

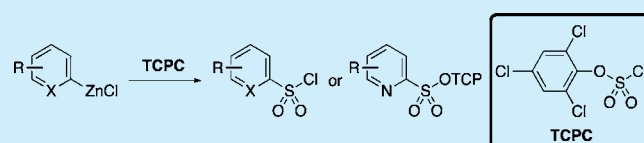
Synthesis of Heteroaryl Sulfonyl Chlorides and 2,4,6-Trichlorophenyl Chlorosulfate

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S Supporting Information

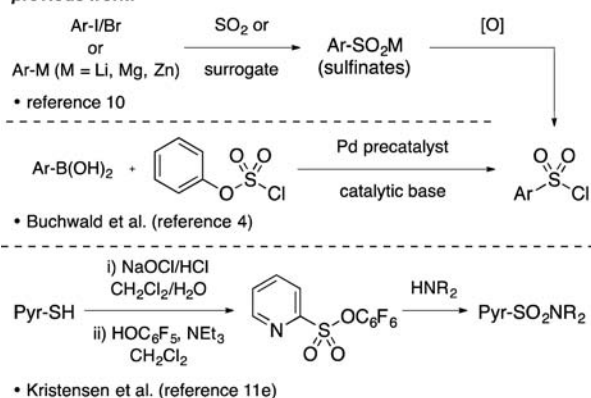
ABSTRACT: A method for the preparation of aryl and heteroaryl sulfonyl chlorides and sulfonamide esters using 2,4,6-trichlorophenyl chlorosulfate (TCPC) is described. The reaction of 2-pyridylzinc reagents with TCPC resulted in 2,4,6-trichlorophenyl (TCP) pyridine-2-sulfonates, and the parent pyridine-2-sulfonate was shown to react with amines. Less electron-rich aryl- and heteroarylzinc reagents reacted with TCPC to afford sulfonyl chlorides that were converted in situ to sulfonamides.



Heterocyclic sulfonamides are a historically significant and still common feature in successful pharmaceuticals and biologically active molecules,¹ yet many examples of their most straightforward synthetic precursors, heterocyclic sulfonyl chlorides, are challenging to synthesize and/or notoriously unstable. The development of an efficient, modular, and general route to sulfonyl chlorides or synthetic equivalents without using toxic, inconvenient reagents such as chlorine gas or sulfonyl chloride is an important unsolved synthetic problem, especially from a discovery chemistry perspective.² Toward this end, our laboratory recently described a palladium-mediated synthesis of sulfonyl chlorides using phenyl chlorosulfate³ and a variety of commercially available arylboronic acids (Figure 1).⁴ The sulfonyl chloride products could either be isolated or reacted with amines to make sulfonamides in a one-pot procedure. However, 3-thienylboronic acid and dibenzofuran-4-boronic acid were the only heteroaryl nucleophiles for which this method could be employed. This inefficiency was due to either protodeboration of the heteroarylboronic acid nucleophiles⁵ or the thermal instability of the electron-deficient heteroaryl sulfonyl chloride products, which in many cases readily decompose at room temperature to give the corresponding chloroheteroarenes and sulfur dioxide.⁶

Many other researchers have contributed to the synthesis of sulfonamides in recent years. Explored by the groups of Willis⁷ and Wu,⁸ an approach to sulfonamides using 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) and a Pd catalyst has been successful with some heterocycles. However, these protocols are mostly limited to iodoarenes and exclusively access *N*-aminosulfonamide products. Wu recently described the reaction of aryl diazonium tetrafluoroborates with DABSO to form sulfonamides, but no heterocyclic examples were reported, and this reaction also was limited to *N*-amino products.⁹ A useful approach targets the more stable sulfinate functional group, which can be oxidized to form sulfonyl chlorides (Figure 1).¹⁰ Organolithium,^{10c} organomagnesium,^{10b,c,h,i} and organozinc^{10g} reagents can be reacted with SO₂ or SO₂ surrogates like DABSO to form sulfonates

previous work:



this work:

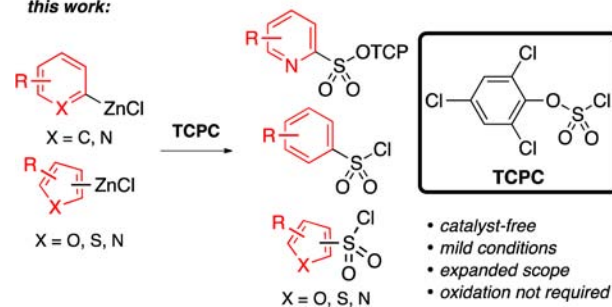


Figure 1. Synthesis of aryl and heteroaryl sulfonyl chlorides and sulfonate esters with 2,4,6-trichlorophenyl chlorosulfate (TCPC).

