Nucleophilic ortho-Allylation of Pyrroles and Pyrazoles: An Accelerated Pummerer/Thio-Claisen Rearrangement Sequence

Andrew J. Eberhart, Claudio Cicoira, and David J. Procter*

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, U.K.
david.j.procter@manchester.ac.uk

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ABSTRACT

Arylsulfanyl groups direct the metal-free, regiospecific, nucleophilic ortho-allylation of pyrroles and pyrazoles. Mechanistic studies support the intermediacy of allylsulfonium salts that undergo facile thio-Claisen rearrangement onto the heterocyclic ring, giving products of coupling. The strategy has been adapted to allow regiospecific propargylation of the heterocyclic substrates.

Functionalized aromatic and heteroaromatic systems form the cores of many pharmaceuticals, agrochemicals, and functional materials. Specifically, substituted pyrroles1–3 and pyrazoles1d–1f with their broad spectrum of biological activities find application in many fungicides, insecticides, herbicides, statins (Lipitor), anti-inflammation (Celebrex),2 and antitumor drugs (Figure 1), thus highlighting the importance of accessing elaborated systems. Functionalization of these heterocycles heavily relies on the electrophilic nature of the systems (exploited in Friedel–Crafts3 type reactions or C–H activation4 processes using transition-metal catalysts) and can be problematic due to regioselectivity issues. Alternative approaches involving the de novo synthesis of the functionalized heterocycles,5 using elaborated building blocks, are therefore often adopted. Although direct metalation6 with stoichiometric reagents and cross-couplings7 of heteroaryl derivatives are known, the use of activating substituents to facilitate nucleophilic substitution is an underexploited approach. In recent years, Pummerer-type8 coupling reactions utilizing sulfoxide substituents have begun to emerge for the nucleophilic alkylation of heteroaromatic9 systems. Oshima and Yorimitsu10a–d as well as Maulide10e–f have recently explored interrupted Pummerer reactions in approaches to benzofurans and α-arylation reactions, while we have explored interrupted Pummerer reactions in approaches to benzofurans and α-arylation reactions, while we have...
reported the allylation\(^{(1a)}\) and propargylation\(^{(1b)}\) of aromatic systems.

**Figure 1.** Selected biologically active pyrroles and pyrazoles.

Herein we report a nucleophilic ortho-allylation of pyrrole and pyrazole sulfoxides, such as 1, that proceeds by a heterocycle accelerated, interrupted Pummerer/thio-Claisen\(^{(12)}\) rearrangement sequence involving allylsulfonium salts 4 (Scheme 1). The procedure is general, metal-free, and regio-specific with regard to both coupling partners.

We began investigating the ortho-allylation reaction of pyrazole sulfoxide 1a with allytrimethylsilane 3a (Table 1). Using our previously established conditions\(^{(11)}\) with TFAA (trifluoroacetic anhydride) as the electrophilic activating agent in MeCN (entry 1), the allylation product 2a was observed as a minor component. Changing the solvent to CH\(_2\)Cl\(_2\) improved the reaction slightly (entries 2–3), while heating was not helpful. The use of Tf\(_2\)O (trifluoromethanesulfonyl anhydride) significantly enhanced the reaction to give 2a in 53\% yield (entry 7).\(^{(13)}\) In contrast, when investigating the reaction of pyrrole sulfoxide 1b, TFAA appears to be the better activating agent (entry 9) and employing MeCN as solvent (entry 10) gave 2b in an excellent yield of 98\%.\(^{(13)}\)

