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Review

Dimethylamino Amination with DMF

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Keywords: Dimethylamination, Dimethylformamide, Quinoline, Pyrazine, Pyridine, Anthraquinone.

Abstract: Dimethylamino group is present in a number of drugs as ampyzine, triampyzine, dimethirimol, aminopyrine and chemical reagents as 4-dimethylamino pyridine and 6-dimethylamino purine. Dimethylamino compounds are also a electrophilic coupling partner in transition metal catalyzed in Suzuki reaction. Earlier it was synthesized by reacting the chloro compounds with dimethylamine. This reaction utilizes high temperature and pressure and most of the time it ended up with a complex reaction mixture and low yield, so it is not a convenient method for synthesis of dimethylamino compounds. Now a day it is synthesized by reacting chloro compounds with dimethylformamide. In this microreview we have summarized all the reports of dimethylamination with dimethylformamide (1954-2010). Dimethylamination with DMF is reported in acid chloride, acid anhydrides, aromatic halo-nitro compounds, pyridines, pyrazines, pyrimidines, 1,3,5-triazines, uracil, quinolines, benzimidazole, benzothiazole, purines and anthraquinones.

1. Introduction

The new milennium has witnessed a gamut of drugs and chemical reagents containing dimethylamino group. It is present in Ampyzine[1] (**I**, central stimulant), Triampyzine[1] (**II**, anticholinergic), Dimethirimol[2] (**III**, fungicide), Aminopyrine[3] (**IV**, antipyretic), 6-Dimethylamino-8-azaadenosine[4] (**V**, antitumour), Altretamine[1] (**VI,** antitumour and male insect chemosterilant) Diphenhydramine[1] (antihistamine), Methadone[5] (narcotic analgesic) and various other drugs as shown in (**Fig.: 1)**. Dimethylamino group is present in a variety of drugs but this group holds a special place in antihistamines as most of them contain dimethylamino group.

Dimethylamino group has emerged as a powerful electrophilic coupling partner in transition metal catalyzed cross coupling reactions forming C-C bond. (Suzuki reaction, **Fig.: 2**). Dimethylamino compounds are converted to trimethyl ammonium triflates by reaction with methyl trifluoro methane sulfonate which reacts

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with a broad range of boronic acids to form carbon–carbon bond.[6]

Due to the wide applicability of dimethylamino compounds efforts are ongoing to synthesize dimethylamino compounds by simple methods. Here in this review we have summarized the synthesis of dimethylamino compounds by dimethylformamide.

2. Dimethylamino Amination in Aromatics

Benzyl chloride and Acid Chloride: Formylation with Dimethylformamide (DMF) was a well reported and studied reaction till Coppinger reported dimethylamination in acid chloride with DMF above 150^0C to give N,N-dimethylamide[13]. He heated acid chloride with DMF at 150^0C to yield the corresponding dimethylamino compound. N,N-dimethylbenzamide was synthesized in 97% yield from benzoyl chloride(**Fig.:3a**). Benzyl chloride was also refluxed with DMF to yield dimethyl benzylamine in 36% yield (**Fig.:3b**).

Halo-nitro-benzene: Wakae and Hamano[7] for the first time in 1963 reported dimethylamination with DMF in halo-nitrobenzene. They synthesized 4-dimethylamino-nitrobenzene in 78% yield by refluxing 1-chloro-4-nitro-benzene with cupric sulfate and DMF. They also synthesized 2,4-dinitro-dimethylaniline in 77% yield in the same way from the corresponding chloro compound. Same results were obtained when cuprous cyanide was used in place of cupric sulfate but the yields decreased significantly. (**Fig.: 4a**). 2-chloro-nitro-benzene was not converted into 2-nitro-dimethylaniline using the same reaction strategy.

On the same time Deorha and Sharma[8] in 1963 independently reported dimethylamino amination with DMF in the presence of copper sulfate (**Fig.: 4b**). They succesfully converted few dihalo-nitro-benzenes and halo-dinitro-benzenes to the corresponding dimethylamino compounds in 61-78% yield. Their results showed that chlorine atoms at *ortho* and *para* positions are replaced by dimethylamino group where as halogen groups at *meta* position to the nitro group are not replaced.

Watanabe[9] studied the reaction of halo-nitro-benzenes with NMF (N-Methyl Formamide) or DMF in the presence of potassium hydroxide at 150^0C-160^0C affording the methyl amino or dimethylamino substituted products respectively in 100% yields. (**Fig. : 4c**).

Cho and park[10] synthesized *p*-dimethylamino-nitrobenzene (86% yield) and *p*-methylamino-nitrobenzene (74% yield) from *p*-nitro-chlorobenzene by reacting them respectively with DMF and NMF in the presence of diethanolamine (**DEA**) at 100^0C (**Fig. 4d**). When diethanolamine was replaced with other ethanolamines including primary (ethanolamine gave 88% yield at 100^0C and 93% yield at 130^0C), secondary (diethanol amine gave 90% yield at 130^0C) and tertiary amines (N-methyldiethanolamine gave 82% yield and triethanolamine gave 21%yield) they also produced the dimethylamino compounds. The order of reactivity towards the formation of dimethylamino compounds among ethanol amines is ethanol amine > diethanolamine > N-methylethanolamine > triethanolamine. When primary amino alcohols (4-amino-1-butanol gave 75% of dimethyl product and 19% of addition product, 6-amino-1-hexanol gave 70% of dimethylamino product and 23% of addition product) were used as catalyst they resulted

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into more addition product than dimethylamino product in comparison to ethanol amines. When other secondary amines with no hydroxy group (dibutylamine and piperidine) were used addition products were obtained. Dibutyl amine gave 25% of addition product and no dimethylamino compound was obtained, where as piperidine gave 5% of dimethylamino product and 95% of addition product. When pyridine was used as a catalyst no reaction took place. When KOH was employed reaction stopped at a certain point and no further progress was observed even after addition of more KOH (yield 35%).

