zation of the bond being broken in the transition state, whereas that for OH insertion from **3** is apparently not affected by remote group R.

Finally, we have not detected trapped products of oxirene, i.e., methoxyoxiranes, in the present reaction system, although these products were not unduly reactive under these conditions of photolysis. This supports the recent calculations[18] which predict the lifetime of oxirene is too short to be trapped chemically.

(17) Su, D. T. T.; Thornton, E. R. *J. Am. Chem. Soc.* **1978**, *100*, 1872–1875.
(18) Strausz, O. P.; Gosavi, R. K.; Denes, A. S.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1976**, *98*, 4784–4786.

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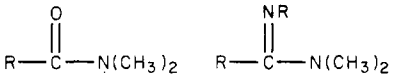
α-Substitution of Amines via Dipole Stabilized Carbanions from Formamidines

Sir:

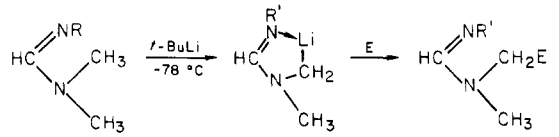
Deprotonation and alkylation of the α carbon of amines has been effected in various ways which involve the use of a masked amino function.[1-3] Prominent among these methods is the use of *N*-nitroso amines[4] and *N,N*-dimethylamides.[5] However, the potential carcinogenicity of the former and the steric bulk required in the latter render these approaches to alkylated amines less than desirable.

N,N-Dimethyl amidines **2** may be considered synthetically equivalent to *N,N*-dimethyl amides **1**. In contrast to amides,



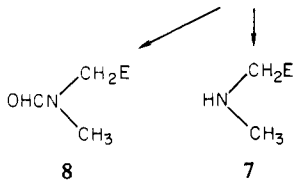
1 **2**

amidines have not been explored with respect to their reaction with strong bases.[6] We now report that amidines may serve as a generally useful precursor to α-substituted amines by metalation of **3**, **4**, or **5** to the dipole-stabilized carbanion, **6**, and treatment



3, R = cyclohexyl
4, R = *n*-Bu
5, R = *t*-Bu

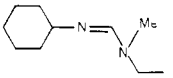
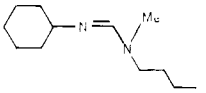
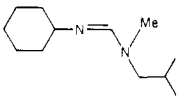
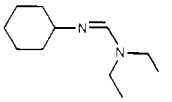
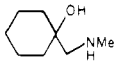
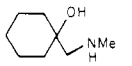
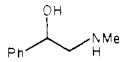
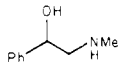
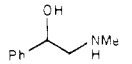
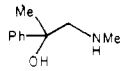
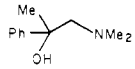
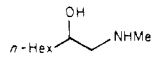
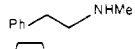
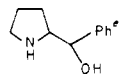
6



8 **7**

with various electrophiles, E. Hydrolysis provides the elaborated amines **7** or the *N*-formyl derivative **8** in good yield (Table I). In this preliminary report, pyrrolidine was also effectively alkylated via its amidine derivative (Table I, entry 14). The formamidines **3–5** as well as that derived from pyrrolidine **9** were prepared from *N,N*-dimethylformamide and *N*-formylpyrrolidine,[7] respectively, in 75–85% overall yield.[8,9]

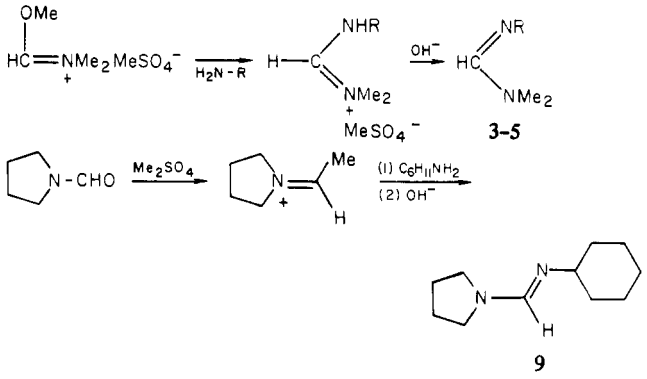
Table I. α-Substituted Amines from Metalation of Formamidines

