

High Yields of *meta*-Substituted Amination Products in the S_NAr Substitution of Benzenes

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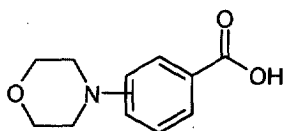
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Abstract: Morpholine substitution in fluorobenzenes containing a *meta*-substituted electron withdrawing group proceeds in DMSO at 100 °C over 60 h to give *meta*-substitution products (by fluoride ion displacement) in pure isolated yields of 19-98%. © 1999 Elsevier Science Ltd. All rights reserved.

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Conventional aromatic nucleophilic substitution with an amine of an aryl halide only proceeds well¹ in the presence of an electron withdrawing group (EWG), and in addition yields of *meta*-substituted products are known² to be low, due to the absence of resonance stabilisation of the intermediate cyclohexadienyl anion. In the last few years, the palladium-catalysed amination of aryl halides has become the method of choice^{3,4} for these nucleophilic aromatic amination reactions, but we required an efficient synthesis of the morpholine-substituted benzoic acids **1a-c**, which could be operated more cost effectively on larger scales, and did not require palladium

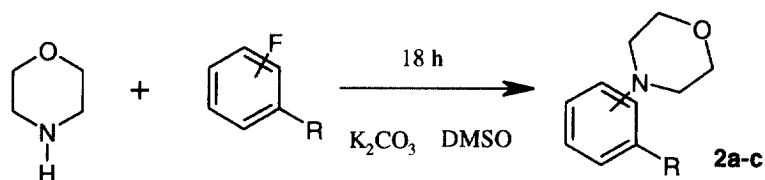


1a, 2-substituted
1b, 3-substituted
1c, 4-substituted

catalysts or the presence of phosphine ligands. Herein we describe the scope of a convenient and improved procedure for the amination (in good yields) of aryl halides, which contain a *meta*-substituted EWG. The acids **1a-c** were conveniently sought *via* the synthesis of their corresponding esters **2a-c** and nitriles **3a-c** (Table 1). Reaction of morpholine with ethyl fluorobenzoates or benzonitriles at 100 °C in DMSO solvent for 18 h and in the presence of anhydrous K₂CO₃, gave adequate yields of the *ortho*- and *para*-substituted derivatives **2a**, **2c**,

3a,3c, but in line with expectations it failed to afford any *meta*-substituted product **2b**, and only a poor 14% yield of **3b** was obtained. In order to improve the yields of *meta*-substituted products, these S_NAr reaction conditions were explored in more detail by further examining the synthesis of **3b**, which contained the stronger cyano-EWG, and thereby offered a greater chance of yield improvement. Using 3-fluorobenzonitrile and morpholine as substrates, in K_2CO_3 /DMSO at 100 °C, and extending the reaction time from 18 to 60 h, doubled the yield of **3b** to 29%. In an attempt to obtain a further yield improvement, homogeneous reaction conditions were investigated with the K_2CO_3 replaced as base by an equivalent amount of morpholine (i.e. a total of 5.5 equivalents); here the yield of **3b** was doubled again to 62%. Increasing the reaction time to 90 h (58%); increasing the reaction temperature to 130 °C (60%); changing the solvent to dimethylacetamide (18%), DMPU (51%) or *N*-methylpyrrolidin-2-one (17%); employing 1,4-azabicyclo[2,2,2]octane (DABCO) catalysis (55%); or increasing the amount of morpholine to an excess of 15 equivalents (46%), could not further increase the

Table I Yields of nucleophilic substitution reactions at 100 °C



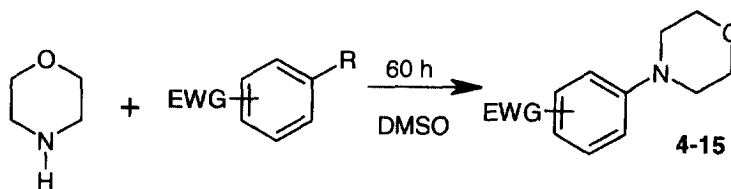
Substituent	R = CO ₂ Et		R = CN	
	Compound	Yield %	Compound	Yield %
2-F	2a	28	3a	82
3-F	2b	0	3b	14
4-F	2c	47	3c	94

62% yield of **3b**. These latter experiments indicated that the substitution conditions employing excess morpholine and no carbonate for 60 h were optimum, and they were adopted as a general procedure. These conditions gave reproducible yields even on a 30 g scale, and were used for the study of the substrate variation shown below (Table 2).

