A Convenient Synthesis of Thieno[2,3-*d*]imidazoles

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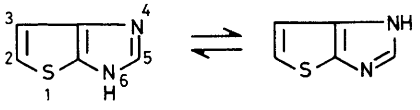
1-Protected and 1,2-diprotected derivatives of 4-bromoimidazole-5-carbaldehyde were prepared from imidazole *via* 2,4,5-tribromoimidazole and reacted with ethyl 2-mercaptoethanoate to give the title compounds.

The parent heterocycle, thieno([2,3-*d*] $\rightleftharpoons$ [3,2,-*d*])imidazole (**1**), is not known in the literature and existing routes to the few known derivatives (mainly 6-substituted), which start either from imidazole[1] or thiophene derivatives,[2—5] are unsatisfactory in that the starting materials are either inaccessible, unstable (2,3-diaminothiophenes are notoriously unstable), or both. We have developed a route to this ring system starting from commercially available imidazole.

2,4,5-Tribromoimidazole (**2**) (71%)[6] was converted into the 1-protected derivatives (**3**)† (Scheme 1, Table 1) and these were treated with either ethereal ethylmagnesium bromide, methyl-lithium, or phenyl-lithium followed by acid, which gave the 1-protected dibromoimidazoles (**4a**—**e**), or with various sodium alkyl-(or aryl-)thiolates either in refluxing propan-2-ol or refluxing *N,N*-dimethylformamide (DMF), which gave the 1,2-diprotected dibromoimidazoles (**4f**—**l**).



(**1**)

Whereas reaction of some of the 1-protected tribromoimidazoles (**3**) with one equivalent of n-butyl-lithium in diethyl ether at −70 °C was found not to be regioselective (both the 2- and 5-bromine atoms react), similar treatment of compounds (**4c**—**e**) and (**4h**—**l**) results in regioselective metal–halogen exchange of the 5-bromine atom. There was no evidence either for metallation of compounds (**4c**—**e**) in the 2-position or of metallation of any of the compounds in the 1- or 2-substituents at this temperature. Addition of DMF to the resulting mixtures gave the *o*-bromoaldehydes (**5**) in reasonable yields.

Each of the *o*-bromoaldehydes (**5a**), (**5b**), (**5f**—**h**) reacted with ethyl 2-mercaptoethanoate in the presence of sodium ethoxide to give the corresponding thieno[2,3-*d*]imidazole (**6**) in good yield. Currently we are studying deprotection of these products with a view to providing a route to the parent heterocycle (**1**).

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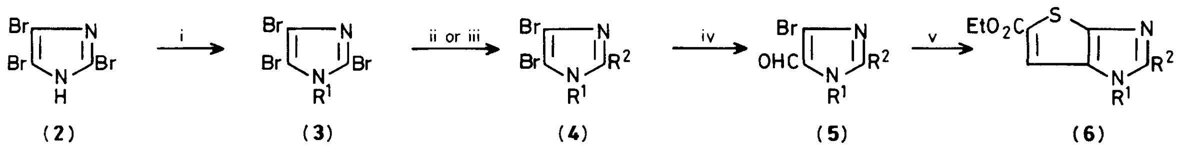
† All new compounds analysed correctly for C, H, and N and possess spectroscopic properties in agreement with the proposed structures.



Scheme 1. *Reagents:* i, R^1Cl–Na_2CO_3–DMF; ii, EtMgBr–Et_2O or tetrahydrofuran, then H^+; iii, R^2SNa–Pr^iOH (refluxing) or DMF (refluxing: lower yields); iv, Bu^nLi–Et_2O, −78 °C, then DMF; v, $EtO_2C{\cdot}CH_2{\cdot}SH$–NaOEt–EtOH.

Table 1. Yields (%) and melting points (°C) for the compounds (**3**)—(**6**).

(**3**)

a; $R^1 = CH_2OMe$ (78) (88—90) (A)[a]
b; $R^1 = CH_2OEt$ (100) (oil)
c; $R^1 = CH_2Ph$ (88) (58—59) (A)
d; $R^1 = CH_2C_6H_4OMe$-4 (90) (69—70) (A)
e; $R^1 = CH_2C_6H_3(OMe)_2$-3,4 (60) (122—124) (B)

(**5**)

a; $R^1 = CH_2Ph$, $R^2 = H$ (53) (59—61) (E)
b; $R^1 = CH_2C_6H_4OMe$-4, $R^2 = H$ (50) (62—64) (A)
c; $R^1 = CH_2C_6H_3(OMe)_2$-3,4, $R^2 = H$ (55) (159—161) (A)
d; $R^1 = CH_2OMe$, $R^2 = SCH_2Ph$ (54) (53—55) (C)
e; $R^1 = CH_2OMe$, $R^2 = SPh$ (51) (oil)
f; $R^1 = CH_2OEt$, $R^2 = SMe$ (53) (79—80) (C)
g; $R^1 = CH_2Ph$, $R^2 = SCH_2Ph$ (54) (oil)
h; $R^1 = CH_2Ph$, $R^2 = SPh$ (52) (73—75) (A)

(**4**)

a; $R^1 = CH_2OMe$, $R^2 = H$ (73) (65—67) (C)
b; $R^1 = CH_2OEt$, $R^2 = H$ (80) (oil)
c; $R^1 = CH_2Ph$, $R^2 = H$ (80) (56—57) (D)
d; $R^1 = CH_2C_6H_4OMe$-4, $R^2 = H$ (73) (64—65) (D)
e; $R^1 = CH_2C_6H_3(OMe)_2$-3,4, $R^2 = H$ (72) (111—113) (A)
f; $R^1 = CH_2OMe$, $R^2 = SEt$ (59) (oil)
g; $R^1 = CH_2OMe$, $R^2 = SPr^n$ (60) (oil)
h; $R^1 = CH_2OMe$, $R^2 = SCH_2Ph$ (62) (oil)
i; $R^1 = CH_2OMe$, R^2 SPh (64) (oil)
j; $R^1 = CH_2OEt$, $R^2 = SMe$ (44) (oil)
k; $R^1 = CH_2Ph$, $R^2 = SCH_2Ph$ (58) (oil)
l; $R^1 = CH_2Ph$, $R^2 = SPh$ (54) (oil)

(**6**)

a; $R^1 = CH_2Ph$, $R^2 = H$ (70) (98—100) (A)
b; $R^1 = CH_2C_6H_4OMe$-4, $R^2 = H$ (68) (84—85) (A)
c; $R^1 = CH_2OMe$, $R^2 = SCH_2Ph$ (65) (83—84) (C)
d; $R^1 = CH_2OEt$, $R^2 = SMe$ (69) (70) (C)
e; $R^1 = CH_2Ph$, $R^2 = SCH_2Ph$ (68) (136—138) (B)
f; $R^1 = CH_2Ph$, $R^2 = SPh$ (69) (73—75) (A)

[a] Solvents: A = ethanol; B = ethyl acetate; C = light petroleum (b.p. 40—60 °C); D = tetrachloromethane–light petroleum (b.p. 40—60 °C); E = ethyl acetate–light petroleum (b.p. 40—60 °C).

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