The lower reactivity of diethanolamine compared to dibutylamine towards direct substitution of *p*-nitrochlorobenzene, which produced addition products seemed to be explained by intramolecular hydrogen bonding in diethanolamine. They noticed that even tertiary ethanolamine such as N-methyldiethanolamine reacted with DMF. They speculated that reaction might proceed according to the scheme as shown in **Fig.: 5** where activated hydroxy group assisted by a neighbouring amine base attack DMF to produce the intermediate **A**. The intermediate **A** then reacted with *p*-nitro-chlorobenzene to produce *p*-dimethylamino-nitrobenzene together with the formate **B**. In the case when R equals H, subsequent intramolecular amidation occurred under the reaction conditions to produce the formamide **C**. When diethanolamine was reacted with DMF, formation of dimethylamine was observed and the formamide **C** was isolated and identified.

In 2004 we synthesized dimethyl-(4-nitro-phenyl)amine in 95% yield by refluxing 1-chloro-4-nitro-benzene with DMF in the presence of potassium carbonate. We further synthesized (2,4-dinitro-phenyl)-dimethylamine in 96% yield from 1-chloro-2,4-dinitro-benzene by reacting it with DMF at 25^0C in the presence of potassium carbonate (**Fig.: 6**). Temperature plays a vital role in dimethylamination of aromatic compounds. The temperature at which chloro group is replaced depends on the activation of the chloro group induced by the nitro group.[11]

3. Dimethyl Aminoamination in Heterocycles

(i) Pyridine: 4-(Dimethylamino)pyridine (DMAP) is a super acylation and alkylation agent. It can be synthesized from 4-chloropyridine by heating it with DMF. In another method (commercially used) 4-pyridyl-pyridinium salt is synthesized from pyridine by reacting it with thionyl chloride and S_2Cl_2. The pyridyl pyridinium salt further reacts with DMF at 155^0C to give DMAP (**Fig.: 7**) in 65-70% yield.[12]

In 1969 Heindel and Kennewell[14] synthesized 2-dimethylamino-5-nitro-pyridine in 94% yield from 2-chloro-5-nitro-pyridine by refluxing it in DMF (**Fig.: 8a**). Substitution with dimethylamino group took place in 2-halopyridine[10] when it was heated with DMF in the presence of diethanolamine (2.5eq. as catalyst) at 130^0C (**Fig.: 8b**). The dimethylamino compound was obtained in 80% yield from 2-chloropyridine where as 92% yield was obtained from 2-bromopyridine.

Watanabe[9] reacted halonitrobenzenes with NMF or DMF in the presence of potassium hydroxide affording the corresponding methylamino or dimethylamino substituted products in 100% yield at 150^0C-160^0C (**Fig.: 8c**).

(ii) Pyrimidines: Griffin etal.[15] firstly reported dimethylamination in pyrimidines. They reacted 2,4-diamino-5-(4-chloro-3-nitro-phenyl)-6-ethyl-pyrimidine with DMF

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and ethanolamine (**EA**) as catalyst to obtain the corresponding dimethylamino compound in 87% yield (**Fig.: 9**). The chloro group was not replaced in the above molecule when DMF was substituted with formamide and N,N-diethyl formamide (**DEF**). They also tried to synthesize N-methylamino substituted compound in the presence of ethanolamine in NMF but only traces of the product were obtained. These compounds acted as inhibitors of dihydrofolate reductase and also showed *in vivo* activity against methotrexate resistant tumor cell lines. 2,4-diamino-6-chloro-pyrimidine[16] which has a less reactive chlorine atom remained unchanged even on heating with DMF-EDA at 120^0C (**Fig. : 10a**). They also obtained 2,4,6 triamino-pyrimidine in 90% yield by heating 6-chloro-2,4-diamino-pyrimidine with DMF at 200^0C (**Fig. : 10b**). When 2-chloropyrimidine[9] was reacted with DMF in the presence of diethanolamine as catalyst at 130^0C it resulted in the formation of corresponding dimethylamino compound in 86% yield (**Fig. 10c**). Dorigo etal.[15] reported that 2-dimethyl-aminopyrimidines possess cardiotonic activities so this seems to be a very convenient method for the synthesis.

2-Amino-4-chloro-6-hydroxy-pyrimidine gave exclusively gave the dimethylamino derivative upon heating in DMF at 90^0C in the presence of 1-2 mole of ethylenediamine (EDA) or ethanolamine instead of the normally expected substitution products[16]. (**Fig.: 10d**) EDA and 2-aminoethanol acted as catalyst for the dimethylamination. The catalytic efficiency was best exhibited by EDA or 2-aminoethanol, moderately by 1,3-diamino propane, N,N and N,N'-dimethylenediamine,2-(methylamino)ethanol or butylamine. No catalytic effect was found with triethylamine or ethyleneglycol. NMF and N-formyl morpholine afforded a moderate yield of the corresponding exchange products along with an appreciable amount of the substitution product. In DEF and N,N-dimethyl acetamide the chloro compounds either remained unreactive or yielded substitution products. Thus the reactivities of the aminating reagents depended upon the combination of the amines and the N-acyl groups.

