



## A high throughput synthesis of aryl triflate and aryl nonaflate promoted by a polymer supported base (PTBD)

Sabine Boisdard, Jaqueline Chastanet and Jieping Zhu \*

*Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-Sur-Yvette, France*

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### Abstract

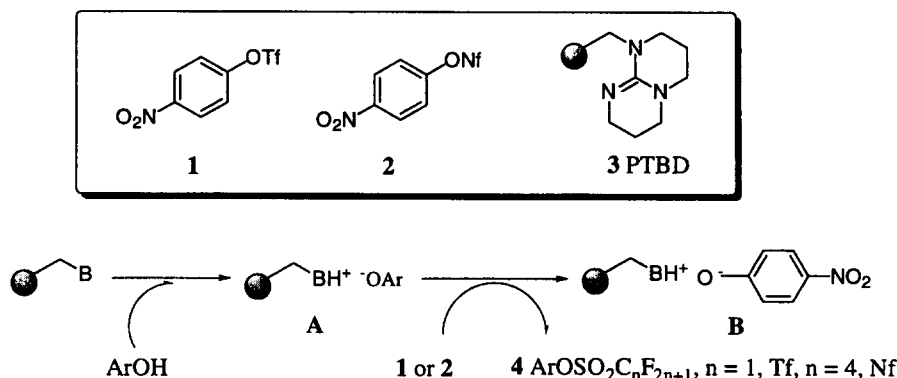
A rapid synthesis of aryl triflate and aryl nonaflate was developed using 4-nitrophenyl triflate and 4-nitrophenyl nonaflate as perfluoroalkanesulfonyl transfer reagents in combination with a polymer supported base (PTBD). Simple filtration of the reaction mixture gave the desired products in high chemical yields and purity. The unique role of PTBD as a base and side product scavenger was demonstrated. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Palladium and nickel catalyzed cross-coupling of aryl triflates,<sup>1</sup> and very recently aryl nonaflates<sup>2</sup> with different organometallic reagents as well as nitrogen- and oxygen-centered nucleophiles<sup>3</sup> are among the most powerful methods for the construction of carbon–carbon and carbon–heteroatom bonds and have found wide applications in modern organic chemistry. Not surprisingly, this efficient methodology has been exploited for the combinatorial synthesis of various biologically important compounds.<sup>4</sup> However, most of the aryl triflates and aryl nonaflates were not commercially available and thus needed to be synthesized in-house for subsequent synthetic applications. From the view-point of combinatorial chemistry, it is thus necessary to develop a high throughput parallel synthesis of these reactive species to meet the current synthetic standards.<sup>5</sup> To the best of our knowledge, such a process has not yet been reported.

Aryl triflates and aryl nonaflates were commonly prepared by reaction of phenols with triflic anhydride<sup>6</sup> and nonafluorobutanesulfonic fluoride<sup>7</sup> in the presence of a base. Other reagents such as imidazole triflate, *N*-phenyltriflimide and *N*-(2-pyridyl)triflimide have been developed by groups of Effenberger,<sup>8</sup> McMurry<sup>9</sup> and Comins,<sup>10</sup> respectively. We have recently shown that 4-nitrophenyl triflate (1) and 4-nitrophenyl nonaflate (2) were efficient perfluoroalkanesulfonyl transfer agents under mild basic conditions.<sup>11</sup> Since 4-nitrophenol, which is acidic in nature, was the only side-product formed besides the desired triflate or nonaflate, we thought it would be possible to develop a high throughput synthesis of aryl triflates and nonaflates using a suitable polymer-supported base.<sup>12</sup> The underlying

\* Corresponding author. Fax: +33 1 69 07 72 47; e-mail: zhu@icsn.cnrs-gif.fr

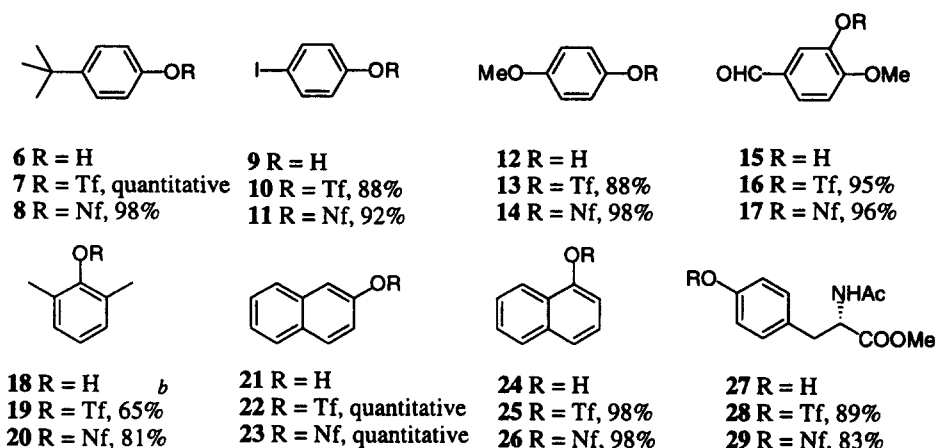
principle is shown in Scheme 1. A characteristic feature of this process is that the polymer-supported base has a dual role. It will first act as a reagent to deprotonate the phenol (salt **A**) and then as a scavenger to trap all the acidic species (salts **A** and **B**). If a slight excess of phenol was used to drive the reaction to completion, simple filtration of the reaction mixture and solvent evaporation might give pure compound **4**, since both starting material and 4-nitrophenol (**5**) will be supported on the polymer via their respective salts **A** and **B**.



