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SYNTHESIS OF 4-SUBSTITUTED 3,5-DICYANO-2,6-PIPERIDINE-DIONES USING LITHIUM NITRIDE AS A CONVENIENT SOURCE OF AMMONIA

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Abstract – A simple and efficient one-pot synthesis of 4-substituted-3,5-dicyano-2,6-piperidinediones was achieved in good yields via the three-component reaction of aldehyde or ketone, ethyl cyanoacetate, lithium nitride (Li_3N) as a convenient source of ammonia in MeOH.

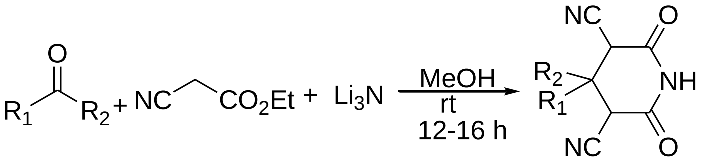
INTRODUCTION

4-Substituted-3,5-dicyano-2,6-piperidinediones exhibit a large range of biological activities such as anticonvulsant, sedative and analgesic activities.[1] They are also useful synthetic intermediates for various pharmaceuticals and active compounds.[2] There are two strategies for synthesis of 4-substituted-3,5-dicyano-2,6-piperidinediones: (1) They are synthetized by Guareschi-Thorpe reaction in following manner: The one-pot, three-component condensation of an aldehyde or ketone with ethyl cyanoacetate and ammonia in alcohol. [2-3] The reaction requires at least 48 hours to proceed to completion, and more typically between 48-168 hours for completion. in addition, current environmental regulations make it impractical to produce gaseous NH_3 in ethanol on a large scale. (2) The other approaches for the preparation of 4-substituted-3,5-dicyano-2,6-piperidinediones using aldehyde or ketone, substituted α-cyanoacetamide, ethyl cyanoacetate in an ethanolic solution of sodium ethoxide at room temperature have also been reported. [1] Substituted α-cyanoacetamide as the starting materia of the route is not easy to obtain. We now report a simple and efficient route to 4-substituted-3,5-dicyano-2,6-piperidinediones using Li_3N as a convenient source of ammonia.

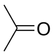
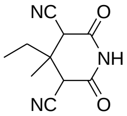
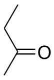
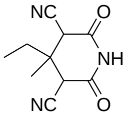
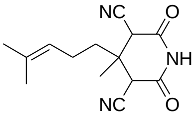
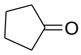
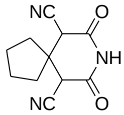
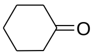
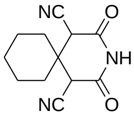
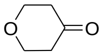
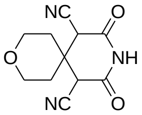
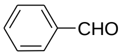
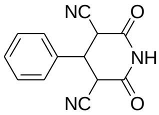
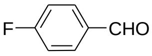
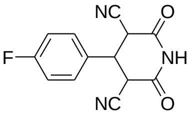
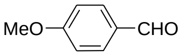
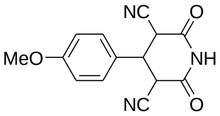
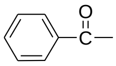
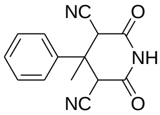
RESULTS AND DISCUSSION

A range of 4-substituted-3,5-dicyano-2,6-piperidinediones was synthesized from a combination of aldehyde or ketone (**1**), ethyl cyanoacetate (**2**) and Li_3N (**3**) in a 1: 2: 2 ratio in an MeOH solution (Table 1). The reaction was completed 12-16 hours at room temperature and the crude product was isolated by precipitation upon addition of hydrochloric acid to the mixture, the separated soild was filtered off and crystallized form the appropriate solvent.

Table 1 Synthesis of 4-substituted-3,5-dicyano-2,6-piperidinediones[a]



1 **2** **3** **4**

Entry	Aldehyde or Ketone	Product **4**	Time (h)	Yield (%)[b]
4a			12	79
4b			12	81
4c			16	76
4d			14	82
4e			14	83
4f			14	76
4g			12	84
4h			12	74
4i			12	78
4j			16	75

[a] Aldehyde or ketone: ethyl cyanoacetate: Li_3N =1: 2: 2; reactions executed in a sealed vessel at room temperature.

