J|A|C|S COMMUNICATIONS

Published on Web 10/28/2010

Palladium-Catalyzed Aminosulfonylation of Aryl Halides

Bao Nguyen, Edward J. Emmett, and Michael C. Willis*

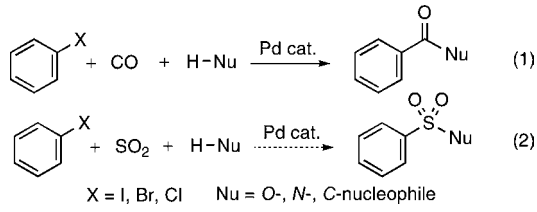
Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford OX1 3TA, U.K.

Received September 8, 2010; E-mail: michael.willis@chem.ox.ac.uk

Abstract: The palladium-catalyzed three-component coupling of aryl iodides, sulfur dioxide, and hydrazines to deliver aryl *N*-aminosulfonamides is described. The colorless crystalline solid DABCO·$(SO_2)_2$ was used as a convenient source of sulfur dioxide. The reaction tolerates significant variation of both the aryl iodide and hydrazine coupling partners.

There is an extensive body of literature documenting the varied coordination modes between sulfur dioxide and metal centers.[1] Despite these numerous reports, applications of sulfur dioxide in transition-metal-catalyzed processes remain scarce.[2,3] A comparison with the transition-metal chemistry of carbon monoxide is striking: catalytic carbonylation processes, such as the palladium-catalyzed conversion of aryl halides into aryl aldehydes, esters, and amides, are established transformations routinely employed in synthetic sequences (eq 1 in Scheme 1).[4] In view of the wide occurrence of sulfonyl motifs ($-SO_2-$) in useful organic functional groups (e.g., sulfones, sulfonates, and sulfonamides) together with the enormous scale of annual sulfur dioxide production,[5] a catalytic method to introduce SO_2 into simple organic molecules would represent an attractive technology. By analogy to established carbonylation chemistry, we were interested in developing palladium-catalyzed reactions to combine aryl halides, sulfur dioxide, and C, O, or N nucleophiles (eq 2 in Scheme 1). The documented examples in which SO_2 undergoes the required insertions into metal−carbon bonds suggested that such reactions are viable.[1−3] In this communication, we report the first examples of the proposed sulfonylation chemistry and in doing so describe a palladium-catalyzed route to *N*-aminosulfonamides.

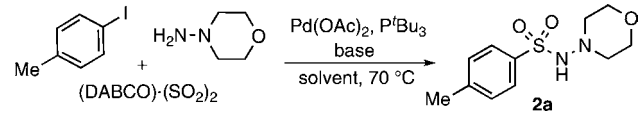
Scheme 1. Palladium-Catalyzed Carbonylation and Sulfonylation Reactions



Exploratory reactions employing a variety of nucleophiles and catalysts in combination with gaseous sulfur dioxide were uniformly unsuccessful. Reasoning that the multiple binding modes and amphoteric nature of sulfur dioxide may be the cause of these difficulties, we explored the possibility of employing an SO_2 equivalent and were attracted to the use of amine−SO_2 charge-transfer complexes. Amine−SO_2 adducts have been known since at least 1900 and have been primarily studied to explore the nature of their structure and bonding.[6] Tertiary amine−SO_2 complexes have received some attention as organic reagents,[7] mainly functioning as dehydrating agents,[8] but as far as we are aware, they have not been exploited as a source of SO_2 for catalysis. We chose to explore the use of the known complex DABCO·$(SO_2)_2$ (**1**; DABCO = 1,4-diazabicyclo[2.2.2]octane),[9] which is an air-stable, colorless solid, in the proposed coupling chemistry. Given the importance of sulfonamides in medicinal chemistry, we decided to focus our initial investigation on the formation of C−SO_2−N linkages.

Using reaction conditions we had previously employed in related palladium-catalyzed aminocarbonylation chemistry,[10] we were able to establish the formation of the key of C−SO_2−N bonds using a hydrazine nucleophile: the coupling of iodotoluene, DABCO·$(SO_2)_2$, and *N*-aminomorpholine was achieved using a $Pd(OAc)_2$/P^{t}Bu$_3$ catalyst in combination with Cs_2CO_3 in toluene at 70 °C, delivering *N*-aminosulfonamide **2a** in 77% yield (Table 1, entry 1). Although the original conditions featured the use of Cs_2CO_3, we found that the addition of the external base was not required when the solvent was changed from toluene to dioxane (entries 3 and 4). We next explored the loading of DABCO·$(SO_2)_2$ needed to maintain an efficient reaction; reducing the amount to 1.1 equiv resulted in an increased yield of 89% (entry 5). However, employing 0.6 equiv of complex **1** (1.2 equiv of SO_2) reduced this to 64% (entry 6). Reasoning that the process no longer had sufficient base, we performed an identical reaction including 0.5 equiv of DABCO, which pleasingly resulted in 99% conversion to sulfonamide **2a** (entry 7).

