Synthesis of 4,4′-Biimidazoles

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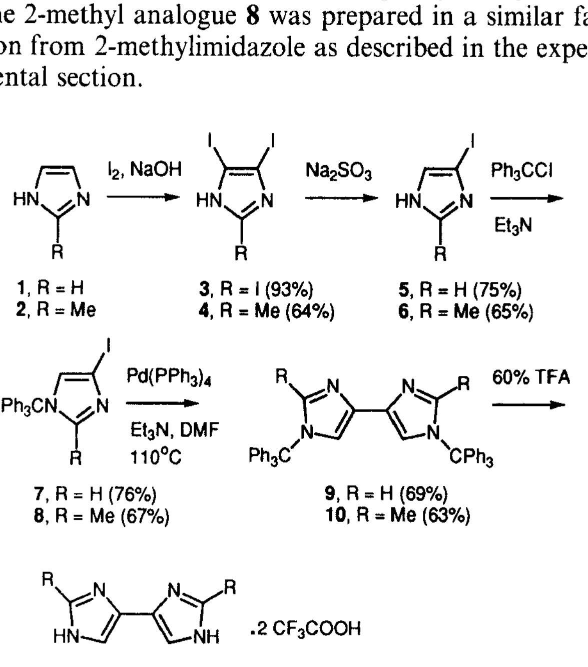
The palladium(0) catalysed coupling reaction of 4-iodo-1-triphenylmethylimidazole (**7**) or its 2-methyl analogue **8** afforded the 4,4′-biimidazoles **9** and **10**, respectively. Treatment of these compounds with 60% aqueous trifluoroacetic acid gave 4,4′-biimidazole and 2,2′-dimethyl-4,4′-biimidazole as their bistrifluoroacetate salts **11** and **12**, respectively.

While the synthesis and chemistry of 2,2′-biimidazoles has been well developed,[1] no such studies on the isomeric 4,4′-biimidazoles have been reported. These latter compounds may potentially be useful as metal ion chelators or as precursors for the synthesis of new heterocyclic compounds. We have found that the palladium(0) catalysed coupling reaction of the readily available *N*-protected 4-iodoimidazoles **7** and **8** proceeds efficiently to give the *N,N*-diprotected 4,4′-biimidazoles **9** and **10**, respectively. As far as we are aware the synthesis of 4,4′-biimidazoles has not been previously reported.

The known 4-iodo-1-triphenylmethylimidazole (**7**)[2] was prepared from imidazole using a modification of the literature procedures by complete ring iodination of imidazole[2,3] followed by selective reductive deiodination with sodium sulfite[4] and finally *N*-triphenylmethylation.[2] The 2-methyl analogue **8** was prepared in a similar fashion from 2-methylimidazole as described in the experimental section.



A degassed solution of **7** or **8** in dimethylformamide containing 5 mol % of tetrakis(triphenylphosphine)palladium(0) and triethylamine (2 molar equiv) was heated at 100–110 °C under an argon atmosphere in a thick walled sealed tube for 24–48 h. The solution was cooled to room temperature and the precipitated product **9** or **10** was collected by vacuum filtration. The yields of **9** and **10** were 69% and 63% respectively. Attempts to couple **5** under the above described conditions were unsuccessful. It thus appears that protection of the imidazole nitrogen is essential to the success of these coupling reactions. It has been reported that the reaction of 2-bromopyridine and palladium(0) gives a 2-pyridylpalladium(II) dimer.[5] An analogous intermediate may be formed in the reaction of **7** or **8** with palladium(0) which then undergoes coupling of the two imidazole moieties to give **9** or **10** respectively. Treatment of **9** or **10** with 60% aqueous trifluoroacetic acid[6] at ambient temperature in the case of **9** and at reflux for 4 h in the case of **10** gave the bistrifluoroacetate salts **11** and **12** of 4,4′-biimidazole and 2,2′-dimethyl-4,4′-biimidazole, respectively.

In summary, we have developed an efficient and convenient synthesis of 4,4′-biimidazole **11** and its 2,2′-dimethyl derivative **12**. The methods described here should have general application to the synthesis of other 4,4′-biimidazoles.

Satisfactory microanalyses were obtained for all new compounds: C ± 0.26, H ± 0.18, N ± 0.39.

4,5-Diiodo-2-methylimidazole (4):

A solution of 2-methylimidazole (**2**; 10.0 g, 0.122 mol) in 2 M aq NaOH (300 mL) was added to a solution of I_2 (61.9 g, 0.241 mol) in $CHCl_3$ (300 mL). The two phase system was stirred until the $CHCl_3$ phase became clear (~ 3 h). The phases were separated and, using $Na_2S_2O_3$ to prevent colouration, the aqueous phase was neutralised with AcOH. The solids were filtered and recrystallised from MeCN to give the title compound as a white solid; yield: 26.05 g (64%) mp 194–195 °C (dec).

