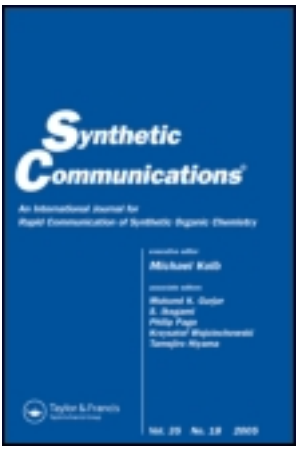

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Convenient Dimethylamino Amination in Heterocycles and Aromatics with Dimethylformamide

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Convenient Dimethylamino Amination in Heterocycles and Aromatics with Dimethylformamide

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ABSTRACT

A convenient dimethylamino amination of various heterocyclic and aromatic compounds having activated chloro group has been carried out in good yields using dimethyl formamide (DMF).

Key Words: Dimethyl amination; Dimethyl formamide; Dimethylamino-purine.

INTRODUCTION

The new millennium has witnessed a gamut of drugs and chemical reagents containing the dimethylamino group. It is present in ampyzine[1]

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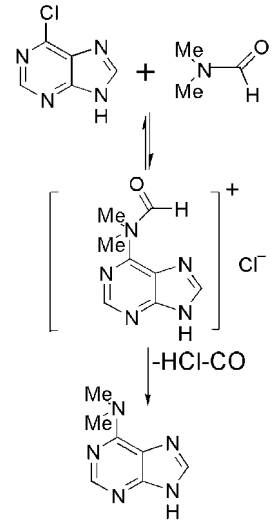
(central stimulant), triampyzine[1] (anticholinergic), dimethirimol[2] (fungicide), aminopyrine[3] (antipyretic), 6-dimethylamino-8-azaadenosine[4] (antitumor), diphenhydramine[1] (antihistamine), methadone[5] (narcotic analgesic), and various other drugs.

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.[6] The 6-DMAP (inhibitor of cyclin dependant kinase [CDK]) is used to study the DNA endoreduplication during elongation and differentiation of primary roots.[7] 6-DMAP is also used to activate embryos and oocytes that give rise to cloned rabbits that are produced by nuclear transfer from adult somatic cells.[8]

The dimethylamino group is mainly introduced by reacting chloro compounds with dimethylamine. As this reaction involves elevated temperature and pressure, it is not a convenient method for synthesis.[9] Most of the time, dimethylamination ends up with very low yield.[10] Coppinger synthesized *N*,*N*-dimethylbenzamide by refluxing benzoyl chloride with DMF.[11] Chloro benzene substituted with nitro group at different positions was refluxed with copper sulfate and DMF to obtain the corresponding dimethylamino compounds.[12]

In this communication, a systematic study is done on the replacement of an activated chloro group with the dimethylamino group in heterocyclic and aromatic compounds by using DMF (Sch. 1).



Scheme 1.

The dimethylamination of 2-chloro-4-piperidino pyrimidine **(2)**, 2,4-dichloro pyrimidine **(3)**, 2,4-dichloro-6-piperidino triazene **(4)**, 2-chloro-4,6-dipiperidino triazene **(5)**, and 4-chloro pyridine **(6)** with DMF yielded the desired dimethylamino products in very good yields (70–96%). There was no reaction in 2-amino-6-chloro pyrazine **(7)** due to the presence of deactivating amino group (Table 1).

The dimethylamino amination of aromatic compounds is temperature dependant. The temperature at which chloro group is replaced depends on the activation of the chloro group induced either by nitrogen atom of heterocyclic ring or nitro group. As nitro group exerts its strong electron withdrawing effect only at the ortho or para positions so only chloro groups at ortho or para positions are replaced and those at meta positions **(10)** are unaffected.

This method of dimethylamino amination by DMF is of great importance in chemical synthesis due to its wide applicability, easy reaction conditions, and high yield. It is also very useful in synthesizing 6-DMAP and various other chemicals of medicinal importance.

