An Efficient and Fast Procedure for the Preparation of 2-Nitrophenylamines under Microwave Conditions

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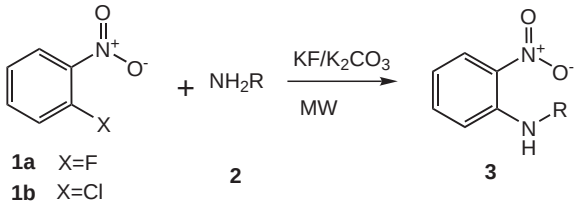
Abstract: 2-Nitrophenylamines were prepared in good yields from 2-chloronitrobenzen (or 2-fluoronitrobenzene) and amines in the presence of anhydrous potassium fluoride under microwave irradiation and solvent free conditions.

Key words: aminations, amines, microwave irradiation, nucleophilic aromatic substitution

Benzimidazoles as pharmacophore or scaffold exhibit many pharmacological activities.[1] In general, 2-nitrophenylamines are important intermediates in the synthesis of this kind of benzo-fused heterocycles. The traditional methods for synthesizing 2-nitrophenylamines often require vigorous conditions and the yields are not satisfactory.[2] The improved procedures[3] often use palladium acetate complexes supported by 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) or 2-(di-*tert*-butylphosphino)biphenyl as catalysts. However these phosphine ligands are expensive. Kulagowski et al.[4] and Lin et al.[5] had reported that 2-fluoronitrobenzene or 2-chloronitrobenzene can react with substituted anilines in the presence of anhydrous potassium fluoride. These reactions were carried out at 160–180 °C for 12–48 hours.

To shorten the reaction time, considerable attention has been focused on microwave assisted organic synthesis. Although it is not very clear why many reactions work extremely well under microwave irradiation, these methods has gained popularity in recent years.[6] Loupy et al.[7] have published a number of reviews on solvent-free reactions under microwave irradiation. This technique has been claimed to be particularly environmentally friendly and decreasing the risk of explosions, since it avoids the use of solvents and offers simple methods of workup. Recent publications also reported that the nucleophilic aromatic substitution reactions could be accelerated in solvent[8] and solvent-free[9] conditions under microwave irradiation. Amination reactions were completed with the unsatisfied yield (17–68%) in the presence of potassium carbonate and cuprous bromide under microwave in the absence of solvent.[10] It encouraged us to investigate if the yield of compound **3** could be increased and the reaction time decreased under microwave irradiation and solvent-free conditions (Scheme 1).

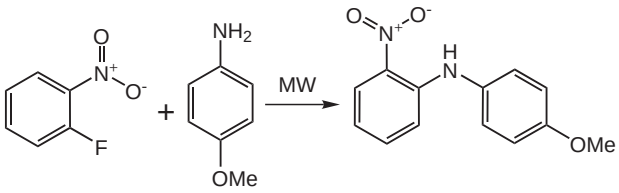


1a X=F
1b X=Cl
2
3

Scheme 1

In the search for optimal reaction conditions, different equivalents of anhydrous potassium fluoride and potassium carbonate were examined. The reaction times were also varied (Table 1). It showed that the best results were obtained when the anhydrous potassium fluoride and potassium carbonate were used in equivalent amount. Due to short reaction times and high yields, the easy work-up procedure by crystallization was possible.

Table 1 Optimization of Reaction Condition for the Synthesis of *N*-(4′-Methoxy-phenyl)-2-nitro-phenylamine



Entry	2-Fluoronitrobenzene (equiv)	*p*-Methoxypheny-lamine (equiv)	Anhydrous KF (equiv)	K_2CO_3 (equiv)	Domestic[a] Microwave, Time (min)	Yield (%)[b]
1	1	2	1	0	20	33
2	1	1	1	0.5	20	60
3	1	1	0	1	20	30
4	1	1	1	1	8	93
5	1	1	1	2	8	90

[a] National™ domestic microwave oven (90 W).
[b] Yield of isolated product, based on 2-fluoronitrobenzene.

It is accepted that thermal effects and specific microwave effects can induce the acceleration of reactions under microwave irradiation.[11] In order to interpret the microwave effect, this reaction was carried out in oil bath under similar conditions (Table 2). It suggested that specific microwave effects play an important role in these reactions.

