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An unusual dehalogenation in the Suzuki coupling of 4-bromopyrrole-2-carboxylates

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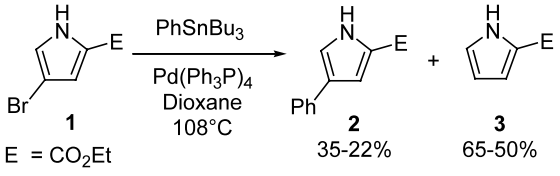
Abstract—An unusual dehalogenation of 4-bromopyrrole-2-carboxylates under Suzuki coupling conditions has been observed. This dehalogenation can be suppressed by protection of the pyrrole nitrogen. Using a BOC protecting group, not only is dehalogenation suppressed, but the protecting group is also removed under the reaction conditions.

Pyrroles are an important family of heterocyclic compounds. In particular, modified pyrroles and polypyrroles are the basis of a wide range of biologically important natural products.[1] Not surprisingly, there are a considerable number of methods available for the preparation of substituted pyrroles. Interestingly, many of these methods involve the final formation of the pyrrole nucleus from functionalized precursors. Far fewer approaches take pyrrole itself and elaborate this core. In part this is doubtless due to the greater difficulties associated with the regiocontrolled functionalization of pyrrole when compared to furan and thiophene.[2]

As part of a program directed at the preparation of members of the lamellarin family of natural products, we were interested in developing a method to install three separate aryl substituents in a regiocontrolled manner on a pyrrole-2-carboxylate ester.[3] Our plan was based on the ability to control the regiochemistry of halogenation of the pyrrole core and using this selectivity to control the location of the three aryl subunits. The beginning of these studies involved the coupling of 4-bromopyrrole-2-carboxylate ethyl ester **1** (Scheme 1). Much to our surprise, the attempted Stille coupling of **1** with tributylphenyltin under standard conditions led to the generation of the desired coupling product **2** as the minor product (<35%), with debrominated compound **3** being the major isolated product (>50%).

Although dehalogenation is not an uncommon side reaction in Stille couplings, it is unusual for it to be the dominant reaction pathway.[4] Indeed, Stille couplings have been employed by Banwell and co-workers in their synthesis of Lamellarins O and Q.[5] Similarly, Scott and co-workers have used a 4-stannylpyrrole carboxaldehyde in the preparation of a number of arylated pyrrole carboxaldehydes.[6] In all of these cases, the yields were >66%.

Faced with this problem, the first alternative that we explored was to change the type of cross-coupling reaction. Our choice was a Suzuki-type coupling, since dehalogenation is far less common in these reactions.[7] As can be seen in Scheme 2, coupling with phenylboronic acid did lead to some improvement in terms of the preparation of the desired coupling adduct **2**. Still, the best result that was obtained was 55% of compound **2** along with 28% of debrominated compound **3**. This ratio proved to be highly variable, with the ratio of these two compounds often times being closer to 1:1, although with good mass recovery (>80%).



Scheme 1. Dehalogenation in the Stille coupling reactions of 4-bromopyrrole-2-carboxylate **1**.

Keywords: Suzuki coupling; pyrroles; dehalogenation; protecting group.

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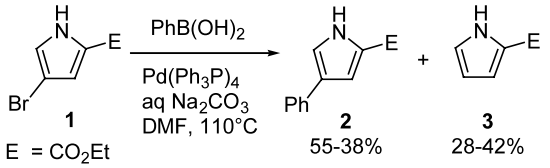
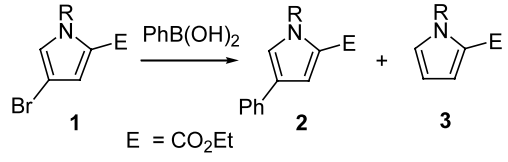


Scheme 2. Dehalogenation in the Suzuki couplings of 4-bromopyrrole-2-carboxylate **1**.

Although the two products could be readily separated by chromatography, the presence of such a significant degree of dehalogenation was troubling. In examining the major differences between our couplings and those reported in the literature, it was noted that in most cases the previous syntheses involve the use of *N*-protected pyrrole esters.[8] To see if the free NH moiety was indeed the source of the problem, protection of the pyrrole amine was explored.[9] The four protecting groups seen in Table 1 were prepared using standard methods. The TIPS group, although ideal due to the ease of its deprotection, failed to survive the reaction conditions required for the coupling (entry 1). Indeed, the TIPS group appeared to be removed at a rate competitive with the coupling reaction, since a nearly 1:1 mixture of coupling product **2** and debrominated product **3** was obtained.

