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Protection of poorly nucleophilic pyrroles

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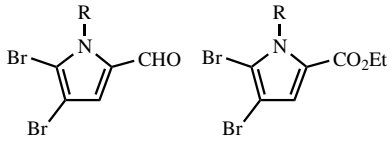
Abstract—A method for the introduction of carbamate protecting groups on the ring nitrogen of electron-deficient pyrroles has been developed using the commercially available chloroformates and stoichiometric tetrabutylammonium iodide. The method is postulated to generate the more reactive iodoformates in situ to facilitate these protection reactions.

During the course of studies on the regioselective coupling of polyhalogenated pyrroles, we were interested in determining what effect the pyrrole nitrogen protecting group would have on the coupling reaction.[1] In particular, initial studies had focused on simple alkyl protecting groups (MEM, BOM, ethyl), but electron-withdrawing protecting groups were also of interest. To that end, aldehyde **1** and ester **2** were targeted (Fig. 1).

The first approach was to protect the pyrrole nitrogen of pyrrole-2-carboxaldehyde or ethyl pyrrole-2-carboxylate as a methyl carbamate or toluenesulfonyl group, followed by halogenation. While the protection proceeded cleanly, halogenation proved to be impossible. Mild conditions such as NBS in DMF afforded only recovered starting material, while more forcing conditions led to either decomposition or, more often, loss of the protecting group.[2] As a result, it appeared that a more reasonable option would be to halogenate the pyrrole first and then protect the nitrogen.



1 R = C(O)OMe **2** R = C(O)OMe
3 R = H **4** R = H

Figure 1. Protected pyrrole targets.

The halogenation to produce aldehyde **3** and ester **4** proceeded cleanly under standard pyrrole bromination conditions (2 equiv of NBS in DMF). Much to our surprise, attempts to install carbamate protecting groups (methyl or *tert*-butyl) all failed under the conventional conditions reported from simple pyrroles, including potassium carbonate in DMF (for the methyl carbamate) and stoichiometric DMAP in acetonitrile at room temperature or at 60 °C with Boc anhydride (for the *tert*-butyl carbamate).[3] The source of this problem was not clear at first. Although steric hindrance could play a role, 5-substituted pyrrole esters have been protected before under relatively normal conditions.[4] At the same time, the vast majority of these reactions have been performed on pyrrole esters with smaller groups at C5 (such as a methyl group).

A second possibility was that the electron-withdrawing effect of the halogens resulted in the poor reactivity of the pyrrole nitrogen. In this case, it must be due to the influence of the bromides at C5 or at C4 and C5, since it is known that ethyl 4-bromopyrrole-2-carboxylate can be protected with a Boc group under the standard conditions used for the protection of pyrroles.[5]

By chance, it was discovered that protection of pyrrole **4** with methyl chloroformate could be accomplished if a large excess (20 equiv) of the chloroformate and the base (potassium carbonate) were used (Scheme 1). Still, this procedure afforded the protected product **2** in somewhat variable yields (54–73%), along with recovered starting material. Further, even the use of a large excess of the chloroformate failed completely in the protection of aldehyde **3**.

Keywords: Halogenation; Pyrrole; Protecting groups; Carbamate.
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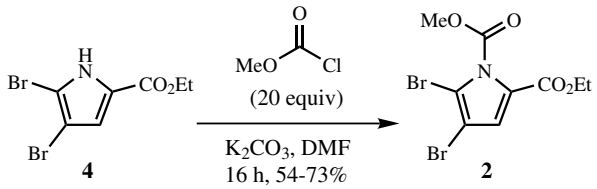


Scheme 1. Protection of pyrrole ester **4**.

In examining alternative methods for protecting the pyrrole nitrogen, it was noted that the conditions we had used earlier to install alkyl protecting groups on the pyrrole nitrogen all employed tetrabutylammonium iodide (TBAI). Without this additive, the reactions never went to completion. Since these reaction conditions are known to generate the corresponding alkyl iodides in situ, it was reasoned that a similar approach might work in the chloroformate reactions. To that end, the reaction of **3** with 5 equiv of methyl chloroformate in the presence of 1 equiv of tetrabutylammonium iodide and 5 equiv of potassium carbonate was undertaken (Table 1, entry 1).[6] Gratifyingly these conditions afforded the desired product **1** in 73% isolated yield.[7]

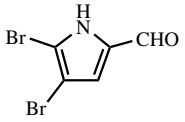
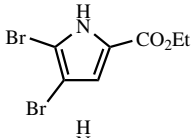
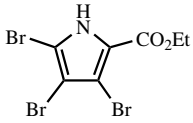
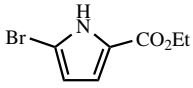
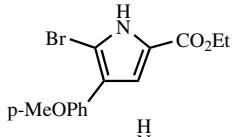
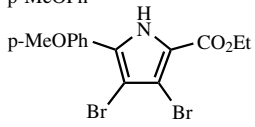
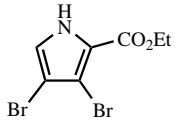
Although the original hypothesis was that the presence of tetrabutylammonium iodide would generate the more reactive iodoformate in situ[8] there was another possibility to consider—that the tetrabutylammonium iodide was simply acting as a phase-transfer catalyst to solubilize the carbonate base in DMF.[9] To differentiate between these two options, the reaction of **3** under the same set of reaction conditions, but using tetrabutylammonium chloride instead of iodide was performed (Table 1, entry 2). After the same reaction time (9 h), the reaction had not quite proceeded to completion, affording 57% of the desired product and 26% of the starting material. As a result, it appears unlikely that a simple phase-transfer argument is the sole reason for the improved reactivity under these conditions, although it may play a role.

