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

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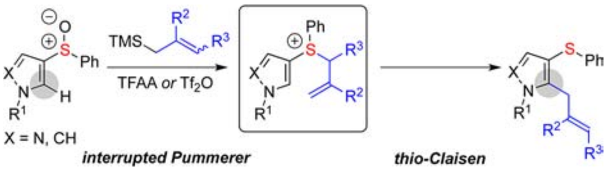
ABSTRACT



Arylsulfinyl 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 pyrroles[1a−c] and pyrazoles[1d−g] 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–Crafts[3] type reactions or C–H activation[4] 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 metalation[6] with stoichiometric reagents and cross-couplings[7] of heteroaryl derivatives are known, the use of activating substituents to facilitate nucleophilic substitution is an underexploited approach. In recent years, Pummerer-type[8] coupling reactions utilizing sulfoxide substituents have begun to emerge for the nucleophilic alkylation of heteroaromatic[9] systems. Oshima and Yorimitsu[10a−d] as well as Maulide[10e−f] have recently explored interrupted Pummerer reactions in approaches to benzofurans and in α-arylation reactions, while we have

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reported the allylation[11a] and propargylation[11b] of aromatic systems.

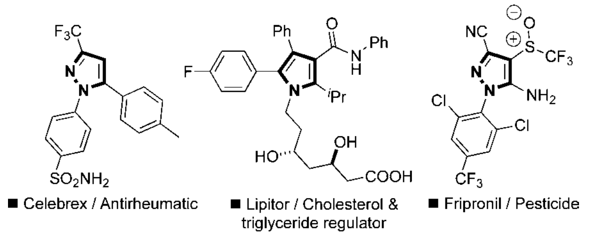
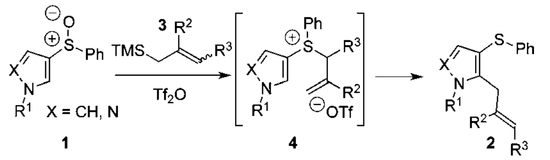


Figure 1. Selected biologically active pyrroles and pyrazoles.

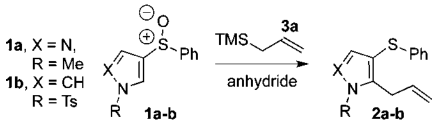
Herein we report a nucleophilic *ortho*-allylation of pyrrole and pyrazole sulfoxides, such as **1**, that proceeds by a heterocycle accelerated, interrupted Pummerer/thio-Claisen[12] rearrangement sequence involving allylsulfonium salts **4** (Scheme 1). The procedure is general, metal-free, and regiospecific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

Scheme 1. Nucleophilic *ortho*-Allylation (X = N, CH)



We began investigating the *ortho*-allylation reaction of pyrazole sulfoxide **1a** with allyltrimethylsilane **3a** (Table 1). Using our previously established conditions[11a] 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_2Cl_2 improved the reaction slightly (entries 2−3), while heating was not helpful. The use of Tf_2O (trifluoromethanesulfonic 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*-Allylation



entry	HetAr	solvent	anhyd.	conditions	yield (%)
1	**1a**	MeCN	TFAA	−40 °C to rt; 2 h	<5
2	**1a**	CH_2Cl_2	TFAA	−78 °C to rt; 2 h	14
3	**1a**	CH_2Cl_2	TFAA	−78 °C to rt; 18 h	24
4	**1a**	DCE	TFAA	−78 to 60 °C 2 h	13
5	**1a**	DCE	Tf_2O	−78 to 60 °C; 2 h	18
6	**1a**	CH_2Cl_2	Tf_2O	−78 °C to rt; 2 h	47
7	**1a**	**CH_2Cl_2**	**Tf_2O**	**-78 °C to rt; 18 h**	**53**
8	**1b**	CH_2Cl_2	Tf_2O	−78 °C to rt; 18 h	14[a]
9	**1b**	CH_2Cl_2	TFAA	−78 °C to rt; 18 h	41[a]
10	**1b**	**MeCN**	**TFAA**	**-40 °C to rt; 18 h**	**98**[a]
11	**1b**	MeCN	TFAA	−40 °C to rt; 2 h	95[a]
12	**1b**	MeCN	TFAA	−40 °C; 2 h	92[a]

