Metallation and Metal–Halogen Exchange Reactions of Imidazoles

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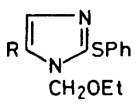
Summary Some reactions (reagents in parentheses) are reported of 1-ethoxymethyl-2-phenylthioimidazol-5-yl-lithium {Me_2S_2, Ph_2S_2, $[(EtO)_2CHCH_2]_2S_2$}, 1-ethoxymethyl-5-methylthio-2-phenylthioimidazol-4-yl-lithium

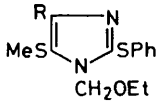
(Me_2S_2, $HCONMe_2$, CO_2), 4,5-dibromo-1-ethoxymethylimidazol-2-yl-lithium (Me_2S_2, Ph_2S_2), and 2-substituted derivatives of 4-bromo-1-ethoxymethylimidazol-5-yl-lithium (*e.g.* with Me_2S_2), prepared by metallation or metal halogen exchange reactions.

ON entering the imidazole field we were surprised to find that some simple derivatives, *e.g.* imidazole-4(5)-thiol, were not available and that the preparation of imidazoles *via* organometallic derivatives has not been exploited.[1] Breslow's group[2] reported recently that attempts to make organometallic reagents from 1-protected 4(5)-bromoimidazoles failed, leading either to reduction or to C-2 metallated derivatives. Our earlier experiences, which we shall report elsewhere, were much the same.

We metallated the 1,2-diprotected imidazole (**1**),[2] in the 5-position with n-butyl-lithium† (this reagent was reported[2] to result in C–S bond cleavage but we have not met this problem) in tetrahydrofuran at −78 °C and treated the resulting imidazol-5-yl-lithium compound with various disulphides to give the 5-substituted derivatives (**2**) [83% yield; δ($CDCl_3$) 7·30s (1H, 4-H), 7·25m (5H, aromatic), 5·50s (2H, NCH_2), 3·45q (2H, OCH_2), 2·35s (3H, SMe), and 1·10t (3H, Me)]; (**3**) [100%; δ($CDCl_3$) 7·50s (1H, 4-H), 7·10—7·40m (10H, SPh), 5·39s (2H, NCH_2), 3·30q (2H, OCH_2), and 0·90t, (3H, Me)]; and (**4**) [61%; δ($CDCl_3$) 7·33s (1H, 4-H), 7·25s (5H, aromatic), 5·50s (2H, NCH_2), 4·57t (1H, CH), 3·30—3·70m (6H, OCH_2), 2·88d (2H, SCH_2), and 1·10q (9H, 3 × Me)] (all oils which were purified by column chromatography).‡



(1) R = H
(2) R = SMe
(3) R = SPh
(4) R = $SCH_2CH(OEt)_2$



(5) R = Li
(6) R = SMe
(7) R = Br
(8) R = CHO
(9) R = COOH

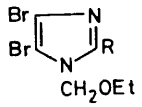
The methyl sulphide (**2**) failed to metallate in the 4-position with n-butyl-lithium or lithium di-isopropylamide under a variety of conditions. However, the use of potassium di-isopropylamide–lithium t-butoxide (KDA)[3] in tetrahydrofuran at −78 °C resulted in metallation in the 4-position as proved by addition of dimethyl disulphide, which gave an inseparable mixture of starting material and 1-ethoxymethyl-4,5-bis(methylthio)-2-phenylthioimidazole (**6**) (ratio 2:1 by ^1H n.m.r. analysis).