Another piece of evidence supporting a direct role of the TBAI in the reaction was the observation that a full equivalent was required in order to effect complete conversion to the desired product. Attempts to use 0.5 equiv of TBAI afforded the product in 40% yield, with the remainder of the material being recovered starting material.

To examine the scope of these conditions, a few similarly hindered and electron-deficient pyrroles were subjected to the same reaction conditions (Table 1, entries 3–10).[7] As can be seen, pyrrole esters were also cleanly protected as carbamates under the TBAI conditions. Indeed, even tribromoesters were readily protected (entry 4).

In the course of these studies, it became clear that the difficulty in protecting pyrroles such as **3** and **4** stems more from an electronic/nucleophilic reason than a steric one. For example, for both monobromide esters in entries 5–8, the compounds could be protected with almost equal efficiency with or without added TBAI

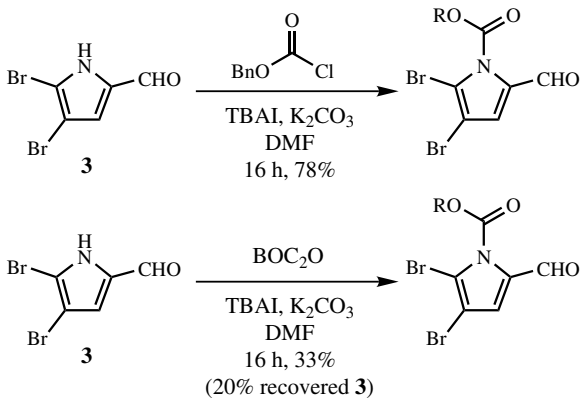
Table 1. TBAI-promoted protection of pyrrole esters and aldehydes with methyl chloroformate

Entry[a]	Substrate	Yield (%)[b]
1		73
2		57[c]
3		82
4		63
5		62
6		60[d]
7		89
8		74[e]
9		91
10		86

[a] Reaction conditions: 5 equiv methyl chloroformate, 5 equiv K_2CO_3, 1 equiv TBAI in DMF for 8 h.
[b] Isolated yield.
[c] Reaction using Bu_4NCl instead of TBAI. Starting material (26%) recovered.
[d] Reaction in the absence of TBAI.
[e] Reaction in the absence of TBAI. Starting material (8%) recovered.

(compare entries 5 and 6, 7 and 8). On the other hand, in any of the other cases, in which two or more bromides were present, the reactions in the absence of TBAI either failed entirely or afforded only modest conversion to the protected products, even after 24 h. This difference between steric and electronic effects is particularly noteworthy in entry 10. This 3,4-dibromopyrrole ester completely lacks any steric hindrance at the C5 position, but fails to afford any of the protected product in the absence of TBAI. As a result, it appears clear that the challenge in protecting these highly halogenated pyrrole esters and aldehydes is more of an electronic effect (poor nucleophilicity) than a steric effect.

The TBAI conditions also worked with other chloroformates, such as benzyl chloroformate to install the synthetically appealing CBz group (Scheme 2).[7] The even less reactive Boc anhydride was also employed under these conditions. Although the reaction did not proceed to completion under the present reaction conditions, it did afford 33% of the Boc protected pyrrole along with 20% of starting material. Curiously, these



Scheme 2. Installation of other protecting groups on aldehyde **3** using TBAI.

same conditions were ineffective with tosyl chloride. Nevertheless, a wide range of carbamates can now be readily prepared from these hindered and electron-deficient pyrroles.

In conclusion, we have developed conditions that are effective for the preparation of carbamates from poorly nucleophilic pyrroles. These conditions are expected to be effective for other poorly nucleophilic nitrogens, such as those found in amides or certain other nitrogen heterocycles.

Acknowledgements

The authors thank the State University of New York and the Research Foundation for financial support.