In contrast to Cho and Park[10], Yamamoto observed[16] that no dimethylamine was produced upon heating a 1:1 mixture of DMF and EDA at 90-100^0C for 2-20 hr. by GLC and ^{1}H NMR. So they suggested that most probably DMF formed a complex with EDA or 2-aminoethanol at 90^0C and this complex subsequently reacted with chloro compounds to give the dimethylamino derivatives at a must faster rate than those of exchange reactions (**Fig.: 11**).

Dimethyl-(4-piperidin-1-yl-pyrimidin-2-yl)-amine was synthesized in 75% yield from 4-piperidino-2-chloropyrimidine by heating it with DMF in the presence of potassium carbonate. Similarly 2,4-dichloropyrimidine yielded a mixture of (2-chloro-pyrimidin-4-yl)-dimethyl amine in 50% yield and N,N,N',N'-tetramethyl-pyrimidine-2,4-diamine in 20% yield when heated with DMF [11] (**Fig.: 12**).

(iii) Pyrazine: Watanbe[9] firstly reported amination in 2-chloropyrazine with NMF or DMF in the presence of potassium hydroxide affording the methylamino or dimethylamino substituted products at 150^0C-160^0C (**Fig.: 13a**). In pyrazines having substitution at different positions the dimethylamino products were obtained in 18-78% yield, whereas the methylamino compounds were obtained in 46-99% yield. As per the results obtained they concluded that this method is especially suitable for the synthesis of 2-dimethyl-aminopyridines and 2-methyl-aminopyridines and pyrazines.

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When the chloropyrazines were heated under reflux in DMF or NMF in the absence of alkali, the starting materials were recovered. 2-chloropyrazine[10] did not reacted with DMF or NMF in the presence of ethanolamine as catalyst at 130^0C (**Fig.: 13b**).

(iv) 1,3,5-Triazine: Dimethylamino amination in triazine is first reported by Agarwal and Chauhan[11] in 2,4-dichloro-6-piperidino triazene and 2-chloro-4,6-dipiperidino triazene. They heated the triazines at 80^0C with DMF and obtained the corresponding dimethylamino compounds in 92% and 95% yields respectively. (**Fig. :14**).
(v) Uracil: 6-dimethylamino-uracil is obtained in 45% yield from 6-chloro-uracil by reacting it with DMF in the presence of EDA (ethylene diamine) as catalyst at 130^0C[16] (**Fig.: 15**)

(vi) Quinoline: In 1969 Heindel and Kennewell[14] observed the anomalous replacement of halogen group by dimethylamino group when they were trying to replace the chloro group of 8-amino-4-chloro-6-methoxyquinoline with 4-diethylamino-3-methylbutylamine.They obtained 8-amino-4-dimethylamino-6-methoxyquinoline in 65% yield. They further extended the use of DMF in dimethylamination and DEF in diethylamination in various substituted quinolines and obtained the dimethylamino or diethylamino products in 76-84% yield **(Fig. :16)**.

In an another study Shinkai etal.[18] treated 4-chloroquinoline with NMF yielding 4-(methylamino)quinoline in 9.4% yield. (**Fig.: 17a**). These type of quinoline moieties having substituents at other positions exhibited nociceptin antagonist and analgesic activity. 2-chloroquinoline[10] reacted with DMF or NMF in the presence of diethanolamine as catalyst at 130^0C resulting in the formation of corresponding dimethylamino (89% yield) or methylamino product (84% yield). (**Fig.:17b**).

Watanabe[9] studied the reaction of haloquinolines (2-chloroquinoline, 4-chloroquinoline and 2,4-dichloroquinoline) with NMF or DMF in the presence of potassium hydroxide affording the methyl amino or dimethylamino substituted products at 150^0C-160^0C. 2-chloro quinoline afforded 100% of the dimethylamino product whereas 77% yield was obtained in case of methylamino product **(Fig.: 18a)**. In 4-chloro quinoline yields were slightly lower having 65% yield in case of dimethylamino product and 69% of methylamino product was obtained. 2,4-dichloro quinoline yielded 23% of 4-chloro-2-dimethylamino quinoline and 44% of 2-chloro-4-dimethylamino quinoline**(Fig.: 18b)**.

(vii) Benzothiazole: Amico etal.[19] for the first time reported dimethylamino amination in heterocycles. They synthesized 2-dimethylamino-benzothiazole in 89% yield by the reaction of 2-chloro benzothiazole with DMF (**Fig. : 19**). They also studied the reaction of other disubstituted formamides (formyl morpholine, formylhexamethylenimine and dibutylformamide) with 2-chloro benzothiazole and obtained the corresponding compounds in 97.5-99.5% yields.

On the basis of this they anticipated that reaction of 2-chlorobenzothiazole with formamide would yield 2-aminobenzothiazole but 2-hydroxybenzothiazole was isolated in 90% yield. On this basis they stated that alkyl halides reacted with formamide (**Fig. :20**) to give formyl amino compounds or formates.

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In an earlier study it was found that alkyl halides reacted with formamides to give formyl amino compounds or formates. The course of the reaction depended upon the structure of the alkyl halide and is predictable and related to the stability of the carbonium ion intermediate. In their opinion reaction proceeded through an SN_2 pathway and not by SN_1.

