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1-PHENYL-2,3-DIAZACYCL[3,2,2]AZINE, A NEW 10-π ELECTRON SYSTEM. INVOLVEMENT OF 3,5-DIDEHYDROIMIDAZO[1,5-a]PYRIDINE?

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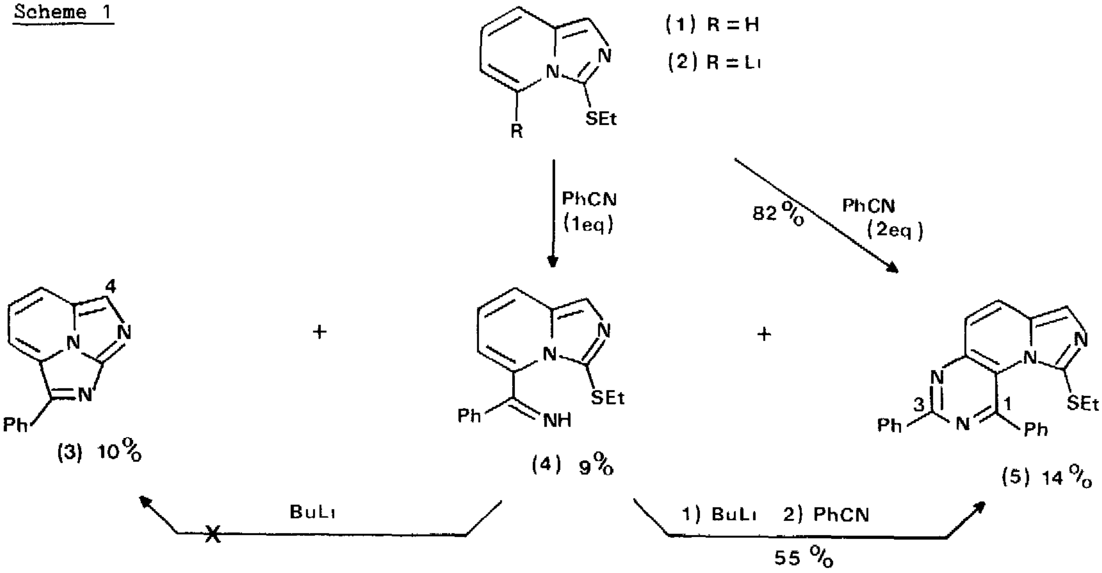
Abstract - 3-Ethylthioimidazo[1,5-a]pyridine reacts with butyl lithium followed by benzonitrile to give the new 10-π electron system, 1-phenyl-2,3-diazacycl[3,2,2]azine, possibly via 3,5-didehydroimidazo[1,5-a] pyridine.

We have recently described the preparation of 5-substituted imidazo[1,5-a] pyridines by reaction of the anion (2) with various electrophiles[1] When we extended this reaction to include benzonitrile as the electrophile we obtained the desired imine (4)[2] together with the cyclazine (3) and the pyrimidine (5) (Scheme 1)[3] To our knowledge the cyclazine (3) is the first example of this 10-π electron system

