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Potassium iodide catalysed monoalkylation of anilines under microwave irradiation

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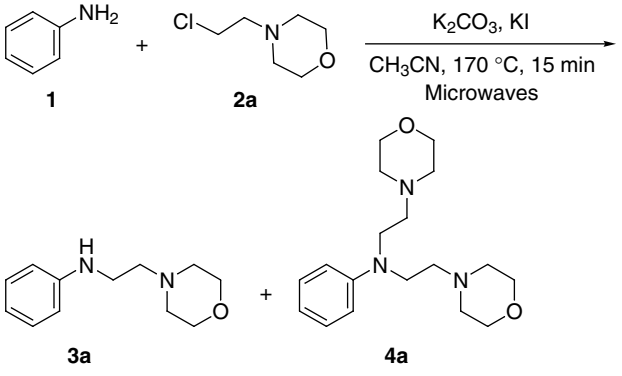
Abstract—A potassium iodide catalysed method for the selective *N*-monoalkylation anilines with alkylhalides and alkyltosylates under microwave irradiation is described. The corresponding *N*-alkylanilines are obtained in good yields with only minor quantities of dialkylation by-products.

N-Alkylation of aniline derivatives is an important reaction in organic synthesis, and provides access to valuable building blocks that are used as intermediates or additives in the preparation of dyes,[1] fluorescence probes,[2] agrochemicals[3] and pharmaceuticals.[4] Although some methods for the direct *N*-monoalkylation of anilines are available, alternative routes are always of interest. Generally, when alkylbromides or alkylchlorides are used as alkylating agents, the reactions proceed slowly and several polyalkylation/halogenated by-products are observed.[5] The most commonly employed alkylating agents are alcohols in the presence of acids (H_2SO_4,[6] H_3PO_4[7]), metals (Raney Ni[8]), Al_2O_3[9] or SiO_2 supported catalysts,[10] under different reaction conditions. Aldehydes and ketones react with aniline derivatives in the presence of hydrogen and a catalyst to yield *N*-alkylanilines.[11]

As part of one of our Drug Discovery programs we became interested in the synthesis of *N*-alkylanilines in a High Throughput Chemistry (HTC) environment, as building blocks for further modifications.

Microwave assisted organic synthesis (MAOS) has become increasingly popular in recent years to improve the yields and shorten reaction times in a variety of reactions.[12] *N*-Alkylation of aliphatic amines under microwave irradiation is a well-documented process.[12d,13] However, to the best of our knowledge, not much attention has been paid to the microwave promoted *N*-alkylation of anilines. Jiang et al. reported in 1996 the *N*-alkylation of anilines with alcohols over Raney nickel under microwave irradiation in a domestic oven.[14] More recently, Khadilkar and Jaisinghani reported in 1999, as a single example, the direct monobenzylation of aniline with benzylchloride on alumina supported potassium carbonate.[15] Dedicated microwave reactors, enable online temperature and pressure monitoring, for the rapid heating of samples under controlled reaction conditions. Herein we report a general, fast and efficient metal-free method for the *N*-alkylation of anilines under microwave irradiation.

Scheme 1 shows the preliminary experiment in our study. Treatment of *N*-(2-chloroethyl)morpholine (**2a**) with a 3-fold excess of aniline (**1**), K_2CO_3 (1 equiv) and



Scheme 1.

Keywords: Microwave assisted synthesis; Aniline; *N*-Alkylation.
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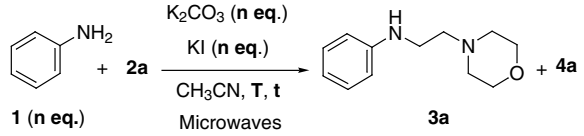
Table 1. *N*-Alkylation of aniline (**1**) with *N*-(2-chloroethyl)morpholine (**2a**) under microwave conditions



Entry	**1** (equiv)	K_2CO_3 (equiv)	KI (equiv)	*T* (°C)	*t* (min)	**3a**:**4a**[a]	Yield[b] (%)
1	3	1	1	170	10	92:8	89
2	3	1	1	110	10	97:3	93
3	3	1	1	80	10	99:1	81
4	3	—	1	110	10	97:3	95
5	3	—	0.1	110	10	97:3	95
6	3	—	0.1	110	5	98:2	84
7	1	—	0.1	110	10	67:33	64

[a] The ratio was determined by LC–MS spectroscopy of the crude reaction mixture.
[b] Yield of isolated product **3a** based on the alkylating agent **2a**.