(viii) Benzimidazole: Soon after the reports of dimethylamination in benzothiazole Joseph and Albert[20] in the similar manner reported dimethylamination in benzimidazole.

They synthesized 2-dimethylamino-benzimidazole in 45% yield by heating 2-chloro- benzimidazole with DMF in a sealed tube and proposed a similar mechanism as shown in (**Fig. : 21**). They also reacted 2,5-dichloro and 2,6-dichloro benzimidazole with DMF and obtained the 2-dimethylamino 5 or 6 chloro benzimidazole in 25% yields. 2-dimethylamino-5 or 6 nitro benzimidazole was synthesized from 2-chloro-5 or 6 nitro benzimidazole in 56% yield.

(ix) Purine: In addition to drugs the dimethylamino group is present in important molecules such as 6-dimethylamino-purine (6-DMAP), a very important chemical present in 0.78-0.08 mol% in the DNA composition of algae.[21] 6-DMAP (inhibitor of cyclin dependant kinase [CDK]) is used to study the DNA endoreduplication during elongation and differentiation of primary roots.[22] 6-DMAP is also used to activate embryos and oocytes which give rise to cloned rabbits which are produced by nuclear transfer from adult somatic cells.[23] Agarwal and Chauhan[11] synthesized 6-DMAP by this method in 96% yield. They proposed a similar mechanism as shown in (**Fig: 22**). 6-DMAP is approximately 7 times higher in cost in comparison to 6-chloropurine. By this method 6-DMAP is synthesized in very high yield which can greatly reduce the cost of 6-DMAP. 2-chloro-6-cyclohexylmethoxy-9-*H*-purine was converted to the corresponding dimethylamino product 6-cyclohexylmethoxy-9H-purin-2-yl)-dimethylamine by heating it with DMF in the presence of ethanol amine at 90^0C (**Fig.: 23**). These molecules are potent inhibitors of cyclin dependant kinases 1 and 2.[24]

4. Anthraquinones

In a similar way Lords and Peters[25] observed the anomalous replacement of halogen group by dimethylamino group during condensation of 1-chloro anthraquinone with aryl amines using DMF as solvent. When 1-chloro-anthraquinone was refluxed with DMF initially 1-dimethylamino-anthraquinone was formed which on prolonged heating resulted in the demethylation and ultimate formation of 1-methylamino anthraquinone as shown in (**Fig.: 24**). A partial dealkylation of 1-dimethylamino anthraquinone to 1-methylamino-anthraquinone is also reported in boiling nitrobenzene, conc. sulphuric acid at 150^0C and in conc. sulphuric acid and boric acid at 130^0C but it was reported for the first time in DMF. 2-chloroanthraquinone similarly gave 2-dimethylamino-anthraquinone which even on prolonged heating did not dealkylated to yield 2-methylamino-anthraquinone as shown in (**Fig**.: **25**).

In dichloro anthraquinones[25] halogen elimination is observed when both the halogen atoms are in the same ring. So with dichloro anthraquinones the reaction with DMF was more complex and the nature of products varied with the reaction time. The reaction in all the disubstituted compounds

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as 1,2 and 1,4 dichloroanthraquinones did not reached to completion. 1,2-dichloro-anthraquinone was converted into a mixture of 2-chloro-1-methylamino-anthraquinone and 1-methylamino-anthraquinone. 1,4-dichloro- anthraquinone gave 1-chloro-4-methylamino-anthraquinone and 1-methylamino- anthraquinone as depicted in (**Fig.: 26**). The chlorine atoms in this case were dehalogenated to give these compounds.

1,5-dichloro anthraquinone, after 21 hrs. under reflux in DMF gave a mixture of 1-chloro-5-dimethylamino-anthraquinone and 1-chloro-5-methylamino-anthraquinone.
Longer reaction times (74hr.) gave these product along with 1,5-bisdimethylamino anthraquinone and even on prolonged heating (250 hr.) gave 5-dimethylamino-1-methylamino and 1,5-bis-(methylamino)-anthraquinone. 1,8-dichloro-anthraquinone and DMF also gave the similar results (**Fig. : 27)**. Dealkyaltion of 1-dimethylamino anthraquinone also occurs in other dipolar aprotic solvents eg. dimethylsulfoxide and dimethylsulphone but does not occurs in comparatively high boiling basic solvents as β-picoline and pyridine or neutral solvents as ethylene glycol mono methyl ester[25].
1 and 2 chloro anthraquinone exclusively gave the dimethylamino derivative upon heating in DMF at 90^0C in the presence of 1-2 mole of ethylenediamine (EDA) or 2-aminoethanol instead of the normally expected substitution products[16].(**Fig.: 28**) EDA and 2-aminoethanol acted as catalyst for the dimethylamination. When 1-chloro anthraquinone was treated with DMF in the presence of EDA 60% of the dimethylamino product was obtained where as with 2-aminoethanol 75% of the product was obtained. With 2-chloroanthraquinone 63% of the dimethylamino product was obtained with EDA and 84% with 2-amino ethanol. When 1-chloroanthraquinone was heated with DMF in the presence of 2-(methylamino)ethanol 5% of the dimethylamino product was obtained. 2-Chloro anthraquinone on treatment DMF in the presence of N,N-dimethylethylenediamine yielded 14% of the dimethylamino product. The catalytic efficiency was best exhibited by EDA or 2-aminoethanol, moderately by 1,3-diaminopropane, N,N and N,N'-Dimethylenediamine (8-14% yield), 2(methylamino)ethanol (5% yield) or butylamine. No catalytic effect was found with triethylamine or ethyleneglycol. NMF (36-41% yield) and N-formyl morpholine (22% yield) afforded a moderate yield of the corresponding exchange products along with an appreciable amount of the substitution product. In DEF and N,N-dimethyl acetamide the chloro compounds either remained unreactive or yielded substitution products. Thus the reactivities of the aminating reagents depended upon the combination of the amines and the N-acyl groups. The use of ethanol as a solvent in the reaction of 1-chloro anthraquinone with DMF and 2-amino ethanol (2 mole eq. each) suppressed the formation of dimethylamino compound (18% yield) and substitution product(12% yield). Temperature plays an important role in the reaction as more substitution product was obtained in comparison to dimethylamino product when 1-chloro-anthraquinone was heated with DMF or N-formyl morpholine in the presence of 2-aminoethanol at a lower temperature of 60^0C.

