Pergamon

Tetrahedron Letters, Vol. 36, No. 23, pp. 3981-3984, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00693-1

DECYCLOPROPYLATION OF 1-CYCLOPROPYL-4-HYDROXY-4-(2-METHYLPHENYL)PIPERIDINE N-OXIDE

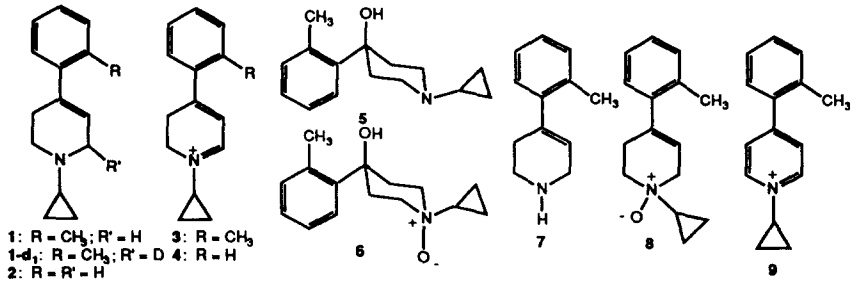
You-Xiong Wang and Neal Castagnoli Jr.*
Department of Chemistry
Virginia Tech, Blacksburg, VA 24061

Summary: Treatment of 1-cyclopropyl-4-hydroxy-4-(2-methylphenyl)piperidine N-oxide with trifluoroacetic anhydride (TFAA) yields the corresponding descyclopropyl secondary amine in excellent yield. This reaction may serve as a model for the mechanism based inactivation of monoamine oxidase B (MAO-B) by cyclopropylamines which recently has been proposed to proceed via a polar mechanism involving a flavin-amine adduct.

Monoamine oxidase (MAO-B) catalyzes the transformation of 1-cyclopropyl-4-(2-methylphenyl)-1,2,3,6-tetrahydropyridine (**1**) to a metabolite displaying UV spectral characteristics (λ_{max} 335 nm) expected for the corresponding 1,2-dihydropyridinium species **3**.[1] This result is not consistent with the generally accepted radical catalytic pathway for MAO-B catalysis[2] in which cyclopropylamines act as mechanism based inactivators rather than substrates.[3] In order to confirm its structure, we undertook the synthesis of the putative dihydropyridinium metabolite **3**.

N-Methyldihydropyridinium derivatives have been prepared by treatment of the corresponding tetrahydropyridine N-oxides[4] with TFAA. A previous attempt to synthesize the dihydropyridinium derivative **4** from 1-cyclopropyl-4-phenyl-1,2,3,6-tetrahydropyridine (**2**) by this reaction, however, failed since, under the somewhat vigorous conditions used, treatment of **2** with *m*-chloroperoxybenzoic acid (*m*-CPBA) led to epoxidation of the tetrahydropyridine double bond in addition to N-oxidation. In order to avoid this problem we elected to carry out the corresponding reaction via the 4-piperidinol N-oxide **6** which was readily prepared by treatment of the piperidinol **5** with *m*-CPBA.[1] Reaction of compound **6** with an excess of trifluoroacetic anhydride at 0 °C followed by treatment of the reaction mixture with HCl in acetic acid to bring about dehydration of the C-4 carbinol, however, did not yield the desired dihydropyridinium product **3**. The ^{1}H NMR spectrum of the crude product showed that the cyclopropyl group was no longer intact while the GC-EI mass spectrum displayed a molecular ion at m/z 173 which corresponds to the secondary amine **7** that

