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ALKYLATION OF N-TRIMETHYLSILYLATED PRIMARY AMINES WITH ARYLETHYLENE OXIDES. AN EFFICIENT SYNTHESIS OF 1-PHENETHANOLAMINES.

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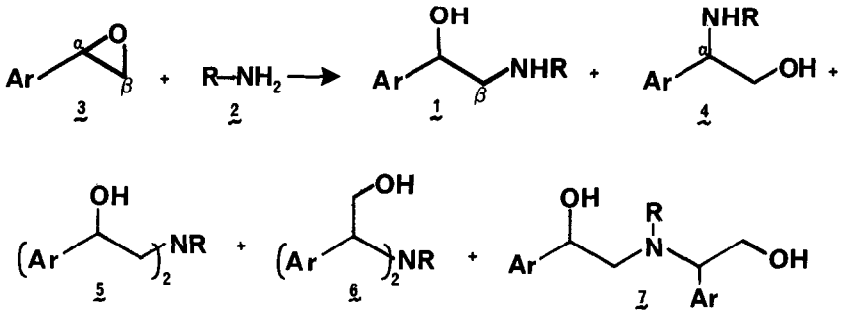
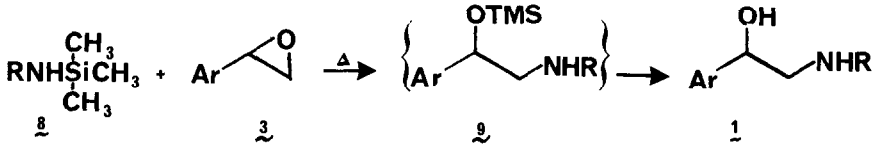
Summary: Reaction of unhindered N-trimethylsilylated primary amines with styrene oxide derivatives provides good yields of 1-phenethanolamines after acidic hydrolysis during work-up. This methodology results in much better conversions and higher yields when compared to direct equimolar alkylations.

In the course of preparing a series of chiral 1-phenethanolamines (1)[1] from the corresponding unhindered primary amines (2), we were posed with the problem of finding the most efficient and direct route for their preparation in optically pure form. Of the numerous classical methods for the synthesis of these pharmaceutically important substances, one of the most direct is the alkylation of the corresponding primary amine (2) with the readily available chiral arylethylene oxide (3).[2,3] Not unexpectedly, direct alkylations with equimolar amounts of 2 and 3 in polar, protic solvents generally gives low yields (ca. 20-50%) of the desired 1-phenethanolamine (1, "β-product") admixed with significant amounts of the 2-phenethanolamine (4, "α-product") and all possible corresponding products of bis-alkylation (5, 6, and 7). Moreover, isolation and purification is almost invariably tedious and difficult (equation 1).

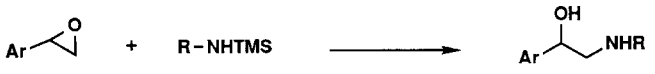


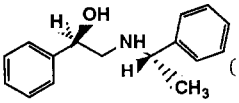
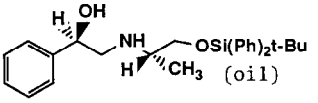
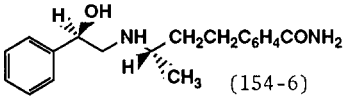
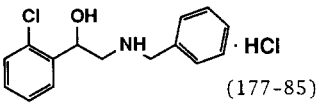
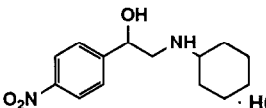
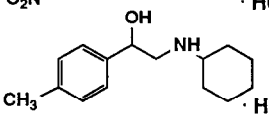
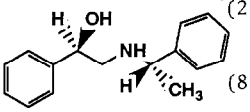
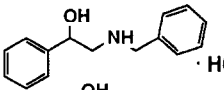
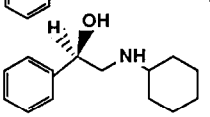
We describe herein mild and operationally simple methodology for this transformation while reducing the formation of undesired products. Reaction of the N-trimethylsilylated amine derivative (8, generated in situ) with 3 in dimethylsulfoxide at 50-75℃ followed by acidic hydrolysis of the intermediate ether 9 provides phenethanolamines in good yields (equation 2).[4,5]



In a typical experimental procedure (see Table) the amine 2 is added to dry DMSO under nitrogen followed by the addition of pure N-(trimethylsilyl)acetamide[6] (1.1 equivalents). After the silylation is complete (<30 min, 25°C) the styrene oxide derivative 3[7] (1.05 equivalents) is added and the solution is warmed (50-75℃) until maximal conversion into 9 is observed (see Table).[8] The mixture is poured onto ice and concentrated hydrochloric acid (>1.2 equivalents) and extracted once with ethyl acetate. The acidic aqueous layer is made basic with sodium hydroxide solution and the resulting free base is isolated by normal extractive methods with ethyl acetate and purified by recrystallization, chromatography on silica gel or by preparation of the hydrochloride salt as indicated in the Table. The exact scope and extensions of this process to mechanistically related reactions are under current investigation in these laboratories.

