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Copper(II) Acetate Promoted Oxidative Cyclization of Arylsulfonyl-*o*-allylanilines

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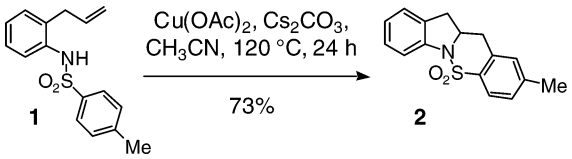
ABSTRACT



Tosyl-*o*-allylaniline 1 undergoes oxidative cyclization to produce tetracycle 2 upon treatment with $Cu(OAc)_2$ and Cs_2CO_3 at 120 °C. The scope of the reaction was extended to other *N*-sulfonylated aromatic systems.

The pursuit of concise methods to assemble chemical complexity is a major focus of the synthetic organic and organometallic chemical community. Reactions that do not require excessive functionalization of the substrates are especially attractive. In this communication we report a direct method for the rapid assembly of heterocyclic systems via a simple oxidative cyclization procedure.

We chose to initiate studies with the *o*-allyl aniline substrate **1** because of its excellent previous performance in aminopalladation reactions.[1] Specific reactions under investigation in our labs include intramolecular aminohalogenation, diamination, and aminocarbonation of olefins. Wacker-type experimental procedures were initially adopted, wherein a catalytic amount of expensive group 10 transition metal, e.g., Pd^{II} or Pt^{II}, would be used in conjunction with less expensive stoichiometric Cu^{II} salts (commonly used to reoxidize Pd^0 to Pd^{II}). In the course of our studies (by carrying out control experiments) we found that the Cu^{II} oxidants are themselves capable of promoting additions of heteroatoms to double bonds.

Reports on the oxidizing powers of Cu^{II} salts have previously appeared,[2] but no examples examining the abilities of these salts to promote the additions of unfunctionalized nitrogens to olefins to form sp^3 carbon centers have previously been reported.

We have recently found that *N*-tosyl-*o*-allylaniline **1** undergoes efficient oxidative cyclization when treated with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 in CH_3CN or DMF at 120 °C. This transformation (cf., **1** → **2**) represents a highly concise heterocycle formation. Conversely, when olefin **1** was treated with catalytic amounts (0.1 equiv) of $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$, the indole product **3**, the result of aminopalladation and subsequent β-hydride elimination, was obtained, in keeping with results reported by Hegedus and others (Scheme 1).[1]

The oxidative cyclization reaction is best performed at 120 °C in a pressure tube in polar solvents such as CH_3CN and DMF (Table 1, entries 4 and 7). The reaction of **1** in THF was incomplete after 24 h (entry 8). The reaction was also much less efficient upon removal of the base (entry 5). Addition of DMSO (4 equiv) neither aided nor impeded the

[†] Assigned the structure of **2** by X-ray crystallography.

(1) (a) Hegedus, L. S. In *Comprehensive Organic Synthesis*; Permagon; New York, 1991; Vol. 4, Chapter 3.1. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800−5807. (c) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164−166.

(2) (a) Rajesawaran, W. G.; Srinivansan, P. C. *Synthesis* **1994**, 270−272. (b) Noto, R.; Gruttadauria, M.; Lo Meo, P.; Frenna, V.; Werber, G. *J. Heterocycl. Chem.* **1995**, *32*, 1277. (c) Tsuji, J.; Kezuka, H.; Toshida, Y.; Takayanagi, H.; Yamamoto, K. *Tetrahedron* **1983**, *39*, 3279−3282. (d) Coda, A. C.; Desimoni, G.; Monaco, H. L.; Quadrelli, P.; Righetti, P. *Gazz. Chim. Ital.* **1989**, *119*, 13−17. (e) Bisiacchi, P.; Coda, A. C.; Desimoni, G.; Righetti, P. P.; Tacconi, G. *Gazz. Chim. Ital.* **1985**, *115*, 119−123. (f) Barun, O.; Ila, H.; Junjappa, H.; Singh, O. M. *J. Org. Chem.* **2000**, *65*, 1583−1587. (g) Wang, S.-F.; Chuang, C.-P.; Lee, J.-H.; Liu, S.-T. *Tetrahedron* **1999**, *55*, 2273−2288.