entry	amidine	electrophile	product	yield, %[a]
1	3	MeI		85
2	3	*n*-PrI		82
3	3	*i*-PrI		*b*
4	3	MeI (twice)		88
5	3	cyclohexanone		45[c]
6	5	cyclohexanone		40[c]
7	3	PhCHO		77[c]
8	4	PhCHO		71[c]
9	5	PhCHO		76[c]
10	3	$PhCOCH_3$		64[c]
11	3	$PhCOCH_3$		67[d]
12	3	*n*-HexCHO		40[c]
13	4	$PhCH_2Br$		54[f]
14	9	PhCHO		57[c]

[a] Yields are based on purified products and have not been optimized. [b] The crude product is a 2:1 mixture of starting material and alkylated product. [c] Product after hydrolysis of the corresponding formamidines. [d] Product after treating the *N*-formyl derivative with $LiAlH_4$. [e] Obtained as a 3:1 mixture of diastereomers. This ratio has the potential of increasing with a systematic survey of reaction conditions. [f] Hydrolyzed with $HCl-H_2O$–MeOH.

(1) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275 and references cited therein.
(2) Barton, D. H. R.; Lamotte, G.; Motherwell, W. B.; Narang, S. C. *J. Chem. Soc., Perkin Trans. 1.* **1979**, 2030.
(3) Hullot, P.; Cuvigny, T. *Bull. Soc. Chim. Fr.* **1973**, 2989.
(4) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15 and references cited therein.
(5) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. Schlecker, R.; Seebach, D.; Lubosch, W. *Ibid.* **1978**, *61*, 512. Hassel, T.; Seebach, D. *Ibid.*, **1978**, *61*, 2237. Seebach, D.; Hassel, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *17*, 274.
(6) Abdullah, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1680, 1722.
(7) Moffat et al. [Moffat, J.; Newton, M. V.; Papenmeier, G. J. *J. Org. Chem.* **1962**, *27*, 4058] reported a general procedure for formylating amines. *N*-Formylpyrrolidine was prepared by mixing equimolar amounts of ethyl formate and pyrrolidine (added together in an ice bath prior to 3 h heating at reflux), and evaporation of the volatiles and bulb-to-bulb distillation [100–120 °C (12 torr)] gave the product in 97% yield. See Also *J. Chem. Soc.* **1948**, 1457.
(8) Formamidines **3–5** and **9** were prepared by treating an ice-cold CH_2Cl_2 solution of the formamidinium salt (prepared from the *N*-formyl compound with 1.0 equiv of dimethyl sulfate with heating for 2 h at 60–90 °C under nitrogen) with 1.0 equiv of the primary amine and stirred at room temperature overnight. The reaction mixture was washed with 10% KOH and the CH_2Cl_2 solution, dried, evaporated, and distilled [**3**, bp 90–110 °C, (12 torr), colorless oil; **4**, bp 155–170 °C; **5**, bp 80–90 °C, (12 torr); **9**, bp 130–150 °C, (12 torr)]. All formamidines showed a singlet at δ 7.1–7.6 for the formyl proton.
(9) Bredereck, H.; Effenberger, F.; Simchen, G. *Chem. Ber.* **1963**, *96*, 1350.

0002-7863/80/1502-7125$01.00/0



9

Metalation of the formamidines could be accomplished quantitatively by addition of *tert*-butyllithium (1.1 equiv, THF, −78 °C), then warming to −25 °C for 1 h and recooling to −78 °C prior to introduction of the electrophile. After being warmed to room temperature, the reaction mixture is quenched with MeOH–H_2O (20 °C, 15 h), providing good yields of the *N*-formyl derivative **8**, which may be isolated. However, hydrolysis of crude **8** (5 equiv of KOH, 2:1 MeOH–H_2O, reflux 18 h) and evaporation of the methanol followed by acidification (HCl), extraction ($CHCl_3$), basification of the aqueous solution, and extraction gave the elaborated amines **7** after bulb-to-bulb distillation.

