Microwave-promoted mono-*N*-alkylation of aromatic amines in water: a new efficient and green method for an old and problematic reaction†

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A greener improvement to direct mono-*N*-alkylation of aromatic amines by alkyl halides was achieved using microwave irradiation in water without any catalyst.

Selective synthesis of *N*-alkylanilines plays a crucial role in organic chemistry due to the relevance of this type of amines as raw materials, intermediates or final products in nearly every field of the chemical industry.[1] Even though many synthetic methods were researched and reported in order to obtain mono- or dialkylarylamines, the preparation of *N*-monoalkylated derivatives *via* direct *N*-alkylation by alkyl halides is one of the most frequently used procedures.[2]

Many recent efforts were made to make this synthesis eco-friendlier: in this way, usual but hazardous volatile organic solvents were replaced with water, using mild basic conditions to reduce the amount of catalysts,[3] and/or conventional heating was substituted by microwave irradiation.[4,5] All the aqueous-mediated methods were efficient and successful but they all needed catalysts and also long reaction times, if MAOS (microwave-assisted organic synthesis) was not used. Moreover the troublesome problem of polyalkylation was only partially solved, working with a near equimolar ratio between arylamine and alkyl halide.[3]

To make the direct *N*-alkylation of aromatic amines fully green, possibly obtaining monoalkylation, we studied the possibility of carrying out the reaction with alkyl halide not only using water as solvent, but moreover avoiding the use of any catalyst, taking advantage of the MAOS technique.

As a basis of this study, a standard reaction between *p*-toluidine[6] and benzyl chloride was carried out in water under microwave irradiation at various times and temperatures (Table 1), using a monomode microwave reactor.

The alkylating reagent was initially added in a 1 : 1 ratio of substrate/halide. The best yield of *N*-benzyl-*p*-toluidine (75%) was achieved at 150 °C in 20 min (Table 1; entry 4): this temperature lies in the lower part of the so-called near-critical region of water[7] and performing the reaction under "superheated conditions" takes advantage of the favorable changes of chemical and physical properties of water at high temperatures and pressures.[8]

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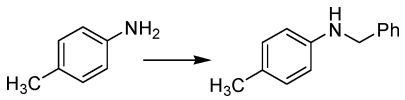
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds. See DOI: 10.1039/b900750d

Table 1 Effects of time and temperature on *N*-benzylation of *p*-toluidine[a]



Entry	Time/min	Temp/°C	Yield (%)[b]
1	10	110	0
2	10	130	5
3	10	150	60
4	20	150	75
5	30	150	75
6	20	150	82[c]

[a] Reaction conditions: *p*-toluidine (3 mmol) and benzyl chloride (3 mmol) in water (1 ml) were irradiated in a monomode microwave reactor. [b] Yield of isolated product. [c] Benzyl chloride: 6 mmol.

Different molar ratios of substrate/halide were also tested, finding that doubling the halide concentration increased the yield of monoalkylated toluidine up to 82% (Table 1; entry 6). It is interesting to note that even with a three-fold excess of the halide, only mono-*N*-alkylation occurred, without trace of the dibenzylated product. In fact, the reaction mixture contained only monoalkyltoluidine and unreacted starting compound.

On the contrary, the recently reported method of aqueous-mediated alkylation with mild base needed a 1 : 1.1 molar ratio to achieve mono-*N*-alkylation, but with a long reaction time and with 10% of dialkylated product.[4]

Parallel experiments were also performed under thermal heating. The reaction between *p*-toluidine and benzyl chloride (1 : 2 molar ratio) in water was carried out in autoclave at 150 °C for 40 min,[9] affording a complex reaction mixture containing starting toluidine as the major product, mono- and dialkyltoluidine as minor products, together with many unidentified products. This finding indicated that microwave irradiation provided higher conversion and selectivity compared to conventional heating conditions.

We experimented with the same reaction also in the presence of bases (Table 2; entries 1–4), with the catalysts frequently used in similar procedures[5,10] (Table 2; entries 5–6), and with organic solvents (Table 2; entries 7–11).

