A Facile Route to Aryl Amines: Nucleophilic Substitution of Aryl Triflates

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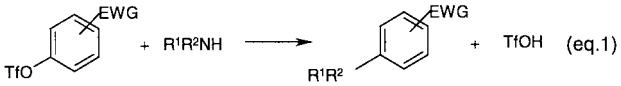
Abstract: The aromatic nucleophilic substitution (S_NAr) between aryl triflates and secondary amines has been studied. In the absence of solvent, the reaction proceeds at room temperature for nitro and cyano activated aryl triflates and requires higher temperatures in the case of carboxy activation. Variable triflate reactivity could be explained in terms of frontier molecular orbital theory. This methodology has been applied for the synthesis of substituted piperidyl pyridines.

Key words: Triflate, S_NAr, amination, aryl amine, frontier orbitals

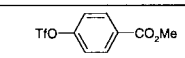
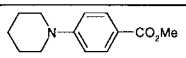
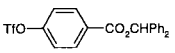
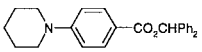
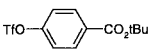
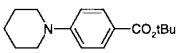
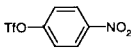
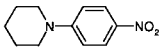
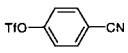
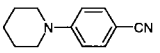
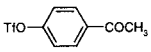
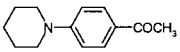
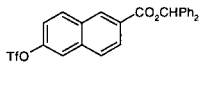
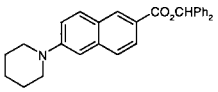
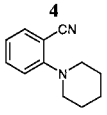
Aryl triflates have been widely used in transition metal catalysed coupling reactions with organometallic reagents.[1] Recently, palladium complexes have been shown to be effective catalysts for the amination of aryl triflates.[2] However, very little attention has been devoted to the study of displacement of the triflate group by amines in S_NAr type reactions.[3,4] In 1990, Kotsuki et al.[3] described the reaction between electron poor aryl triflates and various amines (mainly secondary).



EWG: NO_2, CN, OTf, PhCO

This methodology for the preparation of aromatic amines is very attractive since triflates are readily available from the corresponding phenols.[5] However, the experimental conditions reported by Kotsuki are rather drastic with long reaction times in refluxing acetonitrile and high pressures. In parallel to Kotsuki's work, nucleophilic displacement of triflate by amines has been extensively investigated in

Table 1 Amination of various electron poor triflates with piperidine in the absence of solvent

Entry	Triflate	Product	Temp. (°C)	Reaction Time (h)	Yield [a,b] (%)	mp (°C)
1	 **1a**	 **2a**	100	1.5	35[c]	94
2	 **1b**	 **2b**	110	3	79	142
3	 **1c**	 **2c**	110	7	81	104
4	 **1d**	 **2d**	RT	1	98	103[d]
5	 **1e**	 **2e**	RT	8	84	50
6	 **1f**	 **2f**	100	5	50	87
7	 **3**	 **4**	100	8	32	167
8	 **5**	 **6**	90	2	70	< 50
9			RT	9	ND[e]	

[a] The yields are given for isolated products and refer mainly to single runs. [b] In a typical procedure, a mixture of 1 equiv. triflate and 5 equiv. piperidine is stirred at RT or 100°C until completion of the reaction (monitored by TLC). The crude mixture is purified by flash chromatography on silica gel to afford aryl amine as pure compound (satisfactory ^1H & ^{13}C NMR, IR and mass spectral data). [c] 2.5 equiv. piperidine. [d] Lit. mp[3]: 101-104°C. [e] Not determined.

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our laboratory. We report herein the scope and limitations of this reaction as a synthetic tool and from a mechanistic point of view. An application in medicinal chemistry is presented as well.

Noting the detrimental effect of dilution in kinetics of second order reactions, preliminary experiments were conducted in the absence of solvent. Indeed, we observed that aryl triflates react with piperidine at room temperature in neat conditions, when activated with the nitro or nitrile group (Table 1, entries 4 and 5). In the case of an ester group, the reaction requires higher temperatures (≈ 100 °C) and improved yields were observed with hindered esters that minimise amidation as a competing process (entries 2 and 3). Moreover, it is noteworthy that naphthyltriflate **3** undergoes amination (albeit in poor yield) even though activated by a remote ester group (entry 7).