Scheme 1

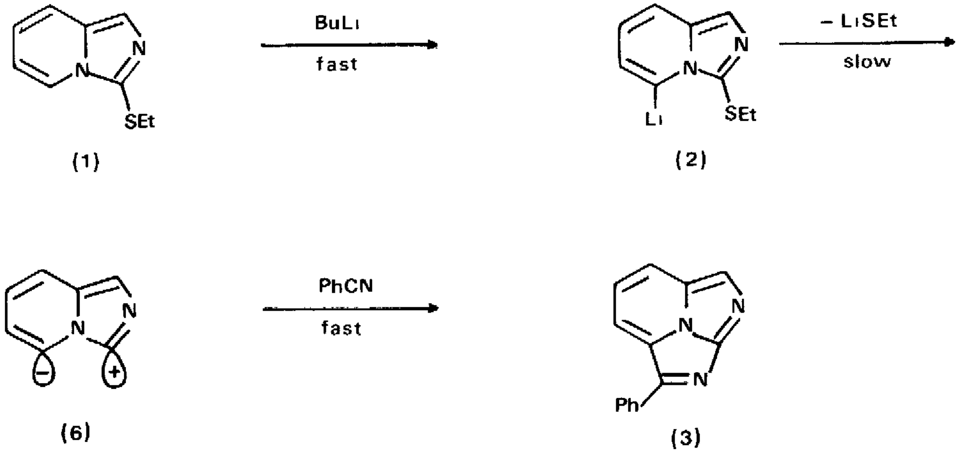


We initially thought that the cyclazine (3) was formed via the anion of the imine (4). However, treatment of the imine (4) in THF at -78° with butyl lithium followed by warming to room temperature and quenching with water returned starting material. We were able to prepare the cyclazine (3) in improved yield (27%)^{4} by adding benzonitrile in one portion to a solution of the anion (2) in THF at -78° The product was isolated by column chromatography on alumina using ether/ethyl acetate (2.1) as eluent to give claret crystals m p. 184-185° (methanol/ethyl acetate). ^{1}H-N M R. δ (CDCl$_3$) 7.3 - 7.6 (3H,m,*m* and *p* phenyl protons), 7 80(1H,t,7Hz,H6), 8 20 - 8.35(2H,m,*o*-phenyl protons) overlain by 8 30(1H,d 7Hz,H5 or H7), 8.45(1H,d,7Hz,H7 or H5), 8.65(1H,s,H4)^{5}, λmax (EtOH)221 (ε = 18,200), 262(22,200), 301(6,600), 488nm(12,200).

The structure of the cyclazine (3) was confirmed by X-ray crystallography Crystal data. $C_{14}H_9N_3$, M_r = 219.25, monoclinic, $P2_1/c$, *a* = 7.59 (2), *b* 8.38 (5), *c* = 17 17(5) Å, β = 102.11 (3)° 1943 Data were collected for *h*0-7*l* with Θ max = 27.5° on a STAD1-2 diffractometer (Mo-Kα radiation). 1150 reflections with *I* > 3σ(*I*) were used in the refinement. *V* = 1067 2Å^{3}, *Z* = 4, *F*(000) = 456, μ = 0.47cm^{-1} The structure was solved by direct phasing methods with the SHELX-76 crystallographic programme system^{6} and was refined to give an *R* value of 0.046.

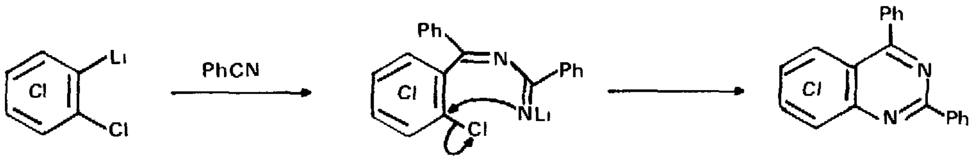
Since (i) the thioether (1) reacts rapidly and quantitatively with butyl lithium to give the anion (2)^{1} and (ii) the anion of the imine(4) is not an intermediate in the formation of the cyclazine (3) it would appear that the carbon-sulphur bond of the anion(2) must be broken before the carbon-carbon or the carbon-nitrogen bond of the cyclazine(3) is formed. It is therefore tempting to speculate that the cyclazine(3) is formed via 3,5-didehydroimidazo[1,5-a]pyridine(6) an intermediate which is related to 1,8-didehydronaphthalene^{7} This possibility is currently under investigation^{8}.

Scheme 2



We confirmed that the pyrimidine(5) was formed via the anion of the imine(4) since treatment of the imine(4) in THF with butyl lithium for 0.5h at -78° followed by benzonitrile gave the pyrimidine(5). The anion(2) reacted with two equivalents of benzonitrile in THF at -78° followed by warming to room temperature to give the pyrimidine (5) as orange micro-crystals in 82% yield, m.p. 167 - 168°(benzene-petroleum ether, b.p. 60 - 80°). ^{1}H-N.M.R. δ(CDCl$_3$/DMSO) 1.57(3H,t,7Hz,CH$_2$*Me*), 3.45(2H,q,7Hz,*CH$_2$*Me), 7.04 and 7.18(2H,ABq,8Hz H(5)C=CH(6)), 7.4 - 7.7(7H,m,H7 and *m* and *p* phenyl protons), 7.83(2H,m,*o*-phenyl(C1)protons), 8.75(2H,m,*o*-phenyl(C3)protons), λmax (EtOH) 223(sh, ϵ =27,600), 265(32,000) 278(sh,27,600), 400 nm (11,100).

