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Microwave-Assisted Amination from Aryl Triflates without Base and Catalyst

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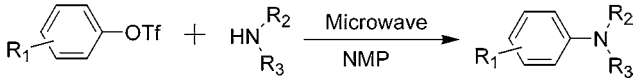
ABSTRACT



Aryl triflates are effectively converted to the corresponding anilines under microwave irradiation in 1-methyl-2-pyridone (NMP) without base and catalyst. Aryl triflates substituted with both electron-poor and electron-rich groups give good to excellent yields. It is noteworthy that the halogenated aryl triflates can chemoselectively react with amines to afford halogenated anilines.

Anilines are very important motifs that have found wide application in fluorescence probes,[1] pharmaceutical and agrochemical industry,[2] photography systems,[3] electronic devices,[4] and natural materials production.[5] Traditional nucleophilic aromatic substitution reactions (S_NAr) of N-nucleophiles are limited to only activated aromatic substrates.[6] The synthesis of anilines by Cu-mediated Ullmann condensation often suffers from severe reaction conditions.[7] In recent years, copper-mediated C−N cross-coupling reactions of arylboronic acids with nitrogen-based nucleophiles[8] and palladium-catalyzed C−N bond formation by exploiting aryl halides or aryl triflates[9] have emerged as powerful tools for preparation of anilines. However, these literature methods require catalysts, long reaction times, sensitive conditions, and/or strong bases. The use of transition-metals and ligands leads to the generation of waste and a number of hazards.[10] The need for clean manufacturing processes demands the development of new strategies for the preparation of anilines.

Microwave-assisted organic synthesis has attracted considerable attention in the past decade.[11] Microwave irradiation often leads to a remarkable decrease in reaction time, increased yields, and easier workup consistent with green chemistry protocols and may enhance the regio- and stereoselectivity of reactions.[12] More recently, it has been reported that aryl halides could couple with amines to give anilines employing microwave techniques in the presence of a strong

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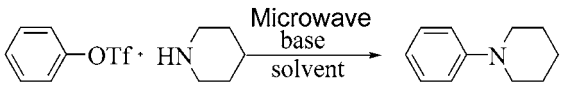
Table 1. Optimization Investigation[a]



entry	base	solvent	temperature (°C)	yield (%)[b]
1	K_2CO_3	NMP	201	<1
2	K_3PO_4	NMP	201	<1
3	KOH	NMP	202	<1
4	NaOH	NMP	202	<1
5	KO^{t}Bu	NMP	203	<1
6	none	NMP	205	83
7	none	DMSO	190	62
8	none	benzene	80	<1
9	none	toluene	110	<1
10	none	CH_3CN	100	<1
11	none	ethanol	87	<1
12	none	DMF	160	35
13	none	H_2O	107	<1

[a] Reaction conditions: PhOTf (2.0 mmol), base (3 mmol), and piperidine (5 mmol) in 10 mL of solvent at the temperature indicated for 45 min. [b] Yields based on GC/MS analysis.

base, but the usage of transition-metal catalysts or phase-transfer catalysts was still unavoidable in some cases.[13] In this paper, we present our studies toward the conversion of aryl triflates, which are easily obtained from phenols,[14] to the corresponding arylamines under the microwave irradiation. The reaction smoothly proceeded within short times in good to excellent yields without any base or catalyst.

We chose to use phenyl triflate as our initial coupling partner in combination with piperidine. The coupling conditions were based on those reported for amination by others employing microwave irradiation.[13] Our primary experiments demonstrated that the microwave heating reactions almost quantitatively resulted in phenol instead of the coupling product when a base such as K_2CO_3, K_3PO_4, KOH, NaOH, or KO^{t}Bu was used (Table 1, entries 1−5). However, we surprisingly found that the C−N coupling product was generated in good yields under base-free conditions (Table 1, entries 6 and 7). Although DMSO as the solvent delivered the expected phenylamine (Table 1, entry 7), it was less effective than NMP. We also tested other solvents such as DMF, benzene, toluene, ethanol, acetonitrile, and water, but they afforded very low yields. The best solvent for the microwave-assisted amination is NMP. It is noteworthy that the reaction tolerated the presence of trace water. The introduction of more than 10% water to the system did not affect the reaction.