[b] Isolated yield

In recent study, we have discoverd that Li_3N as electrode material[4] and catalyst in synthesis of *c*BN[5] in chemistry industry can releases ammonia upon treatment with MeOH along with the corresponding lithium methoxide. Thus, this reagent can serve a dual role as it releases ammonia in situ while generating lithium methoxide with the potential to act as a catalyst (see Figure 1).

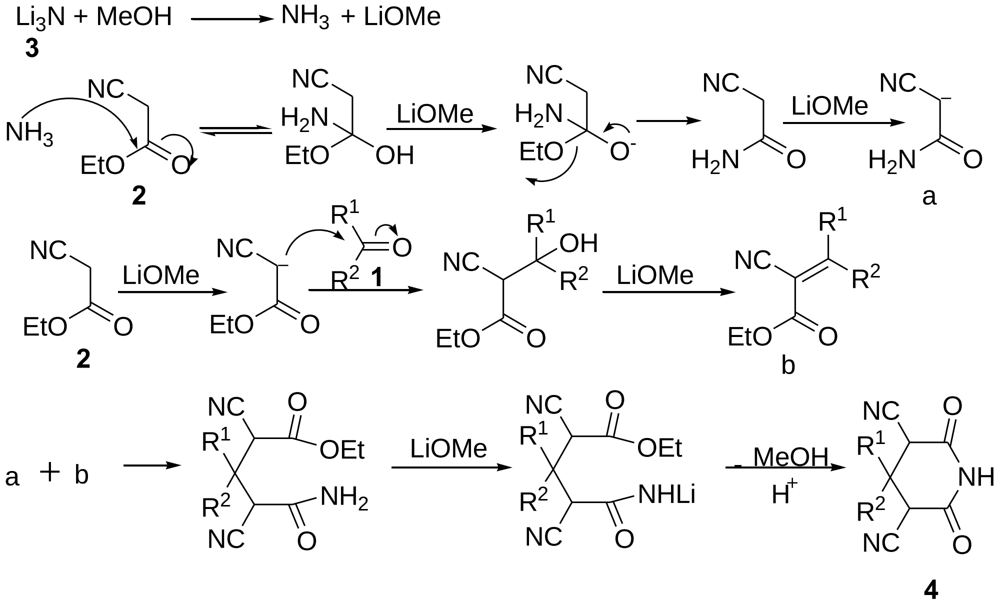


Figure 1. The mechanism of reaction using Li_3N as a source of ammonia

In order to determine the efficiency of Li_3N as a source of ammonia, the same reactions were carried out with ammonia, NH_4Ac and other commercially nitrides (Mg_3N_2, Zn_3N_2, AlN)employed in related condensations. The results summarized in Table 2 revealed that these systems gave lower yields of the desired product or no desired product. The results also emphasized the importance of using lithium methoxide (entry 3), which could improve yield.

Table 2 Synthesis of 4,4-dimethyl-3,5-dicyano-2,6-piperidinediones using different source of ammonia[a]

Entry	Source of Ammonia	Solvent	Yield (%)[b]
1	2 equiv NH_3	H_2O	6
2	2 equiv NH_3	MeOH	24
3	2 equiv NH_3+6 equiv LiOMe	MeOH	58
4	2 equiv NH_4Ac	MeOH	0
5	1 equiv Mg_3N_2	MeOH	31
6	1 equiv Zn_3N_2	MeOH	0
7	2 equiv AlN	MeOH	0

[a] Acetone: ethyl cyanoacetate=1: 2, reactions executed in a sealed vessel at room temperature for 12 h.

[b] Isolated yield

In summary, we first developed a simple and efficient methodology to synthesise a range of 4-substituted-3,5-dicyano-2,6-piperidinediones using Li_3N as a convenient source of ammonia. We believe that this methodology will be a valuable addition to the existing methods in the field of 4-substituted-3,5-dicyano-2,6-piperidinediones.

EXPERIMENTAL

NMR spectra were determined on FT-NMR Avance 400 spectrometer, coupling constants (*J*) were measured in Hz; Elemental analysis were recorded on a PEA-1110 elemental analyzer. Melting points were determined on a Mel-Temp capillary tube apparatus and were uncorrected; Commercially available reagents were used throughout without further purification unless otherwise stated.

