High Pressure Organic Chemistry; XI.[1] A New Convenient Synthesis of Aromatic Amines from Activated Phenols

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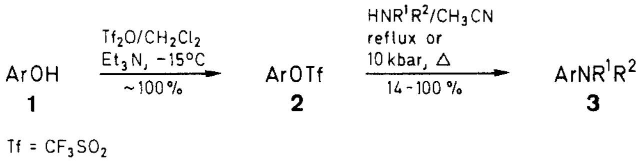
Aryl triflates containing electron-withdrawing substituents efficiently react with amines in refluxing acetonitrile or at 10 kbar pressure to give various aromatic amines.

Aromatic amines are versatile intermediates in industrial, agricultural, and medicinal chemistry.[2] Therefore, development of general and convenient procedures to prepare these molecules is of great importance. Conceptually, one of the effective approaches toward these compounds is the use of aromatic nucleophilic substitution (S_N Ar)[3] with an appropriate amine. Although a number of reports have appeared on this type of transformation, relatively limited methods are available starting from phenols; typically, the Bucherer reaction with ammonium sulfite is well-known.[4] This classical method, while useful, has limitations, this is mainly applicable to naphthols or resorcinols.[5] More flexible methods utilizing thermal rearrangement of quinazolines[6] and substitution of diethyl phosphates with amines[7] are also reported, but both methods suffer from lack of simplicity. In particular cases it has been reported that aryl *p*-toluenesulfonates[8] or aryl trimethylsilyl ethers[9] can react with an amine to provide aromatic amines. However, the method is limited in scope. Herein, we report an alternative, convenient method for the synthesis of aromatic amines from activated phenols via aryl trifluoromethanesulfonates (triflates).

The chemistry of aryl triflates has recently been extensively explored[10] and applied to a variety of chemical transformations of aromatic compounds.[11] In view of the easy preparation of triflates from their readily available phenol precursors.[10,11] an approach utilizing the displacement reaction of the triflate function seems to be attractive. Based on this background our successful results are described below.

The starting aryl triflates **2** were prepared from phenols **1** by treatment with triflic anhydride in the presence of triethylamine. The aryl triflates obtained were easily purified via column chromatography on a short column of silica gel. As expected, these compounds are sufficiently reactive and by simply heating with an amine the desired substitution reaction occurred. (Table 1).

For example, the reaction using a 1 : 3 molar ratio of **2a** to morpholine at reflux in acetonitrile afforded **3a** quantitatively with respect to the triflate. When 4-nitrophenyl *p*-toluenesulfonate was used in place of **2a** for comparison, the reaction occurred slowly (3 days) to afford **3a** in 29% yield.[21] Other reactive amines such as piperidine, pyrrolidine, 1-benzylpiperazine, and benzylamine also gave the desired product in excellent yield. On the other hand, less reactive amines such as diisopropylamine and aniline did not react with **2a** under the refluxing conditions, but at 10 kbar pressure;[22] the products **3e** and **3g** were isolated in 23 and 35% yield, respectively. Since the similar reaction using 4-chloronitrobenzene is unsuccessful at high pressure,[23] the remarkable reactivity of triflate as a leaving group is noteworthy.



1, 2	Ar	1, 2	Ar
a	4-$NO_2C_6H_4$	d	4-$C_6H_5COC_6H_4$
b	2-$NO_2C_6H_4$	e	4-FC_6H_4
c	4-CNC_6H_4	f	1-nitro-2-naphthyl

3	Ar	R¹	R²
a	4-$NO_2C_6H_4$	$-(CH_2)_2O(CH_2)_2-$	
b	4-$NO_2C_6H_4$	$-(CH_2)_5-$	
c	4-$NO_2C_6H_4$	$-(CH_2)_4-$	
d	4-$NO_2C_6H_4$	$-(CH_2)_2N(Bn)(CH_2)_2-$	
e	4-$NO_2C_6H_4$	*i*-Pr	*i*-Pr
f	4-$NO_2C_6H_4$	H	CH_2Ph
g	4-$NO_2C_6H_4$	H	Ph
h	2-$NO_2C_6H_4$	$-(CH_2)_2O(CH_2)_2-$	
i	4-CNC_6H_4	$-(CH_2)_2O(CH_2)_2-$	
j	4-$C_6H_5COC_6H_4$	$-(CH_2)_2O(CH_2)_2-$	
k	4-$TfOC_6H_4$	$-(CH_2)_2O(CH_2)_2-$	
l	1-nitro-2-naphthyl	$-(CH_2)_2O(CH_2)_2-$	

Other less reactive aryl triflates bearing the weaker electron-withdrawing functions of *p*-cyano- or *p*-benzoyl-groups reacted slowly with morpholine at atmospheric pressure. At 10 kbar pressure the reaction was considerably accelerated; **3i** and **3j** were obtained in better yields and in a shorter reaction period. Not surprisingly, even under high pressure conditions no reaction was observed with phenyl triflate, the simplest aryl triflate. Therefore, it can be concluded that the presence of electron-withdrawing substituents on an aromatic ring appears to be essential for the present substitution reaction. Interestingly, reaction of **2e** with morpholine provided only the S_NAr product at fluorine, **3k** instead of the expected triflate substituted compound. This fact implies that in this case a triflate group does not act as a leaving group, but as an electron-withdrawing group.[24]

In conclusion, we have demonstrated that our new method described above can serve as a useful tool for the synthesis of aromatic amines from readily available aryl triflates. In this study we have also clarified the powerful nature of high-pressure techniques for some sluggish reactions.