Attempted metalation of the formamidines **3–5**, **9** with *n*-BuLi or LDA failed to produce any significant levels of α-anions, although several side reactions occurred. Some additional results obtained in this study deserve further comment: (a) Sequential alkylation leads to the α,α'-substituted product and no α,α-substitution is observed. Thus, the acidity of the N–CH_3 group must be considerably greater than that of the N–CH_2R groups (Table I, entry 4). (b) The formamides **8**, obtained on hydrolysis with MeOH–H_2O, can be isolated and reduced[10] ($LiAlH_4$) to furnish tert-*N*-methyl amines (Table I, entry 11).[11]

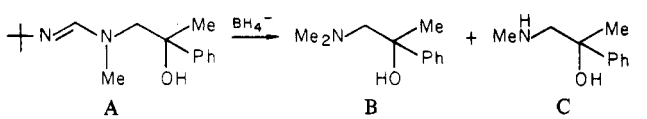
This behavior of formamidines toward *tert*-butyllithium is in sharp contrast to that observed for the corresponding formamides where the formyl proton is removed.[1] Furthermore, metalation of the α-CH_3 proton in the formamidines takes place regardless of the steric bulk of the *N*-alkyl group (*n*-Bu, cyclohexyl, or *t*-Bu) which makes hydrolytic cleavage of the amidine much easier to accomplish, a situation not generally observed in the previous methods.[1-5] Finally, this method should allow, by the use of chiral formamidines, an entry into asymmetric alkylation of the α carbon of amines. This aspect is currently under investigation.[12]

Note Added in Proof: We have recently found that piperidine, diethylamine, and 1,2,3,4-tetrahydroisoquinoline, through their formamidines, are also efficiently alkylated by using this technique.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this work.

(10) Schröter, R. Houben-Weyl In "Methoden der Organische Chemie", 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1957; Vol. XI, part 1, p 583.

(11) The direct reduction of formamidines with $NaBH_4$ (20 °C, 15 h) has the potential for generating the tertiary amine directly. Thus, the amidine A gave a 3:1 mixture of B and C when treated with $NaBH_4$.



A B C

Attempts to increase this ratio using other reducing agents are in progress.

(12) Satisfactory analytical data were obtained for all new compounds.

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A Mechanism for Mitochondrial Monoamine Oxidase Catalyzed Amine Oxidation

Sir:

Mitochondrial monoamine oxidase (MAO, EC 1.4.3,4) is a flavin-dependent enzyme which catalyzes the oxidative deamination of biogenic monoamines to the corresponding aldehydes.[1] Several steps in the oxidation mechanism are known. Concomitant with oxidation of the amine to the iminium ion,[2] the flavin is reduced.[3] The iminium ion is hydrolyzed to the aldehyde,[4,5] and the reduced flavin is reoxidized enzymatically with molecular oxygen.[5] It has been reported that oxidation of the amine occurs when it is in the free base form.[6] The segment of the enzyme-catalyzed reaction which has no substantiation is the mechanism of the amine oxidation. We report here our enzymatic results and nonenzymatic model studies directed toward the elucidation of this mechanism.