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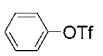
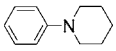
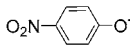
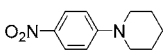
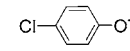
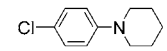
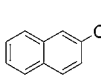
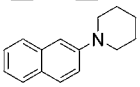
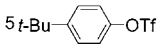
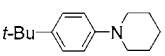
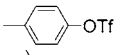
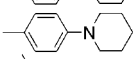
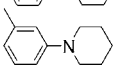
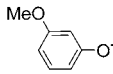
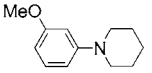
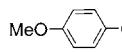
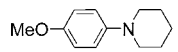
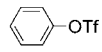
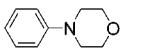
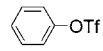
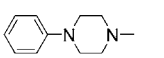
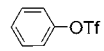
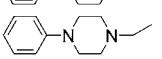
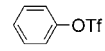
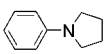
Table 2. Amination of ArOTf and Amines under Irradiation[a]

entry	ArOTf	amine	product	time(min)	yield(%)
1				45	83[b]
2				5	98[b]
3				45	93[b]
4				45	93[b]
5				60	90[b]
6				60	83[b]
7				60	86[b]
8				120	70[b]
9				120	37[b]
10				45	82[b]
11				45	79[b]
12				45	78[b]
13				45	80[b]
14				60	76[b]
15				60	63[b]
16				45	<1[c]
17				45	<1[c]
18				45	<1[c]

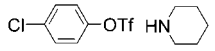
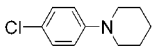
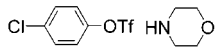
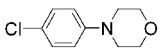
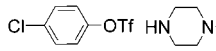
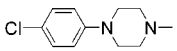
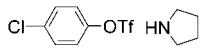
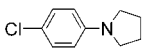
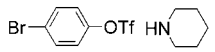
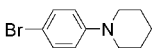
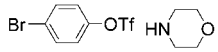
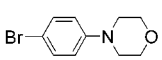
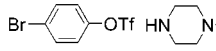
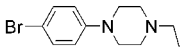
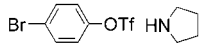
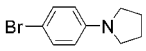
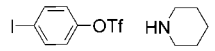
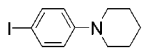
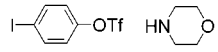
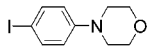
[a] Reaction conditions: ArOTf (2.0 mmol), amines (5 mmol), NMP (10 mL), MW 250 W, reflux, 200−204 °C. [b] Isolated yields. [c] Conversion determined by GC/MS analysis.

With the optimized conditions, we evaluated the microwave heating amination reaction with respect to substituted aryl triflates (Table 2).[15] Electron-poor aryl triflates with a nitro substituent delivered the expected products with excellent yields within 5 min (Table 2, entry 2). The chloro-substituted aryl triflate also afforded a good isolated yield after 45 min (Table 2, entry 3). Alkyl-substituted electron-rich aryl triflates exhibited good reactivity, but longer reaction times were required (Table 2, entries 5−7). Low isolated yields were obtained for the *p*-methoxy-substituted aryl triflate (Table 2, entry 9), while the reaction was shown to tolerate the *m*-methoxy-substituted electron-rich aryl triflate with moderate yield of 70% (Table 2, entry 8).

Variation in the structures of aliphatic amines has little effect on the amination. In all cases, moderate to good

(15) All microwave reactions were conducted in a 50 mL flask with a condenser. Microwave heating was carried out with a single-mode cavity Sanle WHL70S-01 Microwave Synthesizer (Nanjing Sanle Microwave Equipment Corporation).

Table 3. Chemoselectivity of Amination[a]

entry	ArOTf	amine	product	conversion(%)[b]	yield(%)[c]
1				100	93
2				100	90
3				100	90
4				100	91
5				100	92
6				100	94
7				100	89
8				100	92
9				100	87
10				100	95

[a] Reaction conditions: ArOTf (2.0 mmol), amines (5 mmol), NMP (10 mL), MW 250 W, reflux, 200−204 °C, 45 min. [b] Conversion determined by GC/MS analysis. [c] Isolated yields.

conversions occurred for both secondary and primary amines (Table 2, entries 9−15). However, aromatic amines substituted with either electron-withdrawing or electron-donating groups showed no reactivity in amination (Table 2, entries 16−18). Furthermore, we investigated the possibility for this amination using traditional heating methods and found that none of the aryl triflates except for *p*-nitrophenyl triflate were able to react with amines under reflux in NMP for 2 days.

On the basis of the above results and the known S_NAr chemistry, the coupling of aryl triflates and amines to form arylamines under microwave irradiation might involve an S_NAr process.

We also investigated the chemoselectivity for the amination of halogenated aryl triflates. As shown in Table 3, all of chloro-, bromo-, and iodo-aryl triflates could chemoselectively couple with the amines to give corresponding halogenated anilines in 100% conversion yields. To the best of our knowledge, aryl halides could efficiently react with amines to afford C−N coupling products using palladium catalysts.[9,13] In our cases, halide groups did not react even in the presence of excess amines. Therefore, our microwave heating amination provides a highly chemoslective method for preparation of halogenated anilines from halogenated aryl triflates.

In conclusion, we have introduced a general and facile method for the preparation of anilines from aryl triflates under microwave irradiation. The amination reaction proceeded efficiently in the absence of bases and catalysts and was not influenced by trace water. It is noteworthy that halogenated aryl triflates could chemoselectively couple with amines to give halogenated anilines in excellent yields.

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Supporting Information Available: Detailed experimental procedure and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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