IR (Nujol): ν = 1550, 1185, 1020, 968 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.48 (s, CH_3).

MS (FAB): *m/z* (%) = 335 (M + H$^+$, 47), 209 (M + H$^+$ -I, 28), 185 (100), 100 (74).

4(5)-Iodo-2-methylimidazole (6):

A solution of 4,5-diiodo-2-methylimidazole (**4**; 20.0 g, 60 mmol) and Na_2SO_3 (60 g, 0.476 mol) in 30% aq EtOH (1.0 L) was refluxed for 24 h. The solvent was removed almost to dryness to prevent the inorganic salts from precipitating out of the solution and the solid was filtered, washed with H_2O and allowed to air dry to give a white powder of sufficient purity (^{1}H NMR and TLC) to render recrystallisation unnecessary; yield: 8.1 g (65%); mp 141–142 °C. An analytical sample was recrystallised from EtOH; mp 143–144 °C.

IR (Nujol): ν = 3130, 1567, 1167, 1108, 891, 763 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.03 (1 H, s, H-5), 2.45 (3 H, s, CH_3).

MS (CI, + VE): *m/z* (%) = 209 (M + H$^+$, 100), 122 (13), 100 (26).

4-Iodo-2-methyl-1-triphenylmethylimidazole (8):

4(5)-Iodo-2-methylimidazole (**6**; 3.0 g, 14.4 mmol) and chlorotriphenylmethane (4.02 g, 14.4 mmol) were dissolved in anhydr. DMF (30 mL) and the mixture was stirred at r. t. under N_2. NEt_3 (1.46 g, 14.4 mmol) was then added and the solution was stirred for 24 h. The mixture was poured onto ice–H_2O (150 mL), and the solid precipitate was collected by filtration and then recrystallized from EtOAc/hexane to give a white crystalline solid; yield: 4.34 g (67%); mp 194–195 °C (dec).

IR (Nujol): ν = 1217, 742, 701, 667 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.35–7.33 (9 H, m, ArH), 7.13–7.11 (6 H, m, ArH), 6.76 (1 H, s, H-5), 1.64 (3 H, s, CH_3).

^{13}C NMR (CDCl$_3$): δ = 149.2 (C-2), 141.7, 129.8, 128.1, 128.0, 126.7, 78.5 (C-4), 75.4 (Ph$_3\underline{C}$), 17.1 (CH$_3$).

MS (ES, + VE): *m*/*z* (%) = 451 (M + H$^+$, 21), 243 (Ph$_3$C$^+$, 100), 102 (12).

2,2′-Dimethyl-1,1′-di(triphenylmethyl)-4,4′-biimidazole (10):
Compound **8** (4.00 g, 8.89 mmol), NEt$_3$ (1.80 g, 17.8 mmol) and Pd(PPh$_3$)$_4$ (510 mg, 0.44 mmol) were dissolved in anhydr. DMF (15 mL) in a thick walled glass tube. The solution was degassed by bubbling Ar for 10 min, the glass tube was sealed and the mixture was stirred and heated to 110 °C in the dark. After 48 h, the mixture was cooled to r.t. and the precipitate was collected by vacuum filtration. The filtrate was diluted with 5% NaHCO$_3$ (30 mL) and the resulting precipitate was also collected. The combined solids were washed with H$_2$O and cold acetone to leave a light tan solid; yield: 1.81 g (63 %), mp 250–252 °C (dec). Compound **10** was found to be only sparingly soluble in most common organic solvents.

^{1}H NMR (CDCl$_3$): δ = 7.30–7.28 (18 H, m, ArH), 7.22 (2 H, s, H-5, 5′), 7.18–7.16 (12 H, m, ArH), 1.61 (6 H, s, 2 × CH$_3$).

^{13}C NMR (CDCl$_3$): δ = 147.1 (C-2, 2′); 142.5, 134.0 (C-4, 4′), 130.1, 128.0, 127.7, 116.8 (C-5, 5′), 75.0 ($\underline{C}$Ph$_3$), 17.4 (CH$_3$).

MS (ES, + VE): *m*/*z* (%) = 647 (M + H$^+$, 5), 589 (12), 343 (14), 325 (11), 243 (Ph$_3$C$^+$, 100).

HRMS: *m*/*z* calc. for C$_{46}$H$_{38}$N$_4$ 646.3096, found 646.3006.