We propose that MAO catalyzes the oxidation of monoamines by two one-electron transfers from the substrate to the flavin.[7] This type of mechanism has ample precedence in the electrochemical literature.[8] The generally accepted mechanism for the electrochemical oxidation of amines is the radical cation mechanism[8] shown in Scheme I. If this mechanism were applied to the MAO-catalyzed oxidation, it would require that in a slow step a nonbonded electron of the amine nitrogen is transferred to the flavin to give the amine radical cation and the flavin semiquinone radical (Scheme II). This renders the α protons of the amine much more acidic,[8] and thus proton loss would be more facile. The radical generated by proton loss could decompose by two possible routes (Scheme II). Mechanism a shows a second transfer of one electron to the flavin; mechanism b depicts radical combination followed by a two-electron transfer to the flavin. Both mechanisms would generate the same products, the iminium ion and the reduced flavin. Radical intermediates have been suggested and observed in other flavoenzyme-catalyzed reactions.[9]

We recently reported that *N*-cyclopropyl-*N*-arylalkylamines are mechanism-based inactivators of MAO.[10] The mechanism proposed was enzyme-catalyzed oxidation of the *N*-cyclopropyl carbon to give the reactive cyclopropaniminium ion which reacts with an active site nucleophile in a 1:1 stoichiometry. We found[10] that when *N*-[1-^{3}H]cyclopropylbenzylamine (the ^{3}H is on the cyclopropyl carbon adjacent to the N) was used to inhibit MAO, inactivation resulted every time a ^{3}H was removed. Since primary amine substrates of MAO are oxidized at the α-methylene carbons, we carried out an experiment to determine how many times the benzyl methylene carbon is oxidized in *N*-cyclopropylbenzylamine (*N*-CBA) for each *N*-cyclopropyl carbon oxidation. Oxidation of the benzyl methylene carbon should lead to the formation of benzaldehyde (or benzoic acid as a result of air oxidation). Thus, [*phenyl*-^{14}C]*N*-CBA was incubated with MAO until there was no enzyme activity remaining. The small molecules were separated by microdialysis at pH 7.0 and applied to a column of Dowex 50 cation-exchange resin in the protonated form. The ratio of ra-

(1) Kearney, E. B.; Salach, J. I.; Walker, W. H.; Seng, R.; Singer, T. P. *Biochem. Biophys. Res. Commun.* **1971**, *42*, 490.

(2) (a) Patek, D. R.; Chuang, H. Y. K.; Hellerman, L. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1972**, *31*, 420. (b) Hellerman, L.; Chuang, H. Y. K.; DeLuca, D. C. *Adv. Biochem. Psychopharmacol.* 1972, *5*, 327.

(3) (a) Yasunobu, K. T.; Gomes, B. *Methods Enzymol.* **1971**, *17B*, 709. (b) Oi, S.; Yasunobu, K. T. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 631.

(4) Smith, T. E.; Weissbach, H.; Udenfriend, S. *Biochemistry* **1962**, *1*, 137.

(5) (a) Yasunobu, K. T.; Oi, S. *Adv. Biochem. Psychopharmacol.* **1972**, *5*, 91. (b) Houslay, M. D.; Tipton, K. F. *Biochem. J.* **1973**, *135*, 735.

(6) McEwen, C. M., Jr.; Sasaki, G.; Jones, D. C. *Biochemistry* **1969**, *8*, 3952.

(7) Silverman, R. B.; Hoffman, S. J. "Drug Action and Design: Mechanism-Based Enzyme Inhibitors"; Kalman, T. I., Ed.; Elsevier/North Holland: New York, 1979; p 185.

(8) (a) Mann, C. K.; Barnes, K. K. "Electrochemical Reactions in Nonaqueous Systems"; Marcel Dekker: New York, 1970; Chapter 9. (b) Masui, M.; Sayo, H. *J. Chem. Soc. B* **1971**, 1593. (c) Lindsay Smith, J. R.; Masheder, D. *J. Chem. Soc. Perkin Trans. 2*, **1976**, 47.

(9) Palmer, G.; Müller, F.; Massey, V. "Flavins and Flavoproteins"; Kamin, H., Ed.; University Park Press: Baltimore, 1971; pp 123–140.

(10) Silverman, R. B.; Hoffman, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 884.

0002-7863/80/1502-7126$01.00/0