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Imidazolylsulfonates: Electrophilic Partners in Cross-Coupling Reactions

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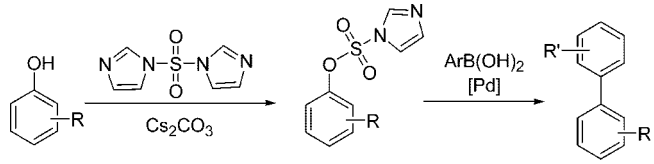
ABSTRACT



Aryl imidazolylsulfonates participate as electrophilic coupling partners in palladium-mediated cross-coupling reactions. The aryl imidazolylsulfonates display good stability while maintaining good reactivity in a variety of palladium-catalyzed coupling reactions. Imidazolylsulfonates are a practical and economic alternative to triflates.

Triflates have long been used in phenol activation toward cross-coupling reactions due to their superior performance as electrophilic coupling partners.[1] Excellent reactivity, however, comes at the expense of stability, and triflates can often suffer from instability. This problem coupled with the high cost of trifluoromethanesulfonic anhydride and triflimide reagents, from which triflates are made, limits their usefulness on larger scales. Recently, the palladium-catalyzed cross-coupling repertoire has been expanded to include aryl tosylates and aryl mesylates as viable electrophilic partners.[2] Aryl tosylates and mesylates are easily prepared and exhibit better stability than triflates and thus are more easily stored and handled. However, reactivity is diminished in palladium-mediated coupling reactions. Successful couplings of these less reactive sulfonates typically require a bulky electron-rich phosphine ligand on the palladium center[2a] and can exhibit marked solvent dependence or substrate specificity.

We report herein the first use of imidazolylsulfonates as effective electrophilic coupling partners in metal-catalyzed coupling reactions. Imidazolesulfonates exhibit markedly improved reactivity over aryl tosylates and improved stability, handling properties, and cost over aryl triflates.

The imidazolylsulfonate moiety was introduced by the Hanessian group as a superb leaving group for sugar compounds.[3] Since then, the imidazolylsulfonate moiety has been reported primarily in the carbohydrate and nucleoside literature as a useful electrophile in several total syntheses of carbohydrate-containing natural products.[4] The imidazolylsulfonate has also been used in the syntheses of a cyclodextrin and of substituted estradiol compounds.[5] More recently, imidazole-1-sulfonyl azide hydrochloride has been introduced as a useful and practical diazo donor reagent that mimics trifluoromethanesulfonyl azide in reactivity.[6]

Given the versatile properties of the imidazolylsulfonate group, we reasoned that aryl imidazolylsulfonates would participate as electrophilic coupling partners in palladium-catalyzed coupling reactions. We anticipated that imidazolylsulfonates would provide enough increased stability and ease of handling to be useful on scale without sacrificing a drastic loss in reactivity compared to aryl triflates.

Hanessian et al. reported two methods for the generation of imidazolylsulfonates. Method A employs a sequential reaction of the hydroxyl compound with sulfuryl chloride

(1) (a) Scott, W.; Crisp, G.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630–4632. (b) For a review of triflate chemsitry, see: Baraznenok, I.; Nenajdenko, V.; Balenkova, E. *Tetrahedron* **2000**, *56*, 3077–3119. (c) For a review of heterocycle synthesis via cross-coupling of triflates, see: Gilson, Z.; Larock, R. *Chem. Rev.* **2006**, *106*, 4644–4680.

