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Der Pharma Chemica, 2010, 2(3): 178-186
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

New reagents from "N, N - Dimethyl amino methoxy methylenium methyl sulphate" - Synthesis of 3-Amino-4-cyano pyrazole

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Abstract

Dimethylamino methylene derivatives of active methylene compounds were prepared using DMF. Me_2SO_4 adduct. These dimethylamino methylene derivatives can be used in the preparation of Fluoroquinolines and heterocycles such as 3-Amino-4-cyano pyrazole.

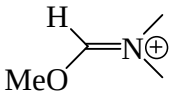
Keywords: Dimethylformamide, Dimethyl sulfate, Active methylene compounds, Dimethylamino methylene derivatives, Fluoroquinolines and pyrazoles.

INTRODUCTION

Heterocycles bearing a pyrazole or pyrazolo pyrimidine moieties are reported to possess various biological activities. Several α-carbon-substituted β-(dimethylamino)enones with general formula **2** have been prepared previously by condensation of active methylene compounds such as 1,3-diketones or β-keto esters, with reactive N,N-dimethylformamide (DMF) derivatives such as N,N-dimethylacetamide dimethyl acetal(DMADMA), N,N-dimethylformamide dimethyl acetal (DMFDMA), N,N-dimethylformamide diethyl acetal (DMFDEA) and *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent, TBDMAM). They have been most frequently used in the synthesis of heterocycles, such as pyrazoles, isoxazoles, pyrimidines and others [1].

Dimethylformamide on treatment with Dimethyl sulphate (Me_2SO_4), an adduct is formed as the methyl sulfate salt **1** [2]. This salt / adduct is useful to the synthesis of enaminones [3], dioxolanes and dioxanes [4], Beckmann rearrangement of cyclohexanone oxime to its corresponding E – caprolactam [5] and in the synthesis of difficult 3 - acyl indazolines [6] and in the synthesis of 2-amino-5-nitro thiazole [7], an intermediate in the preparation of Nitazoxanide.

Industrially both DMF and Me_2SO_4 are available abundantly and the ease of preparation of adduct and its stability prompted us to look into various applications in industry. Our first application came with its usage in fluoroquinolone antibacterial – ciprofloxacin [8]. The next success came with its usage to prepare methyl-3-dimethyl amino acrylate reagent **2**, which was used industrially to prepare number of other fluoroquinoline drugs (viz: sparfloxacin [9]).



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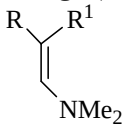


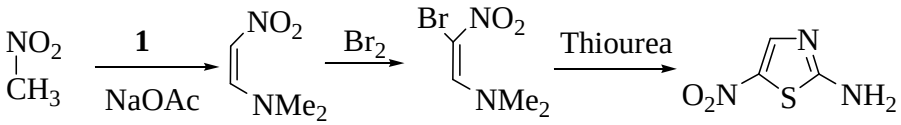
2

RESULTS AND DISCUSSION

a) Reaction with active methylene compounds:

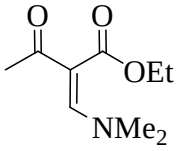
In our quest of exploring the industrial use of this reagent **1**, firstly we concentrated on reaction with active methylene compounds.

The first known report was with cyclopentadienyl sodium to give 6-(dimethylamino) fullvene [2]. The second known report was by Korean team with nitromethane [7] to get compound **3**, which was further converted into 2-Amino-5-nitro thiazole in an overall yield of 32 %.



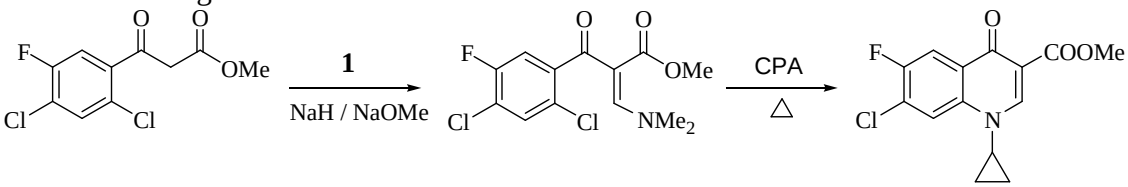
3

In the year 1991 McCombie [3] used triethylamine (TEA) / diisopropylethylamine (DIPEA) as base to prepare 2-Dimethylaminomethylene-3-oxo-butyric acid ethyl ester **4** from ethylacetoacetate.



