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A Very Convenient Dimethylamination of Activated Aromatic Halides Using N,N-Dimethylformamide and Ethanolamines

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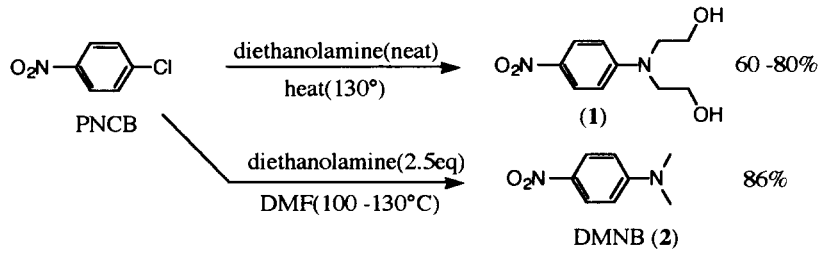
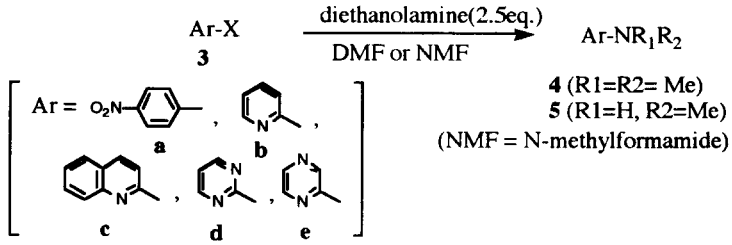
Abstract: A very convenient dimethylamination of activated aromatic halides was achieved by using N,N-dimethylformamide(DMF) and ethanolamines. *p*-Nitrochlorobenzene, 2-halopyridines, 2-chloroquinoline and 2-chloropyrimidine gave the corresponding dimethylamino substituted products when treated with DMF and diethanolamine in 80 -92% yield.

An interesting observation was made while we were optimizing reaction conditions for the nucleophilic substitution reaction of *p*-nitrochlorobenzene(PNCB) with diethanolamine (Scheme 1). When PNCB was treated with diethanolamine(DEA) as a solvent and reagent , 4-N,N-bis-(2'-hydroxyethyl)-aminonitrobenzene(**1**) was obtained as expected. When the same reaction was carried out in N,N-dimethylformamide(DMF), however, dimethylamination product *p*-dimethylaminonitrobenzene(DMNB, **2**) was produced in very good yield.



Scheme 1

Use of DMF as an eqivalent of dimethylamine in the nucleophilic substitution of active halogen atom has not been unknown in the literature. For example, dimethylamination of some heteroaromatic halides such as 2-chloroquinoline, 2-chloro-5-nitropyridine and halogenated anthraquinones was reported when those halides were refluxed in DMF.[1] In other case, N,N-dimethylamides were prepared from acid chlorides or acid anhydrides with DMF at an refluxing temperature with or without an acid catalyst.[2] Use of DMF or N-methylformamide in the presence of KOH(10eq) with some activated heteroaromatic or aromatic halides at an elevated temperature(150 - 190°C), which affords aminated compounds, has been also reported.[3] All these examples, however, require rather high reaction temperature (>150°C). The reactions which demand higher reaction temperature than 150°C are not often recommended in the manufacturing facilities where the steam is used as the heating medium. The substrates used in these literatures are also limited. So, the combination of DMF and diethanolamine could serve as a better way to produce dimethylaminoaromatic compounds when treated with activated halogenated aromatic compounds



Entry No.	Ar-	X	Rxn temp(°C)	Rxn time(h)	formamide used	product	yield(%)
1	**3a**	Cl	130	5.5	DMF	**4a**	86
2	**3a**	Cl	130	11	NMF	**5a**	74
3	**3b**	Cl	130	29	DMF	**4b**	80
4	**3b**	Br	130	13	DMF	**4b**	92
5	**3c**	Cl	130	4	DMF	**4c**	89
6	**3c**	Cl	130	3	NMF	**5c**	84
7	**3d**	Cl	130	0.5	DMF	**4d**	86
8	**3e**	Cl	130	7	DMF	**4e**	0

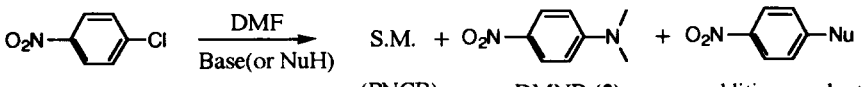
* A typical procedure is described in the references and notes 5.