**Table 1. Optimization of the ortho-Alllylation**

| entry | HetAr | solvent | anhyd. | conditions | yield (%) |
|-------|-------|---------|--------|------------|-----------|
| 1     | 1a    | MeCN    | TFAA   | –40 °C to rt; 2 h | <5        |
| 2     | 1a    | CH\(_2\)Cl\(_2\) | TFAA   | –78 °C to rt; 2 h | 14        |
| 3     | 1a    | CH\(_2\)Cl\(_2\) | TFAA   | –78 °C to rt; 18 h | 24        |
| 4     | 1a    | DCE     | TFAA   | –78 to 60 °C 2 h | 13        |
| 5     | 1a    | DCE     | Tf\(_2\)O | –78 to 60 °C 2 h | 18        |
| 6     | 1a    | CH\(_2\)Cl\(_2\) | Tf\(_2\)O | –78 °C to rt; 2 h | 47        |
| 7     | 1a    | CH\(_2\)Cl\(_2\) | Tf\(_2\)O | –78 °C to rt; 18 h | 53        |
| 8     | 1b    | CH\(_2\)Cl\(_2\) | Tf\(_2\)O | –78 °C to rt; 18 h | 14\(^{14}\) |
| 9     | 1b    | CH\(_2\)Cl\(_2\) | Tf\(_2\)O | –78 °C to rt; 18 h | 41\(^{14}\) |
| 10    | 1b    | MeCN    | TFAA   | –40 °C to rt; 18 h | 98\(^{14}\) |
| 11    | 1b    | MeCN    | TFAA   | –40 °C to rt; 2 h | 95\(^{14}\) |
| 12    | 1b    | MeCN    | TFAA   | –40 °C; 2 h | 92\(^{14}\) |

\(^{14}\) Yields determined by \(^{1}H\) NMR.\(^{(13)}\)

Having identified optimized conditions for the allylation of both pyrazoles and pyrroles, we next investigated the substrate scope. Pleasingly, the ortho-allylation of pyrrole was not restricted with regard to the position of the sulfoxide moiety; both 1b and its regioisomer 1c (entries 1 and 6; Table 2) underwent allylation in high yields. The reaction is also tolerant to various allylsilanes, allowing high yielding allylation when using functionalized silanes 3b–c (entries 2–3) and the extended allylsilanes 3d–e (entries 4–5). Interestingly, the reaction is stereocconvergent with regard to alkene geometry, since both silanes 3d and 3e give products of allylation favoring the E-isomer (entries 4–5).

Although we mainly explored the reactivity with tosyl-protected pyrrole, the unprotected N–H pyrrole 1d also successfully underwent allylation (entry 7). Analogously, phenylsulfinyl-pyrazoles 1a, 1e, 1f, and 1g were successfully allylated under these conditions in good yields (entries 8–10 and 13), showing more efficient reactivity when ortho-allylation at the 4-position of pyrazole is possible.\(^{(14)}\) A variety of commonly used protecting groups are tolerated in the allylation of pyrazoles (entries 9, 10, and 13). Functionalized silanes 3b and 3c can also be used with

\(^{(13)}\) See Supporting Information for complete optimization table.
\(^{(14)}\) This is in agreement with the typical relative reactivities of the positions on pyrazoles; see ref 3.
Table 2. Scope of ortho-Allylation

| entry | reactant | product | yield (%) |
|-------|----------|---------|-----------|
| 1     | 1        | 3a      | 89        |
| 2     | 1        | 3b      | 88        |
| 3     | 1        | 3c      | 86        |
| 4     | 1        | 3d      | 93        |
| 5     | 1        | 3e      | 84        |
| 6     | 1        | 3f      | 49        |
| 7     | 1        | 3g      | 53        |
| 8     | 1        | 3h      | 45        |
| 9     | 1        | 3i      | 82        |
| 10    | 1        | 3j      | 63        |
| 11    | 1        | 3k      | 52        |
| 12    | 1        | 3l      | 77        |
| 13    | 1        | 3m      |           |

| Conditions: entries 1–6: TFAA (2.5 equiv), MeCN, −40 °C to rt, 18 h; entry 7: TFAA (2.5 equiv), CH₂Cl₂, −40 to 0 °C, 2 h; entries 8–13: T[{subscript}2]O (2.5 equiv), CH₂Cl₂, −78 °C to rt, 18 h. ⁶ Crotly-TMS (E/Z, 5/1), giving mixture (E/Z, 11/1). ⁷ Hept-2-en-1-yltrimethylsilane (E/Z, 1/9), giving mixture (E/Z, 17/1). ⁸ 100 °C MW, 2 h. ⁹ 60 °C MW, 2 h. |