5. Dimethylamino Amination in Aliphatics

Acid Anhydride: Coppinger reported dimethylamination in acid anhydride with DMF above 150^0C to give N,N-dimethylamide[13]. He heated acid anhydride

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with DMF at 150^0C in the presence of a drop of conc. Sulphuric acid to yield the corresponding dimethylamino compound. He synthesized N,N-dimethylacetamide in 92% yield from acetic anhydride and N,N-dimethyl succinamic acid in 90% yield from succinic anhydride.

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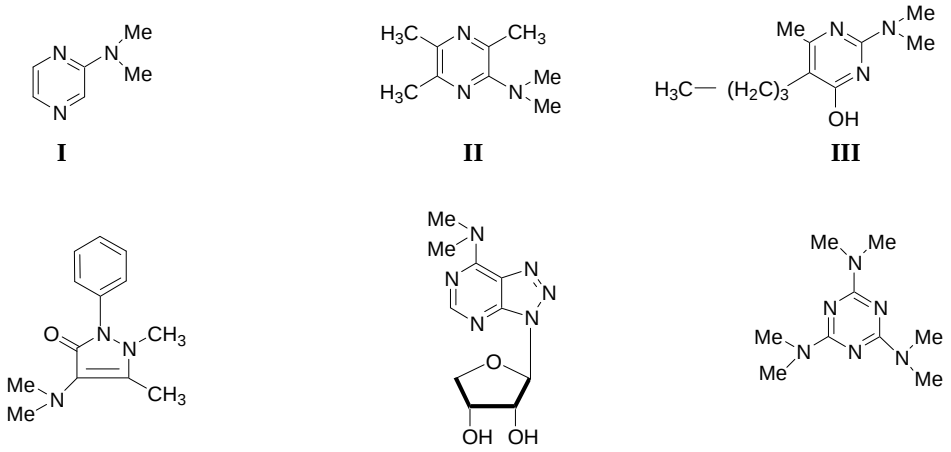

I **II** **III**

IV **V** **VI**

Fig.: 1

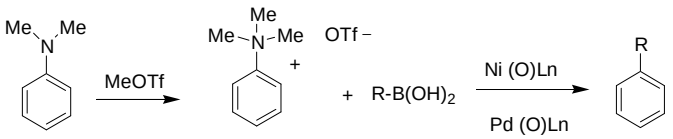

Fig.: 2

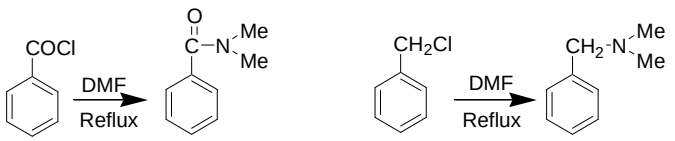

Fig.: 3(a) **(b)**

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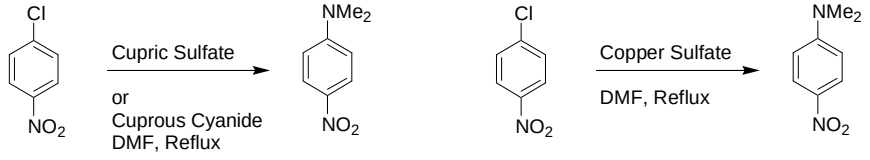

