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Improved yields of *meta*-amination and symmetrical and unsymmetrical diamination of benzenes

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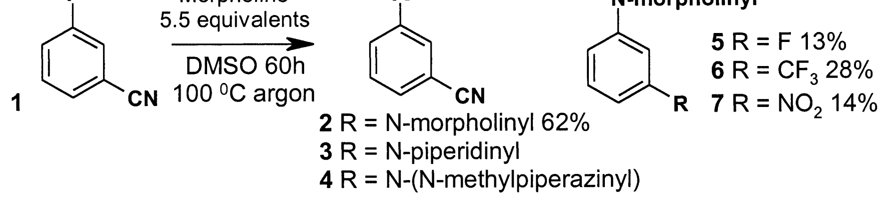
Abstract—Much higher yields were found after shorter reaction times for the *meta*-substituted amination of benzenes in DMPU with microwave heating in a sealed tube (180°C, 5 h), e.g. piperidine and *m*-fluorobenzonitrile **1** gave the *m*-substituted **3** in 92% yield. These modified reaction conditions also afforded a new synthesis of unsymmetrical diamines in >80% yield. © 2001 Elsevier Science Ltd. All rights reserved.

There are two main strategies for the nucleophilic amination of benzenes.[1] Palladium-catalysed amination proceeds in good yields with a range of substrates and is often the synthetic method of choice. Alternatively, a benzene substituted by a leaving group may be reacted with an amine, but the benzene must also contain an *ortho* or *para* electron-withdrawing group (EWG). Another limitation of direct substitution is that synthetic yields in *meta*-substitution have been very poor.[1] Recently we described[2] improved yields of these *meta*-substitutions, but the best yields were obtained only with a strong EWG. Yields in primary amine substitutions were modest, and substitution of a second amine group into dihalo-substituted compounds proceeded in poor yield. Herein, we report an investigation aimed at a significant yield improvement for the direct amination reaction, enabling a wider substrate scope to be used.

Amination of 3-fluorobenzonitrile **1** with 5.5 equivalents of morpholine (Scheme 1) in DMSO at 100°C for 60 h (under conventional atmospheric pressure reaction conditions) had given[2] a 62% yield of **2**. This yield could not be improved[2] by variation of the reaction conditions, including increasing the reaction temperature to 130°C. A more significant increase in reaction temperature was examined with a sealed glass tube (Carius tube) and with a microwave oven, where recent developments[3] allow for sealed tube reactions.

Piperidine substitution in benzenes with a *para*-substituted EWG has been reported[4] (without any yield improvement) in a microwave oven with external reflux. We anticipated, however, that much higher reaction temperatures would be attainable with a Carius tube or in a sealed reaction tube in a microwave oven, and that this might improve the yields of our more difficult *meta*-aminations. Due to the potential for decomposition of DMSO at these higher reaction temperatures (with the risk of a pressure build up), alternative solvents to DMSO were examined for the amination in Scheme 1 (Table 1). The amination yield of **2** obtained with morpholine in sulpholane was much poorer than that found in DMSO (18 versus 62%), but in sulpholane in a sealed tube in a microwave oven at



Scheme 1.

Keywords: amination; aryl halides; substituent effects.

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Table 1. Variation in morpholine aminations of **1** with solvent and heating conditions

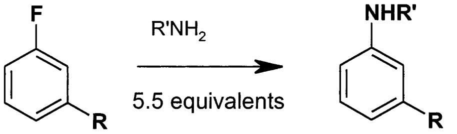
Conditions	Solvent	°C	Time (h)	Yield of **2** (%)
Conventional	Sulpholane	100	60	18
Microwave	Sulpholane	180	2	30
Conventional	DMPU	100	60	51
Carius tube	DMPU	180	5	63
Carius tube	DMPU	180	18	51
Microwave	DMPU	180	2	41
Microwave	DMPU	180	5	80

180°C for only 2 h the yield was improved (30%). Reactions in DMPU gave a small yield improvement in the Carius tube, but decomposition occurred in the 18 h reaction. In a sealed tube in the microwave oven an 80% yield of **2** was obtained after 5 h, compared with 62% in 60 h previously.[2] Under the same reaction conditions, but with piperidine or *N*-methylpiperazine in place of morpholine, the amination yields were 92% of **3** and 93% of **4** (Scheme 1), respectively (originally[2b] 68 and 69% in DMSO at 100°C for 60 h). Thus with DMPU as solvent and shorter reaction times, large yield improvements were found with microwave heating, but in the Carius tube decomposition was observed. These microwave reaction conditions were applied generally to: benzenes with other EWGs; benzenes with a chloro-leaving group; primary amines and disubstitution reactions with difluorobenzenes. The observed yields were compared to those previously obtained[2b] under conventional reaction conditions in DMSO at atmospheric pressure and 100°C for 60 h.