[a] Yields determined by ^1H 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 stereoconvergent 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

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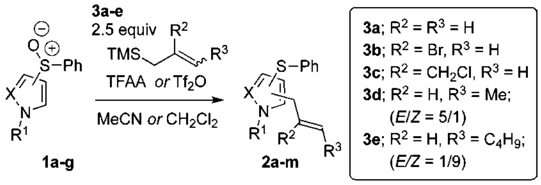
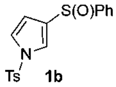
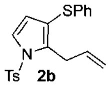
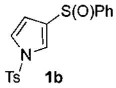
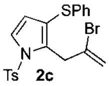
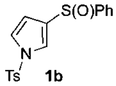
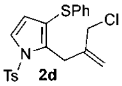
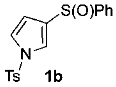
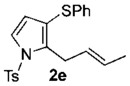
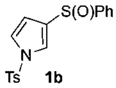
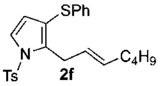
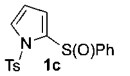
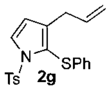
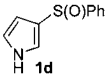
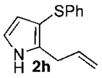
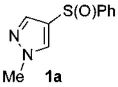
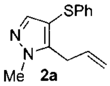
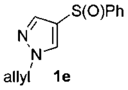
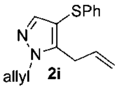
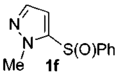
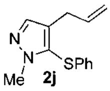
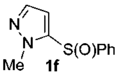
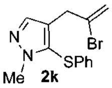
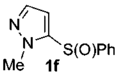
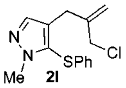
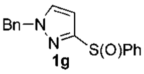
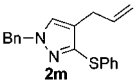
(13) See Supporting Information for complete optimization table.

(14) This is in agreement with the typical relative reactivities of the positions on pyrazoles; see ref 3.

Table 2. Scope of *ortho*-Allylation[a]



3a; $R^2 = R^3 = H$
3b; $R^2 = Br, R^3 = H$
3c; $R^2 = CH_2Cl, R^3 = H$
3d; $R^2 = H, R^3 = Me$; (E/Z = 5/1)
3e; $R^2 = H, R^3 = C_4H_9$; (E/Z = 1/9)

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

[a] Conditions: entries 1–6: TFAA (2.5 equiv), MeCN, −40 °C to rt, 18 h; entry 7: TFAA (2.5 equiv), CH_2Cl_2, −40 to 0 °C, 2 h; entries 8–13: Tf_2O (2.5 equiv), CH_2Cl_2, −78 °C to rt, 18 h. [b] Crotyl-TMS (*E*/*Z*, 5/1), giving mixture (*E*/*Z*, 11/1). [c] Hept-2-en-1-yltrimethylsilane (*E*/*Z*, 1/9), giving mixture (*E*/*Z*, 17/1). [d] 100 °C MW, 2 h. [e] 60 °C MW, 2 h.

phenylsulfinyl-pyrazoles to give products of allylation **2k** and **2l** (entries 11–12).

From a mechanistic perspective, the activation of sulfoxides with TFAA or Tf_2O[15] 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.[16a] Alternatively, the activated sulfoxide could undergo an interrupted Pummerer reaction[11] 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 alkylation 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 alkylations in which **4** acts as an electrophilic alkylating agent.[16a] The lack of crossover products from the reaction of **1b** when 1 equiv of 3-(*p*-tolylthio)-1-tosyl-pyrrole **5b** was present (Scheme 2A) demonstrates the intramolecularity of the alkylation 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 $t_{1/2}$ values as determined by individual reactions for **1b**/**1c**/**1f**/**1a**/diphenylsulfoxide[11a] 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 organosulfanyl[10d,11a,19] groups can be utilized as handles for further manipulation.