directly, or aryl halides can be converted to sulfonates in the presence of an SO₂ surrogate and a Pd catalyst. However, relatively few heterocyclic sulfonamides have been prepared using either of these sulfinate strategies. Notably, sulfonates must be oxidized to form sulfonyl chlorides, so methods that access them require an oxidation step to reach sulfonamide

Received: May 26, 2015

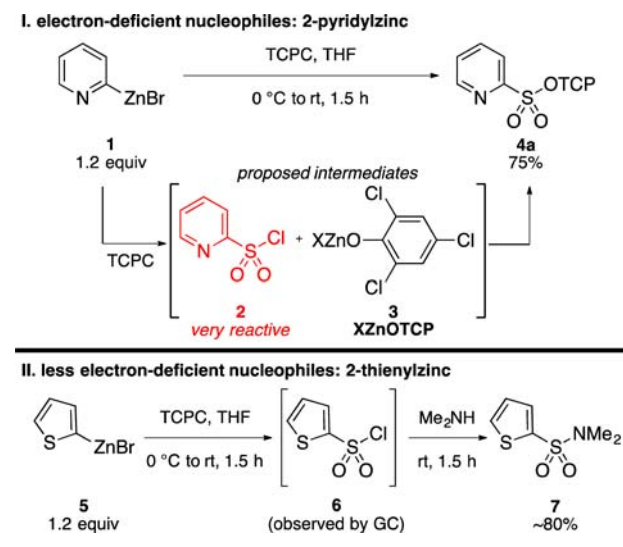
Published: June 11, 2015

products. Although examples of aryl sulfonate esters as shelf-stable alternatives to thermally unstable heterocyclic sulfonyl chlorides have been reported, these compounds are still prepared by using the unstable sulfonyl chlorides in question (Figure 1).¹¹

With the challenge of preparing heterocyclic sulfonamides still remaining, we aimed to increase the scope of our previous chemistry. In this paper, we describe the preparation of aryl and heteroaryl sulfonamides using 2,4,6-trichlorophenyl chlorosulfate (TCPC)¹² and aryl- and heteroarylzinc reagents. Upon reaction with organozinc reagents, this electrophile generates intermediates at the sulfonyl chloride oxidation state that can be directly coupled with amines.

Substituting organozinc reagents for boronic acids has been a powerful and general strategy to enable cross-coupling reactions of heteroaryl carbon nucleophiles,¹³ and the same strategy was proposed for the synthesis of sulfonyl chlorides. This tactic, as in previous endeavors, was in part meant to circumvent the aforementioned protodeboronation problems associated with the corresponding Suzuki–Miyaura coupling reactions of heteroarylboronates.¹⁴ Additionally, initial experiments revealed that organozinc reagents react with aryl chlorosulfates directly, without a transition-metal catalyst (Scheme 1).¹⁵

Scheme 1. TCPC Exhibits Two Modes of Reactivity



In preliminary investigations, two modes of reactivity were observed. Allowing 2-pyridylzinc bromide (**1**) to react with TCPC afforded a 75% yield of 2,4,6-trichlorophenyl (TCP) pyridine-2-sulfonate (**4a**). This product suggests a change of leaving group preference for TCPC when it reacts with the 2-pyridylzinc reagent compared with what we observed in the Pd-catalyzed reaction with arylboronic acids and phenyl chlorosulfate⁴ and with the reactivity of aryl chlorosulfates in general.³ We believe that such a change is unlikely, and instead we propose that although 2,4,6-trichlorophenoxide **3** leaves upon attack of TCPC by the organozinc reagent, an equivalent of the liberated phenoxide subsequently traps the highly reactive pyridine-2-sulfonyl chloride (**2**).¹⁶ This proposed mechanism is consistent with the known reactivities of both aryl chlorosulfates and the electrophile **2**.

