A simple guide for predicting regioselectivity in the coupling of polyhaloheteroaromatics

Scott T. Handy[ab] **and Yanan Zhang**[b]

Received (in Bloomington, IN, USA) 12th September 2005, Accepted 20th October 2005
First published as an Advance Article on the web 21st November 2005
DOI: 10.1039/b512948f

A simple guide for predicting the order and site of coupling (Suzuki, Stille, Negishi, Sonogashira, *etc.*) in polyhaloheteroaromatics based upon the ^{1}H NMR chemical shift values of the parent non-halogenated heteroaromatics has been developed.

Heteroaromatic compounds serve as the core of a wide range of interesting and important compounds and materials. While there are countless ways to prepare such compounds, one method that provides excellent versatility is the family of cross-coupling reactions.[1] These reactions provide a means for installing a wide range of functionalized and non-functionalized carbon and heteroatom substituents with exquisite regiocontrol. As such, they have been employed in countless situations in the synthesis of heteroaromatic compounds.

At the same time, there is a clear limitation to this procedure: the installation of more than one substituent. We have encountered a graphic example of this issue in our recently reported synthesis of lamellarin G trimethyl ether.[2] In this synthesis, each of the three aryl groups on the pyrrole core was installed using a Suzuki cross-coupling reaction (Fig. 1). Such an approach necessitated the use of three sequential halogenation/cross-coupling sequences, thereby insuring that the synthesis could not be less than 6 steps (and is actually 11 steps). Similar issues for the installation of multiple substituents have been encountered by others as well.

A more ideal situation would be to subject polyhalogenated heteroaromatics to a one-pot regioselective polycoupling reaction to directly afford the polysubstituted product. Such a concept raises two main questions: 1. What governs the regioselectivity of coupling in polyhaloheteroaromatics, and 2. Can multiple regioselective couplings be accomplished in a one-pot manner?

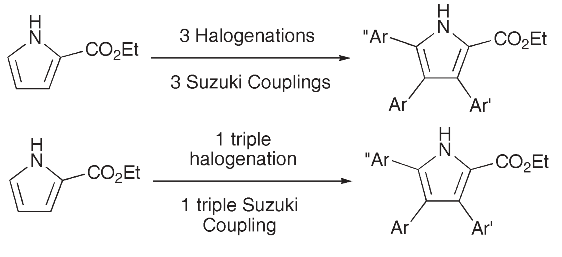


Fig. 1 Sequential *versus* poly coupling approaches.

A number of different groups have studied the regioselective coupling of different polyhaloheteroaromatic systems, often with considerable success.[3–23] What is missing, however, is a method for predicting the regioselectivity of coupling in new polyhaloheteroaromatic compounds. Bridging this gap is the focus of this communication.

Since oxidative addition is often considered to be irreversible and many times, at least in the Suzuki coupling, the rate determining step, it is reasonable to assume that this stage is responsible for the regioselectivity that is observed.[24] The electronic preference for oxidative addition has been reported to parallel that of nucleophilic aromatic substitution (NAS) in the same polyhaloaromatics.[25] While NAS data is not available for many heteroaromatics, the ease of NAS parallels the degree of electron deficiency of the carbon bearing the halogen leaving group.[26]

Electron deficiency for aromatic systems can be determined by calculation, but we sought a general experimental method, particularly one based on NMR spectroscopy. NMR chemical shift values are very sensitive to electronic effects and can afford a picture of the electronic environment of different parts of the molecule. Further, if one makes the assumption that the intrinsic electronics of the heteroaromatic system will be dominant and the influence of the introduction of the halogens comparatively modest, then a very simple method can be envisioned—^{1}H NMR spectroscopy of the parent, non-halogenated heteroaromatic systems. Such a leap is not unreasonable, if one considers the relatively modest electronic effect that bromo and iodo groups (the most common functional groups for cross-coupling reactions) have on electrophilic aromatic substitution reactions. The major advantage of this simplification is the fact that ^{1}H NMR data is already reported and tabulated for an enormous range of substituted and unsubstituted heteroaromatic systems.[27] Further, even in cases where such information is not available, the non-halogenated compounds are the most likely precursors to the polyhalo products. As a result, the identity of the individual aromatic ^{1}H signals can be readily established.