General Procedure: A halobenzene containing an EWG (3 mmol) and a secondary amine (16.5 mmol) were heated for 60 h in DMSO (5ml) at 100 °C. The reaction mixture was poured on to water (50 ml) and solid product collected. The residual aqueous filtrate was extracted with diethyl ether (3x50 ml), washed with saturated brine, and the dried ($MgSO_4$) extracts evaporated. The residue was purified by silica gel column filtration chromatography eluting with 10-20% ethyl acetate in iso-hexane, and after solvent evaporation the residues were combined with the original precipitated solid product. All reactions gave only the isolated products reported, and the starting substituted benzenes.

Variation of the aromatic substrate (Table 2, 4-15) indicated that higher yields in *meta*-substitutions might be obtained than in the previously reported⁵ high pressure reactions, e.g. for **4** 98%, lit.⁵ 77% at 10 kbar and 0% at atmospheric pressure. The high yields in *meta*-substitution reactions were restricted to substrates with fluoride as the leaving group, as there was no reaction with chloro and bromo substituted arenes 5-7. The weaker trifluoromethyl EWG gave only a 19% yield of the substitution product from **8**, and carboxylic acid activation or no substitution gave no reaction (**9** and **10**). The strong electron withdrawal obtained by a combination of CN and CF₃ *meta*-substituted EWGs (**11**) gave an essentially quantitative yield of morpholine. When there was an additional *meta*-substituted fluoro EWG, high substitution yields were obtained for **12** and **13**, together with some di-substitution products (see **14** and **15**). Replacement of morpholine as the basic component by piperidine or *N*-methylpiperazine, afforded equivalent yields with 3-fluorobenzonitrile to those obtained with morpholine (65% and 69% respectively).

Table 2 Substrate variation in reactions with morpholine at 100 °C during 60 h



Compd	EWG	R	% Yield	Compd	EWG	R	% Yield
4	3-NO ₂	F	98	10	H	F	0
5	3-NO ₂	Cl	0	11	3-CN, 5-CF ₃	F	97
6	3-CN	Br	0	12	3-NO ₂ , 5-F	F	62
7	3-CN	Cl	0	13	3-CN, 5-F	F	78
8	3-CF ₃	F	19	14	3-NO ₂ , 5-F	F	37 ^a
9	CO ₂ H	F	0	15	3-CN, 5-F	F	16 ^b

^a Yield of dimorpholino-substituted product isolated with **12**, ^b Yield of dimorpholino-substituted product isolated with **13**.

As the *meta*-substitution yield had been considerably increased under these modified reaction conditions, consideration was given as to whether an alternative reaction mechanism was involved. The other three main mechanisms used^{1,2} to explain nucleophilic aromatic substitution reactions were not supported by experimental evidence. The S_N1 mechanism is inappropriate, and radical and photochemical mechanisms were rejected because no radical initiator was present, and reaction proceeded in the dark to give the same amination yields. The involvement of a benzyne intermediate was discounted because: a) the base used (morpholine) was too

weak; b) fluoride is too poor a leaving group; and c) there was no evidence by TLC, $^1\text{H-NMR}$ or $^{13}\text{C-NMR}$ of *cine*-substituted reaction products. In conventional *ortho/para* substitutions the intermediate anion is stabilised¹ via both canonical resonance structures and the field effects of the EWG; with *meta*-substituted substrates resonance is restricted, and mainly the field effect remains for the stabilisation of reaction intermediates. This hypothesis of field effect stabilisation is supported by: a) the yield variation (Table 2) being related to the Hammett sigma *meta*-values of the EWGs i.e. $\text{NO}_2 > \text{CN} > \text{CF}_3$, which explains the restriction of the reaction to cyano and nitro EWGs; b) the known^{6,7} substitution by the stronger (and anionic) oxygen nucleophiles (such as phenoxide ions) in the presence of strong EWGs. Thus, pending kinetic investigation, the $\text{S}_{\text{N}}\text{Ar}$ mechanism is retained as an explanation for these high yielding *meta*-aminations.

In summary, the enhanced yields of *meta*-substituted products in these nucleophilic amination reactions were based on the identification of favourable reaction conditions, because the precededented poor nucleophilic substitution yields were obtained in our preliminary work (Table 1). The high yielding, but slow substitution process was influenced by: the morpholine concentration; the nature of the substrate EWG; the leaving group and the choice of solvent. The reported general procedure represents an alternative synthetic approach to the well established palladium catalysed amination methods, but is restricted to benzenes substituted with an EWG. The nitro- and cyano-substituted products described offer scope for further transformations to C- and N-substituted benzenes containing cyclic secondary amines.

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