1-Ethoxymethyl-5-methylthio-2-phenylthioimidazol-4-yl-lithium (**5**) was prepared *via* bromination of 1-ethoxymethyl-5-methylthio-2-phenylthioimidazole (**2**) and metal–halogen exchange of the bromine atom in the product (**7**) [(92% yield), m.p. 56—57 °C (from light petroleum) (purified by column chromatography); δ($CDCl_3$) 7·30m (5H, aromatic), 5·51s (2H, NCH_2), 3·46q (2H, OCH_2), 2·30s (3H, SMe), and 1·10t (3H, Me)] with n-butyl-lithium in diethyl ether at −70 °C, and its treatment with dimethyl disulphide yields 1-ethoxymethyl-4,5-bis(methylthio)-2-phenylthioimidazole (**6**) as an oil (purified by column chromatography) [(100% yield); δ($CDCl_3$) 7·23s (5H, aromatic), 5·47s (2H, NCH_2), 3·42q (2H, OCH_2), 2·53s (3H, SMe), 2·28s (3H, SMe), and 1·05t (3H, Me)]. With *NN*-dimethylformamide and carbon dioxide this lithium compound (**5**) yields, respectively, the corresponding aldehyde (**8**) (84%) as an oil [semicarbazone in 70% yield; m.p. 166—167 °C (from carbon tetrachloride–chloroform–light petroleum): ν_{max} (Nujol) 1690 cm^{-1} (CO); δ($CDCl_3$) 9·53s (1H, exchangeable, NH), 7·96s (1H, CH), 7·28s (5H, aromatic), 5·85br.s (2H, exchangeable, NH_2), 5·50s (2H, NCH_2), 3·45q (2H, OCH_2), 2·30s (3H, SMe), and 1·08t (3H, Me)] and acid (**9**) [74%; m.p. 103—104 °C (from chloroform–light petroleum); ν_{max} (Nujol) 1680 cm^{-1} (CO); δ($CDCl_3$) 8·95br.s (1H, exchangeable, CO_2H), 7·30m (5H, aromatic), 5·55s (2H, NCH_2), 3·45q (2H, OCH_2), 2·50s (3H, SMe), and 1·10t (3H, Me).

As far as we are aware, not only is this the first report of a reproducible bromine–lithium exchange reaction of a *mono*bromoimidazole, but 1-ethoxymethyl-5-methylthio-2-phenylthioimidazol-4-yl-lithium (**5**) is the first imidazol-4-yl-lithium compound to be prepared.

Stensio *et al.*[4] have converted 2,4,5-tribromoimidazole into 4(5)-bromoimidazole by its successive treatment with 4 mol. equiv. of n-butyl-lithium and acid and claim to have prepared 4(5)-deuterioimidazole by successive treatment of the monobromo-compound with almost 5 mol. equiv. of n-butyl-lithium, deuteriomethanol, and acid. In our hands 4(5)-monobromoimidazole reacted with 1 mol. equiv. of n-butyl-lithium in diethyl ether or tetrahydrofuran, as expected, in the 1-position; addition of dimethyl sulphate gave mixtures of 4- and 5-bromo-1-methylimidazole [46—63% yield; δ($CDCl_3$) 7·50s (1H, 2-H), 7·27s (1H, 2′-H), 6·97s (1H, 4-H), 6·83s (1H, 5-H), 3·63s (3H, NMe), and 3·56s (3H, NMe′)]. The use of 2 mol. equiv. of n-butyl-lithium gave a similar result.

2,4,5-Tribromoimidazole, prepared (68% yield) by the procedure of Stensio *et al.*[4] was converted at ambient temperature with chloromethyl ethyl ether in benzene in the presence of triethylamine (*cf.* ref. 2) into its 1-ethoxymethyl derivative (**10**) (an oil which was purified by column



(10) R = Br
(11) R = SPh
(12) R = SMe

chromatography) [100% yield; δ($CDCl_3$) 5·40s (2H, NCH_2), 3·65q (2H, OCH_2), and 1·20t (3H, Me)], which, on successive treatment with n-butyl-lithium (in diethyl ether at −70 °C) and diphenyl disulphide, gave 4,5-dibromo-1-ethoxymethyl-2-phenylthioimidazole (**11**) (an oil) [67% yield; δ($CDCl_3$) 7·30m (5H, aromatic), 5·43s (2H, NCH_2), 3·44q (2H, OCH_2), and 1·09t (3H, Me)], also prepared (28%) by bromination of Breslow's compound (**1**). A similar procedure gave the

† We thank Professor R. Breslow and Dr. R. Smiley, Columbia University, New York, for suggesting that we try n-butyl-lithium.

‡ All new compounds analysed correctly for C, H, and N and gave mass spectra consistent with the structures proposed.

methyl sulphide (**12**) (an oil) [68% yield; $\delta(CDCl_3)$ 5·30s (2H, NCH_2), 3·53q (2H, OCH_2), 2·60s (3H, SMe), and 1·19t (3H, Me)]. Further reactions of 4,5-dibromo-1-ethoxymethyl-2-methylthio(and phenylthio)imidazole, (**11**) and (**12**), which we shall report in detail later, have shown that a second bromine atom can be replaced similarly [*e.g.* compound (**7**) is also available by this route]. Thus, starting from a suitably 1-protected 2,4,5-tribromoimidazole, substituents can be introduced one at a time. 2,4,5-Triiodoimidazole can be used also as a starting material.

The discovery of suitable protecting groups for the imidazole 1- and 2-positions (readily removable under mild conditions) is expected to provide an extremely useful route to many imidazoles.

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