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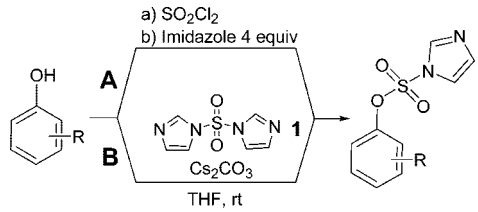
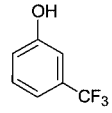
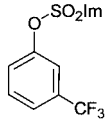
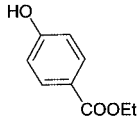
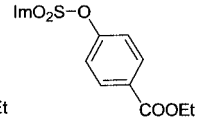
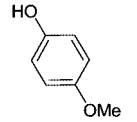
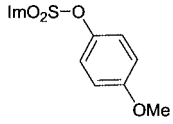
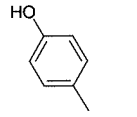
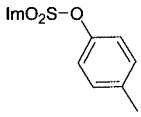
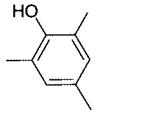
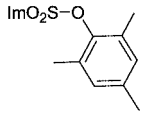
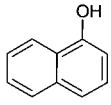
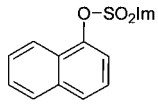
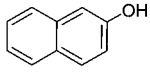
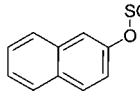
followed by addition of a large excess of imidazole. In Method B, alkoxide formation with sodium hydride was followed by reaction with the commercially available crystalline reagent 1,1′-sulfonyldiimidazole.[4a]

Method A was used initially to generate the aryl imidazolylsulfonates (Table 1, entries 1−3 and 7). Yields were

Table 1. Synthesis of Imidazolylsulfonates



Entry	Phenol	Imidazolylsulfonate	Yield Method A[a]	Yield Method B[b]
1			72%	86%
2			64%	85%
3			46%	93%
4			---	91%
5			---	91%
6			0%[c]	91%
7			---	91%

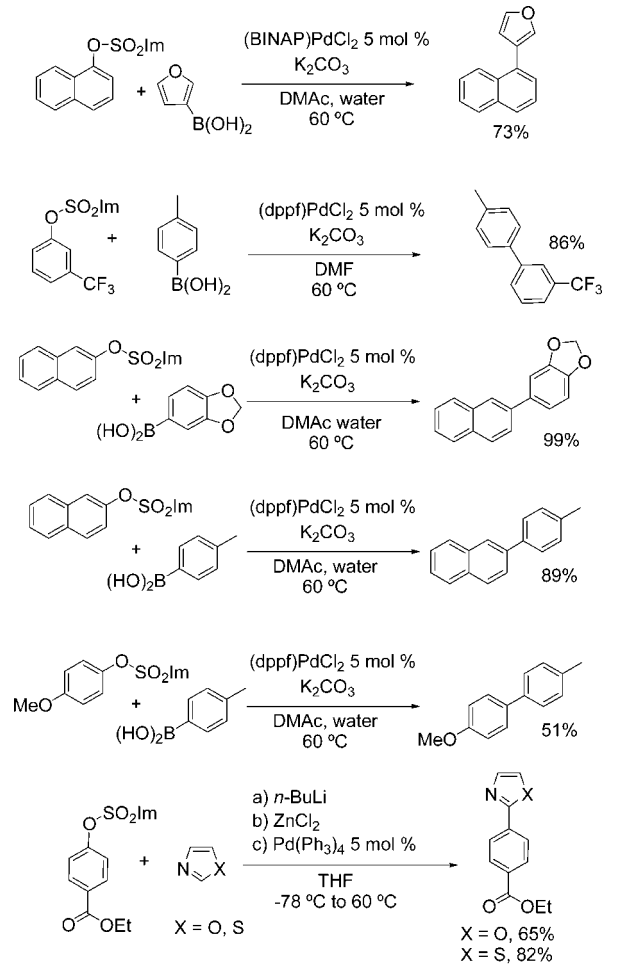
[a] Method A conditions: sulfuryl chloride then imidazole in CH_2Cl_2, 0 °C to rt. [b] Method B conditions: 1,1′-sulfonyldiimidazole plus Cs_2CO_3 in THF at rt. [c] Method A produced 2,4-dichloronaphthol as the only product.

fair to moderate for the phenols, but no desired imidazolylsulfonate product was formed from 1-naphthol (entry 6). Not surprisingly, chlorination is a competitive pathway under these conditions.

A screen of alternatives to replace sodium hydride, called for in Method B, revealed cesium carbonate as the most effective base. Optimal conditions employ a slight excess of the reagent 1,1′-sulfonyldiimidazole[7] with a substoichiometric amount of cesium carbonate in 20 vol of THF at room temperature. Most reactions were complete within 16 h, and yields of the desired imidazolylsulfonates improved to 85% or greater in all cases (Table 1). *o*-Methyl groups do not hinder the reaction (entry 5), and both electron-withdrawing and electron-releasing groups are well tolerated.

