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FORMAMIDINES AS α-AMINO CARBANION PRECURSORS. THE SYNTHESIS OF 2-ARYLPIPERIDINES, -PYRROLIDINES, AND NICOTINE ANALOGS+

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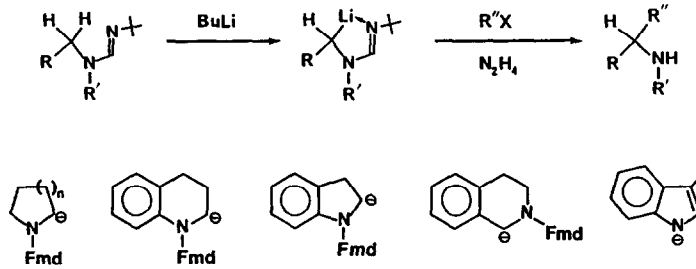
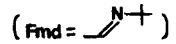
Summary: Metallation of the t-butyl formamidines of benzyl or picolinyl amines followed by alkylation with α,ω-dihaloalkanes gives the title compounds after hydrazinolysis.

Our earlier observation[1] that protons α- to a formamidine moiety can be removed by lithium bases has proven to possess considerable synthetic utility (Scheme 1).[2] This process has been extended to the metallation of various amines whose α-carbanions (A-E) have been alkylated in both chiral[3] and achiral[4] environments furnishing the corresponding enantiomers (D, E) or racemates (A-E). Of interest to us in this program was a method to introduce aryl groups in the α-position which would require alkylation with an

Scheme 1



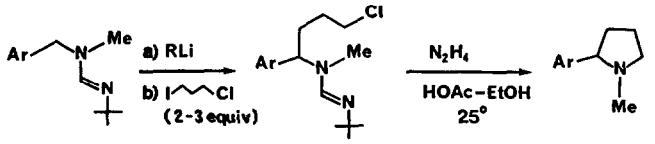
A(n=1-3) B C D E

(Fmd = )

electrophilic aromatic species. Although such species are known[5] from transition metal mediated reactions, we first opted to assess this process by considering a synthesis that involved piperidine and pyrrolidine ring closures. The process we had envisioned and its successful implementation is outlined in Scheme 2, and led to α-aryl or α-pyridyl pyrrolidines 3 in overall yields of 60-72%.[6] The sequence began with the N-methyl-N-aryl methyl-N'-t-butyl formamidine 1 readily prepared by the method in Scheme 4, and

+This paper is warmly dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

Scheme 2



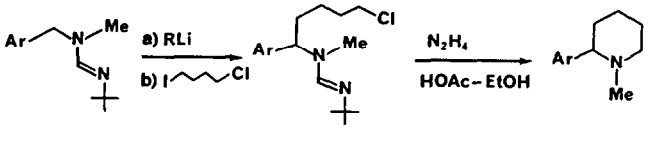
1 2 3

1, Ar	RLi (1.1 equiv)	% 3[6]
Ph	n-BuLi	64
p-ClPh	n-BuLi	63
p-MeOPh	t-BuLi	67
2-Pyridyl	n-BuLi	62
3-Pyridyl	n-BuLi	60 (nicotine)
4-Pyridyl	n-BuLi	72

metallation with n-butyl lithium (THF, -78°, 1.5 h). When Ar in 1 was p-methoxyphenyl the base required was t-butyllithium, due to the lower kinetic acidity. Introduction of 2-3 equiv of 1-iodo-3-chloropropane at -78° followed by warming (1-3 h) to ambient gave the intermediate 2. The latter was immediately treated with a solution of 95% ethanol-acetic acid-hydrazine hydrate (3:1:2)[2] such that the pH of the mixture was ~ 8 and stirred at room temperature (10-15 h). Aqueous workup gave the 2-substituted pyrrolidines 3 in overall yields shown (from 1).

Similarly, 1 was treated with alkyl lithium bases and after addition of 1-iodo-4-chlorobutane gave 4 which was subjected to hydrazinolysis affording 2-aryl piperidines 5 in yields shown[7] (Scheme 3).