4

In the year 1992 we started working on ciprofloxacin process development. We first started using this reagent to prepare intermediate of **6** from **5** [8], which is then converted to ciprofloxacin through **7**.

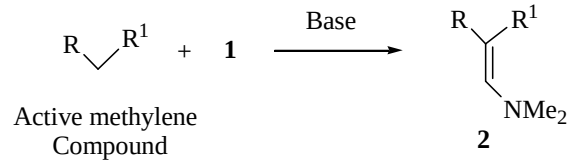


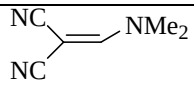
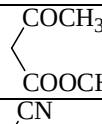
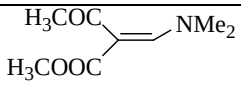
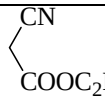
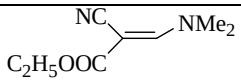
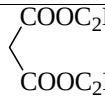
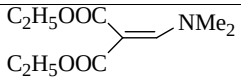
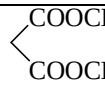
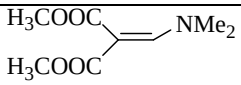
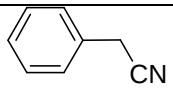
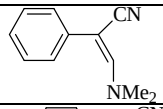
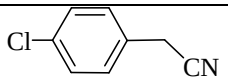
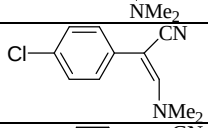
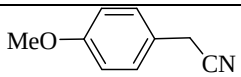
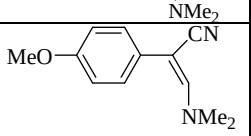
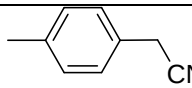
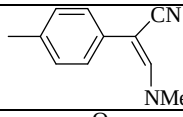
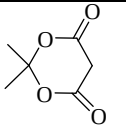
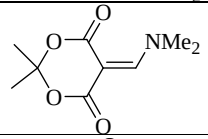
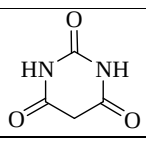
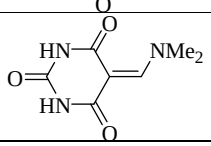
5 (β – Ketoester) **6** **7**

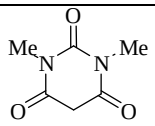
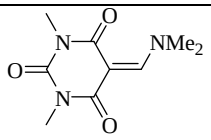
In this paper we report the preparation of enamine derivatives **2a-l** from other active methylene compounds by treatment with DMF.DMS adduct **1**. Most of the products are crystalline solids

with definite melting points. All these derivatives are characterized by their spectral characterization.

Table 1. Enamine derivatives from active methylene compounds 2a-l

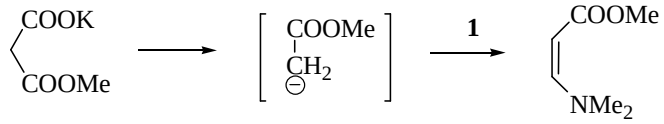


Entry	Active methylene Compound	Product	Yield	Melting range °C	Base used For the reaction
2a			98	82 - 83	TEA
2b			60	60 - 62	DIPEA
2c			70	77 - 79	TEA
2d			80	oil	DIPEA
2e			87	64 - 66	DIPEA
2f			55	79 - 81	DBU
2g			50	88 - 90	DBU
2h			40	84 - 86	DBU
2i			40	89 - 91	DBU
2j			39	118 - 120	DIPEA
2k			60	278 - 279	DBU

2l			74	74 - 76	DBU

b) Preparation of 3-dimethylamino acrylate derivatives:

During our quinoline antibacterial preparations, we were looking for industrial processes for the preparation of methyl-3-dimethylamino acrylate derivative **2**.The literature reports were industrially not feasible because of high cost. We used reagent **1** to prepare compound **2** under decarboxylative conditions. Malonic ester monopotassium salt is known to undergo decarboxylation under mild conditions to generate the anion, which can be reacted insitu with **1** to give **2** [9].