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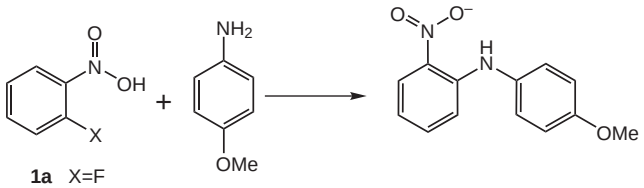
Table 2 Comparison between Heating in Oil Bath (Δ) and Microwave Irradiation (MW)



1a X=F
1b X=Cl

Substrate	Reaction conditions	Yield (%, Δ)[b]	Yield (%, MW)[b,c]
1a	8 min, 90 °C[a]	23	93
1b	10 min, 90 °C[a]	–[d]	90

[a] The temperature measured by immediately introducing a thermometer at the end of irradiation
[b] Yield of isolated product, based on 2-fluoronitrobenzene or 2-chloronitrobenzene;
[c] National™ domestic microwave oven (90 W).
[d] Not detected by TLC.

In order to extend the reaction scope, seven substituted anilines and one aliphatic amine were used in the reaction.[12] All products were purified by the crystallization from petroleum ether and formed in moderate to good yield (60–93%), which are summarized in Table 3. The data indicated that under microwave irradiation and solvent-free condition, aliphatic amines and substituted anilines with electron donating groups react smoothly with compound **1** in the presence of anhydrous potassium fluoride and potassium carbonate. But the substituted anilines with electron withdrawing groups had low yields due to their deactivating effect. It should also be noted that there was no by-product separated under the reaction conditions.

In conclusion a microwave-enhanced method for synthesizing 2-nitrophenylamines has been developed which involves the use of a solvent-free mixture of anhydrous potassium fluoride and cheap potassium carbonate. The process is highly efficient with easy workup.

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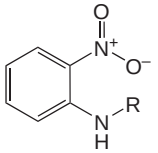
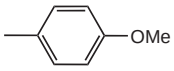
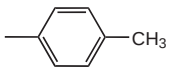
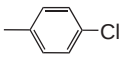
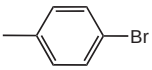
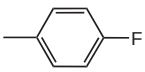
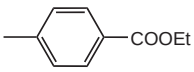
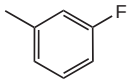
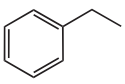
Table 3 Synthesis of N-Substituted 2-Nitrophenylamines (**3a**–**h**)



Product	R	Domestic Microwave,[a] Time (min)	Yield (%)[b]	mp[c] (°C)	Ref.
3a		8	93	83–86	5[d]
3b		8	90	67–70	5[d]
3c		20	75	135–137	4[d]
3d		20	80	148–50	5[d]
3e		20	70	82–83	5[d]
3f		20	60	84–86	–[d]
3g		20	75	63–64	–[d]
3h		2	88	64–66	–[d]

[a] National™ domestic microwave oven (90 W).
[b] All yield listed refer to pure isolated products based on compound **1**.
[c] Uncorrected.
[d] All compounds are characterized by ^{1}H NMR (300 MHz) in $CDCl_3$ and MS. Elemental Analysis were satisfactory for the products **3f**, **3g**, **3h**.

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(12) **General Procedure:** The preparation of *N*-(4′-methoxyphenyl)-2-nitrophenylamine (**3a**) is representative for all synthesis.
p-Methoxy phenylamine (1.1 mmol), anhyd KF (1.1 mmol) and K_2CO_3 (1.1 mmol) were well powdered with a mortar and pestle. 2-Chloronitrobenzene (or 2-fluoronitrobenzene) (1.1 mmol) was then added to the mixture and mixed well in a glass vial. After irradiation under microwave (90 W), the mixture was treated with water and CH_2Cl_2. The organic layer was washed with 10% HCl and brine. The CH_2Cl_2 solution was dried over anhyd Na_2SO_4, evaporated and crystallized from petroleum ether (bp 60–90 °C) to give orange crystals [mp 83–86 °C (lit. ref.[4]: mp 89 °C)]. ^{1}H NMR ($CDCl_3$, 300MHz): δ = 3.85 (s, 3 H, OCH_3), 6.72–8.19 (8 H, aromatic H), 9.41 (s, br, 1 H, NH). MS (EI) *m/z* = 244 [M^+], 229 [$M^+ - 15$].