1,1′-Di(triphenylmethyl)-4,4′-biimidazole (9):
The title compound was prepared from **7**[2] (3.0 g, 6.90 mmol), NEt$_3$ (1.47 g, 13.8 mmol) and Pd(PPh$_3$)$_4$ (300 mg, 0.26 mmol) in DMF (15 mL) in a similar manner to **10** as described above. The solution was stirred and heated at 100 °C for 24 h. The mixture was cooled to r.t. and the precipitated product was collected by vacuum filtration. The solid material was washed with H$_2$O and cold acetone to give a cream solid. Recrystallization from 50% CHCl$_3$/toluene gave the title compound as a white solid; yield: 1.48 g (69 %); mp 279–280 °C (dec).

IR (Nujol): ν = 1216, 1185, 1079, 910, 745, 702, 665 cm^{-1}.

^{1}H NMR (CDCl$_3$): δ = 7.36 (2 H, d, J = 1.6 Hz, H-2,2′), 7.32–7.29 (18 H, m, ArH), 7.28 (2 H, d, J = 1.6 Hz, H-5,5′), 7.19–7.17 (12 H, m, ArH).

^{13}C NMR (CDCl$_3$, in part): δ = 142.7 (C-2,2′), 138.9, 136.7 (C-4,4′), 129.9, 128.0, 127.9, 117.1 (C-5,5′).

MS (ES + VE): *m*/*z* (%) = 619 (M + H$^+$, 61), 241 (Ph$_3$C, 100), 82 (61), 58 (89).

HRMS: *m*/*z* calc. for C$_{44}$H$_{34}$N$_4$ 618.2783, found 618.2778.

4,4′-Biimidazolium Bis(trifluoroacetate) (11):
1,1′-Di(triphenylmethyl)-4,4′-biimidazole (**9**; 1.4 g, 2.25 mmol) was dissolved in 60% CF$_3$CO$_2$H/H$_2$O (60 mL) and stirred at r.t. for 6 h. Precipitated triphenylmethanol was filtered and the solution was evaporated to dryness to leave a yellow oil. Washing with cold MeCN gave **11** as a white solid; yield: 560 mg (69%); mp 203–204 °C.

IR (Nujol): ν = 3159–2243 (NH, br), 1653 (CO$_2$), 1190–1150 (CF$_3$), 842 cm^{-1}.

^{1}H NMR (D$_2$O): δ = 8.12 (2 H, s, H-2, 2′), 7.83 (2 H, s, H-5, 5′).

^{13}C NMR (D$_2$O, MeOH internal standard): δ = 163.9 (q, $J_{C,F}$ = 35.7 Hz, CF$_3\underline{C}$O$_2$), 135.4 (C-2,2′), 120.7 (C-4,4′), 118.0 (C-5,5′), 116.4 (q, $J_{C,F}$ = 290.5 Hz, CF$_3$).

MS (ES, + VE): *m*/*z* (%) = 135 (C$_6$H$_7$N$_4$, 100), 60 (60).

MS (ES, − VE): *m*/*z* (%) = 113 (CF$_3$CO$_2^-$, 94), 69 (CF$_3$, 100).

2,2′-Dimethyl-4,4′-biimidazolium Bis(trifluoroacetate) (12):
Compound **10** (1.5 g, 2.32 mmol) was suspended in 60 % CF$_3$CO$_2$H (100 mL) and refluxed for 4 h until triphenylmethanol precipitated from the refluxing solution. The mixture was cooled to r.t., filtered and the solvent removed to leave a yellow oil. This was washed with a small amount of cold MeCN to give **12** as a light cream powder; yield: 567 mg (63 %); mp 227–228 (dec).

IR (Nujol): ν = 1653 (CO$_2^-$), 1186–1150 (CF$_3$), 665 cm^{-1}.

^{1}H NMR (D$_2$O): δ = 7.59 (2 H, s, H-5,5′), 2.66 (6 H, s, 2 × CH$_3$).

^{13}C NMR (D$_2$O, MeOH as internal standard): δ = 163.0 (q, J = 35.4 Hz, CF$_3\underline{C}$O$_2$), 146.4 (C-2, 2′), 120.2 (C-4, 4′), 116.5 (C-5, 5′), 116.46 (q, J = 289.8 Hz, CF$_3$), 10.8 (2 × CH$_3$).

MS (ES, + VE): *m*/*z* (%) = 163 (C$_8$H$_{11}$N$_4^+$, 100), 82 (C$_8$H$_{12}$N$_4^{2+}$, 58).

MS (ES, − VE): *m*/*z* (%) = 275 (CF$_3$CO$_2$C$_8$H$_{10}$N$_4^-$, 60), 69 (CF$_3^-$, 100).

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