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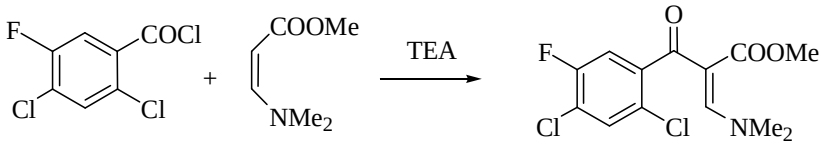
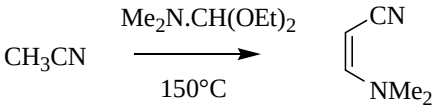
Compound **2** is used to prepare β-keto esters of quinoline antibacterials from the acid chlorides.



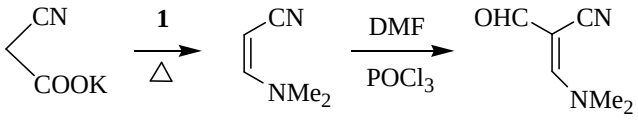
2

Willy et al reported the synthesis of 3-dimethylamino acrylonitrile **8**, which was prepared in poor yields [10], using diethylacetal of dimethyl formamide at 150°C.



8

We developed a simple method for the preparation of compound **8** using the decarboxylative methodology from cyanoacetic acid potassium salt.



8 **9**

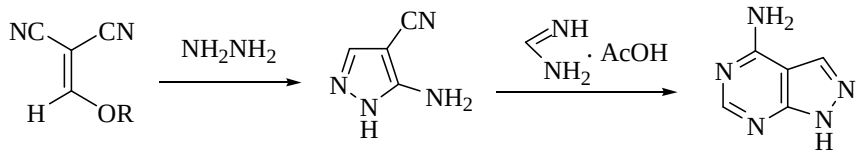
This reagent **8** is confirmed in all respects with the reported in Lit [10]. This is further confirmed by converting it into known 2-cyano-3-dimethylamino acrolien **9**.

c) 3-Amino-4-cyano pyrazole:

3(5)-Amino-4-cyano pyrazole **11** is a critical intermediate for 'Zaleplon' drug [12d] and also for the preparation of 4-amino pyrazolo[3,4-d] pyrimidine (4,APP) **12** compounds [11]. These 4-APP's are known inhibitors of tyrosine Kinase enzymes and are useful for immunoregulation for

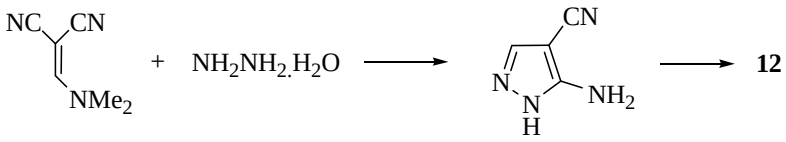
the treatment of cancer ongiogenesis and arteriosclerosis. These pyrazolo pyrimidines are useful for the treatment and prophylaxis for hyperuricemia in mammals [12a]. 4-APP was also reported to have growth inhibition and relief in neurospora crassa and to be a potential antineoplastic agent [12b,c]. Sperti et al [12e] demonstrated that 4-APP as a novel inhibitor of the RNA and DNA depurination induced by Shiga toxin-1. Motta [12f] et al described recently the novel N^2 substituted 4-APP compounds as Adenosine A_3 receptor antagonists (A_3ARs). These receptors are currently of great interest as targets for the therapeutic intervention in many pathological conditions such as renal failure, cardiac and cerebral ischemia, CNS disorders, neurogenarative diseases and inflammatory pathologies such as asthma [13].

4 - Amino pyrazolo [3,4-d] pyrimidine was prepared as follows.



10 **11** **12**

11 was prepared from 2-Methoxymethylene-malononitrile **10** and hydrazine hydrate. We synthesized first time **11** starting from **2a** and the same is converted to **12,** which is confirmed in all respects.



2a **11**

MATERIALS AND METHODS

^{1}H & ^{13}C NMR spectra were recorded using a Bruker 400 Spectrometer (400 & 100 MHz respectively) with TMS as internal standard. IR spectra were recorded on Perkin Elmer Spetrophotometer as KBr pellets or neat. Microanalysis was performed on a Perkin Elmer-240 CHN elemental analyzer. Analytical TLC was conducted on E-Merck 60F254 aluminum-packed silica gel plates (0.2mm). Developed plates were visualized using UV light or Iodine chamber. HPLC spectra were recorded on shimadzu 2010.