With this hypothesis in mind, the existing literature data for regioselectivity in the coupling of five-member heteroaromatics was examined (Fig. 2). For thiazoles (2,4-, 2,5-dibromo, or 2,5-ditrifloxy), the initial site of coupling is always at the more electron deficient center (and thus the carbon with the proton with the larger chemical shift).[3–8] Further, the same selectivity is observed for a wide range of couplings, including Sonogashira couplings,[3,4] Negishi couplings,[5,6] and Stille couplings.[4,7,8] The remaining halogen or halogen equivalent is also capable of coupling, undergoing either Stille[3,7,8] or Suzuki couplings.[5] Dibromoimidazoles behave similarly, with initial coupling

---

[a] *Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132. E-mail: shandy@mtsu.edu; Fax: 615-898-5182; Tel: 615-494-8655*
[b] *Department of Chemistry, Binghamton University, Binghamton, NY 13902*

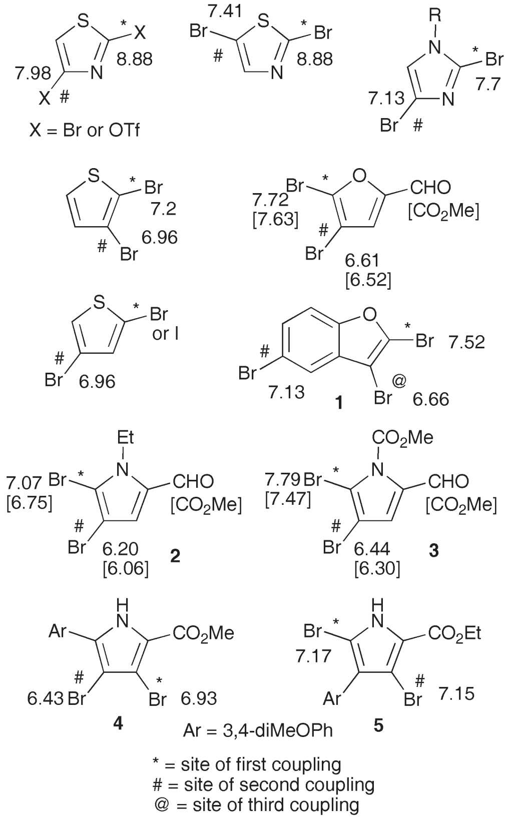


Fig. 2 Five-member heteroaromatics.

(Stille,[9] Kumada, Negishi, or Suzuki[10]) occurring at the C2 position, which is the position with the higher chemical shift value. The Suzuki coupling is particularly noteworthy, since this is the first report in which two halogens are coupled regioselectively under the same coupling conditions in a single pot.[10]

Moving to monoheteroatom-containing heteroaromatics, thiophene again follows the chemical shift trend. In this case, the electronic difference is quite modest as exemplified by a small (0.24 ppm) chemical shift difference between C2 and C3, but is still sufficient to direct the initial coupling to the more electron deficient C2 site for a wide range of couplings (Negishi,[11,14] Sonogashira,[12] Stille,[12] and Suzuki[12,13]). Again, the second bromide is capable of undergoing coupling, although under slightly more vigorous conditions.[13] Furans have been extensively studied by Bach and co-workers and undergo selective coupling (Stille, Negishi, Sonogashira) at the more electron-deficient C5 position.[15] This holds true for both the 2-formyl and 2-carboxylate ester compounds, which display similar levels of electronic differentiation based upon the chemical shift difference between C4 and C5. And a benzo version of these compounds (benzofuran **1**) follows the chemical shift trend for order of coupling.[16] This is a very interesting example, since all three halogens could be coupled in a regioselective manner, employing a Negishi coupling, followed by a Kumada coupling, and finally a second Negishi coupling.