Scheme 1.

Previously, potassium carbonate or cesium fluoride were employed as bases to perform the perfluoroalkanesulfonyl transfer using **1** and **2**.<sup>11</sup> To realize the transformation shown in Scheme 1, an organic base was first sought. Employing 4-*tert*-butyl phenol (**6**) as a testing substrate, DBU was found to be a suitable candidate. Indeed, the reaction between **1** and **6** in DMF in the presence of DBU gave a high yield of 4-*tert*-butyl phenyl triflate (**7**) without the occurrence of a competitive  $S_NAr$  reaction. In accordance with this result, polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD)<sup>13</sup> was selected on the basis of its structural analogy with DBU. In DMF which was previously established as a solvent of choice, the reaction of **6** with **1** gave a rather complex mixture probably due to the high solvating ability of this polar solvent. Indeed, both 4-nitrophenol **5** and 4-*tert*-butyl phenol (**6**) were found in the reaction supernatant. Clearly, a less polar solvent was required to increase the stability of the tight ion-pairs **A** and **B**. As a polar solvent was required for the sulfonyl transfer reaction for its intrinsic ionic mechanism, a compromise of solvent polarity thus needed to be determined. After some trials, it was found that the desired transformation proceeded smoothly when acetonitrile was used as solvent at 80°C. A typical experimental procedure follows: A reaction mixture containing 4-*tert*-butylphenol (**6**, 1.2 equivalents), 4-nitrophenyl triflate (**1**) and PTBD (3 equivalents)<sup>14</sup> in MeCN was heated at 80°C until compound **1** was consumed completely. The reaction mixture was then cooled to room temperature and filtered. Evaporation of the solvent gave 4-*tert*-butylphenyl triflate (**7**) in quantitative yield. Within the limit of detection by <sup>1</sup>H NMR, the purity of **7** was estimated to be higher than 95%. The reaction of **6** with 4-nitrophenyl nonaflate (**2**) under identical conditions afforded 4-*tert*-butylphenyl nonaflate (**8**) in 98% yield. Two additional points deserve to be commented on this transformation. Firstly, the sulfonyl transfer reaction did not take place at room temperature, probably due to the steric hindrance of PTBD around the anion. Secondly, prior formation of polymeric species PTBDH<sup>+</sup> OAr was not required since control experiments indicated that both **1** and **2** were inert towards PTBD under the reaction conditions. It is thus experimentally very simple since all the reaction partners can be directly mixed together.

The established reaction conditions were then applied to diversely substituted phenols and naphthols. As seen in Fig. 1, both electron-rich and electron-poor phenols are suitable substrates. Even a sterically hindered phenol such as 2,6-dimethylphenol (**18**) can be transformed to the corresponding triflate and



Note: <sup>a</sup>all the products have the chemical purity higher than 95% as determined by <sup>1</sup>H NMR as well as HPLC;

<sup>b</sup>moderate yield is due to the volatility of the product

Figure 1. PTBD promoted perfluoroalkanesulfonyl transfer reaction with **1** and **2**<sup>a</sup>

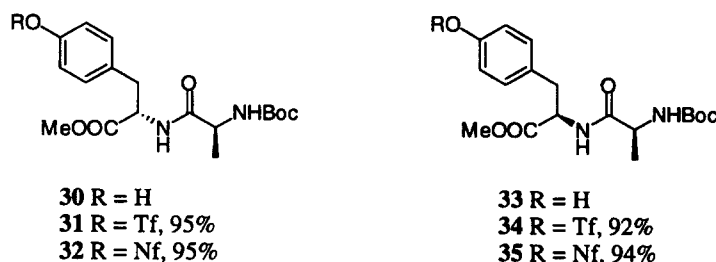


Figure 2.

nonaflate in good yield. The moderate isolated yield of **19** was due to the volatility of the product. A number of functionalities such as aryl iodide, aldehyde, ester and amide were tolerated.