TABLE. PREPARATION OF PHENETHANOLAMINES



Ar =	R =	Conditions/ T(°C)/ t(h)/C(ml/g)	Product Isolated (mp °C)[a]	Yield
C_6H_5- (R)	$C_6H_5\overset{|}{C}HCH_3$ (S)	65/44/1.3	 (82-4)	80[b]
C_6H_5- (R)	TBDPSO$CH_2\overset{|}{C}HCH_3$ (S)	65/25/1.9	 (oil)	69[c]
C_6H_5- (R)	p-$H_2NCOC_6H_4CH_2CH_2\overset{|}{C}HCH_3$ (S)	75/15/1.4	 (154-6)	67[b] 80[d]
o-ClC_6H_5-	-$CH_2C_6H_5$	55/51/2.1	 (177-85)	77[e]
p-$C_6H_4NO_2$	-C_6H_{11}	65/22/2.2	 (240-5)	72[e]
p-$C_6H_4CH_3$	-C_6H_{11}	50/48/1.0	 (204-9)	65[e]
C_6H_5- (R)	$C_6H_5\overset{|}{C}HCH_3$ (S)	45/500/1.6	 (82-85)	79[b]
C_6H_5-	-$CH_2C_6H_5$	57/24/1.9	 (227-31)	61[e] 64[d]
C_6H_5- (R)	-C_6H_{11}	75/41/4.0	 (107-11)	74[b]

a) Compounds prepared gave correct combustion analysis and exhibited satisfactory spectral data (IR,UV,MS,OR, ^1H and ^{13}C NMR). A high degree of homogeneity was suggested by HPLC or GC as well as TLC. Reported melting points are uncorrected. b) Purified by recrystallization of the free base. c) Purified by silica-gel chromatography. d) Yield determined by HPLC versus a purified standard. e) Isolated and purified via the hydrochloride salt.

Acknowledgements

Helpful and stimulating discussions during various stages of this work from Profs. Dave Evans, Leo Paquette, Barry Sharpless, Ted Taylor, and Paul Wender are gratefully acknowledged. In addition, assistance from the Molecular Structure Research Division at Lilly Research Laboratories is appreciated.

References and Notes

1. Currently of interest as drug candidates for the treatment of obesity. Satellite Symposium of the 4th International Congress on Obesity. "Novel Approaches and Drugs for Obesity." New York City, New York, October 3-5, 1983.

2. For a recent review on epoxide chemistry see Smith, J. G. Synthesis 1984, 629.

3. Prepared from optically pure mandelic acid. Eliel, E. L.; and Delmonte, D. W., J. Org. Chem. 1956, 21, 596.

4. Control experiments indicate the α:β ratios are predominantly controlled by use of DMSO as reaction solvent and bis-alkylation products are supressed by silylation of the starting amine. More classical approaches, involve heating the oxirane with excess amine in a polar-protic solvent. See Möller, F., "Methoden der Organische Chemie," 4th ed., Vol. 11-1. Müller, E., Ed., Thiem-Verlag:Stuttgart, 1957; pp. 311-326.

5. For an account of somewhat similar chemistry see Andrews, G. C.; Crawford, T. C.; Contillo, L. G.; Tetrahedron Lett. 1981, 3803 and references therein.

6. N-(Trimethylsilyl)acetamide (MSA) was used as obtained from Aldrich Chemical Corporation. Other trimethylsilylation reagents [N,O-bis(trimethylsilyl)acetamide, N-(trimethylsilyl)imidazole, hexamethyldisilazane, and bis(trimethylsilyl)urea] gave essentially identical experimental results.

7. Styrene oxides employed herein were prepared by direct epoxidation of the corresponding styrenes with m-chloroperoxybenzoic acid derivatives or by the method of Guss. Guss, C. O., J. Am. Chem. Soc. 1952, 74, 2561.

8. Maximum yields of 1 (e.g. entry #1 in Table) are obtained when the DMSO concentration and reaction temperature are adjusted such that the intermediate silylether 9 phase separates during the course of the reaction.

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