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A GENERAL SYNTHESIS OF DIBENZ[C,F]-1-AZA-BICYCLO[3.3.1]-NONANE AND ITS RELATED COMPOUNDS

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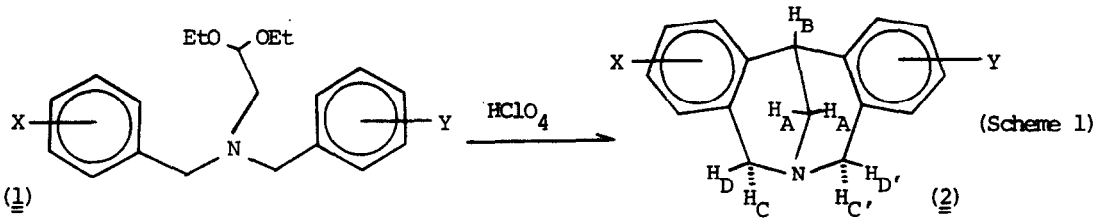
Previous reports describe the acid-catalyzed Friedel-Crafts-type intramolecular cyclization reactions of N-(1,2-diphenylethyl)-aminoacetaldehyde dialkylacetals,[1a,b] N-benzyl-N-phenethyl-aminoacetaldehyde dialkylacetals,[1b] and N,N-dibenzyl-aminoaldehyde dialkylacetals,[1c] of which two benzene rings are each substituted para to the cyclization position with electron donating activating group such as methoxy. We wish to describe here N,N-dibenzyl-aminoacetaldehyde diethylacetals(1), by employing 70% perchloric acid as cyclization catalyst, are effectively double-cyclized to give pharmacologically active dibenz[c,f]-1-aza-bicyclo[3.3.1]-nonanes(2)[2] in high isolated yields without need for electron releasing substituents and indeed, even when electron withdrawing groups such as chlorine or fluorine are present[3] (Scheme 1).



(1) (2) (Scheme 1)

1a: X=3,4-OCH_2O-, Y=H; 1b: X=3-OCH_3, Y=H
1c: X=H, Y=H; 1d: X=3-Cl, Y=3'-Cl; 1e: X=3-F, Y=3'-F

In a typical procedure, compound 1c(1 mmole) was dissolved in 1 ml of 70% $HClO_4$[4] at ca.-30°C and the reaction mixture was allowed to stand overnight at room temperature. The perchlorate of 2(X=Y=H) precipitated,[5] was collected(the yield of the perchlorate was quantitative and its purity was proved by an elemental analysis without further purification), basified with aq. NaOH, followed by extraction with dichloromethane. The resulted dichloromethane solution was concentrated and the residue was chromatographed on a short alumina column to give 2(X=Y=H)(mp 133-4°, 95%).

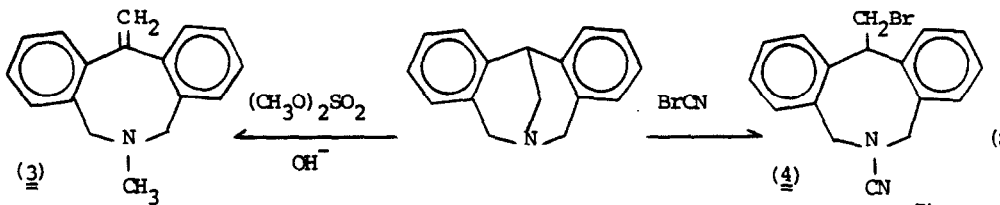
The yields and NMR assignments of the products(2) in Scheme 1 are listed in Table I.

Furthermore, in addition to such efficient double-cyclizations of 1, the product(2)(X=Y=H) was derived to 3 and 4 by Hofmann and von Brown degradations respectively (Scheme 2).

3, mp 60-62° NMR (δ , in $CDCl_3$) 2.32(3H, s), 3.57(4H, s), 5.38(2H, s), 6.95-7.65(8H, m).