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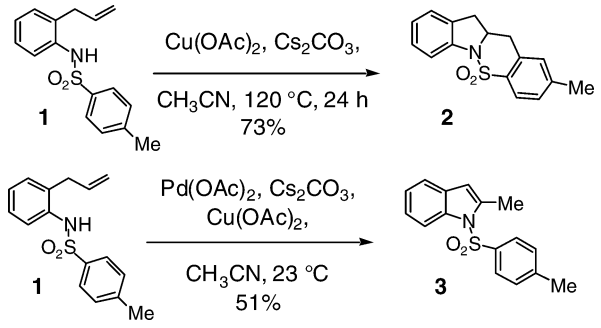
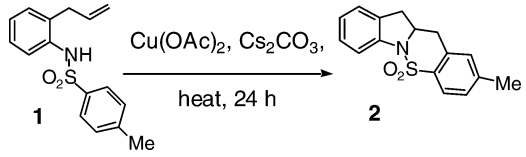
Scheme 1. Divergent Product Formation



progress of the reaction with this substrate. No reaction occurred at 23 or 70 °C in CH_3CN (entries 1 and 2). A 26% yield of **2** was obtained at 90 °C in CH_3CN (entry 3).

Table 1. Effect of Reaction Conditions



entry[a]	solvent	temp (°C)	isolated yield (%)
1	CH_3CN	23	nr[b]
2	CH_3CN	70	nr
3	CH_3CN	90	26
4	CH_3CN	120	73
5[c]	CH_3CN	120	19
6[d]	CH_3CN	120	71
7	DMF	120	69
8	THF	120	51

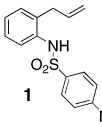
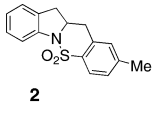
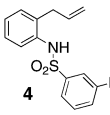
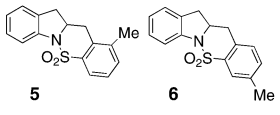
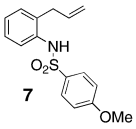
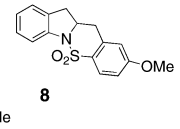
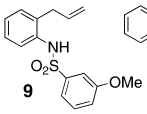
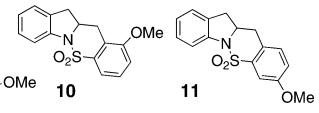
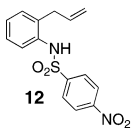
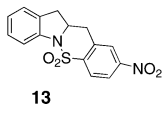
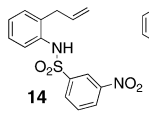
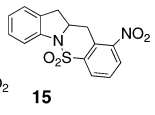
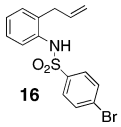
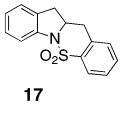
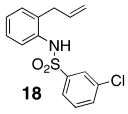
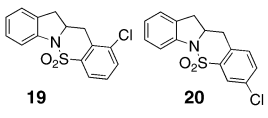
[a] $Cu(OAc)_2$ (3 equiv), Cs_2CO_3 (1 equiv). [b] No reaction. [c] No Cs_2CO_3 was used. [d] DMSO (4 equiv) additive.

The substrate scope was expanded to other arylsulfonyl-*o*-allylaninines in an effort to collect data on the effects of steric and electronic changes on the reaction (Table 2).

We found that the yield and selectivity vary considerably depending upon the electronic nature of the aryl substituent. In general, the reactions of electron-rich substrates **1**, **4**, **7**, and **9** proceeded in good yield. *meta*-Substitution generally led to mixtures of regioisomeric products (see entries 2, 4, and 8). Substrates with electron-withdrawing groups on the sulfonylated aromatic ring reacted more sluggishly, and DMF proved a better solvent than CH_3CN. Addition of DMSO (4 equiv) increased the yields of these reaction, sometimes with significant affect.[3] Neither added HMPA nor pyridine

(3) For studies on the rate-enhancing effects of DMSO in Pd^{II}-catalyzed reactions, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298−5300. (b) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749−7752. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584−3585. (d) Steinhoff, B. A.; Fix, S. R.; Stahl, S. *J. Am. Chem. Soc.* **2002**, *124*, 766−767. (e) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179−4181.

