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Use of the Vinyl Group as an Efficient Protecting Group for Azole N- Atoms: Synthesis of Polyfunctionalized Imidazoles and Thieno[2,3-*d*] ⇌ [3,2-*d*]imidazole

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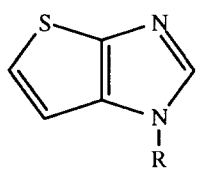
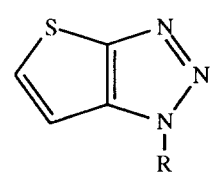
Abstract: 2,4,5-Tribromo-1-vinylimidazole was prepared from 2,4,5-tribromoimidazole and 1,2-dibromoethane and its Br-atoms were replaced regioselectively in the order 2 → 5 → 4 *via* Br → MgBr and other exchange reactions. Efficient removal of the vinyl groups from the resulting polyfunctionalized imidazoles was achieved with ozone or potassium permanganate. An extension of this methodology has allowed the first synthesis of thieno[2,3-*d*] ⇌ [3,2-*d*]-imidazole. © 1997 Elsevier Science Ltd.

Previously we[1-3] have shown that the Br-atoms in 1-protected 2,4,5-tribromoimidazoles can be replaced selectively through Br → Li(or MgBr) exchange strategies in the order 2 → 5 → 4. As a route to polyfunctionalized imidazoles this strategy suffers from the disadvantage, along with metallation and Br → Li exchange reactions of azoles in general,[3-6] that there is no ideal *N*-protecting group for general usage.[2,3,6-10] Some of the reagents required for *N*-protection are prohibitively expensive, especially for large-scale work, whilst others are carcinogenic (*e.g.* $ClCH_2OMe$), and deprotection can present difficulties too. Either because the parent heterocycles are thermally unstable or because they are sensitive to the acidic or basic conditions prevailing during most deprotection procedures, we have failed hitherto to synthesize the parent heterocycles **1** (R = H)[11,12] and **2** (R = H)[13,14] through deprotection of several of their *N*-protected derivatives **1** or **2**, respectively.



1



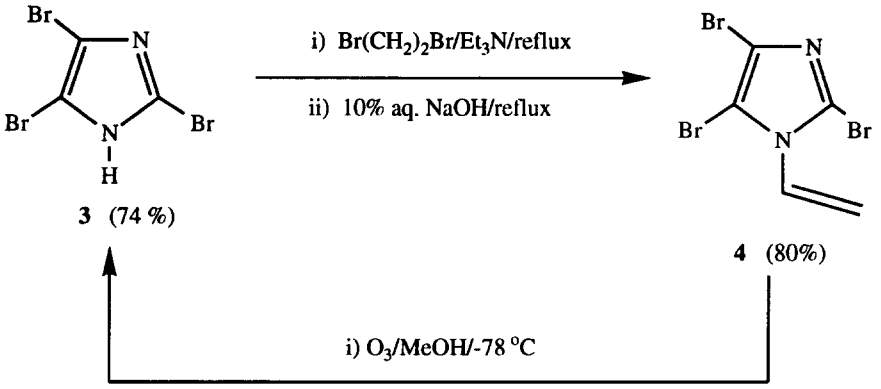
2

Of all the possible *N*-protecting groups perhaps the most surprising to be deployed, albeit on an extremely limited scale, is the *N*-vinyl group.[7,15-18] Van der Stelt *et al.*[7] lithiated commercially available 1-vinylimidazole (BuLi/THF-TMEDA/-60 °C) and quenched the resulting 2-lithiated derivative with variously substituted benzophenones and we[19] have shown that this is a general route for the synthesis of 2-substituted imidazoles (the TMEDA is not essential).

Now we report that our strategy for the synthesis of polyfunctionalized imidazoles can be improved by use of an *N*-vinyl protecting group. The reagent required for the protection step is cheap and

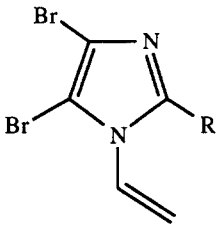
deprotection is efficient and occurs under neutral conditions, which has led to the first synthesis of the parent heterocycle **1** (R = H).

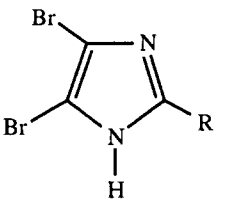
Thus, 2,4,5-tribromoimidazole **3** was converted into its *N*-vinyl derivative **4**[20] in 80% yield by the



SCHEME 1

"one-pot" two-stage process shown in Scheme 1. Regioselective replacement of its 2-Br-atom was possible with ethyl-(Et_2O or THF/0 °C) or phenyl-magnesium bromide (THF/ambient temp.) and the resulting Grignard derivative was quenched with various electrophilic quenching reagents, to give high yields of compounds **5-10**.