Surprisingly, 2- and 4-cyanophenyltriflates **5** and **1e** exhibited similar reaction times at room temperature (entries 5 and 9). The *para* attack might have been expected to be faster considering steric hindrance in the *ortho* position. In addition, it has been reported that amination of halonitrobenzenes proceeds much faster at the *para* position in agreement with optimised $HOMO_{amine}$ - $LUMO_{aryl\ halide}$ interactions when compared to the *ortho* reaction.[6] Therefore, we embarked on semi-empirical molecular orbital calculations in order to estimate the contributions of frontier orbital versus coulombic interactions in triflate reactivity. LUMO energy (E_{EWG}) and electron deficiency at the reaction site (δ^-_{EWG}) were calculated using MNDO and CNINDO programmes respectively.[7] Reactivity of selected electron poor triflates (k_{EWG}) was assessed from detailed kinetic studies.[8]

Interestingly, the relative reactivity of triflates **1b**, **1d**, **1e** and **5** was found to be correlated with softness. The lower the LUMO, the faster the reaction: k_{NO2} (E_{NO2} = -3.655 eV) > $k_{orthoCN}$ (E_{oCN} = -3.416 eV) ≈ k_{paraCN} (E_{pCN} = -3.466 eV) > $k_{CO2CHPh2}$ (E = -3.262 eV).

Moreover, 2- and 4-cyanophenyltriflates turned out to possess LUMOs of equivalent energy in agreement with the observed similar reaction times. On the other hand, no correlation was obtained regarding electron deficiency calculated at the reaction site. For example, it appeared from detailed kinetics studies that the amination rate is 60 times higher in the case of 4-nitrotriflate **1d** when compared to 4-cyanotriflate **1e** whereas the electron deficiency is very similar (δ^-_{NO2} = 0.215, δ^-_{CN} = 0.202). This study leads to the conclusion that the reactivity of aryl triflates towards piperidine is primarily influenced by frontier orbitals interactions rather than coulombic forces.

Next, we investigated the reactivity of 4-cyanophenyltriflate **1e** towards various amines (eq.2).

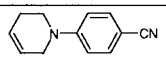
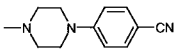
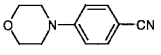
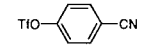
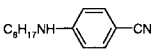
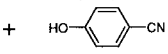
1e **7a-e** **8a-e**

Morpholine, N-methyl piperazine and tetrahydropiperidine gave satisfactory yields in the absence of solvent (see Table 2). However, we observed two limitations to the scope of the reaction:

– With a bulky amine such as diisopropylamine, no reaction occurred and the starting material was recovered.

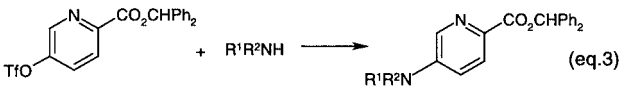
– In the case of octylamine, phenol **9** was isolated as the main product. According to MNDO calculations,[9] octylamine is a harder nucleophile than piperidine. As a result, nucleophilic attack occurs at the harder electrophilic site of the molecule, the sulfur atom, leading to aminolysis of the triflate moiety.

Table 2 Amination of 4-cyanophenyl triflate **1e** with various amines in the absence of solvent

R_1R_2NH	Product	Temp. (°C)	Reaction Time (h)	Yield [a,d] (%)
 **7a**	 **8a**	80	1.5[b]	61
 **7b**	 **8b**	90	2[c]	79[e]
 **7c**	 **8c**	90	2	81[f]
 **7d**	 **8d**	100	1	0
$C_8H_{17}NH_2$ **7e**	 **8e** (6%) +  **9** (73%)	100	3	79

[a] The yields are given for isolated products and refer to single runs .[b] 24h at room temperature. [c] 48h at room temperature. [d] Reactions were performed with 5 equiv. amine and followed by TLC. After completion, crude mixtures were purified by flash chromatography on silica gel. All the isolated compounds gave satisfactory analytical data (^1H and ^{13}C NMR, IR and MS). [e] **8b**: mp = 110°C. [f] **8c**: mp = 84°C, lit. mp[3]: 85°C.