Table 2. Substrate Scope[a]

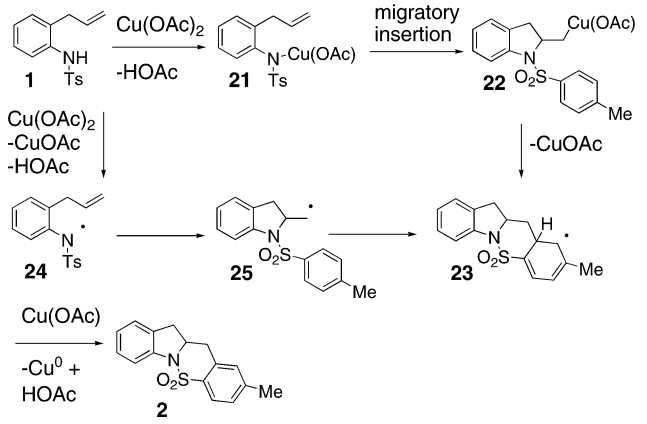
entry	substrate	products	conditions, yield[c] (selectivity)
1[b]			A, 73%
2			A, 51% (**5** : **6** = 2.0 : 1) B, 67% (**5** : **6** = 2.3 : 1)
3			A, 43% B, 63%
4			A, 57% (**10** : **11** = 2.7 : 1) B, 62% (**10** : **11** = 2.7 : 1)
5			B, 24%
6			B, 23%
7			A, 26% B, 54%
8			A, 20% (**19** : **20** = 1.8 : 1) B, 60% (**19** : **20** = 1.8 : 1)

[a] Conditions. **A**: Substrate in DMF (0.08 M) was treated with $Cu(OAc)_2$ (3 equiv) and Cs_2CO_3 (1 equiv). The mixture was heated 24 h at 120 °C in a pressure tube. **B**: DMSO (4 equiv) was added to the reaction mixture. [b] Reaction was run in CH_3CN. [c] Yields refer to the sum of products isolated by chromatography on SiO_2. The remainder of the material was either starting olefin or olefin-isomerized starting material. The structures of the products (e.g., regioisomer) were assigned by analysis of the aromatic region of the ^1H NMR spectra.

provided such yields enhancements. Interestingly, the reaction of the *meta*-substituted nitrosulfonamide **14** provided the *o*-adduct as the sole cyclization product, albeit in low yield (entry 6, Table 2). In the case of the *p*-bromophenylsulfonyl-*o*-allylaniline substrate **16**, the oxidative cyclization to **17** was accompanied by loss of the bromide.

Potential mechanistic sequences for the reaction are proposed in Scheme 2. Thus, one-electron oxidation of the nitrogen (**1** → **24**) followed by 5-*exo*-*trig* intramolecular ring closure generates **25**. Subsequent addition of the primary carbon-based radical onto the aromatic ring, followed by loss of hydrogen radical, would provide **2**. An alternative mechanism would involve nitrogen−copper (II) bond formation

Scheme 2. Proposed Reaction Mechanism



(cf., **21**) followed by intramolecular migratory insertion and subsequent addition to the aromatic ring, possibly via a radical process. The *ortho*-addition preference shown in substrates **4**, **9**, and **14** seems to indicate radical character may be present in the aromatic addition step.[4]

The correlation of substrate reactivity with electron density at nitrogen summarized in Table 2 may indicate either varying degrees of ease of one-electron oxidation in the initiating step or an electrophilic component to the aromatic addition step.

(4) (a) Ito, R.; Migita, T.; Morikawa, N.; Simamura, O. *Tetrahedron* **1965**, *21*, 955. (b) Pryor, W. A.; Davis, W. H., Jr.; Gleaton, J. H. *J. Org. Chem.* **1975**, *40*, 2099−2102.

In support of this mechanism, we note that cyclizations initiated by the formation of nitrogen radicals, though uncommon, do exist.[5] In particular, independent work by Zard,[5d] using *N*-(*O*-ethyl thiocarbonylsulfanyl)amides, and Broka,[5e] using *N*-halogenated substrates, have established that nitrogen radical initiated cascades are useful methods for the synthesis of heterocycles. Nicolaou has also published a recent study using *o*-iodoxybenzoic acid (IBX) to generate nitrogen radicals. [5f]

Further work to expand the substrate scope and to differentiate between the possible mechanistic pathways shown in Scheme 2 will be the subject of future reports.

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Supporting Information Available: Experimental conditions and characterization data, including ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1−14. (b) Zard, S. Z. *Synlett* **1996**, 1148−1154. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. (d) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707−2709. (e) Broka, C. A.; Eng., K. K. *J. Org. Chem.* **1986**, *51*, 5043−5045. (f) See also a recent report using IBX: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kanich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233−2244. (g) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649−9667.