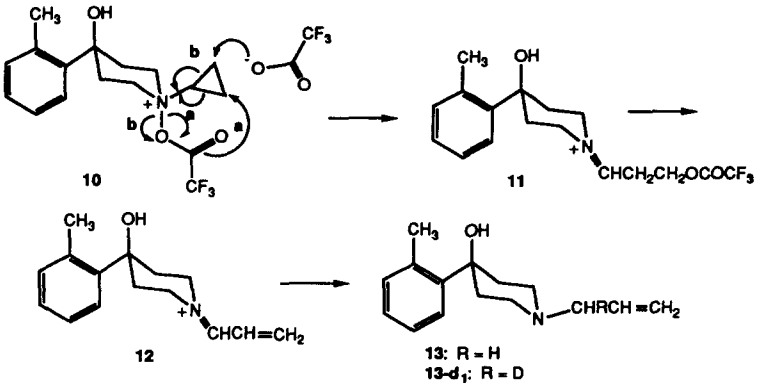
would be formed by decyclopropylation of **6**. Elemental analysis of the oxalate salt isolated from the reaction mixture confirmed the structure of this compound as **7**.[5] In contrast to the behavior of **6**, treatment of the tetrahydropyridine N-oxide **8** with TFAA led to an essentially quantitative yield of the dihydropyridinium product **3** (estimated by ^{1}H NMR analysis which displayed a clean spectrum fully consistent with **3**). Compound **3** proved to be difficult to isolate because of its tendency to undergo autoxidation to the pyridinium species **9**, behavior which has been observed with other dihydropyridinium derivatives.[6] The structure of **3** was confirmed by treatment of the crude reaction mixture with $NaBD_4$ to give the corresponding 1-cyclopropyl-4-(2-methylphenyl)-1,2,3,6-tetrahydropyridine-6d_1(**1-d_1**) which was characterized by ^{1}H NMR and by elemental analysis of its perchlorate salt.[7]



We speculated that the reaction pathway leading to the decyclopropylation of **6** proceeded via the N-trifluoroacetoxy species **10**. An intramolecular rearrangement (pathway **a**) or intermolecular reaction (pathway **b**) would lead to the trifluoroacetoxyethyliminium species **11** that would be expected to undergo rapid elimination to form the eniminium compound **12**. Upon workup, hydrolysis of **12** would yield **7**. Strong evidence to support this proposal was obtained by treating the residue isolated from a reaction mixture containing **6** and TFAA with $NaBH_4$ or (in a separate reaction) $NaBD_4$ in methanol. The expected N-allyl (**13**)[8] and N-allyl-d_1 (**13-d_1**)[9] products obtained in these reactions were characterized by ^{1}H NMR, GC-EI and high resolution EI mass spectral analyses.

Ring expansion[10] and cleavage reactions[11,12] of cyclopropylamines have been reported previously. Most recently, Mariano has found that *trans*-2-phenylcyclopropylamine undergoes oxidative cleavage following initial adduct formation between the primary amine and a model flavin system.[13] Based on the results from these and related studies,[14] Mariano has raised the possibility that MAO catalysis may proceed via a polar addition-elimination mechanism. This proposal has been challenged[15] in part because it does not work with tertiary amines, even though many cyclic tertiary amines which contain the 1,2,3,6-tetrahydropyridine ring system are known to be good substrates for

one or both forms of this enzyme.[16] The results of the present study may add additional credibility to the polar mechanism proposed by Mariano.



Acknowledgement. This research was supported by an NIH grant (NS 28792) and the Harvey W. Peters Center at Virginia Tech.

