Tetrahedron Letters,Vol.30,No.17,pp 2191-2194,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

CYCLIZATION OF ELECTROCHEMICALLY GENERATED NITROGEN RADICALS. A NOVEL SYNTHESIS OF 11-SUBSTITUTED DIBENZO[a,d]CYCLOHEPTENIMINES

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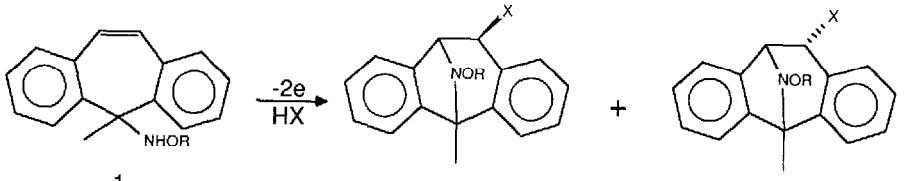
Abstract: A convenient synthesis of 11-substituted dibenzo[a,d]cycloheptenimines proceeding via annelation of electrochemically generated nitrogen radicals is described.

The last four years have seen the development of several new cyclization methods based on the addition of carbon radicals to alkenes.[1] Cyclization of nitrogen based radicals, on the other hand, are less common. Examples include cyclization of olefinic aminium cation radicals generated by the homolysis of N-chloroamines[2a,b] or by the Barton reaction[2c]. A radical chain mechanism was postulated for the annelation of unsaturated hydroxylamines.[3] In this paper we report a novel cyclization based on oxidative addition of aminium radicals to olefins. The two-electron process is initiated by anodic oxidation of a suitably substituted hydroxylamine and is terminated by the nucleophilic solvent. This cyclization was specifically designed for the synthesis of the racemate of the 11-hydroxy metabolite (9)[4a] of the important N-methyl-D-aspartate receptor antagonist MK-0801.[4b]



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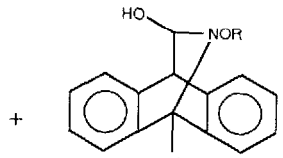

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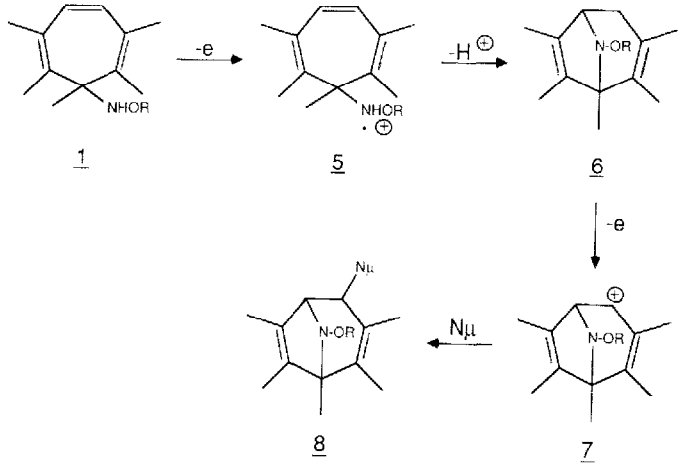
	R	X	Conditions	Yield of 2
a	CH_3	OH	THF, H_2O, $NaBF_4$	55%
b	$COCH_3$	OH	"	70%
c	COOtBu	OH	"	70%
d	CH_3	OCH_3	MeOH, THF, $NaBF_4$	40%
e	CH_3	$OCOCH_3$	CH_3COOH, KOAc	73%
f	CH_3	$NHCOCH_3$	CH_3CN, $NaBF_4$	30%

Anodic oxidation of methoxylamine 1a[5] in aqueous THF afforded the desired exohydroxy derivative racemic 2a in 55% yield in 85% coulombic efficiency, along with two by-products: 3a (7%) and 4 (R = CH_3, 12%). Preparative scale experiments (1-10 g) were conducted at constant potential of 1.2V, in a beaker with a carbon felt anode and a stainless steel cathode. These conditions were based on linear sweep voltametry which indicated a half-wave potential for 1a at 1.3V. For larger preparations (75 g) the current density was controlled at 50-80 mA/cm^2. Acyl hydroxylamines[5] 1b and 1c also serve as starting material providing 2b and 2c in 70% yield. In these cases, however, by-products analogous to 4 were not observed.

