DOUBLE-CYCLIZATION REACTIONS OF 1-DIBENZYLAMINO-2-PROPANONE AND RELATED COMPOUNDS

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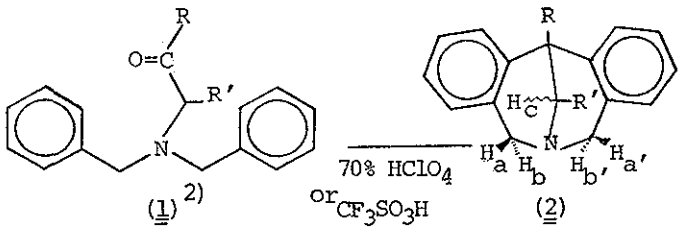
1-Dibenzylamino-2-propanone and its 1-methyl derivative, 2-benzylamino-1-cyclohexanone, 2-benzylamino-1-cyclopentanone, and N,N-dibenzyl-p-X(X=H,Br,NO_2)-phenacylamine, by employing 70%-perchloric acid or triflic acid as cyclization catalyst , afforded 1-aza-5-methy-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene and its 9-methyl derivative, 1-azadibenzo[h,m]tricyclo-[5.3.3.$0^{2,7}$]trideca-8,12-diene, 1-azadibenzo[g,l]tricyclo-[4.3.3.$0^{2,6}$]dodeca-3,6-diene, and 1-aza-5-p-X(X=H,Br,NO_2)-phenyldibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene, in 74-95% isolated yields, respectively.

We reported[1] recently that the perchloric acid catalyzed double-cyclization reactions of N,N-dibenzylaminoacetaldehyde diethylacetals gave pharmacologically active 1-azadibenzo[c,f]-bicyclo[3.3.1]nona-3,6-diene in high isolated yields, independent of the nature of the substituents on the aromatic ring.

In the course of our studies on the enlargement of the scope of the strong acid catalyzed double-cyclization reactions, we wish to describe here the first successful example of the double-cyclization reactions of dibenzylaminoketones(1) with a variety of substituent, by employing 70%-perchloric acid(70-80°C, 3 hrs) or triflic acid(room temperature, overnight) as cyclization catalyst (Scheme 1).



(Scheme 1)

	R	R'
a:	CH_3	H
b:	CH_3	CH_3
c:	$-(CH_2)_4-$	
d:	$-(CH_2)_3-$	
e:	Ph	H
f:	Ph(p-Br)	H
g:	Ph(p-NO_2)	H

Typically, 1-dibenzylamino-2-propanone(1a)(1 mmol) was dissolved in perchloric acid(1 ml) at below 0°C, the reaction mixture was allowed to stand overnight at room temperature, then heated, and cooled. The resulting precipitates of perchlorate of 2a were collected, basified with aq. sodium hydroxide, followed by extraction with dichloromethane. The extracted solution was evacuated and the residue was chromatographed on an alumina column affording 1-aza-5-methyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene(2a)(mp. 124-5°C) in 75% yield. In a similar way, 1-aza-5,9-dimethyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene(2b)(mp.71-2°C) and 1-aza-dibenzo[h,m]tricyclo[5.3.3.$0^{2,7}$]trideca-8,12-diene(2c)(bp.163-6°C /0.005Torr, $HClO_4$salt; mp.≥300°C) were isolated from the reactions of the corresponding 1-dibenzylamino-1-methyl-2-propanone(1b) and

2-dibenzylamino-1-cyclohexanone(2c), in 80% and 92% yield, respectively.

Furthermore, 2-benzylamino-1-cyclopentanone(1d), by using triflic acid,[3] was efficiently double-cyclized to 1-azadibenzo[g,l]-tricyclo[4.3.3.$0^{2,6}$]dodeca-7,11-diene(2d) (mp.161-2°C) in 95% yield, whereas the reaction in perchloric acid was not smoothly undergone double-cyclization affording 2d as a minor product(20%>) and a single-cyclized product(2d')[4] was isolated in 60% yield.