Scheme 2

under milder condition. Herein, we'd like to report the reaction of PNCB, 2-halopyridines, 2-chloroquinoline and 2-chloropyrimidine with DMF(or N-methylformamide) in the presence of diethanolamine. The effect of using other bases(or nucleophiles) than diethanolamine will be also described.

As seen in Scheme 2, several activated aromatic halides undergo dimethylamination nicely with DMF in the presence of diethanolamine. It should be noted that PNCB remains intact when treated with refluxing DMF. In the case of 2-chloropyridine, we believe that this is the first example where DMF is used for the dimethylamination of 2-chloropyridine. It is also interesting to note that 2-N,N-dimethylaminopyrimidine has been previously prepared either by methylation of 2-aminopyrimidine or by cyclization of a diketo compound with 1,1-dimethylguanidine.[4] It is also worthwhile to mention that 2-chloropyrimidine is totally unreactive when treated with DMF only(at reflux temperature, 16 hr). It was reported that 2-dimethylaminopyrimidines seem to possess cardiotonic activities,[4a] and our method seems to be a very covenient way to prepare 2-dimethylaminopyrimidines. As demonstrated in Scheme 2, we believe that this method is very useful and practical in the preparation dimethylaminoaromatic compounds from activated aromatic halides under relatively mild condition.

After this discovery, we were encouraged to examine the possibilities of using other bases(or nucleophiles). Interestingly, all the ethanolamines including primary, secondary and even tertiary amines such as N-methyldiethanolamine and triethanolamine produce DMNB(**2**) when PNCB was treated with DMF in the presence of the ethanolamine(Scheme 3). The order of reactivity toward the formation of DMNB(**2**) among ethanolamines is ethanolamine > diethanolamine > N-methylethanolamine > triethanolamine. Other primary aminoalcohols also produce DMNB(**2**) together with more of addition product **6** than ethanolamine(entry 7,8). When other secondary amines with no hydroxy group were used, addition products were obtained as expected(entry 9,10). With pyridine and K_2CO_3, PNCB remained unreacted (entry 11,13). When KOH was employed, the reaction stopped at a certain point(entry 12) and no further



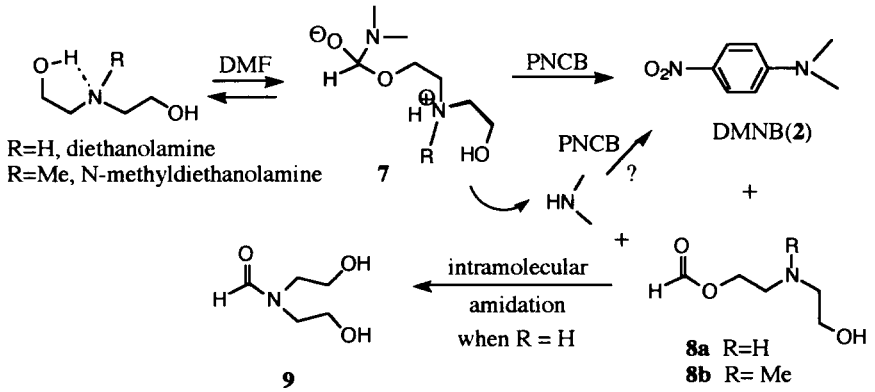
Entry No.	Base(2.5eq) or NuH	Temp. (°C)	Rxn time(h)	Product GC area%* PNCB	2	6**	Isolated % yield of 2
1	ethanolamine	100	6	2.8	88.0	9.2(**6a**)	83
2	ethanolamine	130	6	2.5	93.0	4.5(**6a**)	87
3	diethanolamine	100	24	2.1	97.7	0.2(**1**)	85
4	diethanolamine	130	7	0.7	90.2	9.1(**1**)	86
5	N-methyl-DEA	130	70	18.0	82.0	-	77
6	triethanolamine	130	18	78.8	21.2	-	19
7	4-amino-1-butanol	100	5	5.3	75.8	18.9(**6b**)	80
8	6-amino-1-hexanol	100	4	6.5	70.1	23.4(**6c**)	75
9	dibutylamine	140	6	75.0	-	25.0(**6d**)	-
10	piperidine	100	5	0	5.0	95.0(**6e**)	-
11	pyridine	130	15	99.7	0.3	-	-
12	KOH	130	18	65.0	35.0	-	33
13	K_2CO_3	140	24	100.0	-	-	-

