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SYNTHESIS OF STERICALLY HINDERED 1-ARYLPYRROLIDINES AND 1-ARYLPIPERIDINES BY CONDENSATION OF PRIMARY AROMATIC AMINES WITH CYCLIC ETHERS OR DIOLS

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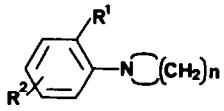
Abstract: A variety of 1-(o-alkylphenyl)- and 1-(o-o'-dialkylphenyl)-pyrrolidines and -piperidines were prepared by the gas phase alumina mediated condensation of tetrahydrofuran (THF), tetrahydropyran (THP) or the corresponding diols with primary aromatic amines in fair to high yield. This methodology can also be used for the synthesis of 1-phenylhexahydroazepine from aniline. A mechanistic interpretation of the catalytic action of alumina is presented.

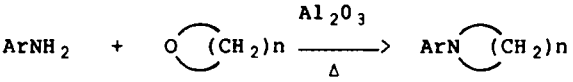
When a need arose to prepare several ortho- and di-ortho-alkylated N-phenyl-pyrrolidines and -piperidines 1 and 2 [2], methodology for such syntheses was found to be limited [3-5]. We now report that the gas phase, alumina-mediated reaction of primary aromatic amines with tetrahydrofuran (THF)[6,7] or



1 n = 4
2 n = 5

tetrahydropyran (THP)[8], (Scheme I) presents a general method for the preparation of a variety of highly hindered 1-aryl-pyrrolidines and -piperidines[9].

Scheme I.



n = 4,5,6

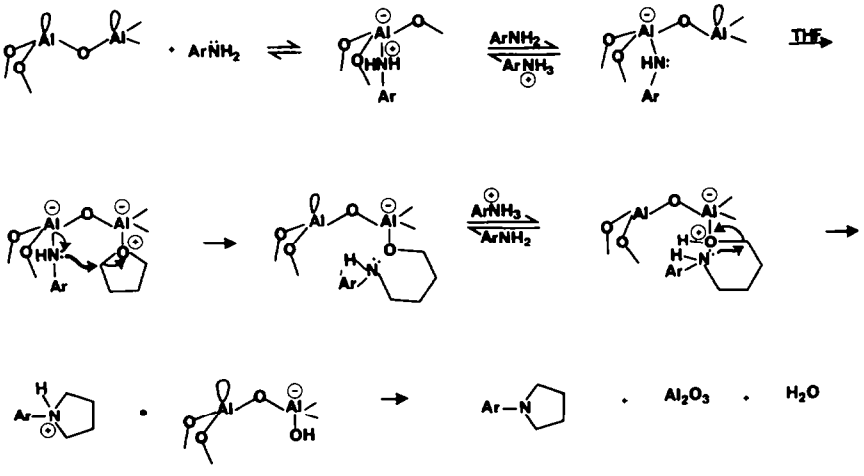
The observation that diols are converted to cyclic ethers over hot alumina[10] prompted us to investigate the effect of substituting 1,4-butanediol and 1,5-pentanediol for THF and THP respectively. The equivalence of the isolated yields (± 3%) of compounds **1b**, **2b**, **2d** and **2e**, prepared by both approaches, indicates that the diol and cyclic ether may be used interchangeably.

Extension of this method to the preparation of 1-phenyl-hexahydroazepine **3**, by condensation of aniline with either oxepane or 1,6-hexanediol resulted in the formation of a mixture of approximately 70% of 3 and 30% of 1-phenyl-2-methyl-piperidine. The ring contraction observed in this case is consistent with the concept of the adsorbed cyclic ether possessing oxonium ion character for its oxygen atom and being capable of undergoing carbonium ion type rearrangements[11]. The use of 1,6-hexanediol resulted in a substantial reduction in the overall yield of cyclic amine products obtained which is most likely due to the relative difficulty of cyclization to the 7-membered cyclic ether on the catalyst surface.