Synthesis of 3-amino-4-cyano-pyrazole (11)

A mixture of Dimethylamino methylene malanonitrile (50.0gm 0.413 M) and 300 ml of methanol was cooled to 20°C in an ice bath, added hydrazine hydrate (28.0 ml) drop wise over a period of 45 minutes. After addition, temperature was raised to 28-30°C and agitated for 3 hrs. (The completion of the reaction was monitored through TLC). Distilled off 60% methanol and cooled to 0-5°C. Stirred for and collected the solids through filtration. White crystalline powder; Yield: 97 %; mp: 170–173 °C (lit: 175-176°C); HPLC purity: > 99 %; FT-IR (cm^{-1}**)**: 3342 (-NH_2), 3147 (-NH), 2237 (-CN); ^{1}HNMR (ppm, DMSO): δ 7.6 (broad, s, 2H, -NH_2), δ 8.06 (s,

1H), δ 8.12 (s, 1H, Ar), δ 13.32 (s, 1H, -NH); ^{13}CNMR (DMSO/TMS): δ 99.92, 132.92, 155.12, 156.17, 158.33; ESI-MS (m/z %): 136.3 (M+1).

Synthesis of 4-amino pyrazolo [3,4-d] pyrimidine (4-APP) (12)

A mixture of compound **11** (25.0 gm 0.231 M) and Formamidine acetate (34.0 gm 0.32 M) in 250 ml of 2-methoxy ethanol was heated to 100°C for 48 hr (The completion of the reaction was monitored by TLC). Cooled to 20-25°C and agitated for 1 hr and collected the solids through filtration. White powder; Yield: 74 %; HPLC purity: >99 %; mp: 353 - 356 °C (lit: >325 °C); FT-IR **(**cm^{-1}**)**: 3317 (-NH_2), 3121 (-NH); ^{1}HNMR (ppm, DMSO): δ 6.31 (broad, s, 2H, -NH_2), δ 8.04 (s, 1H), δ 12.26 (s, 1H, -NH); ^{13}CNMR (DMSO/TMS) δ, 76.77, 115.52, 141.28, 152.96; ESI-MS (m/z %): 109.12 (M+1).

Synthesis of 3-dimethylamino acrylonitrile (8)

a) Synthesis of potassium salt of cyanoacetic acid

To a solution of cyanoacetic acid (85.06 gm, 1M) in 85 ml methanol was added alcoholic potassium hydroxide (56 gm (1M) of KOH dissolved in 224 ml methanol) at 5°C to 10°C over a period of 1 hour. The resulted white slurry was allowed to stir under nitrogen atmosphere at ambient temperature for 6 hrs. Then, again cooled to 5 to 10°C, agitated for 1 hour and collected the solids through filtration under nitrogen atmosphere, which were dried in vacuum at ambient temperature. White powder. Yield: 90 %; mp: 179 – 181 °C; FT-IR (cm^{-1}): 3429 (-COOK), 2253 (CN), 1616 (C=O).

b) Reaction of potassium salt of cyanoacetic acid with DMF. DMS adduct

To potassium cyanoacetate (50 gm, 0.40 M) in 250 ml EDC under nitrogen atmosphere, was added DMF.DMS adduct (113.19 gm, 0.568M) drop wise at 5 to 10°C over a period of 1 hour. The resulted slurry was agitated at ambient temperature for 24 hrs. After usual workup, obtained the desired crude product, which was fractionated using a vigreux column. After discarding a small first fraction, the material boiling at 115°C and 3.0 mmHg was collected (23.5 gm). Yellow liquid. Yield: 60 %; GC purity: 95 – 97 %; FT-IR (cm^{-1}): 2193 (-CN), 1633 (C=C); ^{1}HNMR (ppm, $CDCl_3$): δ 2.8 (broad, s, 6H, -$N(CH_3)_2$), δ 3.7 (d, 1H, *J* = 13 Hz, =CH), δ 6.9 (d, 1H, *J* = 13 Hz, =C-H); ^{13}CNMR ($CDCl_3$/TMS): δ 36.1, 41.4, 59.5, 122.1, 154.1.

