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SYNTHESES OF 1,3-DISUBSTITUTED IMIDAZO[1,5-a]PYRIDINES

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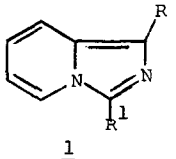
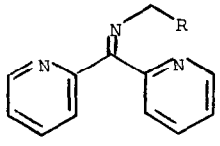
Abstract: Facile syntheses of 1,3-disubstituted imidazo[1,5-a]pyridines have been effected by treatment of ketimines derived from di-2-pyridyl ketone with LDA and benzophenone, reactions of benzyl amine with di-2-pyridyl ketone in boron trifluoride etherate, and reaction of di-2-pyridyl methanamine imines with molecular sieves in benzene.

We wish to report several facile synthetic routes to 1,3-disubstituted imidazo[1,5-a] pyridines 1 which were uncovered during a study of the regiochemistry of electrophilic attack on anions derived from N-alkyl diarylketimines.[1,2]



1

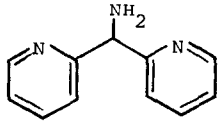
a, R = 2-pyridyl, R^1 = CH_2CH_3
b, R = 2-pyridyl, R^1 = $CH(CH_3)_2$
c, R = 2-pyridyl, R^1 = C_6H_5
d, R = R^1 = C_6H_5
e, R = 2-pyridyl, R^1 = CH_3
f, R = R^1 = 2-pyridyl



2

a, R = CH_2CH_3
b, R = $CH(CH_3)_2$
c, R = C_6H_5

Treatment of imine 2a with LDA at -78°C in THF, followed by a quench with 1N HCl, led to the amine 3 (74%). On the other hand, when 2a or 2b were treated with LDA at -78°C in THF, followed by the addition of one equivalent of benzophenone, imidazo[1,5-a]pyridines 1a (88%)[3,4] and 1b (66%) were isolated, respectively. In the reaction leading to 1a, a quantitative yield of benzhydrol was also obtained. The anions derived from the imines 2a or 2b underwent cyclizations and subsequent oxidations by benzophenone to yield 1a or 1b.



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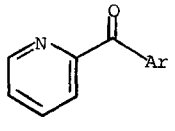


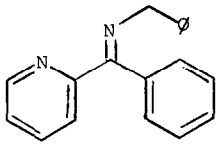
4

a, Ar = 2-pyridyl
b, Ar = C_6H_5

Most prior syntheses of imidazo [1,5-a]pyridines involve the formation of the imidazo ring by dehydrative cyclizations of amides derived from 2-aminomethylpyridines[4,5] and related compounds.[6,7]

In an attempt to synthesize 2c, by heating ketone 4a with benzylamine in the presence of boron trifluoride etherate, it was found that the major product of this reaction was 1c (46%). A small amount of the expected imine 2c (10%) was also isolated. In a similar manner, ketone 4b reacted with benzylamine to give 1d (39%). The imines 2c and 5 which are initially formed undergo rearrangement to the corresponding isomeric imines 6a and 6b, respectively, which then undergo cyclizations followed by air oxidation to yield the imidazo[1,5-a]pyridines.

To test this hypothesis, the imines 6c and 6d were prepared from 3 by reactions with the appropriate aldehydes. These imines underwent cyclizations in the presence of molecular sieves in benzene solutions at room temperature to yield 1e (39%) and 1f (47%),[8] respectively.



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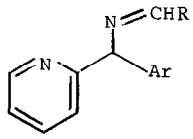

6

a, Ar = 2-pyridyl, R = C_6H_5
b, Ar = R = C_6H_5
c, Ar = 2-pyridyl, R = CH_3
d, Ar = R = 2-pyridyl

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References and Notes

1. Hullot, P.; Cuvigny, T. Bull. Soc. Chim. Fr. 1978, 2989.
2. Kauffmann, T.; Koppelmann, E.; Berg, H. Angew. Chem. Internat. Edit. 1970, 9, 163.
3. 1a; mp 77-78°C; PMR ($CDCl_3$)δ 1.48 (3H, t), 2.07 (2H, q), 6.73 (1H, m), 6.87 (1H, m), 7.04 (1H, m), 7.65-7.80 (2H, m), 8.12 (1H, d), 8.60 (2H, m). Anal. Calcd for $C_{14}H_{13}N_3$: %C, 75.31; %H, 5.87; %N, 18.82: Found: %C, 75.06; %H, 5.97; %N, 18.81.
4. An authentic sample of 1a was prepared by the procedure of Bower and Ramage [J. Chem. Soc. 1955, 2834] from di-(2-pyridyl)methanamine(3) and propionyl chloride.
5. Winterfeld, K.; Franzke, H. Angew. Chem. Internat. Edit. 1963, 2, 736.
6. Katritzky, A. P.; Rees, C. W. Comprehensive Heterocyclic Chem. 1984, 5, 634.
7. Edgar, M. T.; Pettit, G. R.; Krupa, T. S. J. Org. Chem. 1979, 44, 396. This report describes the isolation of an imidazo[1,5-a]pyridine (8%) in the attempted synthesis of an N-benzylidene 2-pyridyl amino acid.
8. 1f; mp 147-147.5°C; PMR ($CDCl_3$)δ 6.83 (1H, m), 7.03-7.15 (2H, m), 7.22 (1H, m), 7.78 (2H, m), 8.30 (1H, m), 8.49 (1H, m), 8.64 (2H, m), 8.78, (1H, m), 10.03, (1H, m). Anal. Calcd. for $C_{17}H_{12}N_4$: %C, 74.98; %H, 4.44; %N, 20.57: Found: %C, 74.87; %H, 4.71; %N, 20.32.

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