KI (1 equiv) in CH_3CN at 170 °C for 15 min. under microwave irradiation led, after aqueous work-up and chromatographic purification, to the *N*-alkyl aniline **3a** in 89% yield. The *N*,*N*-dialkylated product **4a** was isolated in 6% yield.[16]

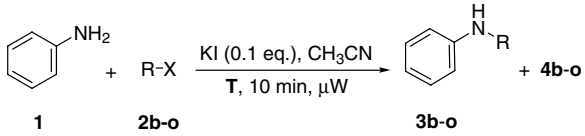
Encouraged by this result, investigations into the conditions suitable for this metal-free selective *N*-alkylation reaction of anilines under microwave irradiation were initiated. The results obtained are summarised in Table 1.

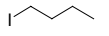
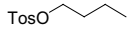
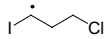
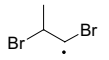
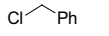
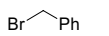
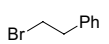
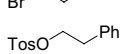
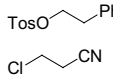
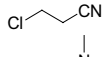
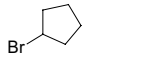
Firstly, the optimal reaction temperature was found to be 110 °C (Table 1, entry 2), lower temperatures (80 °C, Table 1, entry 3) led to a slight decrease in the reaction yield. The use of K_2CO_3 was not necessary (Table 1, entry 4). Additionally, catalytic amounts of potassium iodide could be used without loss in either the selectivity or reaction yield (Table 1, entry 5).[17] When the irradiation time was reduced to 5 min the yield dropped to 84% (Table 1, entry 6). The selectivity and yield were negatively affected by the reduction of the number of equivalents of aniline from 3 to 1 (Table 1, entry 5 vs 7).

We chose as the standard reaction conditions for the selective *N*-alkylation of aniline, irradiation of the alkylating agent with 3 equiv of aniline and a catalytic amount of KI (0.1 equiv) in acetonitrile, heated at 110 °C for 10 min.[18,19]

As shown in Table 2, in general, our microwave conditions worked well for a variety of primary (Table 2, entries 1–10) and secondary (Table 2, entries 11–13) alkylhalides and tosylates.[20] In all cases the reactions were clean and the only significant products formed were those resulting from monoalkylation (**3**) and dialkylation (**4**) of aniline (**1**).[16] Alkyltosylates and secondary alkylbromides (Table 2, entries 2, 8, 11–13) usually required higher reaction temperatures ($T = 170$ °C) to obtain satisfactory yields of the alkylated products. When 1-chloro-3-iodopropane (**2d**) was used the reaction occurred with complete regioselectivity affording *N*-3-chloropropylaniline (**3d**) in 70% yield (Table 2, entry 3). The reaction with 1,2-dibromopropane (**2d**) was also regioselective, the reactivity of the terminal bromide being higher than the secondary one (Table 2, entry 4).

Table 2. Potassium iodide catalysed microwave assisted synthesis of *N*-alkylaniline derivatives **3**[a]

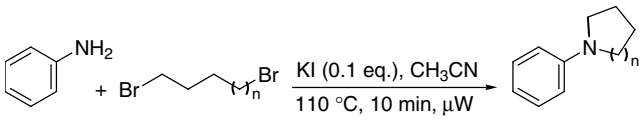


Entry	**2**	X–R	*T* (°C)	**3**:**4**[b]	**3**, Yield[c,d] (%)
1	**2b**		110	88:12	84 (10)
2	**2c**		170	86:14	54 (11)
3	**2d**		110	95:5	70
4	**2e**		110	91:9	57 (7)
5	**2f**		110	80:20	77 (17)
6	**2g**		110	80:20	77
7	**2h**		110	100:0	98
8	**2i**		170	90:10	86 (6)
9	**2j**		170	100:0	83
10	**2k**		110	100:0	98
11	**2l**		170	98:2	71
12	**2m**		170	100:0	98
13	**2n**		170	95:5	92
14	**2o**		170	90:10	67 (4)

[a] The reactions were done on a 1 mmol scale.
[b] The ratio was determined by LC–MS spectroscopy of the crude reaction mixture.
[c] Yield of isolated products **3** based on the alkylating agents **2**.
[d] Yield in parenthesis refers to the isolated *N*,*N*-dialkylated anilines **4**.

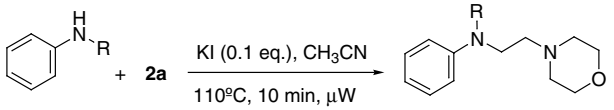
The synthesis of *N*-aryl pyrrolidines (**3r**) and piperidines (**3s**) was achieved in good yields by using as alkylating agents the appropriate dibromoalkanes (**2r**,**s**) (Scheme 2).

To our delight, secondary anilines (**5a**–**c**) were also alkylated in good yields to give the corresponding tertiary amines (**6a**–**c**) without contamination with aniline qua-



Scheme 2.