Finally, the reaction of N,N-dibenzyl-phenacylamine(1e)[5] in triflic acid resulted in 95% yield of 1-aza-5-phenyl-dibenzo[c,f]bicyclo[3.3.1]nona-3,6-diene(2e) (mp.138-9°C), and in the same way, N,N-dibenzyl-p-bromo(1f) and -p-nitro-phenacylamine(1g) gave 1-aza-5-

Table 1 NMR Assignment of Double-Cyclization Products(2)

Comp.*1)	H_a(d)	J_{ab}(Hz)	H_b(d)	$H_{a'}$(d)	$J_{a'b'}$(Hz)	$H_{b'}$(d)	H_c	H_{others}
2a	4.69	(17.5)	3.95				3.26(s,2H)	1.72(s,3H)
2b	4.67	(17.5)	3.98	4.59	(17.5)	3.83	3.30(q,1H)	1.73(s,3H) 1.18(d,J=7Hz,3H)
2c*2)	4.68	(1.75)	3.95	4.57	(17.5)	3.82	3.24(m,1H)	3.11(m,1H) 1.2-1.9(m,7H)
2d*2)	4.73	(17.5)	4.07	4.60	(17.5)	3.89	3.41(m,1H)	2.85(m,1H) 1.4-2.1(m,5H)
2e	4.73	(17.5)	3.97				3.34(s,2H)	
2f	4.72	(17.5)	3.97				3.31(s,2H)	
2g	4.74	(17.5)	3.99				3.34(s,2H)	

*1) 2a-2g(2c: $HClO_4$ salt) gave correct mass spectra and elemental analyses.

*2) ^{13}C-NMR(gated decoupled,ppm down field from TMS, in $CDCl_3$);

2b: 15.50(C_9-CH_3,q), 20.46(C_5-CH_3,q), 36.56(C_5,s), 57.72($C_{2\text{ or }8}$,t), 58.15(C_9,d), 60.26($C_{2\text{ or }8}$,t).

2c: 22.05 25.89 27.95 31.85(-(CH_2)$_4$-), 36.89(C_7,s), 53.64($C_{10\text{ or }11}$,t), 60.07(C_2,d), 60.26($C_{10\text{ or }11}$,t).

p-bromo(2f) (mp.157-8°C) and -p-nitro-phenyl-dibenzo[c,f]bicyclo-[3.3.1]nona-3,6-diene(2g) (mp.236-7°C), in 95% and 74% yield, respectively.

The structures of 2a- 2g depicted in Scheme 1 were identified by their NMR spectra shown in Table 1.

In conclusion, a general synthesis of pharmacologically active 2a and related compounds from the corresponding N,N-dibenzylamino-ketones was achieved.

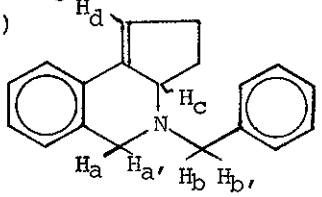
References and Notes

1) H.Takayama, M.Takamoto, and T.Okamoto, Tetrahedron Lett., 1307 (1978).

2) 1a(bp.110-115°C/0.005Torr), 1e(mp.81-2°C), 1f(mp.87-8°C) and 1g(mp.167-8°C) were prepared by the reactions of dibenzylamine with CH_3COCH_2Br, $PhCOCH_2Br$, p-Br and p-NO_2-$PhCOCH_2Br$ in 75-90% yields, respectively. 1b(bp.120-2°C/0.003Torr), 1c(mp.104-5°C) and 1d(mp.74-4°C) were synthesized by the reactions of dibenzylamine with 3-hydroxy-2-butanone, 2-hydroxy-1-cyclohexanone, and 2-hydroxy-1-cyclopentanone, in 50-75% yields. All of them gave acceptable NMR and Mass spectra.

3) In a typical procedure, 1d(1 mmol) was dissolved in triflic acid(1.5g,10mmol) at below 0°C and the reaction mixture was allowed to stand overnight at r.t, poured into cracked ice, basified with aq.NaOH, followed by extraction with CH_2Cl_2. After an usual work up, 2d was isolated.

4) 2d': oil, m/e 261(M^+) 170(M-(C_6H_5-CH_2)), NMR(δ, in $CDCl_3$) 1.68-2.68(4H,m,-(CH_2)$_2$-) 3.13(1H,d,J=13Hz,$H_{a \text{ or } a'}$) 3.34(1H,d,J=15Hz,$H_{b \text{ or } b'}$) 3.49(1H,t,J=6.8Hz,H_c) 3.72(1H,d,J=15Hz,$H_{b \text{ or } b'}$) 4.12(1H,d,J=13Hz, $H_{a \text{ or } a'}$) 6.12(1H,dd,J=5 and 2.5Hz,H_d) 6.83-7.65(9H,m).



5) Hot 70%-$HClO_4$ was not effective, 1e-1g were recovered quantitatively.

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