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Practical Synthesis of Aryl Triflates under Aqueous Conditions

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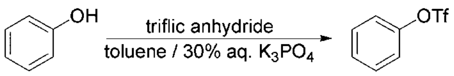
ABSTRACT

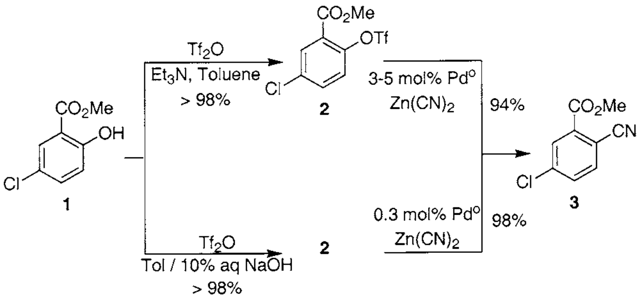


A practical and efficient synthesis of aryl triflates under biphasic basic aqueous conditions is described. The current methodology provides entry into these valuable substrates that omits the use of amine bases and allows facile isolation by simple solvent evaporation after phase separation. Good yields can also be obtained without the use of organic solvent.

Aryl triflates are extensively used as synthetic precursors in a vast array of coupling reactions.[1] Conventional preparation of these substrates involves the treatment of the corresponding phenol with triflic anhydride in the presence of an amine base such as pyridine or triethylamine.[2] More convenient protocols have utilized imidazole triflate,[3] *N*-phenyltriflimide,[4] *N*-(2-pyridyl)triflimide,[5] and recently, polymer-supported *N*-phenyltriflimide.[6] The drawbacks to these specialized reagents are that a prior step is needed for their formation (most derived from triflic anhydride itself) and the relative reactivities of these triflating reagents are often low in comparison to the anhydride.

As part of our ongoing research efforts we recently needed a practical synthesis of ester nitrile **3** that was amenable to large scale. We envisioned arriving at **3** via Pd-catalyzed cyanation of the corresponding aryl triflate **2** (Scheme 1). Our initial efforts toward **3** were via the traditional amine base synthesis[2] of aryl triflate **2** followed by direct Pd-catalyzed cyanation[7] of the crude triflate. We were surprised by the large catalyst loading (3–5 mol % Pd) necessary to achieve complete conversion. Upon closer inspection of the crude aryl triflate by ^{1}H and ^{19}F NMR, it was evident that it was contaminated with 1–3% of triethylammonium triflate. We suspected this ammonium salt might be interfering with the catalytic process.

Scheme 1



Given these results, we hypothesized that formation of the triflate under Schotten–Baumann conditions might prove to be advantageous, eliminating ammonium triflate salts

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(1) For reviews, see: (a) Ritter, K. *Synthesis* **1993**, 735–762. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85–126. (c) Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107–114.

(2) Stille, J. K.; Echavarren, A. M. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486.

(3) Effenberger, F.; Mack, K. E. *Tetrahedron Lett.* **1970**, *11*, 3947–3948.

(4) (a) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *14*, 4607–4610. (b) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982. (c) Bengtson, A.; Hallberg, A.; Larhed, M. *Org. Lett.* **2002**, *4*, 1231–1233.

(5) Comins, D. L.; Dehgani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

(6) Wentworth, A. D.; Wentworth, P., Jr.; Mansoor, U. F.; Janda, K. D. *Org. Lett.* **2000**, *2*, 477–480.

(7) For related procedures involving the Pd-catalyzed cyanation of aryl triflates, see: Drechsler, U.; Hanack, M. *Synlett* **1998**, 1207. Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224–8228.

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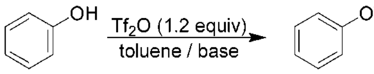
altogether. Gratifyingly, this was demonstrated to be the case. For example, when phenol **1** was dissolved in a biphasic mixture of toluene/10% aqueous NaOH followed by slow addition of triflic anhydride (1.2 equiv), rapid and quantitative formation of triflate **2** was observed. Furthermore, after simple phase separation and azeotropic drying, the crude toluene solution of **2** could be used directly in the Pd-catalyzed cyanation. The crude triflate formed in this manner allowed us to reduce the catalyst loading by 10-fold!