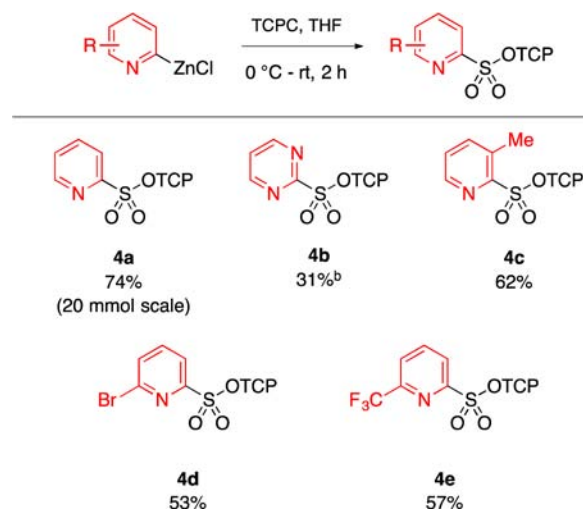
In contrast, combining TCPC and 2-thienylzinc bromide (**5**) afforded thiophene-2-sulfonyl chloride (**6**) (observed by GC),

which was treated in situ with excess dimethylamine to afford sulfonamide **7**. This further substantiates the proposed mechanism of preferential displacement of 2,4,6-trichlorophenoxide over the chloride. Sulfonyl chloride **6** is more stable than **2** and was not observed to react with the phenoxide under these conditions.

The formation of **4a** was surprising but quite advantageous. While pyridine-2-sulfonyl chloride **2** is very unstable, the TCP esters could be stored at room temperature for months without significant decomposition and were isolated by flash chromatography on silica gel. We chose TCPC over phenyl chlorosulfate for this work because TCP sulfonates are more reactive electrophiles than phenyl sulfonates. Caddick has shown that perfluorophenyl and TCP sulfonates are solid, stable, and sufficiently reactive electrophiles that can be used as sulfonyl chloride surrogates.^{11a–d} While Caddick's methods were only extended to a few heteroarylsulfonyl electrophiles, Kristensen further demonstrated that perfluorophenyl sulfonates of electron-deficient heteroarenes are stable alternatives to the corresponding unstable sulfonyl chlorides.^{11e} However, perfluorophenyl chlorosulfate decomposed when we attempted to purify it by silica gel chromatography and was not pursued in light of our success with TCPC.

We were able to generate a series of TCP pyridine-2-sulfonates (Scheme 2), and minimal optimization was required

Scheme 2. Synthesis of 2,4,6-Trichlorophenyl Pyridine-2-sulfonates from 2-Pyridylzinc Reagents and TCPC^a



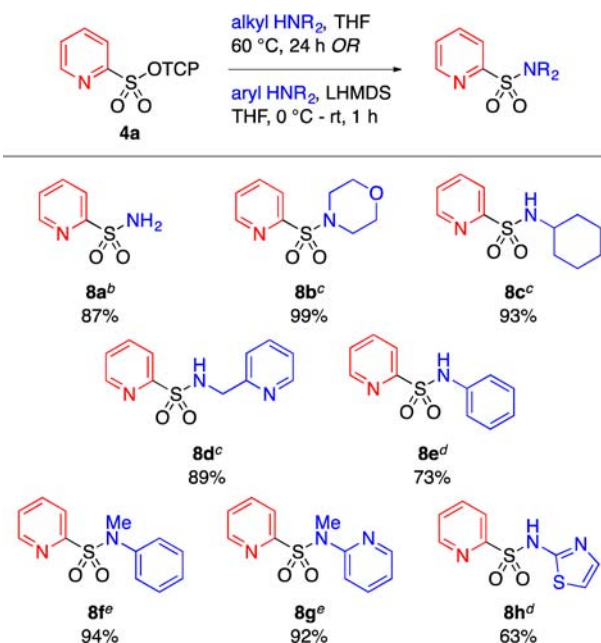
^aReaction conditions: HetArBr (1.0 mmol), *n*-BuLi (1.0 mmol), ZnCl₂ (1.0 mmol), TCPC (1.0 mmol). The reported isolated yields are averages of two runs. ^bReaction conditions: 2-iodopyrimidine (1.0 mmol), *i*-PrMgCl·LiCl (1.0 mmol), ZnCl₂ (1.0 mmol), TCPC (1.0 mmol).

to determine the described reaction conditions. A 1:1 ratio of organozinc reagent to TCPC afforded satisfactory yields of the desired esters. The parent substrate **4a** was prepared on a 20 mmol scale with no additional difficulty. Several substituted pyridines were used, all isolated as solids that were stable in air on the lab bench (**4b–e**). While our laboratory and others have generally found that magnesium–halogen exchange is preferable to lithium–halogen exchange in the preparation of 2-pyridylzinc for Negishi cross-coupling reactions,^{13,17} 2-pyridylzinc mixtures prepared from Grignard reagents consistently afforded lower yields of the sulfonate esters when

reacted with TCPC. This is seen in the yield of **4b**, where the only successful method for preparing the 2-pyrimidinylzinc reagent was by use of magnesium–iodine exchange.