Table 3. Potassium iodide catalysed microwave assisted *N*-alkylation of *N*-alkylaniline derivatives **5**[a]



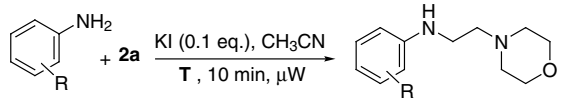
5a-c **6a-c**

Entry	5	6, Yield[b] (%)
1	**5a**	95
2	**5b**	90
3	**5c**	92

[a] The reactions were done on a 1 mmol scale.
[b] Yield of isolated products **6** based on the alkylating agent **2a**.

ternisation by-products.[16] The first results obtained are shown in Table 3.

Table 4. *N*-Alkylation of substituted anilines (**7**) with *N*-(2-chloroethyl)morpholine (**2a**) under microwave conditions[a]



7a-i (3 eq.) **8a-i**

Entry	7	T (°C)	8, Yield[b] (%)
1	**7a**	110	92
2	**7b**	110	70
3	**7c**	110	90
4	**7d**	170	95
5	**7e**	170	67
6	**7f**	170	98
7	**7g**	190	84
8	**7h**	170	89
9	**7i**	170	90

[a] The reactions were done on a 1 mmol scale.
[b] Yield of isolated products **8** based on the alkylating agent **2a**.

N-Alkylation of substituted anilines was also examined. *N*-(2-Chloroethyl)morpholine (**2a**) was chosen as the model alkylating agent. The results are summarised in Table 4. Electron rich anilines (Table 4, entries 1–3) were easily alkylated under our standard reaction conditions (μW, 110 °C, 10 min). The reaction with *para*-hydroxyaniline was chemoselective leading to the corresponding *N*-alkyl derivative in good yield (Table 4, entry 3). The *N*-alkylation of electron poor anilines required higher temperatures (170 °C) to achieve high yields (Table 4, entries 4–9). When the reaction was performed with *ortho*-nitroaniline (**7g**) the reaction mixture needed to be heated at 190 °C, probably due to the steric hindrance caused by the *ortho*-substituent.

In summary, we have developed a general and efficient metal-free method for the *N*-alkylation of anilines under microwave irradiation.[21,22] Studies on the scope and limitations of this methodology are undergoing and will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.10.002.

References and notes

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16. The excess of aniline can be easily recovered during the HPLC purification step.
17. When the reaction was carried out without K_2CO_3 and KI the product **3a** was obtained in 7% yield after microwave irradiation at 110 °C for 10 min.
18. The structure of the compounds **3a**–**c**, **3f**–**o**, **3r**–**s**, **8a**,**e** and **8g**–**h** was confirmed by comparison with authentic samples purchased from different vendors. All new monoalkylation compounds were fully characterised by ^1H, ^{13}C NMR and high resolution mass spectrometry.
19. When the reaction mixture was heated at 110 °C (oil bath temperature) for 10 min into a sealed tube the monoalkylation product **3a** was obtained in 60% yield.
20. When the alkylation reaction with **2b**,**h** or **2k** was performed in an open vessel with a catalytic amount of KI (0.1 equiv) in refluxing acetonitrile (traditional heating) for 1 h, the corresponding products **3b**,**h** or **3k** were obtained in 57%, 52% and 80%, respectively.
21. *Representative procedure*: To a solution of *N*-methylaniline (**5a**, 321 mg, 3 mmol) in acetonitrile (3 mL) in a microwave Emrysprocess™ vial *N*-(2-chloroethyl)morpholine (**2a**, 150 mg, 1 mmol) and KI (16.6 mg, 0.1 mmol) were added. The vial was sealed and heated in a Emrys™ optimiser microwave at 110 °C for 10 min. The cooled reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed successively with $NaHCO_3$ (aqueous saturated solution) and brine. Volatiles were evaporated and the residue thus obtained was purified by HPLC chromatography to give *N*-methyl-*N*-[3-(*N*′-morpholyl)ethyl]aniline (**6a**, 339 mg, 95%) as a violet oil. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, $J = 7.6$ Hz, 2H), 6.70 (d, $J = 8.1$ Hz, 2H), 3.72 (t, $J = 4.5$ Hz, 4H), 3.48 (t, $J = 7.5$ Hz, 2H), 2.94 (s, 3H), 2.54 (t, $J = 7.7$ Hz, 2H), 2.51 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.2, 129.4, 116.5, 112.3, 67.0, 55.4, 54.2, 50.2, 38.7. HRMS calcd for $C_{13}H_{21}N_2O$ 221.1654, found 221.1658.
22. Typical pressures for reactions carried out at 110 °C, 170 °C and 190 °C are, respectively, 1.1, 6.5 and 12 bar.