The activation of sulfoxides with TFAA or Tf₂O allows for two plausible mechanisms. In a vinylogous Pummerer reaction,⁹b N-lone pair donation with concomitant triflate expulsion could form an extended thionium ion, allowing direct nucleophilic attack at the heterocycle followed by rearomatization.⁶a Alternatively, the activated sulfoxide could undergo an interrupted Pummerer reaction¹¹ followed by a thio-Claisen rearrangement and rearomatization. The former pathway could in theory lead to regioisomeric products of allylation, whereas the process described shows complete ortho-selectivity. Moreover, the use of the extended alkenylsilanes 3d and 3e (entries 4 and 5) selectively produced linear allylation products from double-allylic inversion. This strongly suggests a pathway proceeding through a sigmatropic rearrangement of allylsulfonium salt 4. Alternatively, allylsulfonium salt 4, from an interrupted Pummerer reaction, could participate in intermolecular Friedel–Crafts type allylations in which 4 acts as an electrophilic allylating agent.⁶a The lack of crossover products from the reaction of 1b when 1 equiv of 3-(p-tolylthio)-1-tosyl-pyrrrole 5b was present (Scheme 2A) demonstrates the intramolecularity of the allylation and rules out an intermolecular Friedel–Crafts-type process. The experiment resulted in complete allylation of the starting sulfoxide 1b and recovery of 5b. Similar results were obtained from an analogous reaction of sulfoxide 1h in the presence of sulfide 5a.

The relative ¹⁄₂ values as determined by individual reactions for 1b/1c/1f/1a/diphenylsulfoxide¹¹a are 1500:1500:1020:3.2:1 (±10%), respectively.¹⁶b In addition, competition experiments reacting pyrrole sulfoxide 1b in the presence of 1c and analogously, pyrazole sulfoxide 1a in the presence of 1f, with limiting allylTMS, showed a preference for the consumption of sulfoxides 1b and 1a, suggesting steric factors control the formation of 4 (Scheme 2B).¹⁷ Furthermore, competitions between 1a and 1i, and 1b and 1i, with limiting allylTMS indicated a preference for consumption of the heterocyclic substrates (Scheme 2C). These results, in conjunction with the relative reaction rates, suggest that rearrangement onto the heterocyclic systems is accelerated: the overall allylation process to form 2a and 2b is much faster comparatively to the allylation of diphenyl sulfoxide, and the intramolecular competition shows complete selectivity for reaction on the heterocyclic ring.

A proposed mechanism for the ortho-allylation of pyrrole and pyrazole sulfoxides involves an interrupted Pummerer reaction of the activated sulfoxide 6, to form allylsulfonium salt 4, which can then undergo a thio-Claisen rearrangement followed by rearomatization to give the product 2 (Scheme 3).¹⁸ The products of ortho-allylation are rich in synthetic potential, as both the allyl and organosulfanyl¹⁶d,¹¹a,¹⁹ groups can be utilized as handles for further manipulation.

Footnotes:
(15) The activation of sulfoxides with TFAA or Tf₂O is well documented; see ref 8.

(16) See Supporting Information for (a) a schematic of alternative reaction pathways and (b) a table of relative reaction ¹⁄₂.

(17) Formation of allylsulfonium salt from diphenyl sulfide is fast; see ref 11.

(18) Preliminary studies show that similar products can be obtained from the corresponding sulfides using allyl iodide and silver tetrafluoroborate. However, complex mixtures of multiple allylation products as well as regioisomers are obtained.
Preliminary studies show how the process can be exploited in a tandem nucleophilic ortho-allylation/electrophilic substitution sequence in the formation of 7a, or as part of an approach to more complex heterocycles such as 7b (Scheme 4).

Furthermore, under the conditions developed here, propargylsilanes in conjunction with pyrazole and pyrrole sulfoxides give the respective products of nucleophilic ortho-propargylation 8a and 8b in high yields (Scheme 5).

In summary, pyrrole and pyrazole sulfoxides undergo ortho-allylation by a heterocycle-accelerated interrupted Pummerer/thio-Claisen rearrangement sequence. The operationally simple and metal-free process allows the addition of allylic and propargylic nucleophiles with C–H substitution and shows complete regiospecificity with regard to both coupling partners.

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Supporting Information Available. Optimization table, additional mechanistic studies, experimental procedures, characterization data, $^1$H and $^{13}$C spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.