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Fast Synthesis of Aryl Triflates with Controlled Microwave Heating

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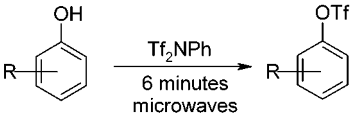
ABSTRACT



Synthesis of aryl triflates from phenols using *N*-phenyltriflimide requires only 6 min for completion when conducted with controlled microwave heating. The methodology was applied to both solution- and solid-phase conditions. Ten different aryl triflates were synthesized and isolated in good yields. Applications in high-throughput chemistry are suggested.

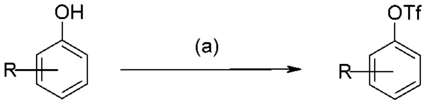
In high-throughput chemistry there is a need to decrease the reaction times as well as effectuate the purification procedures. Conceptual and technological solutions to these issues have been the subjects of intensive research. Automated and focused microwave flash heating was recently proven to improve the preparative efficiency and to dramatically reduce reaction times for several different types of organic transformations.[1]

Aryl triflates are useful starting materials in many types of palladium- and nickel-catalyzed coupling reactions.[2] The most common procedure for the preparation of aryl triflates is to react triflic anhydride with a phenol in the presence of a base.[3] Triflic anhydride is, however, a low temperature, nonselective reagent, and consequently its use in high-throughput synthesis of functionalized aryl triflates is limited. An alternative route to aryl triflates is to use *N*-phenyltriflimide, a stable and crystalline triflating agent that often results in improved selectivity.[4]

In most cases, reaction times between 3 and 8 h are needed when employing *N*-phenyltriflimide.[5] We aimed at finding conditions for the reduction of the reaction time in order to make the triflation more adoptable to high-throughput chemistry. A general method was desired, although primarily we were interested in making triflates from salicylic aldehydes for further use as precursors for annulation reactions.

Herein we describe the first protocol for fast microwave-promoted triflatation of phenols (Scheme 1).

Scheme 1[a]



1 **2**

[a] Reagents and conditions: (a) Tf_2NPh (1.0 equiv), K_2CO_3 (3.0 equiv), THF, 120 °C (microwave heating), 6 min.

Nine different phenols (**1a**−**i**) were selected as starting materials. The selection was made to include both electron-donating and electron-withdrawing substituents. K_2CO_3 was chosen due to its ability to act as a drying agent as well as a base.

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(1) Recent reviews: (a) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (b) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406−416. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105.

(2) Ritter, K. *Synthesis* **1993**, 735−762.

(3) Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000**, *56*, 3077−3119.

(4) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607−4610.

(5) (a) Crisp, G. T.; Turner, P. D. *Tetrahedron* **2000**, *56*, 407−415. (b) Wentworth, A. D.; Wentworth, P., Jr.; Mansoor, U. F.; Janda, K. D. *Org. Lett.* **2000**, *2*, 477−480.

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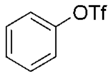
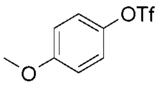
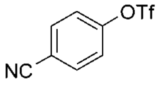
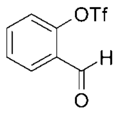
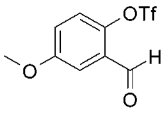
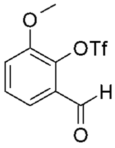
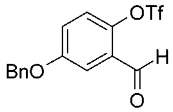
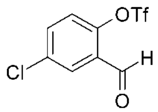
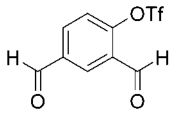
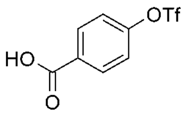
Aryl triflates have proven to be surprisingly stable at high temperatures.[6] Thus, the heating was not foreseen to cause any serious decomposition problems. Despite that, we decided not to conduct the reaction above 120 °C, to make it compatible with more thermosensitive functional groups.

The results from the study are outlined in Table 1. Using controlled microwave heating we succeeded in reducing the reaction time to 6 min.[7] The reactions were found not to be sensitive to air or moisture; hence there was no need for an inert atmosphere. All the phenols were smoothly converted to triflates in isolated yields between 69 and 91%.

There was no clear correlation between the reaction outcome and the electron density of the substituents, and a formyl group in the ortho-position did not reduce the yield to any extent. The highly electron-poor 5-nitrosalicylic aldehyde and the sterically hindered 3-formyl-5-methylsalicylic aldehyde (not reported) could also be triflated with this method, as deduced from GC-MS and crude NMR, but the formed products were very insoluble and for this reason difficult to fully purify. It is notable that, employing only 1 equiv of the triflimide, all reactions delivered full conversion of the starting phenol. This nonexcess stoichiometry results in less demanding purification and good atom economy.