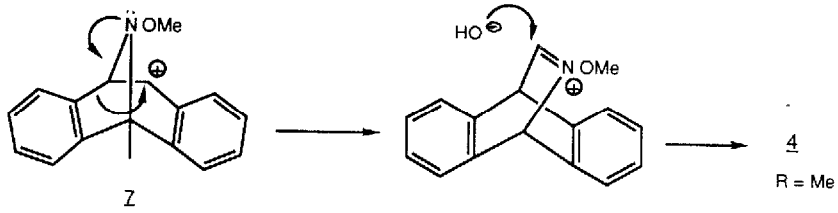
Other nucleophilic solvents can also terminate the reaction. Thus oxidation of 1a in methanol, acetic acid and acetonitrile afford the analogous methoxy (2d), acetoxy (2e) and acetamido (2f) derivatives. An O-substituted hydroxyamine is essential for this cyclization. The unsubstituted hydroxylamine (1, R = H) and the amino (1, H replaces OR) derivatives did not react analogously.

We propose the following mechanistic pathway for the cyclization: anodic, one-electron oxidation generates the radical cation 5 which adds



rapidly to the double bond. The electron rich carbon radical thus produced (6) is readily oxidized to carbocation 7. Selective nucleophilic attack on 7 from the less hindered exo side leads to the observed product 8. Inherent to the success of this sequence is the fact that the electron rich carbon radical (6) is oxidized more readily than the electrophilic nitrogen radical 5. This sequence is electronically and functionally equivalent to the reaction of electrophilic carbon radicals with olefins.[6]

The major by-product 4, is clearly the result of a rearrangement of the intermediate carbocation 7 as shown. We have reported earlier the non-oxidative, thermal and base catalyzed cyclization of 1 (R = H) and 1a leading to 2 (X = H, R = H or CH_3)[5]. Even though a radical mechanism has been postulated for this type of ring closure[3], the relationship with our current reaction is not clear.



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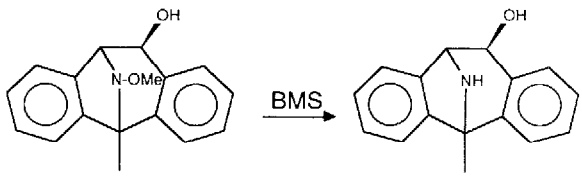
The synthesis of racemic 9 was completed by reductive cleavage of the methoxyl group of 2a. This was accomplished by reaction with an excess of borane-methyl sulfide, followed by hydrolysis with methanolic sulfuric acid. The overall isolated yield of electrochemical annelation and demethoxylation was 50%. Resolution provided the optically pure d-isomer.[8]



2a 9

Acknowledgements: We thank Mr. R.A. Reamer and Ms. L.DiMichele for their help in the identification of new compounds, Drs. L.F. Colwell and H.G. Ramjit for the mass spectra and Dr. R.D. Larsen for useful suggestions.

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7. ^{1}H NMR ($CDCl_3$) 2a (syn & anti.) δ 2.01, 205 (2 singlets, 3H total), 3.67, 3.73 (2 singlets, 3H total); 4.41, 4.68 (2 doublets, 1H total, J=12 Hz each) 4.82, 5.05 (2 doublets, 1H total, J=1 Hz each) 7.05-7.45 (m,8H). 4 2.18 (s,3H), 3.70 (s,3H), 4.34 (d,1H,J=3 Hz) 4.68 (s, 1H) 7.05-7.46 (m,8H). 9 1.91 (s,3H), 4.44 (d,1H,J=1 Hz), 4.59 (d,1H, J=1 Hz) 7.15-7.40 (m,8H). The active protons (NH, OH) are broadened into the baseline.
8. Resovled with di-p-toluoyl-D-tartaric acid and isolated as the maleate salt, $[\alpha]_D$ (+) 109.2° (C=1 in methanol), by R.D. Larsen and P.J. Reider of these laboratories.

(Received in USA 6 February 1989)