References and notes

1. The importance of these protecting groups in avoiding dehalogenation as a competing reaction has been reported earlier. Handy, S. T.; Bregman, H.; Lewis, J.; Zhang, Y. *Tetrahedron Lett.* **2003**, *44*, 427–430.
2. For example, treatment of methyl carbamate protected pyrrole-2-carboxaldehyde with NBS in a mixture of trifluoroacetic acid and sulfuric acid afforded 4,5-dibromopyrrole-2-carboxaldehyde in which the carbamate group had been cleaved.
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5. See Ref. 1 and Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456–2466.
6. Representative experimental procedure: To a solution of 270.4 mg (1.07 mmol) of **3** in DMF (3 mL) was added sequentially 505 mg (5.34 mmol) of methylchloroformate, 738.6 mg (5.34 mmol) of potassium carbonate and 395.0 mg (1.07 mmol) of tetrabutylammonium iodide. The resulting mixture was stirred at room temperature for 8 h. The reaction mixture was quenched with 50 mL of water and extracted with diethyl ether (2×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The resultant residue was purified by flash chromatography. Elution with 1:5 ethyl acetate–hexane afforded 241.2 mg (72.6%) of **1** as a red solid.
7. All new compounds exhibit spectral data consistant with the structures indicated. Representative data: Methyl 4,5-dibromo-2-formylpyrrole-1-carboxylate: ^{1}H NMR (360 MHz $CDCl_3$) 9.32 (s, 1H), 6.94 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (90 MHz $CDCl_3$): δ 178.43, 178.21, 132.88, 125.06, 118.91, 100.48, 35.93; IR (neat) 3103, 2949, 2923, 2830, 1663, 1511, 1356. 1-Methyl-2-ethyl 4,5-dibromopyrrole-1,2-dicarboxylate: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.0 (s, 1H), 4.26 (q, 2H), 3.95 (s, 3H), 1.32 (t, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 159.72, 128.54, 124.05, 119.16, 113.42, 98.64, 60.34, 35.76, 14.25; IR (neat) 3040, 2950, 1708, 1442, 1310, 1251, 908, 736. 1-Methyl-2-ethyl 3,4,5-tribromopyrrole-1,2-dicarboxylate: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.32 (q, 2H), 3.89 (s, 3H), 1.31 (t, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 158.41, 128.63, 124.13, 121.03, 112.47, 104.64, 61.52, 35.74, 14.29; IR (neat) 2950, 1706, 1461, 1407, 1323, 1243, 909, 742. 1-Methyl-2-ethyl 5-bromopyrrole-1,2-dicarboxylate: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 6.92 (d, 1H, $J = 3.6$), 6.19 (d, 1H, $J = 3.6$), 3.92 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 160.82, 123.39, 118.02, 111.89, 110.99, 51.15, 34.49; IR (neat) 2950, 1710, 1461, 1435, 1412, 1315, 1243, 1118, 904, 745. 1-Methyl-2-ethyl 3,4-dibromo-5-(4′-methoxyphenyl)pyrrole-1,2-dicarboxylate: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.27 (d, 2H, $J = 7.2$), 6.99 (d, 2H, $J = 7.2$), 3.89 (s, 3H), 3.85 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 160.63, 160.19, 138.37, 131.89 (2C), 121.62, 120.92, 114.00 (2C), 107.37, 101.64 (one other aromatic signal worth 2C's), 55.27, 51.39, 36.26; IR (neat) 2950, 2915, 2847, 1697, 1608, 1574, 1539, 1452, 1439, 1368, 1249, 1208, 1178, 1102, 1054, 1022, 840, 763. 1-Methyl-2-ethyl 5-bromo-4-(4′-methoxyphenyl)pyrrole-1,2-dicarboxylate: ^{1}H NMR ($CDCl_3$, 360 MHz): δ; ^{13}C NMR ($CDCl_3$, 90 MHz): δ; IR (neat) 3061, 2950, 2916, 2843, 1699, 1612, 1571, 1456, 1374, 1249, 1211, 1178, 1056, 1018, 841, 763. 1-Benzyl-4,5-dibromo-2-formylpyrrole-1-carboxylate: ^{1}H NMR (360 MHz $CDCl_3$): δ 9.35 (s, 1H), 7.36–7.26 (m, 3H), 7.11 (d, 2H, $J = 3.6$ Hz), 7.03 (s, 1H), 5.71 (s, 2H); ^{13}C NMR (90 MHz $CDCl_3$): δ 177.75, 177.32, 136.03, 132.38, 128.61, 127.71, 126.80, 125.48, 118.41, 101.06, 51.13; IR (neat) 3110, 3031, 2944, 2917, 2824, 1669, 1604, 1515, 1496, 1392. 1-*tert*-Butyl-4,5-dibromo-2-formylpyrrole-1-carboxylate: ^{1}H NMR (360 MHz $CDCl_3$): δ 9.70 (s, 1H), 7.06 (s, 1H), 1.64 (s, 9H); ^{13}C NMR (90 MHz $CDCl_3$): δ 178.60, 178.19, 134.53, 122.30, 111.75, 105.26, 29.63, 27.57; IR (neat) 3119, 2981, 2928, 2857, 1774, 1673, 1534, 1291. 1-Methyl-2-ethyl-3,4-dibromopyrrole-1,2-dicarboxylate: ^{1}H NMR ($CDCl_3$, 360 MHz): δ 6.82 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz): δ 160.18, 128.04, 127.36, 107.03, 100.14, 51.40, 38.77; IR (neat) 3117, 2951,

1704, 1516, 1488, 1431, 1373, 1343, 1244, 1194, 1113, 1068, 956, 820, 759.

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