Fig.: 4 (a) **(b)**

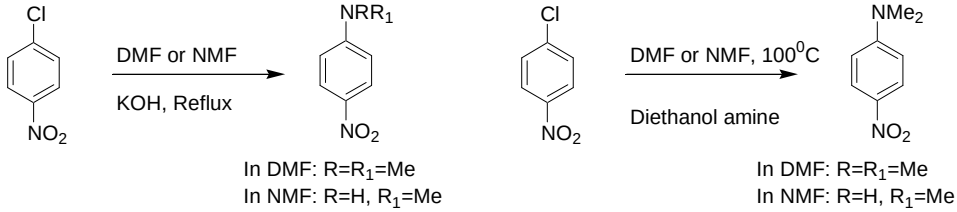

Fig. : 4 (c) **(d)**

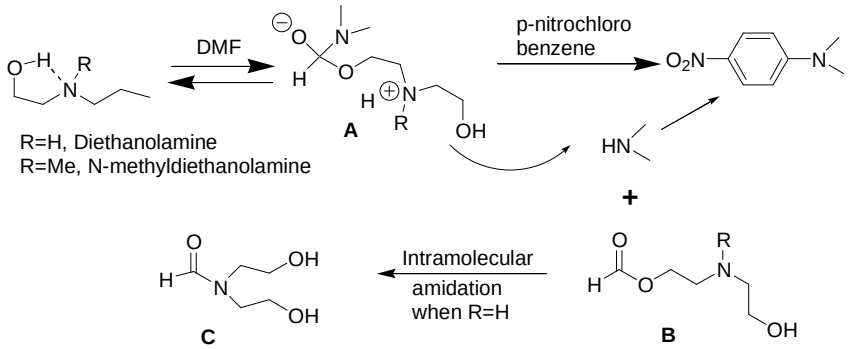

Fig. 5

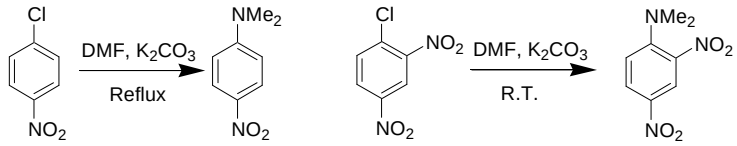

Fig. : 6

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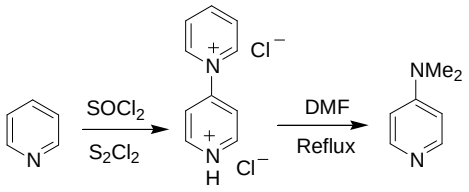


Fig.:7

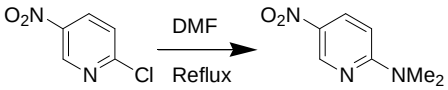
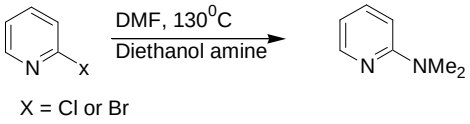


Fig. : 8a



8b

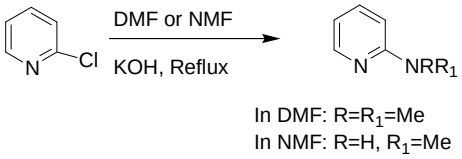


Fig. : 8c

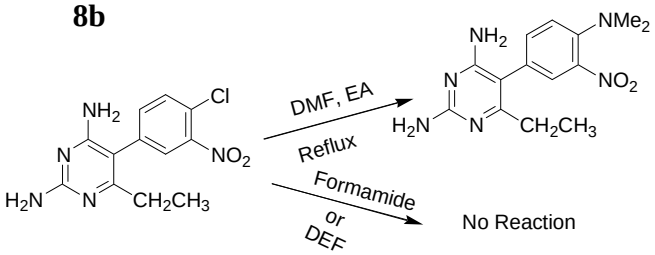


Fig:9

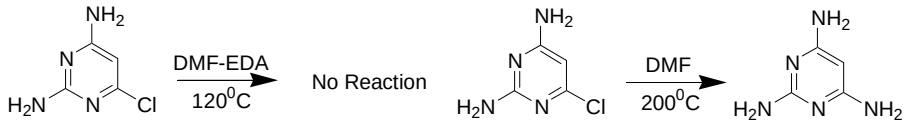


Fig:10 (a) **(b)**

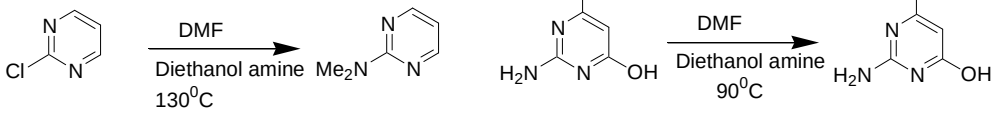


Fig. :10c **(d)**

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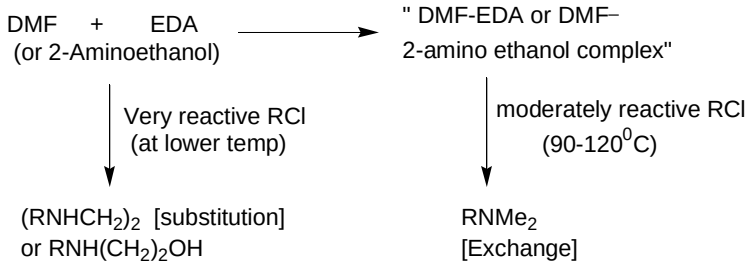