To demonstrate the utility of TCP pyridine-2-sulfonates, **4a** was converted to *N*-alkyl and *N*-aryl sulfonamides in good yields (Scheme 3). The ester is not as reactive as pyridine-2-

Scheme 3. Preparation of Pyridine-2-sulfonamides^a



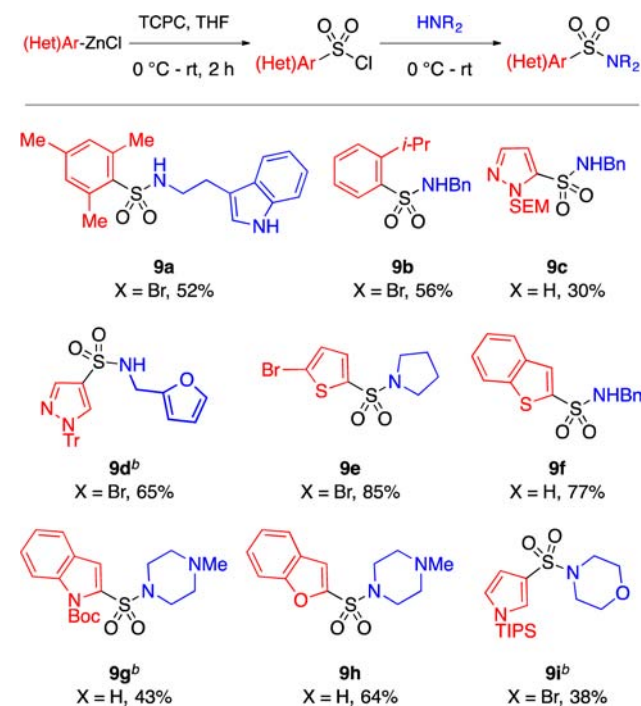
^aThe reported isolated yields are averages of two runs. ^bReaction conditions: **4a** (1.0 mmol), 56% aqueous NH_4OH (2 mL), 1 h. ^cReaction conditions: **4a** (1.0 mmol), amine (2.0 mmol). ^dReaction conditions: **4a** (1.0 mmol), amine (2.0 mmol), LHMDS (2.0 mmol). ^eReaction conditions: **4a** (1.0 mmol), amine (1.2 mmol), LHMDS (1.2 mmol).

sulfonyl chloride, and while this imparts the benefit of bench stability, more vigorous conditions are required in order to react this electrophile with amines. Heating to 60 °C was sufficient for ammonia and alkylamines (**8a–d**), but strong base (LHMDS) was required for *N*-aryl- and *N*-heteroaryl amines (**8e–h**).

We then showed that the scope of TCPC with less electron-deficient aryl- and heteroarylzinc reagents is quite broad (Scheme 4). Of note, sterically encumbered arylzinc reagents represent suitable nucleophiles for the sulfonylation reaction (**9a** and **9b**). Sulfonamides attached at the 2- and 3-positions of pyrazole were both prepared in useful yields (**9c** and **9d**), as well as two thiophene-based sulfonamides (**9e** and **9f**). Lastly, three examples of electron-rich five-membered heterocycles were converted to sulfonamides (**9g–i**).

The underexplored reagent TCPC has been shown to facilitate a new and convenient way to prepare aryl and heteroaryl sulfonyl chlorides. No transition-metal catalyst is required for the reaction, and using organozinc reagents enabled the functionalization of heterocycles. A broad range of amines and electron-rich (hetero)arylzinc reagents were suitable coupling partners, enabling the rapid synthesis of a diverse set of sulfonamides. TCPC also allowed for the preparation of TCP pyridine-2-sulfonates, bench-stable alternatives to pyridine-2-sulfonyl chlorides that are still reactive

Scheme 4. Preparation of (Hetero)aryl Sulfonamides with Organozinc Reagents and TCPC via Sulfonyl Chlorides^a



^aReaction conditions: $(\text{Het})\text{Ar-H/Br}$ (1.0 mmol), *n*-BuLi (1.0 mmol), ZnCl_2 (1.0 mmol), TCPC (1.0 mmol), amine (2.0 mmol). The reported isolated yields are averages of two runs. ^bSame as the general procedure, except that TCPC was added at –78 °C with subsequent warming to rt overnight.

with both alkyl- and arylamines. For both classes of heterocycles, these protocols take advantage of the modularity of the sulfonamide functional group when generating molecular diversity. This modularity and the operational simplicity of the procedures described herein suggest that TCPC may serve as a useful and practical reagent in drug discovery or medicinal chemistry efforts.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and experimental and spectroscopic data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01540.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Institutes of Health for financial support of this project (GM58160), a supplement for J.R.C. under Award 3-R01-GM046059-20S, and a fellowship to J.R.D. (1F32GM099202). This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This material is based upon work supported by the National Science Foundation Graduate

Research Fellowship under Grant 1122374. The Varian 300 and 500 MHz NMR spectrometers used for portions of this work were purchased with funds from NSF (Grants CHE-9808061 and DBI-9729592). The authors thank Dr. Yiming Wang (MIT) for help in preparing this article.