EXPERIMENTAL

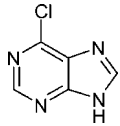
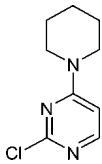
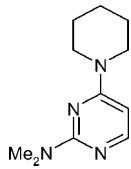
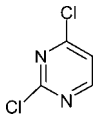
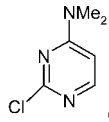
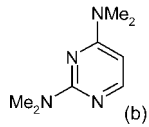
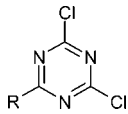
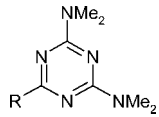
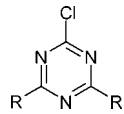
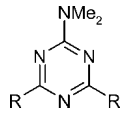
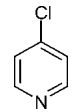
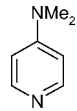
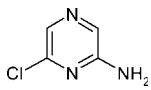
IR spectra were recorded on Beckman Aculab-10, Perkin Elmer 881, and FTIR 8210 PC, Shimadzu spectrophotometers either on KBr discs or in neat. Nuclear Magnetic Resonance (NMR) spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometers using TMS as an internal reference. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Argon/Xenon (6 KV, 10 mA) as the FAB gas. Chemical analysis were carried out on Carlo-Erba-1108 instrument. The melting points were recorded on an electrically heated melting point apparatus and are uncorrected.

Dimethylamino Amination Procedure

0.5 gm of the chloro compounds were heated with 15 mL of DMF and K_2CO_3 for 10 hr. The DMF was removed under reduced pressure and 5% sodium hydrogen carbonate solution was added. The compound was extracted with chloroform and dried over Na_2SO_4 and concentrated to afford the product which on crystallization with chloroform and hexane afforded the pure dimethylamino compounds.

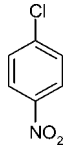
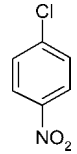
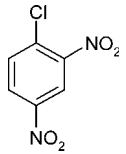
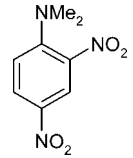
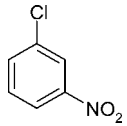
2-*N*,*N*-Dimethylamino-4-piperidinopyrimidine (2). M.P. 76–78°C, MS 207 (M^{+1}), IR (KBr) 3017, 2940, 2858, 1648, 1586, 1487 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 7.91 (d, 1H, $J = 6.12$ Hz), 5.84 (d, 1H,

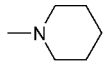
Table 1. Dimethylamino amination of heterocyclic and activated nitro halo compounds.

Entry	Starting	Product	Temp (°C)	Yield (%)
1			120	96
2			150	75
3		 (a)  (b)	100	50 20
4			80	92
5			80	95
6			80	75
7		No reaction		

(*continued*)

Table 1. Continued.

Entry	Starting	Product	Temp (°C)	Yield (%)
8			140	95
9			25	96
10		No reaction		

R = 

$J = 6.13$ Hz), 3.59 (t, 4H, $J = 5.1$ Hz), 3.12 (s, 6H), 1.62 (bs, 6H), ^{13}C 162.2 (C), 162.0 (C), 156.2 (CH), 91.9 (CH), 44.8 (CH_2), 36.8 (N–CH_3), 25.5 (CH_2), 24.7 (CH_2). Anal. calcd for $C_{11}H_{18}N_4$: C, 64.05; H, 8.79; N, 27.16. Found: C, 64.38; H, 8.56; N, 26.88.

***bis*-2,4-(*N*,*N*-Dimethylamino)-6-piperidino-triazene (4).** M.P. 72–74°C, MS 251 (M^{+1}), IR (KBr) 3016, 2943, 2860, 1620, 1466, 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 3.76 (t, 4H, $J = 5.2$ Hz), 3.11 (s, 12H), 1.59 (m, 6H), ^{13}C 170.2 (C), 163.60 (C), 45.5 (CH_2), 36.32 (N–CH_3), 25.8 (CH_2), 24.3 (CH_2). Anal. calcd. for $C_{12}H_{22}N_6$: C, 57.57; H, 8.86; N, 33.57. Found: C, 57.28; H, 8.94; N, 33.62.

2-*N*,*N*-Dimethylamino-4,6-*bis*-piperidino-triazene (5). M.P. 102–103°C, MS 291 (M^{+1}), IR (KBr) 3002, 2928, 2848, 1632, 1443, 1397 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 3.73 (t, 8H, $J = 5.1$), 3.08 (s, 6H), 1.57 (bs, 12H), ^{13}C 166.62 (C), 165.73 (C), 44.48 (CH_2), 36.26 (N–CH_3), 26.235 (CH_2), 25.71 (CH_2). Anal. calcd for $C_{15}H_{26}N_6$: C, 62.04; H, 9.02; N, 28.94. Found: C, 61.76; H, 8.94; N, 28.72.

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