* GC area % was readjusted to 100% (**PNCB** + **2** + **6**)
** **6a** Nu=$N(CH_2CH_2OH)_2$, **6b** Nu=$NH(CH_2)_4OH$, **6c** Nu=$NH(CH_2)_6OH$, **6d** Nu=$N[(CH_2)_3CH_3]_2$ **6e** Nu= 

Scheme 3

progress was observed even after addition of more KOH(1.0 -2.5 eq) under the reaction condition described in Scheme 3.

The lower reactivity of diethanolamine compared to dibutylamine toward direct substitution of PNCB, which produce addition products, seems to be explained by intramolecular hydrogen bonding in diethanolamine(Scheme 4). It is interesting that even tertiary ethanolamine such as N-methyldiethanolamine reacts with DMF. We speculate that the reaction might proceed according to Scheme 4, where



Scheme 4

activated hydroxy group assisted by an neighbouring amine base attack DMF to produce the intermediate **7**. The intermediate **7** then seems to be captured by PNCB to produce DMNB(**2**) together with the formate **8**.[6] In case of **8a**, where R equals hydrogen, subsequent intramolecular amidation occurs under the reaction condition to produce the formamide **9**. When diethanolamine was reacted with DMF only (130°C), generation of dimethylamine was observed and the formamide **9** was actually isolated and identified.[6]

Finally, the reactivity of ethanolamines with other formamides than DMF should be also mentioned. As seen in Scheme 2, diethanolamine reacts with N-methylformamide in the presence of PNCB to produce 4-N-methylaminonitrobenzene(entry 2). We treated formamide (NH_2COH) with ethanolamine and PNCB(100°C, 1 day) hoping that unsubstituted aromatic amine(p-nitroaniline) be obtained, however, only unreacted PNCB was recovered, although the consumption of ethanolamine was observed by gas chromatography. When dimethylacetamide was reacted with PNCB in the presence of ethanolamine, DMNB(**2**) and addition product **6a** were produced in ca. 1:1 ratio.

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5. A typical procedure is as follows: A mixture of PNCB (2.0g, 12.6mmol), diethanolamine (3.37g, 2.5eq.) and DMF(5 ml) was heated to 130°C. After 5.5 hr, the reaction mixture was concentrated under vacuum. Water(30 ml) was added to the residue with stirring. The resulting solids were filtered. At this time excess diethanolamine, byproduct **9** were easily removed because of high water solubility. The solids were washed with ethanol(2 - 3ml) to give bright yellow crystals of **2** (1.80g, 86% yield). M.p. 163.2 -164.8°C(lit. 163 -164°C)[3]
6. It was observed that the rate of consumption of diethanolamine(DEA) in DMF only (130°C) was quite slower than in DMF with substrates such as PNCB or 2-bromopyridine. Under the typical reaction condition, ca. 0.8eq. of DEA was consumed after 5.5hr when o-nitrotoluene was used instead of PNCB. On the other hand, ca.2.2 eq. of DEA was consumed after 5.5hr when PNCB was present. Dimethylamide from the intermediate **7** seems to attack PNCB, however, it is not clear that free dimethylamine also attacks PNCB. The formamide **9** was independently prepared by a known procedure (reaction of methyl formate with diethanolamine)[7] and compared. ^{1}H NMR(300MHz, DMSO d-6)δ 7.97(s, 1H), 4.76 (br, 2H), 3.47(t, 4H), 3.30(m, 4H).
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