Alkyl protecting groups were more stable to the reaction conditions (Table 1, entries 2 and 3) and did indeed suppress any dehalogenation. This observation supported our concerns regarding the free NH group being the factor leading to dehalogenation. At the same time, these alkyl protecting groups could be difficult to remove following the coupling reaction. From this perspective, a BOC group appeared to be ideal. Indeed, the Suzuki coupling of BOC-protected **1** with phenyl boronic acid led to almost exclusive preparation of compound **2** in which the protecting group has been removed under the reaction conditions, but presumably only after coupling has occurred (entry 4).[10]

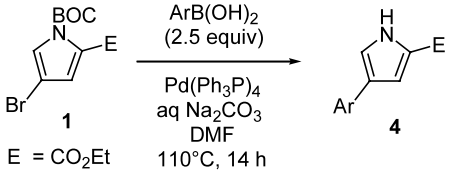
Table 1. Influence of pyrrole protecting group on the degree of dehalogenation



Entry	R[a]	%**2**/%**3**[b]
1	TIPS	48/35[c]
2	Me	75/–
3	Bn	72/–
4	BOC	68/5[c]

[a] $Pd(Ph_3P)_4$ (2 mol%), aq. Na_2CO_3/DMF, 110°C.
[b] Isolated yield.
[c] Protecting group lost, R = H in products

Table 2. Suzuki couplings with BOC-protected systems



Entry	Ar	%Yield[a]
1	3,4-Dimethoxyphenyl	80 (58)[b]
2	4-Fluorophenyl	68
3	3-Isopropoxy-4-methoxyphenyl	82
4	2,3,4-Trimethoxyphenyl	84 (65)

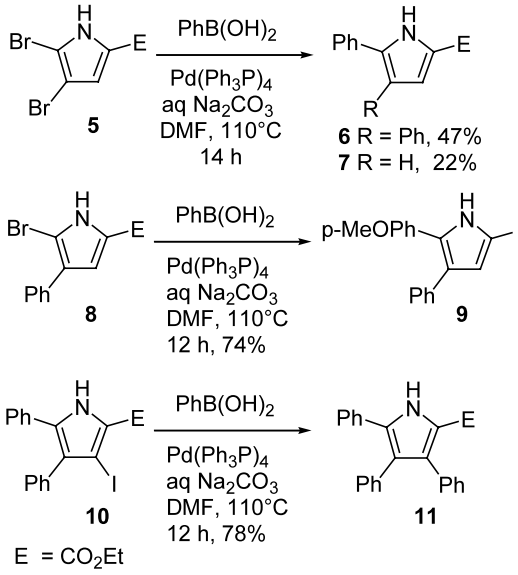
[a] Isolated yield.
[b] 1.2 equiv. of boronic acid.

With these improved conditions in hand, a series of couplings with BOC-protected pyrrole **1** were explored (Table 2).[11] As can be seen, these reactions afford uniformly good results. Although the use of only slight excess of the boronic acid (1.2 equiv.) afforded the coupling products in 58–65% yield, these yields could be further improved by using a larger excess of the boronic acid (2–3 equiv.). In this way, 68–84% yields of the 4-arylated products **4** can be readily obtained with only trace amounts (<5%) of the dehalogenation product **3**.

With respect to the dehalogenation reaction, the exact combination of electronic and regiochemical effects required for it to occur are not yet clear. Examining first 4-halopyrrole esters, good yields have been reported for the coupling of an unprotected 5-alkyl-3,4-dibromopyrrole ester,[12] 3,5-dialkyl-4-bromopyrrole ester,[12] and 3,4-dibromopyrrole ester.[5] Seemingly, all of these reports are at variance with our observations with pyrrole ester **1**, although in every case the exact electronics and substitution pattern are different. We have also noted that 4,5-dibromopyrrole ester **5** exhibits dehalogenation, but only at C4, affording a mixture of bis-coupling product **6** and mono-coupling product **7** (Scheme 3).

For 5-halopyrrole esters, very little information is available. The only substrates that have been reported are not protected (compound **8** and a 3,4-extended 5-bromopyrrole ester reported by Murashima).[13] In all cases, no significant dehalogenation was reported.

Finally, for 3-halopyrrole esters, the reports again are conflicting. We have observed no dehalogenation in the Suzuki coupling of an unprotected substrate such as **10**. Similarly, a 1,4,5-trialkylated-3-trifloxypyrrole ester is reported to afford an excellent yield of the desired coupling product.[14] On the other hand, Ghosez has noted significant dehalogenation in the coupling of an *N*-tosylated 2-vinyl-iodopyrrole.[15] This dehalogenation can be controlled by modification of the palladium catalyst.



Scheme 3. Couplings with 3-halo, 5-halo, and 4,5-dihalo pyrrole esters.