Our own efforts have focused on pyrroles. Here a series of dibromo compounds **2**, **3**, **4**, and **5** have all been studied (Fig. 2).[17] Under Suzuki coupling conditions [Pd(Ph$_3$P)$_4$, Na$_2$CO$_3$, DMF, 90 °C], all of these substrates follow the expected trend of the more electron deficient (and thus the larger chemical shift) site undergoing coupling first.[18]

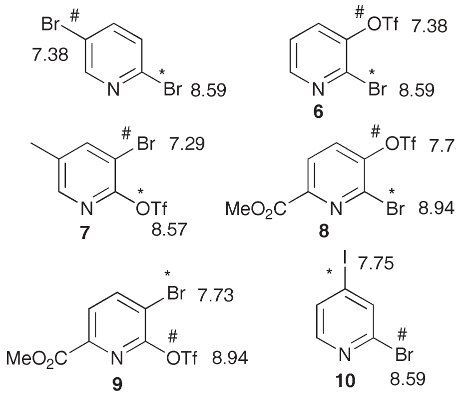
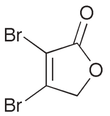


Fig. 3 Six-member heteroaromatics.

Six-member heteroaromatics follow the same guidelines (Fig. 3). Thus, 2,5-dibromopyridine has been noted to undergo selective coupling at the C2 position using a Kumada,[19] Sonogashira,[20] or Suzuki coupling.[21] The pyridine compounds also provide an interesting opportunity to explore the effect of having different halogens or halogen equivalents in the same molecule. Thus, both pyridine **6** and regioisomer **7** undergo selective coupling at the more electron deficient C2 position.[22] Interestingly, this same observation does not hold true for isomers **8** and **9**. In this case, the bromide underwent the first coupling, regardless of position. In the case of pyridine **10**, Kumada couplings occur first at the less electron deficient C4 position with the more reactive iodide.[23] Coincidentally, this is the second example of both halogens of a dihalo-system being able to be coupled in the same reaction pot. Based upon the observations of these "mixed halogen" systems, it is reasonably clear that the ^{1}H NMR chemical shift method (and thus the electronic preference of the heteroaromatic ring) can be overcome by halogens of sufficiently different intrinsic reactivity.

Finally, there is evidence that the results of heteroaromatic systems can be extended to other types of coupling partners. Thus, 2,3-dibromofuranone **11** undergoes a regioselective Stille coupling at the more electron deficient C3 site and then undergoes coupling at the C2 position with some difficulty.[28] Although there are few other examples of couplings on nonheteroaromatic polyhalo-systems, it does have promise to be an interesting avenue of future research.


11

In conclusion, the ^{1}H NMR method for predicting the site and order of coupling on polyhaloheteroaromatics has much promise in simplifying the practical utilization of such substrates in organic synthesis. There is the potential for limitation in this method for predicting the order of coupling in systems with more than two halogens, since the installation of the first substituent will influence the electronics of the heteroaromatic core. In the one existing example (benzofuran **1**), the ^{1}H NMR method is accurate, but more study is required before a clear determination of this possible limitation can be made. Such efforts are underway in this laboratory and will be reported in due course.

Notes and references

1 For a recent and thorough monograph covering cross-coupling reactions, see: *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley Interscience, New York, 2002, vol. 1.

2 S. T. Handy, Y. Zhang and H. Bregman, *J. Org. Chem.*, 2004, **69**, 2362.

3 N. D. P. Cosford, L. Tehrani, J. Roppe, E. Schweiger, N. D. Smith, J. Anderson, L. Bristow, J. Brodkin, X. Jiang, I. McDonald, S. Rao, M. Washburn and M. A. Varney, *J. Med. Chem.*, 2003, **46**, 204.

4 K. C. Nicolaou, N. P. King, M. R. V. Finlay, Y. He, F. Roschangar, D. Vourloumis, H. Vallberg, F. Sarabia, S. Ninkovic and D. Hepworth, *Bioorg. Med. Chem.*, 1999, **7**, 665.