Fig. : 11

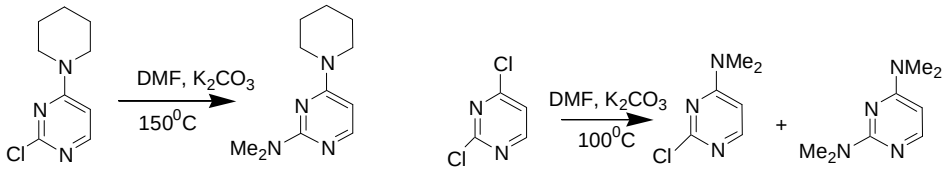

Fig. : 12

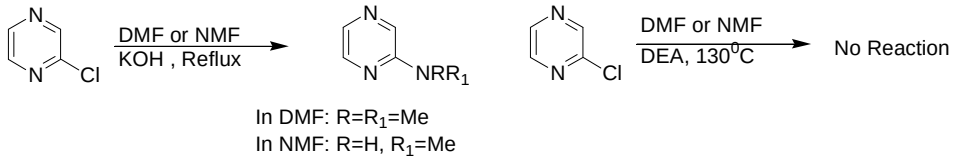

Fig. : 13a **(b)**

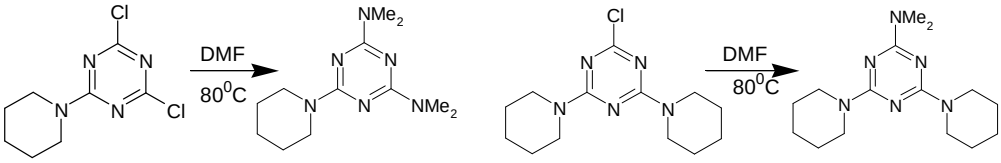

Fig. :14

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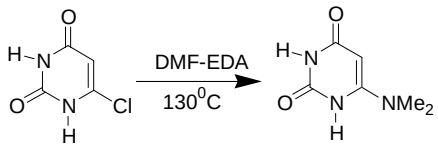


Fig.: 15

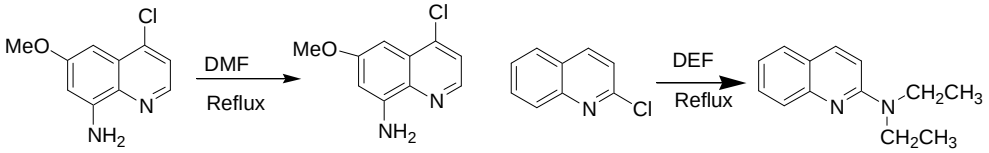


Fig. : 16

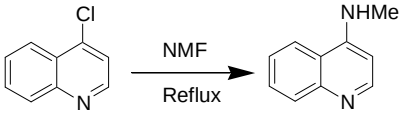
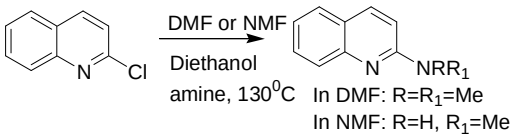


Fig. :17a



(b)

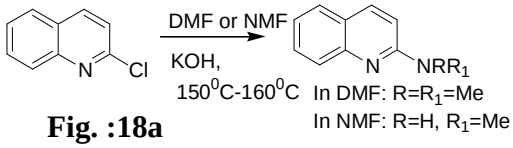


Fig. :18a

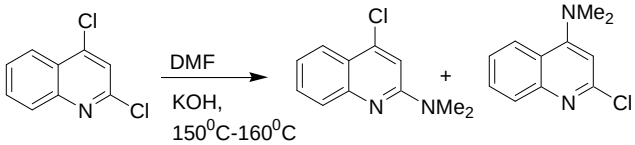


Fig.: 18b

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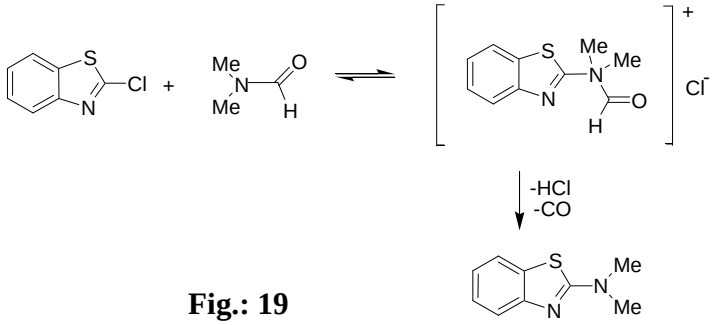

