**	e	**8c**	−77.6	>95	90
5	+28	96	**7**	+75.1	**9**	−19.7	95	87
					8a'	−42	>95	70
					8c'	−48.2	>95	75

a) $c = 1$ in methanol. b) Determined by HPLC analysis of Mosher esters. c) Determined by ^{1}H NMR using 1,1'-binaphthyl-2,2'-diylphosphoric acid (Ref. 11). d) Overall isolated yield based on starting acetophenone. e) Not measured as the product was partially hydrolyzed under the reaction conditions. In this case the mixture was carried through the subsequent steps during which time the hydrolysis was complete.

standard work up and chromatography gave amine **8a**. Compound **8a'** was prepared by the reductive methylation of **8a** with refluxing formic acid and 37% aq. formaldehyde solution. Amines **8b**, **8c**, and **9** were obtained by catalytic hydrogenation (Pd/C, H_2, CF_3COOH) of the azides **6b**, **6c** and **7** respectively. Dimethylamino derivative **8c'** was prepared from **6c**, (Raney Ni/HCHO/CF_3COOH, MeOH, H_2, 60 psi),[13] in one step.

In summary, an efficient method for the preparation of α-arylethylamines in >95% *ee* and in high yield was achieved using a recoverable chiral auxiliary as a catalyst for asymmetric induction in one of the key steps. Further modifications, we believe, could make this method an attractive one even for large scale purposes.

Acknowledgement: We thank Dr. M.J. Shapiro and his group for NMR measurements and Mr. L. Janaskie for HPLC determinations.

References and Notes:

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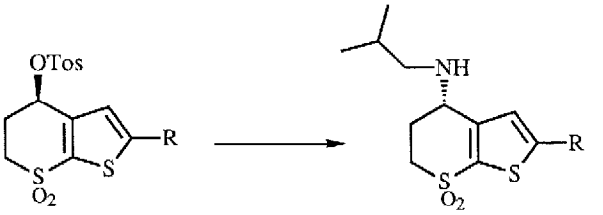
5. To our knowledge, this transformation is not reported in the literature. While our work was in progress, the Merck group (ref. 7) presented the following approach which is complementary to the one we presented in this communication.



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10. The displacement with the azide is an instantaneous reaction. Hydrazoic acid in toluene is made following the literature method (H. Wolff, *Organic Reactions*, Robert E. Krieger Publishing Company, Huntington, New York, **1975**, Vol. *3*, p. 327).

Hydrazoic acid is very poisonous and explosive, all reactions involving it should be carried out in a well-ventilated hood. If some hydrazoic acid has been inhaled accidentally, resulting in a feeling of pressure in the head, the drinking of a few ml of 96% alcohol has been suggested to relieve these symptoms. It has a pungent odor.

A typical procedure which is illustrated with example **4a** is as follows: To a stirred solution of **4a** (0.201g, 1mmol), triphenylphosphine (0.314g, 1.2 mmol), and hydrazoic acid (1.4 ml of 0.97 M solution in toluene, 1.3 eq) at 0°C, diethyl azodicarboxylate (0.209g, 1.2 eq) was added dropwise. The mixture was stirred for 2 h. at ambient temperature, diluted with water and extracted with EtOAc. The organic extracts were dried, evaporated and the residue thus obtained was chromatographed on SiO_2 to give the azide **6a** (0.224g, yield ~100%); IR (neat) 2101 cm^{-1}, MS (Isobutane/DCI): m/z(%) 227(4) - 225(4.7) (M^+), 200(75), 198(83), 185(93), and 183(100); NMR ($CDCl_3$): 7.42-7.7.55 (m, 2H), 7.2 7.3 (m, 2H), 4.58 (q, J = 7.5Hz, 1H), and 1.52 (d, J = 7.5Hz, 3H) ppm.

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13. The original method[14] for the reduction of azides to amines with Raney Ni was modified by the addition of 37% aq. formaldehyde solution to give the dimethylamino derivative.

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(Received in USA 21 August 1991)