Scheme 3

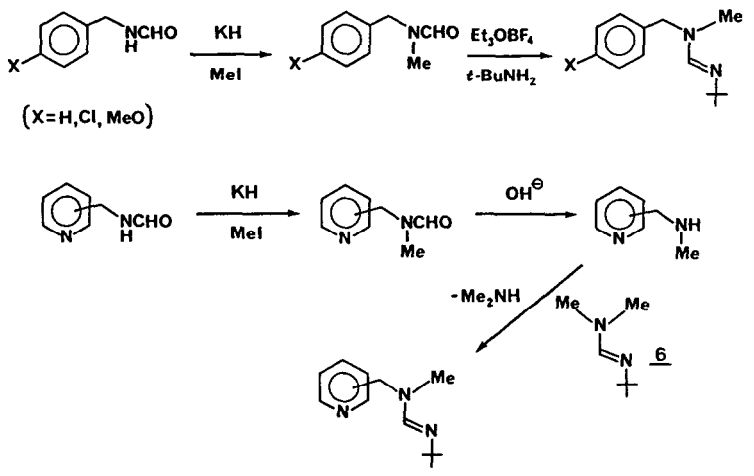


1 4 5

1, Ar	RLi (1.1 equiv)	% 5
Ph	n-BuLi	67
p-ClPh	n-BuLi	67
p-MeOPh	t-BuLi	61
2-Pyridyl	n-BuLi	66
3-Pyridyl	n-BuLi	62 (ref 7)
4-Pyridyl	n-BuLi	77

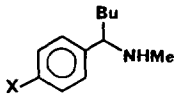
The starting material for these studies, e.g. 1, were all prepared in good overall yields starting from the corresponding benzyl amines or picolinyl amines according to Scheme 4.

Scheme 4

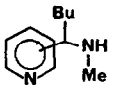


The formamides of the aryl methyl amines (HCO_2Et, 25°, 8 h) were treated with KH (THF, 0°) and methyl iodide (1.2 eqiv, 0°-25°) to give the N-methyl formamides (80-90%) which were treated with 1.2 equiv Et_3OBF_4 in 1,2-dichloroethane (reflux 8 h). The reaction mixture was cooled to room and t-butylamine was added. After stirring overnight and quenching in 10% NaOH, the mixture was extracted ($CHCl_3$) and concentrated to furnish the formamidines. For the picolinyl series, the N-methyl formamides were hydrolyzed in methanolic KOH and then heated with the dimethylamino formamidine 6 as described previously.[2a] The pyridine nitrogen precluded the use of the Meerwein reagent in this preparation. As expected the use of mono halides in this process leads to good yields of the α-alkyl benzyl amines 7 or the corresponding picolinyl amines, 8. Thus, alkylation of 1 with n-butyl bromide

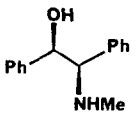
furnishes, after hydrazine treatment, the α-n-butyl derivatives, whereas addition of benzaldehyde to 1 (Ar = Phenyl) gives, after hydrazinolysis, a single amino alcohol 9



7a, X=Cl(74%)
7b, X=MeO(72%)



8a, 2-Pyr(52%)
8b, 3-Pyr(71%)
8c, 4-Pyr(81%)



Syn-9

assigned the syn configuration based on the ^{1}H-NMR (270 MHz) which showed proton couplings of 5.87 Hz. The latter is the subject of further study to determine the scope and extent of acylic stereocontrol.

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6. A similar scheme has been reported which employed benzylnitrosamine to prepare 2-phenyl-N-benzyl piperidine in 33% yield; cf. R. R. Fraser, G. Boussard, I. D. Postecu, J. J. Whiting, Y. Y. Wigfield, Can. J. Chem. 51, 1109 (1973).

7. Nicotine, obtained in this study was identical to an authentic sample from Eastman Kodak. The other products gave satisfactory analyses and were shown by vpc to be greater than 95% pure. N-Methyl anabasine (5, Ar = 3-pyridyl) is reported. NMR spectrum: G. F. Alberici, J. Andreux, G. Adam, Tetrahedron Letters 24, 1937 (1983); mp of dipicrate, 236-238°, K. H. Buechel and F. Korte, Chem. Ber. 95, 2438 (1962) report 237-239°.

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