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

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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–Crafts³ type reactions or C–H activation⁴ processes using transition-metal catalysts)

(2) Lipitor (1st) and Celebrex were in the 50 top selling drugs in 2011: http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011. 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 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-Claisen¹² rearrangement sequence involving allylsulfonium salts **4** (Scheme 1). The procedure is general, metal-free, and regiospecific with regard to both coupling partners.



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

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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





entry	HetAr	solvent	anhyd.	conditions	yield (%)
1	1a	MeCN	TFAA	$-40~^\circ\mathrm{C}$ 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 ₂ O	-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
^{<i>a</i>} 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 vielding 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 tosylprotected 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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⁽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



^{*a*} 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: Tf₂O (2.5 equiv), CH₂Cl₂, –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 sulf-oxides 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 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 orthoselectivity. 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 $1500:1500:1020:3.2:1 (\pm 10\%)$, 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 allyITMS, 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 allyITMS 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.

⁽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, $-40~^\circ C$ to rt, 18 h. b Tf₂O (2.5 equiv), CH₂Cl₂, -78 to 60 $^\circ C$ 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

Scheme 4. Ortho-Allylation and Product Manipulation







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, ¹H and ¹³C spectra, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.