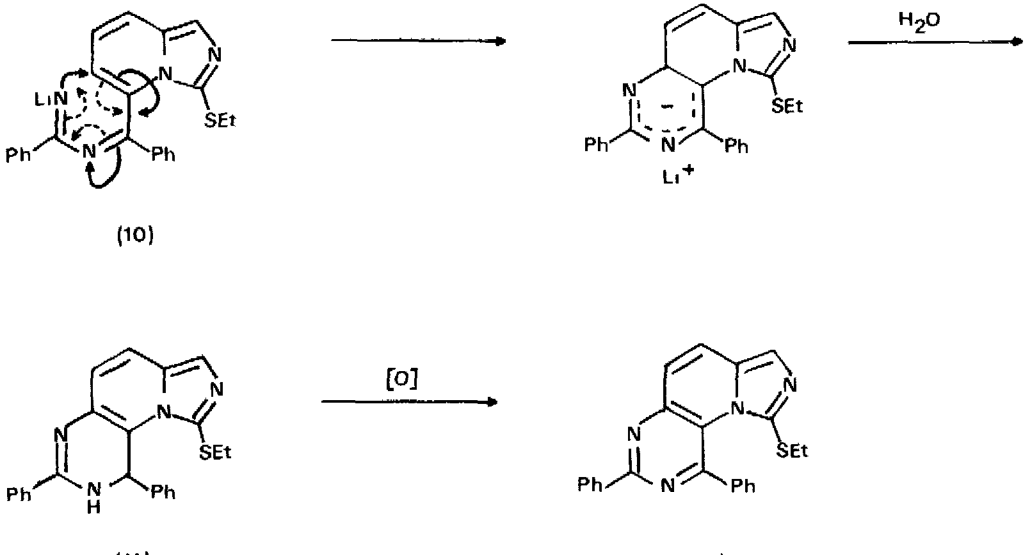
The formation of the pyrimidine(5) is related to previous work where halo[9] or alkoxy[10] aryl lithiums have been found to react with benzonitrile to give pyrimidines, for example(7)→(9)[9]. It has been suggested that the intermediate anions e.g. (8) cyclise by nucleophilic displacement of the leaving group.



(7) (8) (9)

However, it might appear that the presence of a leaving group is unnecessary. In our case one can envisage cyclisation of the conjugated imine(10) occuring either by attack of the anion at the now electron deficient carbon (solid arrows) or by an electrocyclic reaction (broken arrows), followed by oxidation of the dihydro-pyrimidine (11) on work up (Scheme 3).

Scheme 3



(10)

(11) (5)

References and notes

1. P. Blatcher and D. Middlemiss, Tetrahedron Letters, 1980, 2195.
2. Tan crystals, m.p. 98-99° (petroleum ether, b.p. 60-80°). ^{1}H-N.M.R. ($CDCl_3$) 1.05(3H,m,CH_2Me), 2.73(2H,q,CH_2Me), 6.5-6.9(2H,m,H6 and H7), 7.2-7.8(6H,m,Ph and H8) overlain by 7.70(1H,s,H1), 10.15(1H, broad s, NH) max ($CHBr_3$) 3260(NH), 1598, 1575 cm^{-1} (C=C;C=N) max (EtOH) 223(sh, =23,000); 245.5(sh,16,400), 290.5 (3,600), 353.5nm(2,300).
3. Yields refer to analytically pure material.
4. The conditions for the formation of the cyclazine(3) have not yet been optimised.
5. In imidazo[1,5-a]pyridine this proton appears at 7.45. A similar downfield shift of ca. 1 ppm has been observed in a related cyclazine; see M. De Pompei and W.W. Paudler, J.Org.Chem., 1976, 41, 1661.
6. G.M. Sheldrick, SHELX-76 programme for crystal structure determination, 1976, University of Cambridge. Supplementary X-ray data submitted for deposition at the Cambridge Crystallographic Data Centre.
7. Current evidence suggests that 1,8-didehydronaphthalene undergoes concerted 1,2-addition to olefins; C.W. Rees and R.C. Storr, Chem.Comm., 1965, 193; R.Hoffmann, A.Imamura and W.J. Hehre, J.Amer.Chem.Soc., 1968, 90, 1499; C.W. Rees and R.C. Storr, J.Chem.Soc. (C), 1969, 765; J. Meinwald, L.V. Dunkerton and C.W. Gruber, J.Amer.Chem.Soc., 1975, 97, 681.
8. A [2 + 8]cycloaddition between the thioether(1) and benzonitrile followed by loss of ethane thiol is unlikely since addition of butyl lithium to a solution of the above in THF at -78° did not give any of the cyclazine(3). However, the possibility that the anion(2) undergoes [2 + 8]cycloaddition with benzonitrile followed by loss of lithium thioethoxide has not yet been ruled out.
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10. W.J. Houlihan and A.J. Pieroni, J.Het.Chem., 1973, 10, 405; A.C. Ranade, R.S. Mali,R.M. Gridwani and H.R. Deshpande, Chem. and Ind., 1977, 310; A.C. Ranade, R.S. Mali and H.R. Deshpande, Experientia. 1979, 35, 574.

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