With a general method in hand to make the required aryl imidazolylsulfonates, we next turned our attention to their performance in cross-coupling reactions. The aryl imidazolylsulfonates were subjected to typical Suzuki−Miyaura and Negishi-type conditions, and the expected products were isolated in good yields (Scheme 1).[8] A variety of palladium

Scheme 1. Imidazolylsulfonates in Suzuki−Miyaura and Negishi Cross-Coupling Reactions[a]

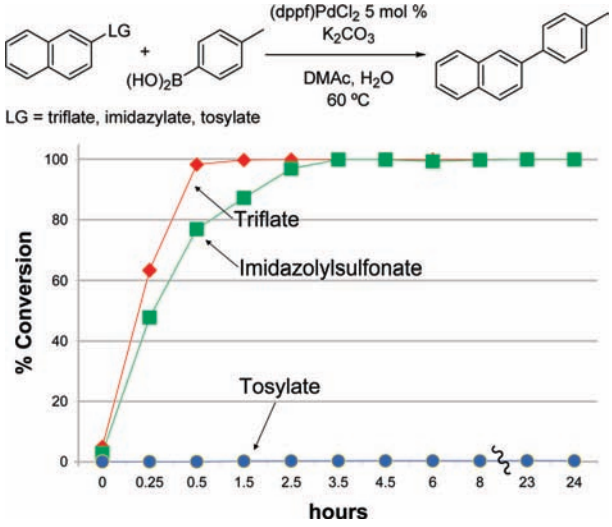


[a] Isolated yields were not optimized.

catalysts were used successfully to effect the couplings. The reactions were achieved in a variety of solvents as well. Addition of lithium chloride showed no benefit or detriment: yield and rate were essentially unchanged in THF.[9] Moreover, the aryl imidazolylsulfonates exhibited good shelf life; coupling yields were not reduced by using imidazolylsulfonates that had been stored at ambient temperature for 7 months.

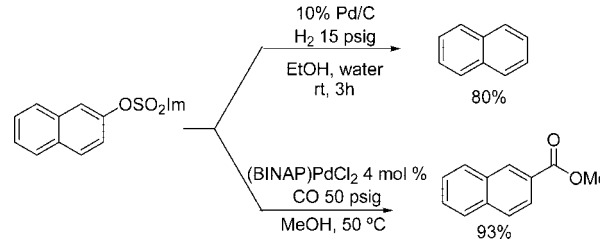
Preliminary comparative rate studies revealed that the reactivity of naphthyl imidazolylsulfonates is similar to that of naphthyl triflates (Scheme 2). The conversion rate is somewhat slower: the 2-naphthyl triflate conversion was 98% in 30 min, whereas the analogous 2-nathphyl imidazolylsulfonate required 2.5 h to reach full conversion. In sharp contrast, the 2-naphthyl tosylate analogue was inert under the same conditions.

Scheme 2. Suzuki Cross-Coupling Reactivity Comparison: Triflate versus Imidazylate versus Tosylate



Imidazolylsulfonates are also useful intermediates for functional group transformation of the phenol (Scheme 3).

Scheme 3. Hydrogenolysis and Carbonylation Reactions of 2-Naphthylimidazolylsulfonate



Reduction of 2-naphthol imidazolylsulfonate was achieved under very mild hydrogenolysis conditions to produce naphthalene in good yield. Palladium-catalyzed carbonylation to generate the ester also proceeded in excellent yield under exceedingly mild conditions.[10]

An important added benefit to using imidazolylsulfonates is the inherent potential for self-destruction of the cross-coupling byproduct imidazolesulfonic acid. Recently, there has been a greater regulatory focus on alkyl and aryl sulfonates as potential genotoxic impurities (PGIs).[11] The byproduct of the imidazolylsulfonate cross-coupling is imidazolesulfonic acid (Scheme 4).[12] Unlike tosic, methanesulfonic, and triflic acids, imidazolesulfonic acid hydrolyzes in the presence of water and acid to produce imidazole and sulfuric acid, and thus the potential formation of alkyl or aryl sulfonates from the residual sulfonic acid is eliminated. The imidazolylsulfonate moiety is conveniently designed for degradation under aqueous and acidic conditions.