5 T. Bach and S. Heuser, *Tetrahedron Lett.*, 2000, **41**, 1707.

6 T. Bach and S. Heuser, *J. Org. Chem.*, 2002, **67**, 5789; T. Bach and S. Heuser, *Angew. Chem., Int. Ed.*, 2001, **40**, 3184.

7 A. Dondoni, M. Fogagnolo, A. Medici and E. Negrini, *Synthesis*, 1987, 185.

8 J. Shao and J.S. Panek, *Org. Lett.*, 2004, **6**, 3083.

9 D. Wang and J. Haseltine, *J. Heterocycl. Chem.*, 1994, **31**, 1637.

10 I. Kaswasaki, M. Yamashita and S. Ohta, *J. Chem. Soc., Chem. Commun.*, 1994, 2085.

11 K. Tamao, K. Nakamura, H. Ishii, S. Yamaguchi and M. Shiro, *J. Am. Chem. Soc.*, 1996, **118**, 12496.

12 R. Pereira, B. Iglesias and A. R. de Lera, *Tetrahedron*, 2001, **57**, 7871.

13 B. Raju, C. Wu, A. Kois, E. Verner, I. Okun, F. Stavros and M.F. Chan, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2651.

14 J. O. Karlsson, S. Gronowitz and T. Frejd, *J. Org. Chem.*, 1982, **47**, 374.

15 T. Bach and L. Krueger, *Eur. J. Org. Chem.*, 1999, 2045; T. Bach and L. Krueger, *Tetrahedron Lett.*, 1998, **39**, 1729; T. Bach and L. Krueger, *Synlett*, 1998, 1185.

16 T. Bach and M. Bartels, *Synlett*, 2001, 1284; T. Bach and M. Bartels, *Tetrahedron Lett.*, 2002, **43**, 9125.

17 S. T. Handy, I. Vulfova, J. J. Sabatini and Y. Zhang, Unpublished results.

18 Interestingly, the regioselectivity for compound **5** can be reversed using EtOH/toluene as the solvent. The reason for this solvent-induced reversal of regioselectivity is not clear, but can be extended to 2,3-dibromothiophene as well. The only related report was a reversal of regioselectivity upon the addition of copper iodide as a co-catalyst: K.-M. Ryu, A. K. Gupta, J. W. Han, C. H. Oh and C.-G. Cho, *Synlett*, 2004, 2197; W.-S. Kim, H.-J. Kim and C.-G. Cho, *J. Am. Chem. Soc.*, 2003, **125**, 14288.

19 A. Minato, K. Suzuki, K. Tamao and M. Kumada, *J. Chem. Soc., Chem. Commun.*, 1984, 511.

20 J. W. Tilley and S. Zawoiski, *J. Org. Chem.*, 1988, **53**, 386.

21 S. T. Handy, T. Wilson and K. Minassian, Unpublished results.

22 T. R. Kelly and F. R. Lang, *J. Org. Chem.*, 1996, **61**, 4623.

23 X.-F. Duan, X.-H. Li, F.-Y. Li and C.-H. Huang, *Synthesis*, 2004, 2614.

24 Although this is the general assumption, it may not always hold true. For example, see: A. H. Roy and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 1232; P. Espinet and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 4704.

25 J.-F. Fauvarque, F. Pfleuger and M. Troupel, *J. Organomet. Chem.*, 1981, **208**, 419.

26 T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper & Row Publishers: New York, 1987, pp. 640–643.

27 The ^{1}H NMR data in Fig. 2 and 3 (except for the pyrrole data, which was determined experimentally) are from: E. Pretsch, P. Buehlmann and C. Affolter, *Structure Determination of Organic Compounds*, Springer-Verlag: Berlin, 2002, pp. 186–197.

28 R. Rossi, F. Bellina and E. Raugei, *Synlett*, 2000, 1749.