Synthesis of methyl-2-(dimethylamino) ethyl acrylate (4)

a) Preparation of monopotassium salt of methyl malonate

To a solution of Diethyl malonate (100 gm, 0.625 M) in 100ml methanol was added alcoholic potassium hydroxide (1.0 M) (35.0 gm of KOH dissolved in 140ml methanol) at 5 to 10°C over a period of 1 hour. The precipitated white solid was agitated continuously for 6 hrs under nitrogen atmosphere at room temperature and again cooled in an ice bath. Stirred for 1 hour and collected the solids through filtration under nitrogen atmosphere, which was dried under vacuum at ambient temperature. White powder; Yield: 85 %; mp: 201-205°C; FT-IR (cm^{-1}): 1733 (ester C=O), 1600 (C=O of –COOK).

b) Reaction o fmonopotassium salt of methyl malonate with DMF. DMS adduct

A solution of monopotassium methyl malonate (76 gm, 0.487 M) in 380 ml EDC under nitrogen atmosphere was cooled in an ice bath and DMF.DMS adduct (135 gm, 0.682 M) added with

stirring. The resulted slurry was allowed to stir at ambient temperature (20 - 25°C) for 24 hrs. After usual workup obtained the crude product, which was recrystallised from isopropyl ether (41 gm). Yellow crystalline solid. Yield: 65 %; GC purity: > 99%; mp: 41- 44°C; FT-IR (cm^{-1}): 1680 (ester C=O), 1612 (C=C); ^{1}HNMR (ppm, $CDCl_3$): δ 2.8 (s, 6H, -N(CH_3)$_2$) , δ 3.6 (s, 3H, -CH_3), δ 4.49 (d, 1H, *J* = 13 Hz, =C-H), δ 7.4 (d, 1H, *J* = 13 Hz, =C–H); ^{13}CNMR ($CDCl_3$/TMS): δ, 41.4, 51.2, 98.2, 153.1, 166.0.

General Procedure for the synthesis of β-dimethyl amino acrylates (2a-l).

To a stirred solution of active methylene compound (1.0 M) and adduct **1** (1.5 M) in ethylene dichloride under nitrogen atmosphere was added the base (2.0 M) at 10°C to room temperature. The temperature of the reaction mixture was raised to 50°C and then to reflux temperature if required. The completion of the reaction was checked on precoated silica gel plates and observed under UV light or Iodine vapours. After cooling the reaction mixture to ambient temperature (20 - 25°C) and then treating with water the organic layer was separated. The aqueous layer was extracted with EDC. The combined organic portions were washed with water (till pH comes to neutral) and then dried over Na_2SO_4. Evaporation of the solvent and purification of the residue in desired solvent furnished the β-dimethyl amino acryl derivatives.

Synthesis of Dimethylamino methylene malanonitrile **(2a)**

White crystalline powder. Yield: 72 %; GC Purity: > 99 %; mp: 82-83 °C; FT-IR (cm^{-1}): 2213 & 2199 (-CN), 1649 (C=C); ^{1}HNMR (ppm, $CDCl_3$): δ 3.2 (s, 3H, N-CH_3), δ 3.3 (s, 3H, N-CH_3), δ 7.0 (s, 1 H, =CH); ^{13}CNMR ($CDCl_3$/TMS): δ 38.20, 47.61, 49.02, 115.33, 117.21 and 158.01; Anal. Calcd. for $C_6H_7N_3$ (121.14): C, 59.48; H, 5.82; N, 34.68. Found: C, 59.18; H, 6.30; N, 36.07.

Synthesis of Methyl-2-acetyl-3- (dimethylamino) acrylate **(2b)**

Yellow crystalline powder. Yield: 60 %; GC Purity: > 98 %; mp: 60-62 °C; FT-IR (cm^{-1}): 1694 (ester C=O), 1625 (C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 2.3 (s, 3H, -CH_3), δ 2.9 - 3.1 (s, 6H, -N(CH_3)$_2$), δ 3.7 (s, 3 H, -OCH_3), δ 7.7 (s, 1H, =CH); ^{13}CNMR ($CDCl_3$/TMS): δ 29.30, 41.61, 47.42, 51.01, 102.22, 157.01, 168.53 and 195.30; Anal. Calcd.for $C_8H_{13}NO_3$ (171.19): C, 56.12; H, 7.65; N, 8.18. Found: C, 54.57; H, 7.02; N, 8.24.