This methodology is not applicable to the synthesis of cyclic amines from *p*-chloro- or *p*-bromoaniline, due to loss of the halogen substituent on the catalyst surface and the resulting formation of complex mixtures. Neither was the reaction suitable for the sythesis of *N*-arylazetidines using oxetane, 2,2-dimethyl-1,3-propanediol or 3-hydroxypropylaniline due to the marked propensity for the formation of unsaturated, rather than cyclic, products.

The observations noted in this study, as well as the observations made by Bourns *et al*. in a related investigation[8], suggest a simple mechanism for these transformations which appears not to have been considered previously (Scheme II). This mechanistic interpretation accounts for all of the known facts about the reaction including the need to pre-heat the catalyst bed at 400°C to remove residual water (and thereby increasing the number of Lewis acid sites), the gradual degradation of the catalyst by the slow conversion of δ-alumina to corundum, and the advantage of using excess amine in the reaction[12].

Scheme II. Mechanistic Interpretation



This procedure provides for a simple efficient route to hindered 1-arylpyrrolidines and 1-arylpiperidines which are not accessible by other methodologies.

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and they, as well as reported boiling points are uncorrected. IR spectra were recorded on either Perkin-Elmer 710-B or 237-B spectrophotometers. ^{1}H NMR spectra were obtained on a Varian EM-360L spectrometer with tetramethylsilane as an internal standard. Mass spectra were run on a DuPont 21-490 spectrometer. All organic chemicals were commercially available used as received. Fisher Indicating Alumina (8-14 mesh) used as catalyst. The apparatus was of the same basic design as described by Bourns, Embleton, and Hansuld[8]. All new compounds were submitted to Galbraith Laboratories, Inc. for microanalysis, with satisfactory results within the usual limits (± 0.3%).

General Procedure: The catalyst was activated by heating at 400°C for 72 hours, followed by cooling to the desired reaction temperature. A 2:1 molar ratio (amine:cyclic ether or α,ω-diol) of mixed reactants was added dropwise (2 drops/sec.) to the column in a slow stream of nitrogen. The scale of the reaction was 0.5 to 0.25 mole in cyclic ether or diol. The gaseous products were condensed, and sodium chloride was added to salt out the organic material. The organic layer was separated, dried over sodium sulfate and fractionally distilled in vacuo through a 12 cm. Vigreux column. The unreacted starting amine was recovered, and the yield of product was calculated on the basis of the amount of starting amine consumed. The yields, specific conditions, physical properties and derivatives for each cyclic amine product are tabulated in Table I. Spectral data are presented in Table II.

Preparation of 1-Phenylhexahydroazepine,3: Using the general procedure outlined above, 102.1 g (1.1 moles) of aniline and 55.0 g (0.55 moles) of oxepane were condensed over alumina at 340°C. A 63% yield of a narrow boiling fraction containing approximately 70% 1-phenylhexahydroazepine and 30% 1-phenyl-2-methylpiperidine was obtained bp 71-74°C (0.3 mm). The isomeric impurity may be separated chromatographically (silica gel/pet. ether) to afford 1-phenylhexahydroazepine bp 76°C (0.3 mm) [Lit. [13] bp. 146-148°C (12 mm)]; HCl salt mp 194-196°C [Lit.[13] mp 194°C]; ^{1}H NMR (CCl_4): δ 1.53 (s broad, 8H), 3.35 (t, J=6 Hz, 4H), 6.25-6.63 (m,3H), 6.80-7.23 (m,2H); mass spectrum (40 eV), m/e (relative intensity): 175 (M+, 100), 146 (97). Use of the corresponding diol in place of the cyclic ether reduces the yield of product to ca. 25%. ^{1}H NMR absorptions corresponding to the isomeric impurity include a methyl doublet at δ 0.92 (J=6Hz), and partially resolved multiplets at δ 1.33 and δ 3.02. The structure of the major product was further verified by comparison with an authentic sample of 1-phenylhexahydroazepine prepared by an adaptation of the method of Bunnett and Brotherton[14]. To 4.29 g (0.11 mole) of freshly prepared sodium amide was added 16.9 mL (0.15 mole) of hexamethyleneimine. The resulting mixture was heated to ca. 100°C for 20 minutes after which time bromobenzene (7.86 g, 0.05 mole) was added dropwise. A vigorous reaction ensued with the evolution of ammonia, but the reaction subsided when all of the bromobenzene had been added. The resulting mixture was refluxed for 16 hours, cooled, and cautiously treated with 25 mL of water and 50 mL of benzene. The benzene layer was separated and washed with three 50 mL portions of 5% hydrochloric acid, and the combined acid extracts were made strongly basic with 20% sodium hydroxide solution. The oil which separated was extracted into ether, dried over sodium sulfate, filtered, concentrated and the oil distilled under reduced pressure to give 8.5 g (97% yield) of 1-phenylhexahydroazepine, bp 75-76°C (0.3 mm), having an NMR spectrum identical to that described above.