REFERENCES

(1) (a) Drews, J. *Science* **2000**, *287*, 1960–1964. (b) Chrusciel, R. A.; Strohbach, J. W. *Curr. Top. Med. Chem.* **2004**, *4*, 1097–1114. (c) Malawska, B. *Curr. Top. Med. Chem.* **2005**, *5*, 69–85. (d) Olson, R. E.; Albright, C. F. *Curr. Top. Med. Chem.* **2008**, *8*, 17–33. (e) Sun, D.; Wang, M.; Wang, Z. *Curr. Top. Med. Chem.* **2011**, *11*, 1464–1475.

(2) Wright, S. W.; Hallstrom, K. N. *J. Org. Chem.* **2005**, *71*, 1080–1084 and references therein.

(3) Buncel, E. *Chem. Rev.* **1970**, *70*, 323–337.

(4) DeBergh, J. R.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10638–10641.

(5) (a) Lennox, A. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664–674. (b) Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469–483.

(6) Kwart, H.; Body, R. W. *J. Org. Chem.* **1965**, *30*, 1188–1195 and references therein.

(7) (a) Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372–16373. (b) Emmett, E. J.; Richards-Taylor, C. S.; Nguyen, B.; Garcia-Rubia, A.; Hayter, B. R.; Willis, M. C. *Org. Biomol. Chem.* **2012**, *10*, 4007–4014.

(8) Li, W.; Li, H.; Langer, P.; Beller, M.; Wu, X.-F. *Eur. J. Org. Chem.* **2014**, 3101–3103.

(9) Zheng, D.; An, Y.; Li, Z.; Wu, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2451–2454.

(10) (a) For a recent review of sulfonates in organic synthesis, see: Aziz, J.; Messaoudi, S.; Alami, M.; Hamze, A. *Org. Biomol. Chem.* **2014**, *12*, 9743–9759. (b) Woolven, H.; Gonzalez-Rodriguez, C.; Marco, I.; Thompson, A.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876–4878. (c) Deeming, A.; Russell, C. J.; Willis, M. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 1168–1171. (d) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 10204–10208. (e) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 4404–4407. (f) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226–6229. (g) Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* **2014**, *16*, 154–157. (h) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. *J. Org. Chem.* **2003**, *68*, 8274–8276. (i) Chen, C. C.; Waser, J. *Org. Lett.* **2015**, *17*, 736–739.

(11) (a) Caddick, S.; Wilden, J. D.; Bush, H. D.; Wadman, S. N.; Judd, D. B. *Org. Lett.* **2002**, *4*, 2549–2551. (b) Caddick, S.; Wilden, J. D.; Judd, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 1024–1025. (c) Caddick, S.; Wilden, J. D.; Judd, D. B. *Chem. Commun.* **2005**, 2727–2728. (d) Wilden, J. D.; Geldeard, L.; Lee, C. C.; Judd, D. B.; Caddick, S. *Chem. Commun.* **2007**, 1074–1076. (e) Bornhold, J.; Fjære, K. W.; Felding, J.; Kristensen, J. L. *Tetrahedron* **2009**, *65*, 9280–9284.

(12) TCPC has made a few appearances in the literature. See: (a) Takiura, K.; Honda, S. *Yakugaku Zasshi* **1967**, *87*, 1248–1255. (b) Doucet-Baudry, G. C. R. *Seances Acad. Sci., Ser. C* **1968**, *267*, 1057–1059. (c) Hedayatullah, M.; Leveque, J. C.; Denivell, L. C. R. *Seances Acad. Sci., Ser. C* **1972**, *274*, 1937–1940.

(13) (a) Yang, Y.; Oldenhuis, N. J.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 615–619. (b) Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. *Org. Lett.* **2013**, *15*, 5754–5757.

(14) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

(15) The more reactive nucleophile 2-pyridylmagnesium chloride afforded only an 11% yield of the desired sulfonate ester **4a** upon treatment with TCPC at -78 °C. Under the same reaction conditions, 2-pyridyllithium also resulted in a low yield of **4a** (<10%).

(16) Kristensen^{11e} reported that **2** can react with pentafluorophenol in the presence of triethylamine to form pentafluorophenyl pyridine-2-sulfonate in 76% yield.

(17) Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010**, *75*, 8330–8332.