On the basis of this finding, we explored the scope and limitation of aryl triflate formation under these new conditions. Using phenol as our standard substrate, we first examined the effect of the aqueous base used in the biphasic reaction with toluene (Table 1). Of these, 30% (w/v) aqueous solutions of K_3PO_4 routinely provided the highest assay yields.

Table 1. Effect of Aqueous Base on Triflate Formation[a]

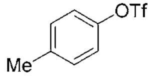
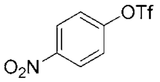
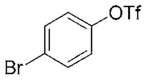
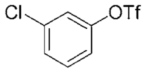
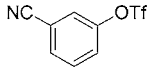
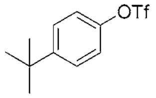
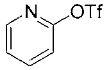
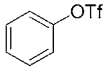
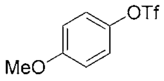
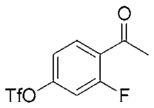


entry	(w/v) base	yield[b]
1	10% NaOH	57%
2	15% KOH	75%
3	5% LiOH	87%
4	40% CsOH	77%
5	30% K_2CO_3	55%
6	30% K_3PO_4	95%

[a] Reactions conducted at 0 °C with slow addition of Tf_2O (1.2 equiv) to a biphasic toluene/base (3.0 equiv) mixture of the phenol. [b] Yield based on quantitative HPLC analysis of the toluene solution using an analytically pure sample of the aryl triflate as a standard.

After identifying aqueous K_3PO_4 as the optimum base, the scope of the reaction with respect to substitution on the phenol was investigated. The results of our study are outlined in Table 2. A variety of substituents are tolerated, and even 2-pyridone (entry 7) was converted to the corresponding triflate in good yield. In most cases, the reactions are instantaneous and all can be performed in an open-air flask.[8] Furthermore, good yields can be obtained in the absence of any organic solvent (entries 3−5 and 8−10). Finally, isolation of the triflate is easily accomplished by simple evaporation of the organic solvent after phase separation to give the products in >95% purity.

Table 2. Synthesis of Aryl Triflates[a]

entry	product	isolated yield[b]
1	 **4**	81%
2	 **5**	64%
3	 **6**	91% 90%[c]
4	 **7**	85% 88%[c]
5	 **8**	95% 66%[c]
6	 **9**	92%
7	 **10**	68%
8	 **11**	95% 92%[c]
9	 **12**	94% 88%[c]
10	 **13**	92% 75%[c]

[a] Reactions conducted at 0 °C with slow addition of Tf_2O (1.2 equiv) to a toluene/30% (w/v) aqueous K_3PO_4 biphasic mixture of phenol followed by warming to ambient temperature for 30 min. [b] Products isolated in >95% purity (based on HPLC, ^1H, and ^{13}C analysis) by simple evaporation of solvent after phase separation. Yields have not been optimized and are a direct reflection of the percent of conversion based on quantitative HPLC analysis after 30 min. [c] Reactions performed in the absence of organic solvent with products isolated by subsequent toluene extraction.

In conclusion, we have identified a convenient aqueous synthesis of aryl triflates that allows for the direct isolation of these valuable substrates without the use of amine bases, expensive triflating agents, or chromatography. Further investigations, including the extension of this methodology to other substrates, are continuing.

Supporting Information Available: Characterization data, including ^1H, ^{13}C, and ^{19}F NMR spectra for all aryl triflates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) **Typical Procedure.** To a cooled (0 °C) biphasic mixture of toluene (10 mL), 30% (w/v) aqueous K_3PO_4 (10 mL), and the phenol (5 mmol) was added dropwise Tf_2O (6 mmol) at a rate to maintain the reaction temperature <10 °C. The reaction was allowed to warm to ambient temperature and stirred for 30 min. The layers were separated, and the toluene layer was washed with water (10 mL) and then concentrated to give the corresponding triflate.