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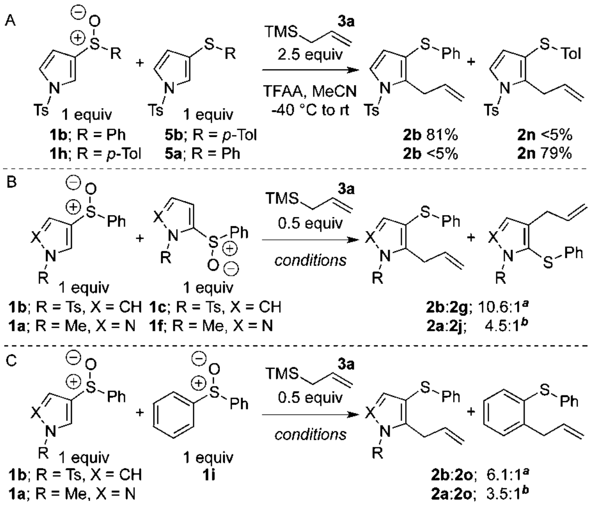
(15) The activation of sulfoxides with TFAA or Tf_2O is well documented; see ref 8.

(16) See Supporting Information for (a) a schematic of alternative reaction pathways and (b) a table of relative reaction $t_{1/2}$.

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

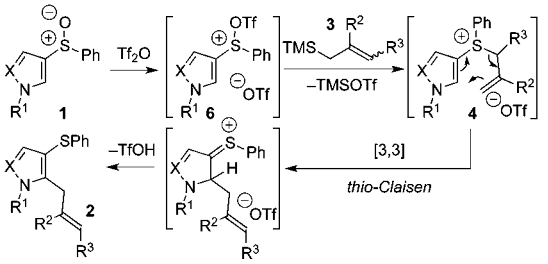
(18) Preliminary studies show that similar products can be obtained from the corresponding sulfides using allyl iodide and silver tetrafluoroborate. However, complex mixtures of multiple allylation products as well as regioisomers are obtained.

Scheme 2. Competition Experiments



[a] TFAA (2.5 equiv), MeCN, −40 °C to rt, 18 h. [b] Tf_2O (2.5 equiv), CH_2Cl_2, −78 to 60 °C MW, 2 h.

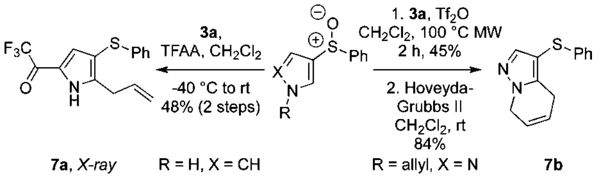
Scheme 3. Mechanism of *ortho*-Allylation (X = N, CH)



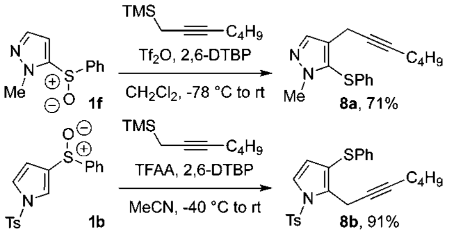
Preliminary studies show how the process can be exploited in a tandem nucleophilic *ortho*-allylation/electrophilic substitution sequence in the formation of **7a**, or as part of an approach to more complex heterocycles such as **7b** (Scheme 4).

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).

Scheme 4. *Ortho*-Allylation and Product Manipulation



Scheme 5. *Ortho*-Propargylation of Pyrroles and Pyrazoles (2,6-DTBP = 2,6-Di-*tert*-butylpyridine)



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.

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(19) (a) For a review on transition metal catalyzed C−C bond formation reactions, see: Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674. (b) For recent examples, see: Kanemura, S.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Synthesis* **2008**, 2659. (c) Hooper, J. F.; Chaplin, A. B.; González-Rodríguez, C.; Thompson, A. L.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2906.