Table 1. Effect of the Amount of DABCO·$(SO_2)_2$ and Base on the Preparation of Aminosulfonamide **2a**[a]



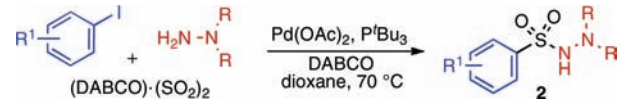
entry	base (equiv)	equiv of DABCO·$(SO_2)_2$	solvent	yield (%)[b]
1	Cs_2CO_3 (2.2)	2.2	toluene	77
2	−	2.2	toluene	12
3	Cs_2CO_3 (2.2)	2.2	dioxane	17
4	−	2.2	dioxane	83
5	−	1.1	dioxane	89
6	−	0.6	dioxane	64
7	DABCO (0.5)	0.6	dioxane	99[c]

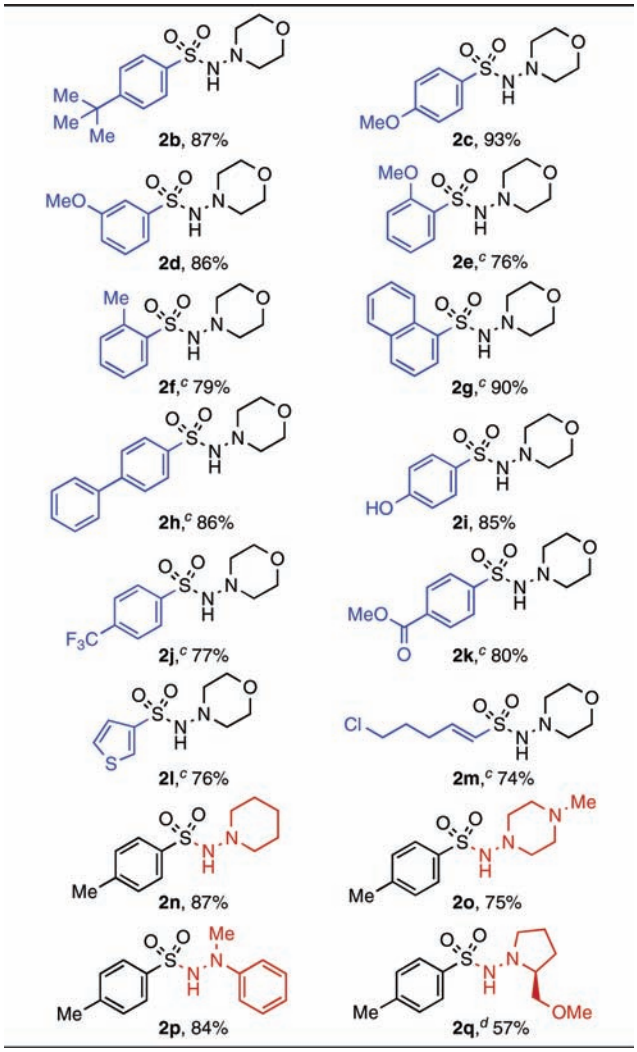
[a] Conditions: iodotoluene (1.0 equiv), hydrazine (1.5 equiv), DABCO·$(SO_2)_2$ (as indicated), $Pd(OAc)_2$ (10 mol %), P^{t}Bu$_3$·HBF$_4$ (20 mol %), solvent, 70 °C, 16 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Corresponding to a 93% isolated yield.

Table 2 documents the scope of the developed aminosulfonylation chemistry. We first evaluated a range of aryl iodide coupling partners and were able to introduce a variety of electron-donating substituents using the optimized conditions (products **2b**−**d**). However, although both *p*- and *m*-iodoanisole were effective substrates, the use of the ortho isomer resulted in only moderate yields. For slow-reacting substrates, we found that the use of 1.1 equiv of DABCO·$(SO_2)_2$ without the addition of extra DABCO was more efficient; under these conditions *o*-iodoanisole was

10.1021/ja1081124 © 2010 American Chemical Society

Table 2. Scope of Pd-Catalyzed Coupling of Aryl Iodides, DABCO·$(SO_2)_2$, and Hydrazines[a,b]





[a] Conditions: aryl halide (1.0 equiv), hydrazine (1.5 equiv), DABCO·$(SO_2)_2$ (0.6 equiv), DABCO (0.5 equiv), $Pd(OAc)_2$ (10 mol %), P^tBu_3·HBF_4 (20 mol %), 1,4-dioxane, 70 °C, 16 h. [b] Isolated yields. [c] DABCO·$(SO_2)_2$ (1.1 equiv.) was used, and no DABCO was added. [d] With 95% conversion.