Acknowledgements: The authors gratefully acknowledge the gift of o-isopropylaniline and di-o-alkylanilines, furnished by Ethyl Corporation.

TABLE I. Reaction Conditions and Physical Constants for 1-Aryl Cyclic Amines

No.	R_1	R_2	Catalyst Temp.,°C	Alkylating Agent	% Yield[a]	BP,°C (mm)	n_D^{20}	Derivative MP,°C[b] Picrate	Methiodide
1a	CH_3	H	320	THF	68	58-59(0.5)[c]	1.5612[d]	101.5-102[e]	174-175 dec.
1b	CH_3	4-CH_3	275	THF	67	84-85(1.0)	1.5328	159-160.5	127.5-5-128
			275	Diol	69[f]				
1c	CH_3	5-CH_3	285	THF	75.5	78-79(0.7)	1.5552	149-150.5	164-164.5 dec.
1d	CH_3	6-CH_3	330	THF	55	125-127(20)[g]	1.5349[h]	154-155	79-80.5 dec.
1e	C_2H_5	6-C_2H_5	300	THF	47.5	74-74.5(0.45)	1.5282	155-156.5	i
1f	i-Pr	H	300	THF	77.6	57-58(0.3)	1.5412	108-109.5	159-159.5 dec.
1g	CH_3	6-i-Pr	290	THF	45.3	52 (0.2)	1.5250	160.5-162	i
1h	C_2H_5	6-i-Pr	290	THF	30.4	65-65.5(0.2)	1.5247	147-148.5	i
1i	C_2H_5	6-sec-Bu	300	THF	52.4	69.5-71.5(0.2)	1.5222	131-132.5 dec.	i
1j	CH_3	6-t-Bu	300	THF	0[j,g]				
2a	CH_3	H	340	Diol	50	61-62(0.5)[k]	1.5419[l]	153-154[m]	114-115 dec.
2b	CH_3	4-CH_3	340	THP	73	62-62.5(0.3)	1.5365	145-146.5	i
			340	Diol	75[f]				
2c	CH_3	5-CH_3	340	THP	68.2	58-60(0.3)	1.5348	n	
2d	CH_3	6-CH_3	340	THP	30	58(0.3)	1.5361	106-108 dec.	i
			340	Diol	33[f]				
2e	C_2H_5	6-C_2H_5	340	THP	22[o]	87.5(0.5)	1.5252	i	p
			340	Diol	19[f,o]				
2f	i-Pr	H	350	THP	80	54.5-56(0.3)	1.5289	140.5-142	i

a. Yield based on amine consumed. b. Picrates recrystallized from 95% EtOH; methiodides recrystallized from 1:4 EtOH/EtOAc. c. Lit[3b] bp 114°C (11 mm). d. Lit.[3b] n_D^{20} 1.5593. e. Identical to lit value [6a] f. Spectral and physical properties of products identical with productes synthesized with cyclic ether. g. Lit.[3b] bp 110°C (9mm). h. Lit [3b] n_D^{25} 1.5328. i. No crystalline product obtained. j. Approximately 35% yield of o-toluidine,5% yield of N-(o-tolyl)pyrrolidine and considerable amounts of polymeric residue obtained. k. Lit[8] bp 65-66°C (0.6 mm). l. Lit.[8] n_D^{25} 1.5392. m. Lit. mp 153.8-154[8]. n. No picrate or methiodide obtained; hydrochloride salt mp 177-178°C acetone). o. Product purified by preparative TLC followed by distillation at reduced pressure. p. Not attempted.