In all the aqueous mediated conditions the yields were lower than that of the standard procedure, thus proving that the presence of bases and/or catalysts negatively affected the course and the yield of the reaction. Moreover, if organic solvents were used instead of water, the reaction didn't occur in the absence of

Table 2 Effects of bases, catalysts and solvents on the *N*-benzylation of *p*-toluidine[a]

Entry	Base	Catalyst	Solvent	Yield (%)[b]
1	KOH	—	H_2O	40
2	TEA	—	H_2O	35
3	K_2CO_3	—	H_2O	45
4	$NaHCO_3$	—	H_2O	48
5	—	KI	H_2O	40
6	—	CuI	H_2O	0
7	—	—	DMF	0
8	—	—	DMSO	0
9	—	—	Dioxane	0
10	—	—	MeCN	0
11	—	KI	MeCN	10[c]

[a] Reaction conditions: *p*-toluidine (3 mmol) and benzyl chloride (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product. [c] Dialkylated compound was the major product.

bases and/or catalysts, and anyway the yields are very poor and dialkylation occurred preferentially.

Now that optimised conditions had been established, the reaction was attempted with a range of different alkyl halides. With all halides, the alkylation was achieved with high yield and selectivity (Table 3; entries 1–6), without trace of dialkylated product[11] and with no difference between bromo or iodoalkane (Table 3; entries 1–2).

Only with α,ω-dibromoalkanes selective mono-alkylation did not occur. As already reported, although in slightly different reaction conditions,[12] with 1,4-dibromobutane a cyclocondensation took place *via* double *N*-alkylation of starting aniline to obtain *N*-arylpyrrolidine (Table 3; entry 7).

With 1,2-dibromoethane intramolecular cyclization didn't occur, but two different alkylation products were obtained (Table 3; entry 8): *N*,*N*′-di-*p*-tolylethylenediamine, corresponding to mono-alkylation for each bromine of the halide, and *N*,*N*′-di-*p*-tolylpiperazine, corresponding to a particular dialkylation involving a second molecule of the halide. Even increasing the excess of halide up to ten fold, the final yields and the ratio between the two products remained practically the same, together with the formation of by-products (detected by HRMS).

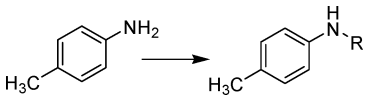
Then the reaction was tested with different starting arylamines and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride as alkylating agent.

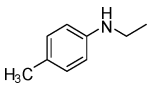
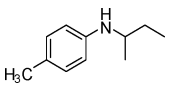
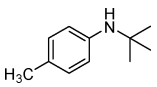
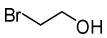
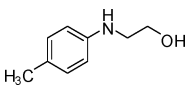
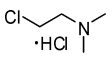
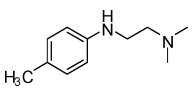
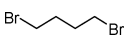
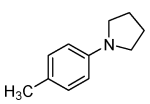
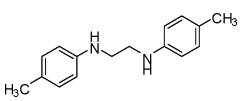
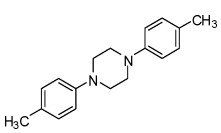
We chose this alkyl halide among the tested ones for its interesting features. It allows easy functionalization of aromatic amines with a dialkylaminoalkyl chain, which is one of the most common substituents in many pharmaceutical products,[13] and is usually obtained by substitution of aryl halides and not by direct alkylation of arylamines.[14] Moreover, it must be used as the hydrochloride to avoid aziridinium formation and the hydrochloride is water soluble, so optimal for our reaction conditions, but, on the contrary, not useful with conventional organic solvents, as commonly required.

The results are summarised in Tables 4 and 5.

Aniline and toluidines were easily alkylated in good yields (Table 4, entries 1–3).