With developed methodology for the synthesis of aryl amines, we investigated the amination of aryl triflate **10**[10] in relation to a medicinal project.



10 **7** **11**

Triflate **10** turned out to be very reactive towards several functionalised amines (Table 3). Indeed, detailed kinetic studies revealed that **10** reacts with piperidine 10 times faster than 4-cyanophenyltriflate **1e** (and hence 6 fold slower than 4-nitrophenyltriflate **1d**). According to CNINDO calculations, **10** is a softer electrophile than **1e** and

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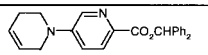
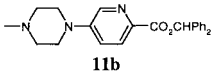
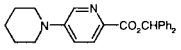
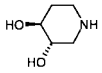
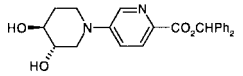
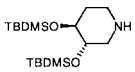
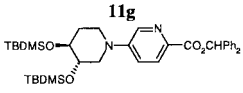
is harder than **1d** regarding their LUMO energy.[11] Furthermore, **10** exhibits a reduced electron deficiency at the reaction site ($\delta^- = 0.177$) when compared to **1e** and **1d** confirming predominant frontier orbital interactions in triflate reactivity.

Table 3 Amination of triflate **10** with various functionalised amines

Amine[a]	Product	Temp. (°C)	React. Time	Yield (%)
 **7a**	 **11a**	60[b]	2	60[d]
 **7b**	 **11b**	70[b]	1	76[e]
 **7f**	 **11f**	70[b]	15min	75[f]
 **7g**	 **11g**	100	3	17[c]
 **7h**	 **11h**	100	6	75[c]

[a] 5 equiv. unless otherwise indicated. [b] Heating was necessary to obtain a homogeneous medium. [c] 2 equiv. amine. [d] **11a**: mp=121°C. [e] **11b**: mp=128°C. [f] **11f**: mp=143°C.

In the case of racemic *trans*-dihydroxy piperidine **7g**,[12] it was necessary to add DMF because of the heterogeneity of the reaction medium. This resulted in a low yield (17 %) of aminated product **11g**. The yield was dramatically improved by protecting the two hydroxyl groups as *tert*-butyl dimethylsilyl ethers. Accordingly, the reaction could be carried out in neat conditions and the racemic product **11h** was isolated in 75 % yield.[13]

In conclusion, we have demonstrated that the reaction between secondary amines and electron deficient aryl triflates does not require drastic conditions as reported. In the absence of solvent, aryl triflates undergo nucleophilic substitution with various amines either at room temperature or at 60-100°C depending on the activating substituent. Kinetic studies have shown that the reactivity of triflates towards secondary amines is mainly controlled by frontier orbitals interactions rather than coulombic forces. In addition, we have successfully applied our methodology to the preparation of functionalised piperidylpyridines.

Acknowledgement

We are grateful to the Analytical Department (HMR, Romainville) for performing the spectral analyses and to Branislav Musicki and John Weston (Medicinal Chemistry Department) for helpful discussions.

References and Notes

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(2) For excellent recent reviews see: Hartwig, J.F. *Synlett* **1997**, 329; Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2046; Frost, C.G.; Mendonca, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615.

(3) Kotsuki, H.; Kobayashi, S.; Suenaga, H.; Nishizawa, H. *Synthesis* **1990**, 1145.

(4) For the nucleophilic amination of N^2-aromatic triflates see: Chayer, S.; Essassi, E. M.; Bourguignon, J. J. *Tetrahedron Lett.* **1998**, *39*, 841; Cappelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Bruni, G.; Romeo, M. R.; Menziani, M. C.; De Benedetti, P. G.; Langer, T. *J. Med. Chem.* **1998**, *41*, 728; Arcadi, A.; Cacchi, S.; Fabrizi, G.; Manna, F.; Pace, P. *Synlett* **1998**, 446; Steinbrecher, T.; Wameling, C.; Oesch, F.; Seidel, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 404; Megati, S.; Goren, Z.; Silverton, J. V.; Orlina, J.; Nishimura, H.; Shirasaki, T.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **1992**, *35*, 4098; Saari, W. S.; Halczenko, W.; King, S. W.; Huff, J. R.; Guare Jr, J. P.; Hunt, C. A.; Randall, W. C.; Anderson, P. S.; Lotti, V. J.; Taylor, D. A.; Clineschmidt, B. V. *J. Med. Chem.* **1983**, *26*, 1696.