Synthesis of Ethyl-2 -cyano-3-(dimethylamino) acrylate **(2c)**

Pale yellow crystalline powder. Yield: 70 %; mp: 77-79 °C; FT-IR (cm^{-1}): 2203 (-CN), 1698 (ester C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 1.3 (t, 3H, *J* = 7 Hz, -CH_3), δ 3.2 (s, 3H, N-CH_3), δ 3.38 (s, 3H, N-CH_3), δ 4.22 (q, 2H, *J* = 7 & 20 Hz, -CH_2) and δ 7.69 (s, 1H, =CH); ^{13}CNMR ($CDCl_3$/TMS): δ 14.31, 38.30, 47.52, 60.60, 70.15, 118.0, 157.3 and 166.67; Anal. Calcd.for $C_8H_{12}N_2O_2$ (168.19): C, 57.12; H, 7.19; N, 16.65. Found: C, 56.86; H, 8.33; N, 17.26.

Synthesis of 2-dimethylamino methylene-1, 2-butanedioic acid diethyl ester **(2d)**

Yellow liquid. Yield: 80 %; GC purity: > 95 %; FT-IR (cm^{-1}): 1682 (C=O), 1610 (C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 1.25 (t, 3H, *J* = 6.5 Hz, -CH_3), δ 1.30 (t, 3H, *J* = 6.5 Hz, –CH_3), δ 2.99 (s, 6H, -N(CH_3)$_2$), δ 4.14 – 4.24 (q, 4H, *J* = 6.5 & 19 Hz), δ 7.4 (s, 1H, =CH); ^{13}CNMR ($CDCl_3$/TMS): δ 14.12, 14.29, 45.50, 59.70, 60.42, 92.90, 153.23, 167.31 & 167.4.

Synthesis of 2-dimethylamino methylene-1,2-propanedioic acid dimethylester **(2e)**
Pale Yellow crystalline powder. Yield: 87 %; mp: 64-66 °C; GC purity: > 99 %; FT-IR (cm^{-1}): 1715 (C=O), 1693 (C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.0 (s, 6H, $(-CH_3)_2$), δ 3.70 (s, 3H, N-CH_3), δ 3.77 (s, 3H, N-CH_3), δ 7.55 (s, 1H, =CH); ^{13}C NMR ($CDCl_3$/TMS): δ 51.15, 51.45, 91.79, 153.95 & 167.54.

Synthesis of Phenyl-3-(dimethylamino) acrylonitrile **(2f)**
Pale yellow crystalline powder. Yield: 55 %; mp: 79 – 81 °C; FT-IR (cm^{-1}): 2177 (-CN); ^{1}HNMR (ppm, $CDCl_3$): δ 3.18 (s, 6H, $-N(CH_3)_2$, δ 6.88 (s, 1H, =CH), δ 7.1 - 7.3 (m, 5H, aromatic); ^{13}CNMR ($CDCl_3$/TMS): δ 42.41, 76.52, 121.0, 123.81, 124.93, 128.60, 136.52 and 149.80; Anal. Calcd.for $C_{11}H_{12}N_2$ (172.23): C, 76.71; H, 7.02; N, 16.26. Found: C, 76.30; H, 8.22; N, 16.37.

Synthesis of 4-chlorophenyl-3-(dimethylamino) acrylonitrile **(2g)**
Yellow crystalline powder. Yield: 50 %; mp: 88 – 90 °C; FT-IR (cm^{-1}): 2183 (-CN), 823 (C-Cl); ^{1}HNMR (ppm, $CDCl_3$): δ 3.2 (s, 6H, $-N(CH_3)_2$), δ 6.8 (s, 1H, =CH), δ 7.1 - 7.2 (m, 4H, aromatic); ^{13}CNMR ($CDCl_3$/TMS): δ 42.51, 75.82, 120.60, 124.93, 124.94, 128.61, 130.42, 135.11 and 149.7; Anal. Calcd.for $C_{11}H_{11}N_2Cl$ (206.6): C, 63.92; H, 5.36; N, 13.55. Found: C, 63.72; H, 5.87; N, 13.85.