In conclusion, we have demonstrated the practical and scalable synthesis of aryl imidazolylsulfonates and their

(2) (a) Roy, A.; Hartwig, J. *J. Am. Chem. Soc.* **2003**, *125*, 8704–8705. (b) Nguyen, H.; Huang, X.; Buchwald, S. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819. (c) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346–9349. (d) Steinhuebel, D.; Baxter, J.; Palucki, M.; Davies, I. *J. Org. Chem.* **2005**, *70*, 10124–10127. (e) Baxter, J.; Steinhuebel, D.; Palucki, M.; Davies, I. *Org. Lett.* **2005**, *7*, 215–218. (f) Wu, J.; Zhu, Q.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670–673. (g) Molander, G.; Yun, C. *Tetrahedron* **2002**, *58*, 1465–1470. (h) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457–3460. (i) Huffman, M.; Yasuda, N. *Synlett* **1999**, 471–473. (j) For an example of Sonogashira coupling of a vinyl tosylate, see: Woo, J.; Walker, S.; Faul, M. *Tetrahedron Lett.* **2007**, *48*, 5679–5682. (k) Fu, X.; Zhang, S.; Yin, J.; Schumacher, D. *Tetrahedron Lett.* **2002**, *43*, 6673–6676. (l) For reductive deoxygenation of aryl mesylate, see: Sajiki, H.; Mori, A.; Mizusaki, T.; Ikawa, T.; Maegawa, T.; Hirota, K. *Org. Lett.* **2006**, *8*, 987–990. (m) For an amination of mesylates, see: So, C.; Zhou, Z.; Lau, C.; Kwong, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1–6.

(3) (a) Hanessian, S.; Vatèle, J.-M. *Tetrahedron Lett.* **1981**, *37*, 3579–3582. (b) Vatèle, J.-M.; Hanessian, S. *Tetrahedron* **1996**, *52*, 10557–10568, and references therein.

(4) (a) Ingram, L.; Taylor, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3503–3506. (b) Beaudion, S.; Kinsey, K.; Burns, J. *J. Org. Chem.* **2003**, *68*, 115–119. (c) Ma, T.; Pai, B.; Zhu, Y.; Lin, J.; Shanmuganathan, K.; Du, J.; Wang, C.; Kim, H.; Newton, M.; Cheng, Y.; Chu, C. *J. Med. Chem.* **1996**, *39*, 2835–2843. (d) Ahmed, F.; David, S.; Vatèle, J.-M. *Carbohydr. Res.* **1986**, *155*, 19–31. (e) David, S.; Malleron, A.; Dini, C. *Carbohydr. Res.* **1989**, *158*, 193–200. (e) Duan, S.; Binkley, E.; Binkley, R. *J. Carbohydr. Chem.* **1998**, *17*, 391–396. (f) Tann, C.; Brodfuehrer, P.; Brundidge, S.; Sapino, C.; Howell, H. *J. Org. Chem.* **1985**, *50*, 3644–3647. (g) Chou, T.; Becke, L.; O'Toole, J.; Carr, M.; Parker, J *Tetrahedron Lett.* **1996**, *37*, 17–20. (h) Alais, J; David, S. *Carbohydr. Res.* **1992**, *230*, 79–87. (i) Best, W.; Macdonald, J.; Skelton, B.; Stick, R.; Tilbrook, D.; White, A. *Can. J. Chem.* **2002**, *80*, 857–865. (j) Meloncelli, P.; Stick, R. *Aust. J. Chem.* **2006**, *59*, 827–833.

(5) (a) Teranishi, K.; Hisamatsu, M.; Yamada, T. *Tetrahedron Lett.* **2000**, *41*, 933–936. (b) Fevig, T.; Mao, M.; Katzenellenbogen, J. *Steroids* **1988**, *51*, 471–479. (d) Ahmed, F.; David, S.; Vatèle, J.-M. *Carbohydr. Res.* **1986**, *155*, 19–31.