Fig.: 19

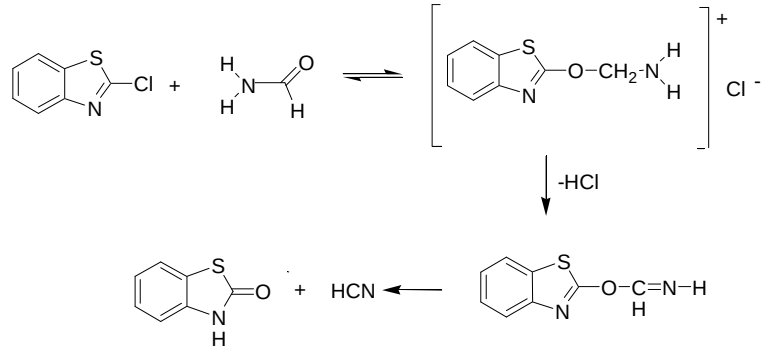

Fig.: 20

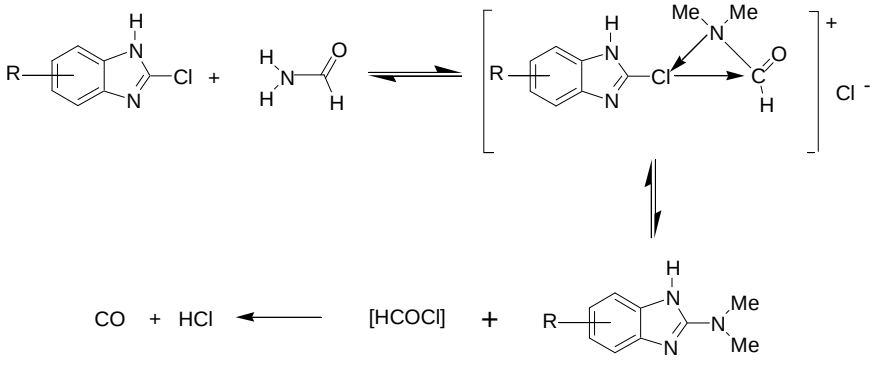

Fig: 21

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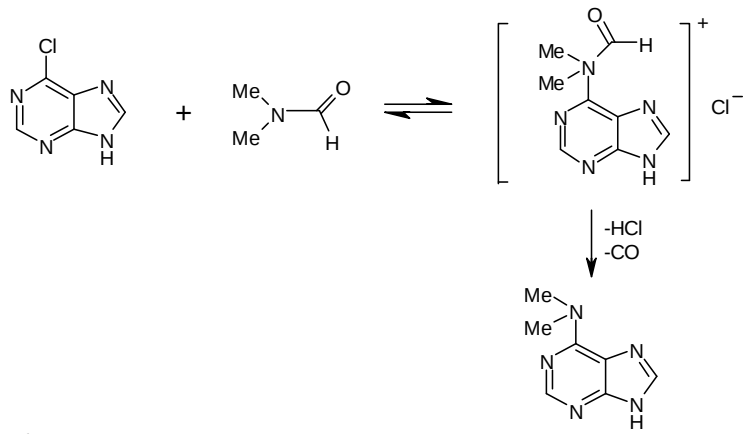

Fig.: 22

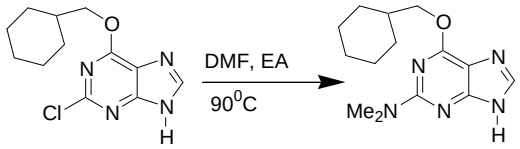

Fig.: 23

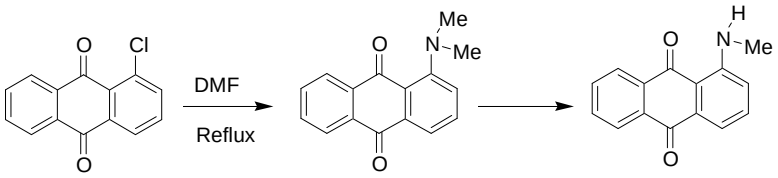

Fig.: 24

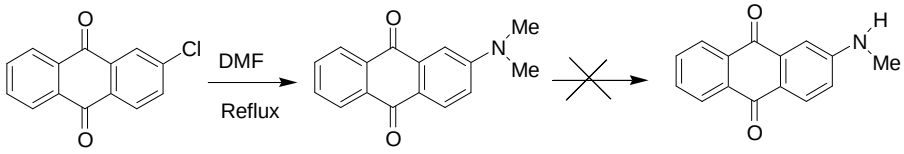

Fig.: 25

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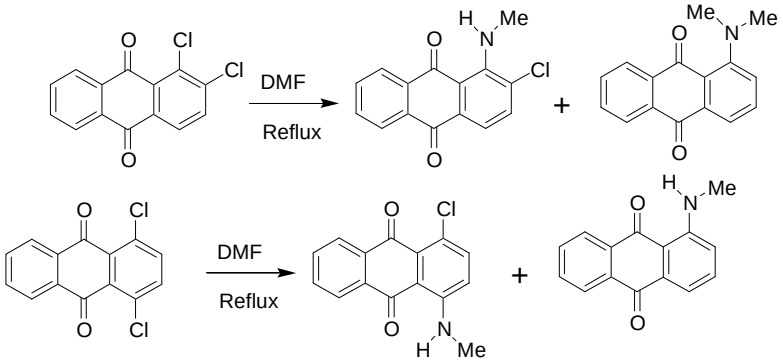

Fig.: 26

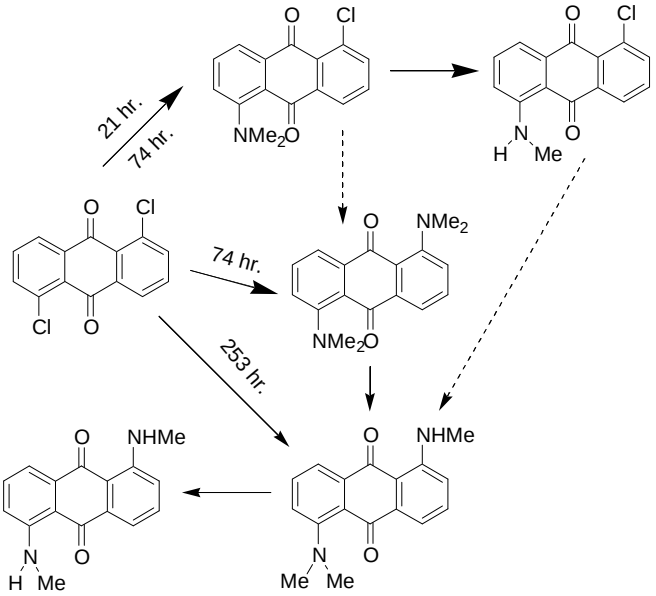

Fig.: 27

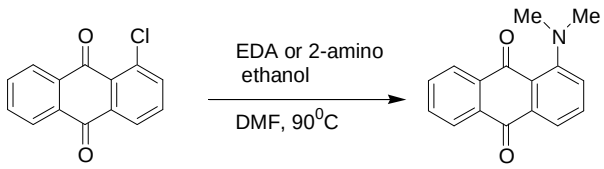

Fig. : 28

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