Sealed tube reactions in DMPU in a microwave oven at 180°C for 5 h

Morpholine gave only a modest yield improvement during displacement of *m*-fluorobenzenes containing weaker EWGs than cyano; e.g. with *m*-difluorobenzene (structures in Scheme 1), 13% of **5** versus 8% in DMSO; with *m*-trifluoromethyl fluorobenzene 28% of **6** versus 19% in DMSO. Chlorine replacement with morpholine in *m*-chlorobenzonitrile and *m*-chloronitrobenzene did not proceed at all[2b] under the conventional DMSO reaction conditions, but under the microwave conditions a 12% yield of **2** and a 14% yield of **7** was isolated. Under the microwave oven conditions primary amines consistently afforded better yields in reactions with **1** (Table 2).

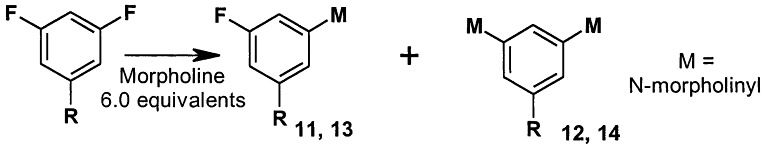
Table 2. Reactions of primary amines under microwave reaction conditions



Compound	R	Amine R′NH$_2$	Conditions	Yield (%)
8	CN	$MeS(CH_2)_3NH_2$	Conventional	31
8	CN	$MeS(CH_2)_3NH_2$	Microwave	56
9	CN	Allylamine	Conventional	19
9	CN	Allylamine	Microwave	29
10	CN	Benzylamine	Conventional	33
10	CN	Benzylamine	Microwave	42

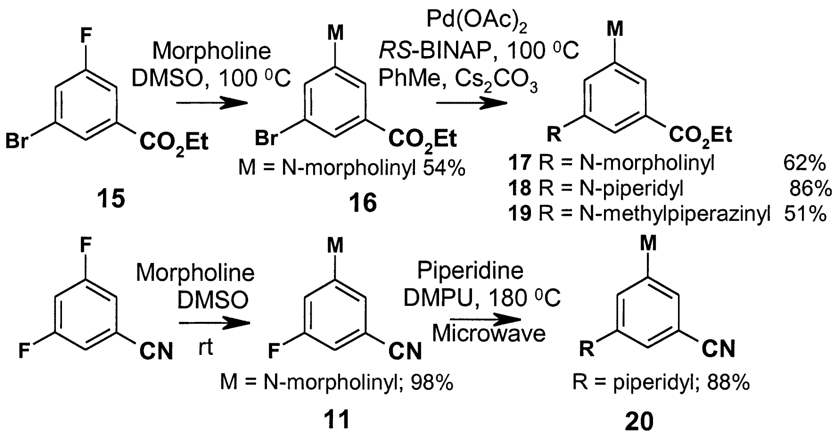
For palladium-catalysed diamination of *m*-dibromobenzenes good yields (45–83%) have been reported[5] by Beletskaya with morpholine and piperidine, but the desired symmetrical diamines had to be separated from dehydrohalogenation products. By contrast, our microwave conditions in DMPU with an EWG present gave high disubstitution yields (Table 3) of the symmetrical compounds **12** and **14**. Unsymmetrical diamines were not described by Beletskaya,[5] and we have prepared these in two ways. Firstly, we used the rare[6] chemical **15** (Scheme 2) with our conventional DMSO conditions for introduction of the first amino group to afford **16** (under microwave conditions, mixtures were obtained due to some amide formation). Introduction of the second amine group to give **18**, and separately **19**, was then effected via palladium-catalysed amination[1] with bromide as the leaving group. Secondly, we re-examined in DMSO, the diaminations of *m*-difluorobenzenes containing EWGs under milder

Table 3. Reaction of excess morpholine with difluorobenzenes



Compounds	R	Reaction conditions	% Mono substitution	% Di substitution
11 and **12**	CN	Conventional rt	98[a]	0
11 and **12**	CN	Conventional 100°C	62	37
11 and **12**	CN	Microwave	5	65
13 and **14**	NO_2	Conventional rt	91[a]	0
13 and **14**	NO_2	Conventional 100°C	78	16
13 and **14**	NO_2	Microwave	7	76

[a] Reaction allowed to reach completion by TLC.



Scheme 2.

reaction conditions. Introduction of the first amino group proceeded regioselectively at room temperature over 3–10 days (Table 3) or in a period of hours at 100°C to afford **11**, and **13**. Substitution of the second amino group had previously proceeded[2b] in poor yield, making access to unsymmetrical diamines difficult. Now, unsymmetrical substitution was achieved via the monosubstituted **11** (Scheme 2) in >80% yield. Piperidine was introduced as the second amino group under the microwave conditions to give the unsymmetrical diamine **20** in 88% yield.

In summary, microwave heating at 180°C in a sealed tube raised all of the *m*-amination yields in a shorter reaction time than with the conventional DMSO reaction conditions for 60 h. Diaminations were achieved in high yield for symmetrical and unsymmetrical substrates without the use of transition metals.

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