A potential problem associated with this new procedure is the inherent high basicity of PTBD that may cause racemization of base-sensitive chiral compounds. To evaluate this point, a pair of diastereomers: L-N-Boc-Ala-L-Tyr methyl ester (**30**) and L-N-Boc-Ala-D-Tyr methyl ester (**33**) were prepared and their reactions with **1** and **2** were examined (Fig. 2). Under standard conditions, both dipeptides were converted into their respective triflates and nonaflates in excellent yields.<sup>15</sup> More importantly, comparison of <sup>1</sup>H NMR spectra (in DMSO for better resolution) and HPLC analysis (column: Nova-Pak, silica; eluent: heptane:EtOAc:AcOH=75:25:0.2) showed that less than 5% epimerization occurred in these sulfonyl transfer reactions.

Finally, the free PTBD base can be recovered from salts **A** and **B** by washing with diluted acid, base, H<sub>2</sub>O and organic solvents, successively.<sup>13a</sup> With the same loading as the virgin one, the reaction of dipeptide **30** with **2** in the presence of recycled PTBD gave nonaflate **32** in comparable yield.

In conclusion, we have developed a rapid synthesis of aryl triflates and aryl nonaflates using 4-nitrophenyl triflate and 4-nitrophenyl nonaflate as perfluoroalkylsulfonyl transfer agents in combination with a polymer-supported base (PTBD). The role of PTBD was unique in this study as it served not only as a base to activate phenols but also as a scavenger for trapping the acidic components (the starting phenol and the so-produced 4-nitrophenol).<sup>16</sup> The procedure developed should be easily adapted for automated parallel chemical synthesis.

## Acknowledgements

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## References

1. (a) Ritter, K. *Synthesis* **1993**, 735–762; (b) Stanforth, J. P. *Tetrahedron* **1998**, *54*, 263–303.
2. (a) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203–208; (b) Lipshutz, B. H.; Buzard, D. J.; Yun, C. S. *Tetrahedron Lett.* **1999**, *40*, 201–204.
3. (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046–2067; (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
4. Pavia, M. R.; Whitesides, G. M.; Hangauer, D. G.; Hediger, M. E. Patent WO 95-04277, 1995 (*C. A.* **1995**, *123*, 198439z). For compilations, see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527–4554; (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643–5678; (c) Booth, A.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1998**, *54*, 15385–15443.
5. For reviews, see: (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600; (b) Balkenhohl, F.; Von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2289–2337.
6. Subramanian, L. R.; Hanack, M.; Chang, L. W. K.; Imhoff, M. A.; Schleyer, P. R.; Effenberger, F.; Kurtz, W.; Stang, P. J.; Dueber, T. E. *J. Org. Chem.* **1976**, *41*, 4099–4103.
7. (a) Niederprüm, H.; Voss, P.; Beyl, V. *Liebigs Ann. Chem.* **1973**, 20–32; (b) Subramanian, L. R.; Bentz, H.; Hanack, M. *Synthesis* **1973**, 293–294.
8. Effenberger, F.; Mack, K. E. *Tetrahedron Lett.* **1970**, 3947–3948.
9. (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982; (b) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 4607–4610.
10. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
11. (a) Zhu, J.; Bigot, A.; Tran Huu Dau, M. E. *Tetrahedron Lett.* **1997**, *38*, 1181–1182; (b) Neuville, L.; Bigot, A.; Tran Huu Dau, M. E.; Zhu, J. *J. Org. Chem.* **1999**, in press.
12. Booth, R. J.; Hodges, J. C. *Acc. Chem. Res.* **1999**, *32*, 18–26; (b) Obrecht, D.; Villalgordo, J. M. In *Tetrahedron Organic Chemistry Series*; Baldwin, J. E.; Williams, R. M., Series Eds. Solid-supported combinatorial and parallel synthesis of small-molecular-weight compound libraries. Elsevier Science: Oxford, UK, 1998.
13. Tamura, Y.; Fukuda, W.; Tomoi, M. *Synth. Commun.* **1994**, *24*, 2907–2914; (b) Xu, W.; Mohan, R.; Morrissey, M. M. *Tetrahedron Lett.* **1997**, *38*, 7337–7340, and references cited therein.
14. The loading of PTBD (Aldrich) is 3.2 mmol base per gram.
15. All new compounds described gave spectral data consistent with the assigned structures.
16. Ion-exchange resin serves as a reagent and product scavenger, see: Kulkarni, B. A.; Ganesan, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2454–2455.