coupled in 76% yield (**2e**). With the use of either set of conditions as appropriate, substrates featuring a variety of functional groups, including free hydroxyl (**2i**), electron-withdrawing trifluoromethyl (**2j**) and methyl ester (**2k**), and 3-thienyl (**2l**), were smoothly coupled. An *E*-configured alkenyl iodide was also employed, allowing the ready preparation of alkenyl aminosulfonamide **2m**. Although aryl iodides were the most efficient substrates, the corresponding aryl bromides could be employed, albeit to deliver products in reduced yields. For example, sulfonamide **2a** was isolated in 93% yield when iodotoluene was used but only 56% yield when bromotoluene was employed and the reaction was performed at the increased temperature of 90 °C. Several alternative hydrazine coupling partners were also utilized successfully (**2n**−**q**).[11] Finally, a preparative-scale reaction employing 500 mg of iodotoluene (2.29 mmol) using the standard reaction conditions delivered aminosulfonamide **2a** in 92% isolated yield.

In conclusion, we have shown for the first time that it is possible to prepare C−SO_2−N linkages using a palladium-catalyzed aminosulfonylation process. Key to the success of the chemistry was the use of solid DABCO·$(SO_2)_2$ as an easy to handle equivalent of sulfur dioxide. With this reagent, it was possible to achieve efficient aminosulfonylation reactions between a range of aryl iodides and *N*,*N*-dialkylhydrazines, providing aryl *N*-aminosulfonamides in good to excellent yields. The reactions are operationally simple and employ only a slight excess (1.2 equiv) of sulfur dioxide. Studies aimed at elucidating the mechanism of the process and developing related transformations are underway.

Acknowledgment. We thank the EPSRC for the award of an Advanced Research Fellowship (to M.C.W.).

Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Kubas, G. J. *Acc. Chem. Res.* **1994**, *27*, 183. (b) Schenk, W. A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 98. (c) Kubas, G. J. *Inorg. Chem.* **1979**, *18*, 182. (d) Mingos, D. M. P. *Transition Met. Chem.* **1978**, *3*, 1.
(2) For a review, see: Pelzer, G.; Herwig, J.; Keim, W.; Goddard, R. *Russ. Chem. Bull.* **1998**, *47*, 904.
(3) Alkene hydrosulfination: (a) Klein, H. S. *Chem. Commun.* **1968**, 377. (b) Herwig, J.; Keim, W. *J. Chem. Soc., Chem. Commun.* **1993**, 1592. (c) Herwig, J.; Keim, W. *Inorg. Chim. Acta* **1994**, *222*, 381. (d) Keim, W.; Herwig, J.; Pelzer, G. *J. Org. Chem.* **1997**, *62*, 422. Sulfinic acid synthesis from an aryldiazonium salt: (e) Pelzer, G.; Keim, W. *J. Mol. Catal. A: Chem.* **1999**, *139*, 235. Alkene−SO_2 copolymerization: (f) Wojcinski, L. M.; Boyer, M. T.; Sen, A. *Inorg. Chim. Acta* **1998**, *270*, 8. Sulfolene formation from dienes and SO_2: (g) Dzhemilev, U. M.; Kunakova, R. V. *J. Organomet. Chem.* **1993**, *455*, 1.
(4) For reviews, see: (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (b) Brennführer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, *1*, 28. (c) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.
(5) *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Elvers, B., Hawkins, S., Russey, W., Eds.; VCH: Weinheim, Germany, 1994; Vol. A25.
(6) (a) Divers, E.; Ogawa, M. *J. Chem. Soc., Trans.* **1900**, *77*, 327. Selected examples: (b) Moede, J. A.; Curran, C. *J. Am. Chem. Soc.* **1949**, *71*, 852. (c) Hata, T.; Kinumaki, S. *Nature* **1964**, *203*, 1378. (d) van der Helm, D.; Childs, J. D.; Christian, S. D. *Chem. Commun.* **1969**, 887. (e) Douglas, J. E.; Kollman, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 5226. (f) Wong, M. W.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7527.
(7) Eugéne, F.; Langlois, B.; Laurent, E. *J. Org. Chem.* **1994**, *59*, 2599.
(8) (a) Olah, G. A.; Vankar, Y. D. *Synthesis* **1978**, 702. (b) Olah, G. A.; Vankar, Y. D.; Gupta, B. G. B. *Synthesis* **1979**, 36. (c) Olah, G. A.; Vankar, Y. D.; Fung, A. P. *Synthesis* **1979**, 59. (d) Olah, G. A.; Vankar, Y. D.; Arvanaghi, M. *Synthesis* **1979**, 984. (e) Olah, G. A.; Arvanaghi, M.; Vankar, Y. D. *Synthesis* **1980**, 660.
(9) Santos, P. S.; Mello, M. T. S. *J. Mol. Struct.* **1988**, *178*, 121.
(10) Tadd, A. C.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583.
(11) Attempts to substitute the hydrazine nucleophiles with primary amines resulted in the recovery of unreacted starting materials.

JA1081124