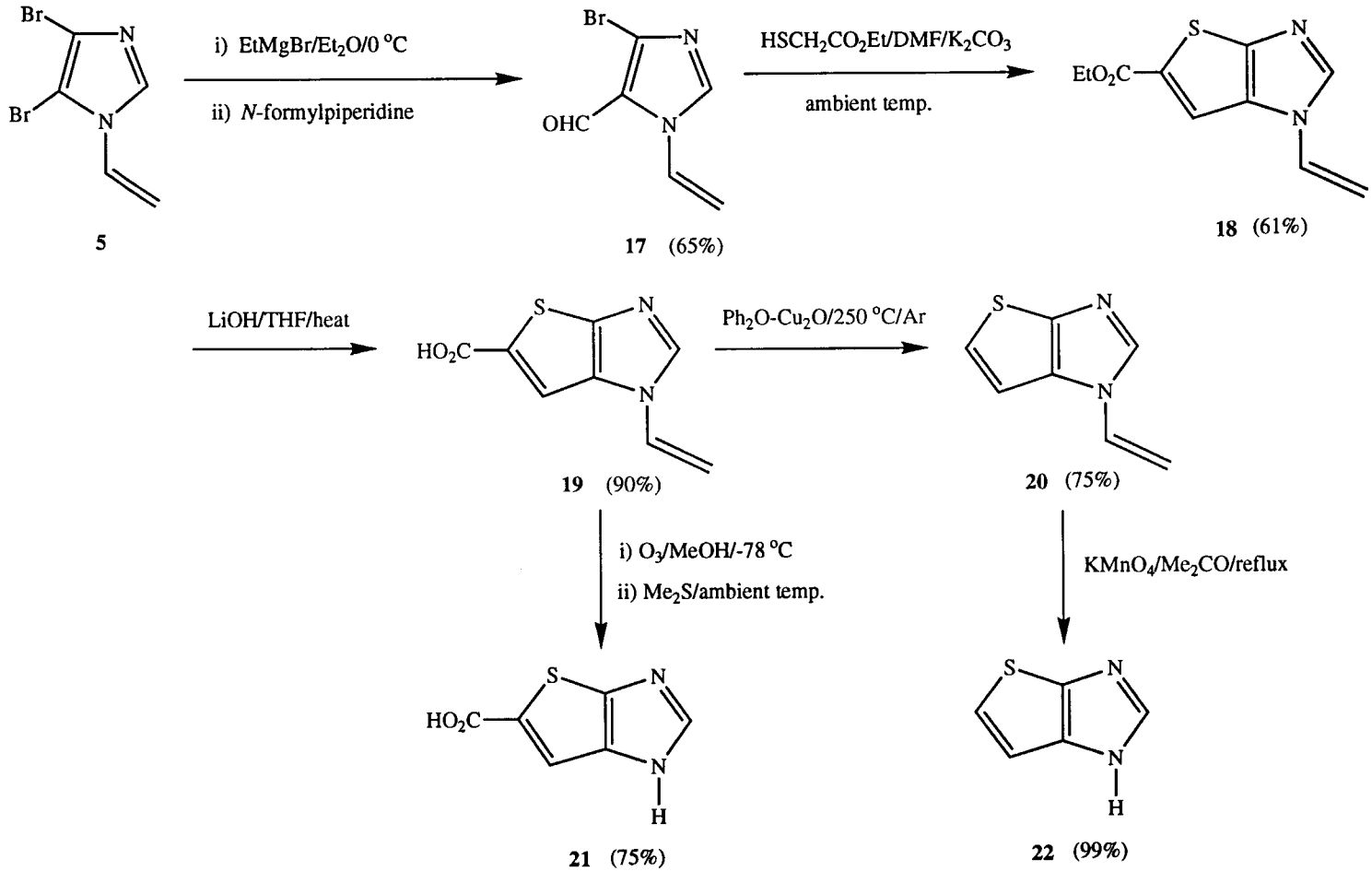


5 R = H (81%)
6 R = SMe (82%)
7 R = SPh (79%)
8 R = CH(OH)Me (82%)
9 R = CH_2OH (65%)
10 R = CHO (75%)

11 R = H (87%)
12 R = SMe (75% crude)
13 R = SPh — unstable
14 R = CH(OH)Me (88%)
15 R = CH_2OH (87%)
16 R = CHO (67%)

The vinyl group was removed efficiently from all these compounds by treating them with ozone in methanol at -78 °C in the presence of dimethyl sulfide, to give compounds **11-16**. Compounds **12** and **13** are unstable; the latter decomposed during work-up. 2,4,5-Tribromo-1-vinylimidazole **4** was deprotected similarly (Scheme 1).

4,5-Dibromo-1-vinylimidazole **5** was reacted with ethylmagnesium bromide regioselectively at position-5 and the resulting Grignard compound formylated with *N*-formylpiperidine, to give 4-bromo-1-vinylimidazole-5-carbaldehyde **17** (Scheme 2). Unlike imidazol-5-yllithium compounds, which undergo


Br
Br
N
N
i) EtMgBr/Et2O/0 °C
ii) N-formylpiperidine
OHC
HSCH2CO2Et/DMF/K2CO3
ambient temp.
EtO2C
S
5
17 (65%)
18 (61%)
LiOH/THF/heat
HO2C
Ph2O-Cu2O/250 °C/Ar
19 (90%)
20 (75%)
i) O3/MeOH/-78 °C
ii) Me2S/ambient temp.
KMnO4/Me2CO/reflux
H
21 (75%)
22 (99%)

SCHEME 2

transmetallation reactions readily to give the corresponding imidazol-2-yllithium derivatives, the corresponding Grignard reagents are more stable.[2,3]

Thienoimidazole **18** was prepared in the usual way[11,12] and its ester group was hydrolysed, which gave a high yield of the corresponding acid **19**. Decarboxylation of this acid was achieved by heating it to 250 °C (Woods metal bath) in diphenyl ether in the presence of copper(I) oxide. Both acid **19** and its decarboxylated product **20** were deprotected in high yield, in the former case as before and, in the latter case, with potassium permanganate in refluxing acetone (Scheme 2), to give acid **21** and the novel thieno[2,3-*d*] ⇌ [3,2-*d*]imidazole **22**, respectively. The parent heterocycle **22** can be kept at ambient temperature (preferably at 0°C) for several weeks but is unstable in the presence of acid or alkali.

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