Table 3 *N*-Alkylation of *p*-toluidine with different alkyl halides[a]



Entry	Alkyl halide	Product	Yield (%)[b]
1			85
2			88
3			73
4			68
5			66
6			90
7			85
8			20
			20

[a] Reaction conditions: *p*-toluidine (3 mmol) and alkyl halide (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product.

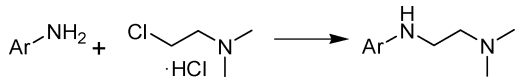
Activated anilines were well derivatized, as in the case of *o*-anisidine (Table 4, entry 4), but if a strong deactivating group was also present, as in the case of 2-methoxy-4-nitroaniline, the yield was considerably reduced (Table 4, entry 5).

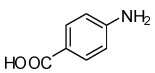
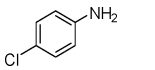
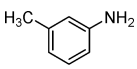
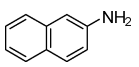
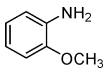
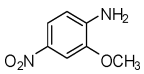
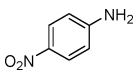
The *N*-alkylation of electron-poor anilines took place with variable yields, from a low yield for 4-nitroaniline to a moderate yield for 4-aminobenzoic acid (Table 4, entries 6–7), up to a satisfactory yield for *p*-chloroaniline (Table 4, entry 8). Anyway the reaction mixture contained only monoalkylarylamine and unreacted starting product.

Naphthylamines were also monoalkylated with very good yields (Table 4, entries 9–10).

Heteroaryl amines, such as 2-aminopyridine and 1-aminoisoquinoline, didn't react in this condition, probably owing to their deactivation properties (Table 4, entries 11–12).

Table 4 *N*-Alkylation of different arylamines[a]



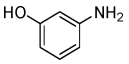
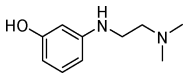
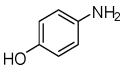
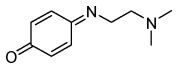
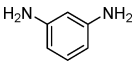
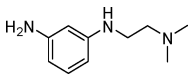
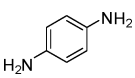
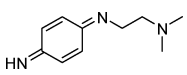
Entry	Arylamine	Yield (%)[b]	Entry	Arylamine	Yield (%)[b]
1		89	7		35
2		74	8		67
3		82	9		78
4		72	10		75
5		20	11		—
6		10	12		—

[a] Reaction conditions: arylamine (3 mmol) and 2-chloro-*N,N*-dimethylethylamine hydrochloride (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product.

The reaction with hydroxyanilines was chemoselective achieving only the mono-*N*-alkyl derivatives (Table 5, entry 1–2), but in the case of *p*-hydroxyaniline the product was easily oxidized to the corresponding quinone (Table 5, entry 2). In a similar way, with phenylenediamines only one amino group preferentially reacted, although with moderate yield (Table 5, entry 3), and with *p*-phenylenediamines only the corresponding quinoneimine was formed (Table 5, entry 4).

In conclusion, we have set up a green way to mono-*N*-alkylated aromatic amines under microwave irradiation. The reaction was carried out in water at 150 °C with twice the amount of the appropriate alkyl halide and without any catalyst. This synthetic procedure works very well with a variety of arylamines and in a satisfactory way also with deactivated amines; it allows only mono-*N*-alkylated products to be obtained and it is chemoselective in the presence of more than one functional group. The reaction is efficient, rapid and clean. Indeed, the described method could be a useful synthetic way to achieve alkylarylamines avoiding the use of organic solvents and catalysts or additives.

Table 5 *N*-Alkylation of hydroxyanilines and phenylenediamines[a]

Entry	Alkyl halide	Product	Yield (%)[b]
1			45
2			n.d.[c]
3			32
4			n.d.[c]

[a] Reaction conditions: arylamine (3 mmol) and 2-chloro-*N,N*-dimethylethylamine hydrochloride (6 mmol) in water (1 ml) were irradiated at 150 °C for 20 min. [b] Yield of isolated product. [c] Yield not determined: structures identified by HRMS analysis.

Notes and references

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