Synthesis of 2-(4-methoxyphenyl)-3-dimethylamino acrylonitrile **(2h)**
Pale Yellow crystalline powder. Yield: 40 %; mp: 84 - 86°C; FT-IR (cm^{-1}): 2178 (-CN); ^{1}HNMR (ppm, $CDCl_3$): δ 3.2 (s, 6H, $-N(CH_3)_2$), δ 3.7 (s, 3H, $-OCH_3$), δ 6.7 (s, 1H, =CH), δ 6.84 (d, 2H, *J* = 7.2 Hz, Ar), δ 7.22 (d, 2H, *J* = 7.2 Hz, Ar); ^{13}CNMR ($CDCl_3$/TMS): δ 30.80, 42.31, 55.26, 76.32, 114.0, 114.30, 121.31, 125.32, 126.23, 129.0, 149.0 and 157.4. Anal. Calcd.for $C_{12}H_{14}N_2O$ (202.2): C, 71.262; H, 6.97; N, 13.85. Found: C, 71.03; H, 7.75; N, 14.42.

Synthesis of 2-(4-methy phenyl)-3- dimethylamino acrylonitrile **(2i)**
White crystalline solid. Yield: 40 %; mp: 89 - 91°C; FT-IR (cm^{-1}): 2176 (-CN); ^{1}HNMR (ppm, $CDCl_3$): δ 2.3 (s, 3H, $-CH_3$), δ 3.2 (s, 6H, $-N(CH_3)_2$), δ 6.84 (s, 1H, =CH), δ 7.0 (d, 2H, *J* = 8 Hz, Ar), δ 7.2 (d, 2H, *J* = 8 Hz, aromatic); ^{13}CNMR ($CDCl_3$/TMS): δ 20.81, 42.40, 121.12, 123.90, 129.32, 133.50, 134.71 and 149.30; Anal. Calcd.for $C_{12}H_{14}N_2$ (186.2): C, 77.38; H, 7.57; N, 15.04. Found: C, 77.22; H, 8.96; N, 15.67.

Synthesis of 5-dimethylamino methylene-2, 2-dimethyl-(1,3)-dioxane-4, 6-dione **(2j)**
White crystalline solid. Yield: 39 %; mp: 118 –120°C; HPLC purity: > 99.5 %; FT-IR (cm^{-1}): 1729 (C=O), 1669 (C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 1.72 (s, 6H), δ 3.31 (s, 3H, N-CH_3), δ 3.41 (s, 3H, N-CH_3), δ 8.13 (s, 1H, =CH); ^{13}CNMR ($CDCl_3$/TMS): δ 26.41, 43.81, 48.59, 83.89, 102.77 and 160.82.

Synthesis of 5-dimethylamino methylene pyrimidine-2,4,6-trione **(2k)**
Yellow solid. Yield: 60 %; mp: 278–279 °C; HPLC purity: > 98 %; FT-IR (cm^{-1}): 3523, 3432 (-NH), 3169, 3068 (-NH), 1688 (C=O), 1650 (C=O), 1614(C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.24 (s, 3H, N-CH_3), δ 3.39 (s, 3H, N-CH_3), δ 8.01 (s, 1H, =CH), δ 10.35 (s, 2H, -NH); ^{13}CNMR ($CDCl_3$/TMS): δ 44.57, 48.57, 89.27, 151.45, 161.35 & 163.73; ESI-MS (m/z %): 184.1 (M+1).

Synthesis of 5-dimethylamino methylene N, N'-dimethyl pyrimidine 2,4,6-trione **(2l)**
Yellow crystalline powder. Yield: 74 %; mp: 74–76 °C; HPLC purity: > 99 %; FT-IR (cm^{-1}): 3467 (-NH), 1643 (C=O); ^{1}HNMR (ppm, $CDCl_3$): δ 3.31 (s, 6H, N-$(CH_3)_2$), δ 3.38 (s, 3H, N-CH_3), δ 3.43 (s, 3H, N-CH_3) & δ 8.14 (s, 1H, =CH); ^{13}CNMR ($CDCl_3$/TMS): δ 27.75, 44.69, 48.79, 90.29, 152.34 & 162.07; ESI-MS (m/z %): 212 (M+1).

CONCLUSION

In conclusion, we have demonstrated the usefulness of DMF.Me_2SO_4 adduct to prepare number of dimethylamino methylene derivatives from active methylene compounds. These dimethylamino methylene derivatives can be efficiently converted to pyrazoles, thiazoles, isoxazoles and others, which are important building blocks for many heterocyclic derivatives.

Acknowledgments
The authors greatly acknowledge their thanks to Mr. Venkat Jasti, CEO, Suven Life Sciences Ltd, Hyderabad for providing excellent facilities to carry out this work and K. Latha for generating data on compounds **2j, 2k** and **2l**.

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