Table 1. Compounds 3 Prepared

Product	Amine	Reaction Conditions	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)
3a	morpholine	reflux, 24 h	100	151–152	149.5–150[12]
3b	piperidine	reflux, 12 h	100	101–102.5	103–104[13]
3c	pyrrolidine	reflux, 12 h	100	170.5–171	170[14]
3d	1-benzylpiperazine	reflux, 12 h	87	117.5–118.5	121[15]
3e	diisopropylamine	reflux, 24 h	0	–	–
3e	diisopropylamine	10 kbar, 62 °C, 45 h	23	93.5–94.5	$C_{12}H_{18}N_2O_2$ (222.3)
3f	benzylamine	reflux, 24 h	61	148–149	145–146[16]
3g	aniline	reflux, 24 h	0	–	–
3g	aniline	10 kbar, 100 °C, 20 h	35	130–132	131–132.5[17]
3h	morpholine	reflux, 12 h	100	oil[c]	$C_{10}H_{12}N_2O_3$ (208.2)
3i	morpholine	reflux, 72 h	80	75–76.5	85[18]
3i	morpholine	10 kbar, 62 °C, 20 h	88	–	–
3j	morpholine	reflux, 48 h	56	140–142	140[19]
3j	morpholine	10 kbar, 62 °C, 20 h	62	–	–
3k	morpholine	10 kbar, 62 °C, 50 h	14	oil	$C_{11}H_{12}F_3NO_4S$ (311.3)[d]
3l	morpholine	reflux, 24 h	100	69.2–70.2	79[20]

[a] Yield of isolated pure products based on **2**.

[b] Satisfactory microanalyses obtained: C ±0.09, H ±0.02, N ±0.08.

[c] Bp 165–170 °C/2 Torr.

[d] Characterized by MS determination of the accurate molecular mass: **3k** requires: 311.0439; found: 311.0433 (−0.6 ppm).

Table 2. Spectroscopic Data of **3e**, **3h**, **3k** Prepared

Product	IR (neat/Nujol) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
3e	1600, 1300	1.35 (12H, d, J = 6.8), 4.01 (2H, septet, J = 6.8), 6.77 (2H, d, J = 9.4), 8.06 (2H, d, J = 9.4)
3h	1605, 1520	3.05 (4H, m), 3.83 (4H, m), 6.9–7.2 (2H, m), 7.50 (1H, ddd, J = 8.5, 7.3, 1.6), 7.76 (1H, dd, J = 7.8, 1.6)
3k	1600, 1510	3.16 (4H, m), 3.86 (4H, m), 6.88 (2H, d, J = 9.2), 7.17 (2H, d, J = 9.2)

Melting points are uncorrected. IR spectra were recorded on a JASCO A-302 IR spectrophotometer. ^{1}H-NMR spectra were obtained at 90 MHz on a Hitachi R-90H spectrometer.

Aryl Triflates 2; General Procedure:

To a mixture of phenol **1** (1 mmol) and Et_3N (303 mg, 3 mmol) in CH_2Cl_2 (3–5 mL) at −15 °C is added a solution of triflic anhydride (423 mg, 1.5 mmol) in CH_2Cl_2 (1 mL). After the reaction is complete (TLC monitoring, usually ca. 10 min), the mixture is diluted with CH_2Cl_2 (10 mL) and washed with sat. $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer is dried (Na_2SO_4) and evaporated. The residue is purified by column chromatography on a short column of silica gel (CH_2Cl_2) to give almost quantitatively the aryl triflates **2**, which are sufficiently pure for further reactions.

Aromatic Amines 3; General Procedures:

At Atmospheric Pressure: A mixture of the aryl triflate **2** (1 mmol) and the amine (3 mmol) in anhydrous CH_3CN (5 mL) is refluxed under N_2 for the time indicated in Table 1. After evaporation of the solvent, the crude product is purified by column chromatography on silica gel (hexane/EtOAc) to afford the aromatic amine **3**.

At 10 Kbar Pressure: A mixture of the aryl triflate **2** (0.5 mmol) and the amine (1.5 mmol) in anhydrous CH_3CN (1.5 mL) is placed in a Teflon reaction vessel and allowed to react[22] at the temperature and time indicated in Table 1. After evaporation of the solvent, the crude product is purified by preparative TLC to afford **3**.

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(24) Aromatic fluorides bearing electron-withdrawing groups are well-known to undergo the aromatic nucleophilic substitution with various nucleophiles. See Ref. 3.