(5) A typical procedure is as follows: To a mixture of 4-hydroxybenzonitrile (5g, 42 mmol) in dichloromethane (200 ml) was added at 0°C triethylamine (8.7 ml, 62.4 mmol) and then slowly trifluoromethanesulfonic anhydride (8.4 ml, 49.9 mmol). The resulting mixture was stirred 2 h at 0°C then quenched with water. The organic layer was separated, washed with water and dried over anhydrous magnesium sulfate. After filtration and concentration at reduced pressure, the crude mixture was purified by flash chromatography on silica gel (diethyl ether/cyclohexane: 20/80 v/v) to afford **1e** (8.46 g, 80 % yield). TLC, SiO_2, ether/cyclohexane: 1/1 (v/v), $R_f = 0.48$. IR ($CHCl_3$, ν cm^{-1}): 2235 (CN); 1430, 1140 (OSO_2CF_3). ^1H NMR (250 MHz, $CDCl_3$, ppm): δ 7.80, 7.43 (4H, AA'BB' system). Analyses for the elements C, H, F, N, S were within ± 0.2% of theoretical values.

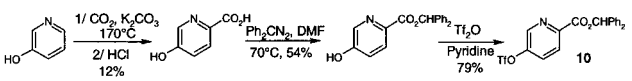
(6) For a comprehensive textbook on frontier orbital theory, see: Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976. For a discussion on aromatic nucleophilic substitution with aryl halides see chapter 3, 68-69 and references cited therein.

(7) Low energy conformations were identified using force field calculations (in-house software). Following MNDO or CNINDO/2 calculations (programmes implemented in QCPE package), relevant frontier orbitals were assigned based on electronic density at the reaction site.

(8) Only triflates reacting cleanly (yield > 70%) were considered. Amination reactions were performed at 25°C using a thermostated water bath. Product formation and triflate consumption were followed by HPLC.

(9) E_{HOMO} piperidine = -10.066 eV; E_{HOMO} octylamine = -10.435 eV

(10) Prepared according to the following Scheme:



Scheme

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(11) Calculated LUMO energies with CNINDO: E_{1b} = 0.0349 eV ; E_{10} = 0.0622 eV ; E_{1e} = 0.0799 eV.
(12) Takemura, S.; Miki, Y.; Uono, M.; Yoshimura, K.; Kuroda, M.; Suzuki, A. *Chem. Pharm. Bull.* **1981**, *29*, 3026.
(13) Preparation: A mixture of triflate **10** (340 mg, 0.78 mmol) and amine **7h** (542 mg, 1.56 mmol) was stirred 6h at 100°C and then purified by flash chromatography on silica gel with a 15/85 (v/v) diethyl ether / cyclohexane mixture to give **11h** (371 mg, 75% yield). TLC, SiO_2, ether/cyclohexane 2/8 (v/v): R_f = 0.40. IR ($CHCl_3$, ν cm^{-1}): 1716, 1577, 1555, 1495, 1258, 835. ^1H NMR (250 MHz, $CDCl_3$, ppm): δ 0.04, 0.05, 0.08 and 0.09 (s, 3H), 0.77 and 0.91 (s, 9H), 1.53 (dq, J = 13 Hz, J= 4 Hz, 1H), 2.12 (m, 1H), 3.4-3.6 (m, 5H), 3.71 (m, 1H), 7.06 (dd, J = 9 Hz, J= 3 Hz, 1H), 7.18 (s, 1H), 7.25-7.50 (m, 10 H), 8.02 (d, J = 9 Hz, 1H), 8.36 (d, J = 3Hz, 1H). ^{13}C NMR (50 MHz, CD_3COCD_3, ppm): δ -4.86, -4.77, -4.71, -4.60, 17.81, 17.98, 25.62, 25.80, 28.7, 42.0, 50.0, 69.90, 70.75, 77.05, 118.7, 126.38, 127.32, 127.76, 128.44, 135.36, 136.67, 140.42, 148.88, 164.28. MS *m/e* (relative intensity): 632 (M^+, 25), 575 (12), 422 (75), 167 (100), 73 (12).

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