4, mp 185-187°(decomp.) IR(KBr) 2195 cm^{-1}(C≡N), NMR (δ , in $CDCl_3$) 4.21(2H, d, J=8.0 Hz), 4.33(2H, d, J=16.0 Hz), 4.73(2H, d, J=16.0 Hz), 4.86(1H, t, J=8.0 Hz), 7.05-7.45(8H, m).

Both transformations provide useful synthetic entries into the dibenz[c,f]azocine derivatives which also have pharmacologically interesting properties.[6]



(Scheme 2)

Table I Reactions of N,N-Dibenzyl-aminoacetaldehyde diethylacetals(1)[7] with $HClO_4$

1			2		NMR (δ , $CDCl_3$) of 2					
					H_A(doublet)	H_B(triplet)	H_C(doublet)	H_D(doublet) [H_C'(doublet)	H_D'(doublet)]	
X	Y	yield(%)*a		mp(C)	J_{AB}(Hz)			J_{CD}(Hz)		
3,4-OCH_2O-	H	72	(2a)	150-1°	3.33	2.1	3.58	3.80 [3.90	17.5	4.46 4.58]
3-OCH_3	H	80	(2b)	oil	3.33	2.4	3.62	3.84 [3.84	17.5	4.58 4.58] *c
H	H	95	(2c)	133-4°	3.38	1.8	3.73	3.93	17.5	4.57
3-Cl	3'-Cl	33, 82*b	(2d)	160-1°	3.34	2.0	3.69	3.89	17.5	4.52
3-F	3'-F	87*b	(2e)	166-8°	3.33	1.5	3.71	3.88	17.5	4.54

*a) The isolated yield shown was unoptimized. All products gave correct elemental analyses and mass spectra. *b) After standing overnight at room temperature, the reaction mixture was heated at 70-80°C for 1 hr. *c) The signals were overlapped each other and broadened slightly.

Further studies along the scope and the limitation of the strong acid catalized double-cyclization reactions are in progress.

References and Notes

1) S.F.Dyke, Advance in Heterocyclic Chem., 14, 279 (1972); J.M.Bobbitt, ibid., 15, 99 (1973). 1a) A.R.Battersby, and D.A.Yeowell, J. Chem. Soc., 1988 (1958). 1b) D.W.Brown, S.F.Dyke, G.Hardy, and M.Sainsbury, Tetrahedron Lett., 2609 (1968); 1515 (1969); D.W.Brown, S.F.Dyke, and M.Sainsbury, Tetrahedron, 25, 101 (1969); M.Sainsbury, D.W.Brown, S.F.Dyke, and G.Hardy, ibid., 25, 1881 (1969). 1c) J.M.Bobbitt, and S.Shibuya, J. Org. Chem., 35, 1181 (1970).

2) Compound 2(X=Y=H) displayed a remarkable antihistaminic activity(our unpublished result).

3) The reaction of 1(X=4-NO_2 , Y=H) in 70% $HClO_4$ at 70-80°C was complex, but in CF_3SO_3H at room temperature afforded double-cyclized product(2) in 65% yield.

4) When less than 60% $HClO_4$ was employed, the double-cyclization reaction did not proceed.

5) When necessary, the reaction mixture was cooled in a refrigerator for a while.

6) S.Casadio, G.Pala, E.Crescenzi, E.M.Uberti,G.Coppi, and C.Turba, J. Med. Chem., 11, 97 (1968)

7) Symmetrical 1 (X=Y) were synthesized by the reactions of $NH_2CH_2CH(OEt)_2$ with 2 equiv. of (substituted)benzylhalogenides in boiling aq. alcohol in the presence of K_2CO_3(yields, 80%<). Unsymmetrical 1 (X≠Y) were prepared by the condensation of (substituted)benzaldehydes with $NH_2CH_2CH(OEt)_2$, catalytic hydrogenation, followed by the reactions with the corresponding benzylhalogenides (yields, 70%<). All compounds of 1 gave correct NMR and mass spectra.