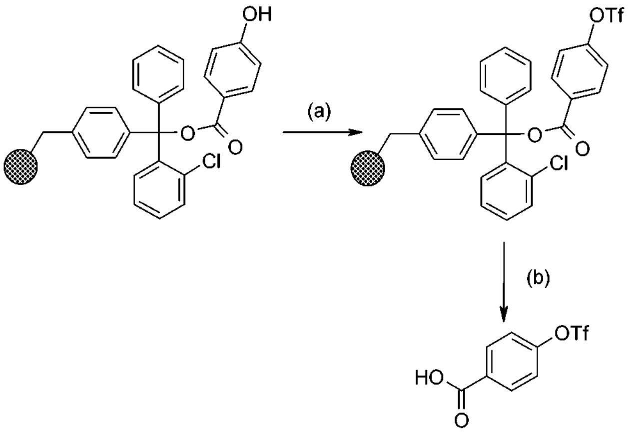
Table 1. Synthesis of Aryl Triflates

entry	product		isolated yield[a] (%)
1		**2a**	69
2		**2b**	80
3		**2c**	91
4		**2d**	78
5		**2e**	87
6		**2f**	73
7		**2g**	69
8		**2h**	69
9		**2i**	90
10		**2j**[b]	80

[a] >95% pure according to GC-MS. Compounds **2a**−**h** were purified with flash chromatography. Compound **2i** was purified through washing with hot THF. [b] Synthesized on solid support.

4-Hydroxybenzoic acid (**1j**), coupled to a 2-chlorotrityl linker, was chosen for solid-phase triflate synthesis (Scheme 2). Liquid Et_3N was used as base instead of K_2CO_3, and 2-chlorotrityl polystyrene resin was utilized due to the mild cleaving conditions required.[8]

Scheme 2. Fast Solid-Phase Synthesis[a]



[a] Reagents and conditions: (a) Tf_2NPh (1.0 equiv), Et_3N (3.0 equiv), THF, 120 °C (microwave heating), 6 min; (b) 1% TFA/CH_2Cl_2, rt, 1 h.

Rewardingly, the fast methodology was easily transferred to the solid-phase conditions and compound **2j** was isolated in 80% yield after cleavage (Table 1, entry 10). No hydrolysis of the liberated triflate was detected.

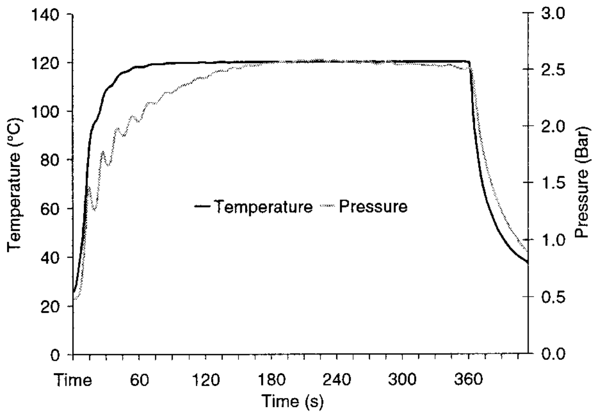


Figure 1. Temperature and pressure profiles for a representative triflation reaction (entry 2).

THF is not an ideal solvent for rapid microwave heating in sealed reaction vessels. This has been attributed to the relatively low boiling point and a low tan δ of the solvent.[9] Despite that, the reaction mixture could be heated to 120 °C in less than 1 min and the pressure did not exceed 5 bar in any of the reactions (Figure 1).

In summary, we have developed a convenient microwave-assisted, high-speed method for synthesis of aryl triflates. One successful example of solid-phase synthesis is given, which indicates that the method easily can be adopted for use on solid support.

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Supporting Information Available: Complete Experimental Section with full analytical characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. v. R.; Effenberger, F.; Kurtz, W.; Stang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099−4103.

(7) **General experimental procedure:** The phenol (2.0 mmol), *N*-phenyl-bis(trifluoromethane-sulfonimide) (2.0 mmol, 710 mg), K_2CO_3 (6.0 mmol, 830 mg), and 3.0 mL of THF were mixed in a septum-capped tube. The reaction mixture was heated to 120 °C for 6 min in a SmithSynthesizer.

(8) Barlos, K.; Chatzi, O.; Gatos, D.; Stavropoulos, G. *Int. J. Peptide Protein Res.* **1991**, *37*, 513−520.

(9) Tan $\delta = 0.047$ at room temperature; Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213−224.