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A DIRECT METHOD FOR THE SUBSTITUTION OF IMIDAZO[1,5-a]PYRIDINES AT POSITION 5

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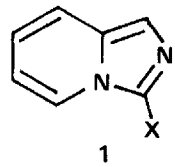
Abstract - 3-Ethylthioimidazo[1,5-a]pyridine lithiates at carbon 5. Quenching of the anion with an electrophile followed by desulphurisation gives 5-substituted imidazo[1,5-a]pyridines.

Imidazo[1,5-a]pyridine (1a) undergoes electrophilic substitution at position 1[1] and lithiation at position 3[2]. To our knowledge there are no reports on the direct substitution of the pyridine ring[3]. As part of a general programme aimed at the synthesis of imidazo[1,5-a] pyridines we wanted a direct method for the introduction of substituents at position 5.

Our strategy was to protect position 3 with a group that would (i) direct lithiation to position 5 and (ii) be easily removed under mild conditions. To this end we chose to investigate the lithiation of the thioether (1b)[4].



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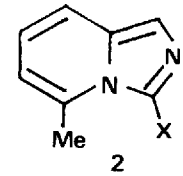

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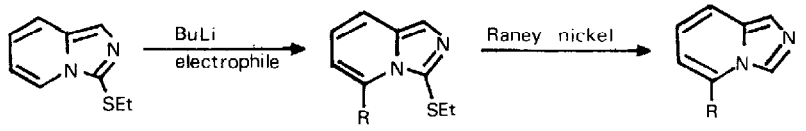
a X = H
b X = SEt

Addition of n-butyl lithium (1.1 equiv.) to (1b)[5] in THF at -78° followed by quenching with methyl iodide (1.1 equiv.) and allowing to warm to room temperature gave 3-ethylthio-5-methylimidazo[1,5-a]pyridine (2b) bp 150° (0.04 mmHg)[6] in 97% yield. ^{1}H-N.M.R. δ ($CDCl_3$) 1.31 (3H,t,SCH_2Me), 2.97(3H,s,5-Me), 3.14(2H,q,SCH_2), 6.25(1H,d,H6), 6.60(1H,q, H7), 7.28(1H,d,H8) 7.50(1H,s,H1). Desulphurisation of (2b) with Raney nickel[7] in refluxing ethanol (1h) gave 5-methylimidazo[1,5-a]pyridine(2a) in quantitative yield[8]. The anion of (1b) reacts with a variety of electrophiles. Some other examples are given in the table.

Table



1b 3 4

Electrophile	R	Yield of (3)[a]	Yield of (4)[a]
PhCHO	CH(OH)Ph	71	65
EtCHO	CH(OH)Et	60	50[b]
Ph_2CO	$C(OH)Ph_2$	71[b]	56
$ClCO_2Et$	CO_2Et	76	43
Et_2CO	$C(OH)Et_2$	29[c]	-

(a) yield of analytically pure material; (b) yield of hydrochloride salt;

(c) 51% based on recovered starting material.

References and notes

1. J.D. Bower and G.R. Ramage, J.Chem.Soc., 1955, 2834.

2. W.W. Paudler, C.I.P. Chao and L.S. Helmick, J.Het.Chem., 1972, 9, 1157.

3. Imidazo[1,5-a]pyridines with substituents in the 6-membered ring can be prepared from the appropriate pyridine by the method of Bower and Ramage (ref.1) but the syntheses are long (up to 8 stages) and share no common intermediate; D.Middlemiss and K.Mills, unpublished results.

4. Alkylthio groups are known to coordinate lithium and direct the position of metallation; see B.M. Trost, M. Reiffen and M. Crimmin, J.Amer.Chem.Soc., 1979, 101, 257. We chose the ethylthio rather than the methylthio group to avoid possible metallation next to sulphur; see H. Gilman and F.J. Webb, J.Amer.Chem.Soc., 1949, 71, 4062.

5. Prepared in quantitative yield from the corresponding thiol (J.E. Kuder, PhD thesis, University of Ohio, 1968) by reaction with ethyl iodide (1.1 equiv.) in acetone at 45° with K_2CO_3 (2 equiv.) as base.

6. Kugelrohr oven temperature.

7. For method of preparation see L.F. Fieser and M.Fieser, 'Reagents for Organic Synthesis', Wiley, New York, 1967, Vol. 1, 729.

8. Identical to authentic material; see W.W. Paudler and J.E. Kuder, J.Het.Chem., 1966, 3, 33.

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