TABLE II. Spectral Data for 1-Aryl Cyclic Amines

No.	^{1}H NMR (CCl_4), δ(J,Hz)	IR (neat), cm^{-1}(intensity) νC-N(aliphatic)- νC-N(aromatic)	
1a	1.70-2.03(m,4H),2.24(s,3H),3.08 (t,J=7Hz,4H), 6.50-7.14(m,4H)	1189 (m)	1314 (s)
1b	1.70-2.04(m,4H),2.19(s,6H),3.03 (t,J=7Hz,4H),6.67-6.88(m,3H)	1210 (m)	1320 (s)
1c	1.70-2.03(m,4H),2.21(s,3H),2.25(s,3H), 3.08(t,J=7Hz,4H),6.39-6.62(m,2H)	1192 (m)	1315 (s)
1d	1.79-2.12(m,4H),2.24(s,6H),3.18 (t,J=7Hz,4H),6.93-7.12(m,3H)	1192 (s)	1315 (s)
1e	1.19(t,J=8Hz,6H),1.81-2.15(m,4H),2.57 (q,J=8Hz,4H),3.17(t,J=7Hz,4H),6.94(s,3H)	1193 (m)	1360 (s)
1f	1.20(d,J=7Hz,6H),1.80-2.15(m,4H),3.02(t, J=7Hz,4H),3.46(hept.,J=7Hz,1H),6.85-7.42 (m4H)	1183 (m)	1355 (m)
1g	1.15(d,J=7Hz,6H),1.80-2.15(m,4H),2.17(s, 3H),3.15(t,J=7Hz,4H),3.12(hept.J=7Hz,1H), 6.78-7.07 (m,3H)	1187 (m)	1355 (m)
1h	1.17(c,J=Hz,6H),1.20(t,J=7Hz,3H),1.85- 2.15(m,4H),2.58(q,J=7Hz,2H),3.17(t,J=7Hz, 4H),3.20(hept.J=7Hz,1H),6.98(s,3H)	1170 (m)	1350 (m)
1i	0.63-1.00(m,3H),1.22(t,J=7Hz,6H),1.40- 1.75 (m,4H),2.52(q,J=7Hz,2H),3.03 (hept, J=7Hz,1H),3.18(t,J=6Hz,4H),6.98(s,3H)	1163 (m)	1345 (m)
2a	1.35-1.87(m,6H),2.24(s,3H),2.78(t, distorted,4H),6.60-7.17(m,4H)	1225 (s)	1374 (s)
2b	1.38-1.90(m,6H),2.19(s,6H),2.75(t, distorted,4H),6.69-6.92(m,3H)	1227 (s)	1380 (s)
2c	1.34-1.87(m,6H),2.19(s,3H),2.24(s,3H), 2.77(t,distorted,4H),6.49-7.01(m,3H)	1247 (s)	1385 (s)
2d	($CDCl_3$)1.53-1.91(m,6H),2.27(s,6H),3.05 (t,distorted,4H),6.94-7.18(m,3H)	1215 (s)	1385 (s)
2e	1.18(t,J=8Hz,6H),1.42-1.87(m,6H),2.58 (q,J=8Hz,4H), 3.02(t,distorted,4H),6.93(s,3H)	1214 (m)	1364 (m)
2f	1.18(d,J=7Hz,6H),1.45-1.85(m,6H),2.77(t, distorted,4H),3.45(hept,J=7Hz,1H,6.78- 7.25(m,4H)	1217 (s)	1375 (m)

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9. The only unsuccessful case encountered in this study occurred with 2-methyl-6-t-butylaniline **1j**, which eliminated 2-methylpropene under the reaction conditions, to yield N-(2-methyl-phenyl)pyrrolidine upon subsequent reaction with THF. This elimination presumably arises via a cyclic transition state involving β-hydrogen abstraction by the nitrogen in an intermediate aluminoanilide (cf: Ecke, G.G.; Napolitano, J.P.; Filbey, A.H.; Kolka, A.J. J. Org. Chem. **1957**, 22, 639).

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