In light of these results, there are still a number of questions concerning the electronic and regiochemical features that facilitate the dehalogenation reaction of halopyrrole esters. What can be stated with assurance is that the 4 position of unsubstituted pyrrole-2-carboxylates is particularly prone to dehalogenation under cross-coupling conditions. This dehalogenation can be avoided by use of a protecting group on the pyrrole nitrogen. With a BOC group, the protecting group is also cleaved under the coupling conditions, thereby avoiding a separate deprotection step. The mechanism of this facile dehalogenation and its implications for Suzuki couplings of halopyrroles in general is currently under investigation and will be reported in due course.

Acknowledgements

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9. Interestingly, as we were pursuing these investigations, Dr. Cai of Hoffmann-La Roche informed us of a similar observation that they have made in the coupling of 3-bromoindoles in which protection of the indole nitrogen is required to avoid extensive dehalogenation.
10. This deprotection appears to be a thermal reaction. We have noted that simply heating a solution of pyrrole ester **1** in DMF to 120°C for 6 h is sufficient to completely remove the BOC group. Lower temperatures (100°C) do not cleave the BOC group. For similar observations, see: (BOC removal), Fuerstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275–8280. (BOC retained), Johnson, C. K.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025–1027.
11. General procedure for the coupling reaction: To a round-bottom flask was added 100 mg (0.32 mmol) of BOC-protected pyrrole ester **1**. DMF (2.5 mL) was added and the mixture stirred under argon. To this solution was then added sequentially 33 mg (0.016 mmol) of palladium tetrakis-triphenylphosphine and 167 mg (0.79 mmol) of 2,3,4-trimethoxyphenylboronic acid. The mixture was heated to 70°C and 540 mg (2.88 mmol) of sodium carbonate dissolved in minimal water added. The reaction was then heated to 110°C for 14 h. After cooling to rt, the reaction was diluted with water (15 mL) and extracted with diethyl ether (3×15 mL). The organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. Chromatography (20% ethyl acetate/hexanes) afforded 82.0 mg (84%) of ethyl 4-(2′,3′,4′-trimethoxyphenyl)pyrrole-2-carboxylate as a white solid. ^{1}H NMR (360 MHz, $CDCl_3$) 9.16 (br s, 1H), 7.41 (m, 1H), 7.20 (m, 1H), 7.18 (d, 7.2 Hz, 1H), 6.70 (d, $J=7.2$ Hz, 1H), 4.33 (q, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 1.37 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) 161.14, 152.11, 150.87, 142.77, 122.66, 122.15, 122.09, 121.60, 121.40, 113.69, 107.69, 60.86, 60.34, 60.24, 55.98, 14.43. Spectral data for other coupling products: ethyl 4-(4′-iso-

propoxy-3′-methoxyphenyl)pyrrole-2-carboxylate: ^{1}H NMR (360 MHz, $CDCl_3$) 10.10 (br s, 1H), 7.11–7.08 (m, 2H), 7.02 (s, 1H), 6.91 (d, $J=7.2$ Hz, 1H), 6.79 (d, $J=7.8$ Hz, 1H), 4.52 (septet, 1H), 4.26 (q, 2H), 4.33 (s, 3H), 1.37 (d, $J=7.6$ Hz, 6H), 1.34 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) 160.55, 150.00, 146.30, 126.63, 125.33, 123.52, 119.90, 115.42, 115.24, 111.60, 102.80, 71.31, 60.81, 55.89, 22.06, 14.37. Ethyl 4-(4′-fluorophenyl)pyrrole-2-carboxylate: ^{1}H NMR (360 MHz, $CDCl_3$) 9.51 (br s, 1H), 7.47–7.44 (m, 2H), 7.17–7.14 (m, 2H), 7.06–7.01 (m, 2H), 4.25 (q, 2H), 1.37 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) 161.52 (d, J(C,F) = 243 Hz), 161.22, 130.64 (d, J(C,F) = 2.7 Hz), 126.69 (d, J(C,F) = 7.2 Hz), 125.81, 123.67, 119.21, 115.51 (d, J(C,F) = 20.7 Hz), 112.29, 60.55, 14.38. Ethyl 4-(3′,4′-dimethoxyphenyl)pyrrole-2-carboxylate: ^{1}H NMR (360 MHz, $CDCl_3$) 9.13 (br s, 1H), 7.16–7.13 (m, 2H), 7.09 (s, 1H), 7.06 (d, $J=8.2$ Hz, 1H), 6.86 (d, $J=8.2$ Hz, 1H), 4.34 (q, 2H), 3.94 (s, 3H), 3.88 (s, 3H), 1.37 (t, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) 161.04, 149.11, 147.72, 127.63, 126.75, 123.54, 118.76, 117.51, 112.15, 111.52, 108.88, 60.43, 55.91, 55.82, 14.41.

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