(6) Goddard-Borger, E.; Stick, R. *Org. Lett.* **2007**, *9*, 3797–3800.

(7) (a) Staab, H.; Wendel, K. *Angew. Chem.* **1961**, *73*, 26. (b) Staab, H.; Wendel, K. *J. Liebigs Ann. Chem.* **1966**, *694*, 86–90. (c) 1,1′-Sulfonyldiimidazole has been used recently as an imidazole transfer reagent; see: Keith, J. *J. Org. Chem.* **2008**, *73*, 327–330.

(8) (a) For recent reviews of the Suzuki−Miyaura coupling reaction see: Doucet, H. *Eur. J. Org. Chem.* 2008, *7*, 1133−1155 and(b) Alonso, F.; Beletskaya, I.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101. (c) For a recent review of Negishi couplings, see: Negishi, E.-I. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257. (d) Reeder, M.; Gleaves, H.; Hoover, S.; Imbordino, R. Pangborn. *J. Org. Proc. Res. Dev.* **2003**, *7*, 696–699. (e) Anderson, B.; Becke, L.; Booher, R.; Flaugh, M.; Harn, N.; Kress, T.; Varie, D.; Wepsiec, J. *J. Org. Chem.* **1997**, *62*, 8364–8369. (f) Anderson, B.; Harn, N. *Synthesis* **1996**, *5*, 583–585. (g) Crowe, E.; Hossner, F.; Hughes, M. *Tetrahedron* **1995**, *51*, 8889–8890.

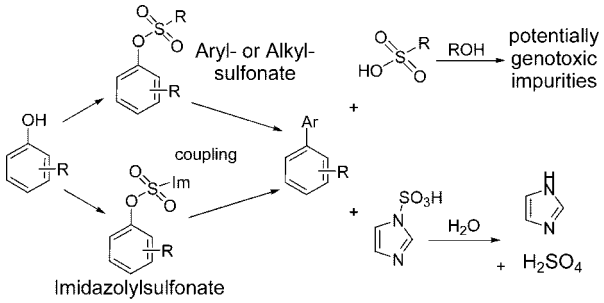
(9) (a) Scott, W.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040. (b) Echavarren, A.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486. (c) Casado, A.; Espinet, P.; Gallego, A. *J. Am. Chem. Soc.* **2000**, *122*, 11771–11782.

(10) Albaneze-Walker, J.; Bazaral, C.; Leavey, T.; Dormer, P.; Murry, J. *Org. Lett.* **2004**, *6*, 2097–2100.

(11) (a) Elder, D.; Teasdale, A.; Lipczynski, A. *J. Pharm. Biomed. Anal.* **2008**, *46*, 1–8. (b) Snodin, D. *Reg. Toxicol. Pharm.* **2006**, *45*, 79–90. (c) Glowienke, S.; Frieauff, W.; Allmendinger, T.; Martus, H.-J.; Mueller, L. *Mutat. Res.* **2005**, *581*, 23–34. (d) Committee for Medicinal Products (CHMP); *Guideline on the Limits of Genotoxic Impurities*; European Medicines Agency: London, 2008 (CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006).

(12) (a) Staab, H. *Angew. Chem.m Int. Ed. Engl.* **1962**, *1*, 351–367. (b) Botchkavvieva, T; Passet, B. *Zh. Obshch. Khim.* **1983**, 2221–2222.

Scheme 4. Degradation of Imidazolesulfonic Acid Post-Coupling



utility in palladium-mediated reactions. Imidazolylsulfonates act as fully competent electrophilic coupling partners in Suzuki−Miyaura and Negishi-type couplings, as well as participants in both hydrogenolysis and carbonylation reactions. Imidazolylsulfonates are a practical and economical alternative to triflates for a variety of palladium catalyzed reactions. Further development of coupling reactions is underway in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental and characterization data details. This material is available free of charge via the Internet at http://pubs.acs.org.

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