References and Notes

(1) Rimoldi, J. M.; Wang, Y.-X.; Nimkar, S. K.; Kuttab, S. H.; Anderson, A. H.; Burch, H.; Castagnoli, Jr., N. *Chem. Res. Tox.* **1995**, submitted.
(2) Silverman, R. B. In *Advances in Electron Transfer Chemistry*, Mariano, P. S. (Ed.) Academic Press; Greenwich, CT 1992; Vol. 2; pp 177-213.
(3) Silverman, R. B; Zelechonok, Y. *J. Org. Chem.* **1992**, *57*, 6374.
(4) Kalgutkar, A.; Castagnoli, Jr. N. *J. Med. Chem.* **1992**, *35*, 4165.
(5) Spectral data for **7**: GC (temperature program: 100 °C for 2 min then 25 °C/min to 275 °C) R_t 5.60 min -EIMS, m/z 173 ($M^{\cdot+}$); ^{1}H NMR ($CDCl_3$) δ 7.01-7.19 (m, 4H, Ph-H), 5.53 (bs, 1H, C5), 3.44 (m, 2H, C6), 3.01 (t, 2H, C2), 2.23 (s, 3H, CH_3), 2.22 (m, 2H, C3). Anal. (oxalate salt) Calcd for ($C_{14}H_{17}NO_4 \cdot 0.1\ H_2O$): C, 63.42; H, 6.47; N, 5.29. Found: C, 63.39; H 6.55; N 5.24.
(6) Wu, E.; Shinka, T.; Caldera-Munoz, P.; Yoshizumi, H.; Trevor, A.; Castagnoli, Jr. N. *Chem. Res. Tox.* **1988**, *1*, 186.
(7) Spectral data for **1-d$_1$**: GC (temperature program: 100 °C for 2 min then 25 °C/min up to 275 °C) R_t 6.60 min -EIMS m/z 214 ($M^{\cdot+}$); ^{1}H NMR (DMSO-d_6) δ 7.08-7.17 (m, 4H, Ph-H), 5.59 (bs, 1H, C5), 3.49 (bs, 1H, C6), 3.09 (t, 2H, C2), 2.48 (t, 2H, C3), 2.28 (s, 3H, CH_3), 2.02 (m, 1H, cyclopropyl CH),

0.83 and 0.63 (m, 4H, cyclopropyl CH_2CH_2). Anal. ($HClO_4$ salt) Calcd for ($C_{14}H_{18}DClNO_4$): C, 57.23; H+D, 6.72; N, 4.45. Found: C, 56.99; H+D, 6.36; N, 4.43.

(8) Spectral data for **13**: GC (temperature program: 100 °C for 2 min then 25 °C/min to 275 °C) R_t 6.35 min -EIMS m/z 231 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 7.17-7.40 (m, 4H, Ph-H), 6.00 (m, 1H, propenyl CH), 5.33 (m, 2H, $=CH_2$), 3.28 (d, 2H, propenyl CH_2), 3.05 (m, 2H, C6), 2.78 (t, 2H, C2), 2.62 (s, 3H, CH_3), 2.39 (t, 2H, C5), 2.06 (m, 2H, C3). High resolution EIMS ($M^{\cdot+}$): Calcd: 231.1623145. Found: 231.163300.

(9) Spectral data for **13-d_1**: GC (temperature program: 100 °C for 2 min then 25 °C/min to 275 °C) R_t 6.35 min -EIMS m/z 232 ($M^{\cdot+}$); ^1H NMR ($CDCl_3$) δ 7.14-7.40 (m, 4H, Ph-H), 5.98 (m, 1H, propenyl CH), 5.27 (m, 2H, $=CH_2$), 3.18 (d, 1H, propenyl CHD), 2.96 (m, 2H, C6), 2.69 (t, 2H, C2), 2.63 (s, 3H, CH_3), 2.34 (t, 2H, C5), 2.03 (m, 2H, C3). High resolution EIMS ($M^{\cdot+}$): Calcd: 232.1685912. Found: 232.169006.

(10) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26.
(11) Sayre, L. M.; Singh, M. P.; Kokil, P. B.; Wang, F. *J. Org. Chem.* **1991**, *56*, 1353.
(12) Hiyama, T.; Koide, H.; Nozaki, H. *Bull. Chem. Soc. Japan* **1975**, *48*, 2918.
(13) Kim, J. M.; Hoegy, S. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1995**, *117*, 100.
(14) Kim, J. M.; Bogdan, M. A.; Mariano, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 10591.
(15) Silverman, R. B.; Lu, X. *J. Am. Chem. Soc.* **1994**, *116*, 4129.
(16) Altomare, C.; Carrupt, P.-A.; Gaillard, P.; El Tayar, N.; Testa, B.; Carotte, A. *Chem. Res. Tox.* **1992**, *5*, 366.

(*Received in USA* 23 *February* 1995; *revised* 3 *April* 1995; *accepted* 7 *April* 1995)