General Procedure for the Preparation of 4. To a stirred solution of aldehyde or ketone (10 mmol) and ethyl cyanoacetate (2.26 g, 20 mmol) in MeOH (5 mL) at 8 °C in a 10 mL, lithium nitride (0.7 g, 20 mmol) was added in a single portion. The reaction mixture was sealed immediately and stirred at rt for 12-16 h. The mixture was then acidified by hydrochloric acid (15mL in 50 mL water) and the separated soild was filtered off and crystallized form MeOH to give **4** as a white soild.

4,4-Dimethyl-3,5-dicyano-2,6-piperidinedione (4a) : mp 215-217°C (lit.,[2b] mp 214-216°C); IR (KBr) *v*: 3211 (NH), 2242 (CN), 1723, 1698 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.02 (s, 1 H, NH), 4.42 (s, 2 H, CH), 1.28 (t, *J*=7.5 Hz, 6 H, CH_3); Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.49; H, 4.70; N, 21.89.

4-Ethyl-4-methyl-3,5-dicyano-2,6-piperidinedione (4b) : mp 188-190°C (lit.,[2b] mp 191-193°C); IR (KBr) *v*: 3240 (NH), 2225 (CN), 1743, 1702 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.92 (s, 1 H, NH), 4.51 (s, 2 H, CH), 1.28-1.23 (m, 2H, CH_2), 1.16 (t, *J*=7.3 Hz, 3H, CH_3), 0.96-0.92 (m, 3H, CH_3); Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.44; H, 5.45; N, 20.39.

4-Methyl-4-(4-methylpent-3-enyl)-3,5-dicyano-2,6-piperidinedione (4c) : mp 192-193°C; IR (KBr) *v*: 3235 (NH), 2240 (CN), 1730, 1698 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.08 (s, 1 H, NH), 5.12 (m, 1 H, CH=), 4.43 (s, 2 H, CH), 2.10-2.06 (m, 2H, CH_2),1.29-1.25 (m, 2H, CH_2), 1.20 (t, *J*=7.2 Hz, 3H, CH_3), 0.92-0.89 (m, 3H, CH_3); Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found: C, 64.70; H, 6.75; N, 16.35.

6, 10-Dicyano-8-azaspiro[4,5]decane-7,9-dione (4d) : mp 162-163°C (lit.,[1] mp 166 °C); IR (KBr) *v*: 3212 (NH), 2243 (CN), 1745, 1708 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.94 (s, 1 H, NH), 4.63 (s, 2 H, CH), 1.75-1.69(m, 8H, CH_2); Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.84; H, 5.15; N, 19.41.

1, 5-Dicyano-3-azaspiro[5,5]undecane-2,4-dione (4e) : mp 196-198°C (lit.,[1] mp 200 °C); IR (KBr) *v*: 3201(NH), 2239(CN), 1732, 1712 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.02 (s, 1 H, NH), 4.53 (s, 2 H, CH), 1.69-1.43(m, 10H, CH_2); Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.41; H, 5.60; N, 19.21.

7,11-Dicyano 3-Oxa-9-azaspiro[5.5]undecane-8,10-dione (4f) : mp 196-198°C. IR (KBr) *v*: 3234 (NH), 2219 (CN), 1734, 1705 (C=O) 1185 (C-O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.10 (s, 1 H, NH), 4.92 (s, 2 H, CH), 3.72-3.66 (m, 4 H, OCH_2),1.72-1.68 (m, 4H, CH_2); Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.76; N, 18.02. Found: C, 56.45; H, 4.68; N, 18.15.

4-Phenyl-3,5-dicyano-2,6-piperidinedione (4g) : mp 248-249°C (lit.,[1] mp 255°C); IR (KBr) *v*: 3305 (NH), 2260 (CN), 1712, 1692 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.02 (s, 1 H, NH), 7.45-7.32 (m, 5 H, ArH), 4.96-4.87 (m, 2 H, CH), 4.40-4.32 (m, 1 H, CH); Anal. Calcd for $C_{13}H_9N_3O_2$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.65; H, 5.58; N, 22.35.

4-(4-Fluorophenyl)-3,5-dicyano-2,6-piperidinedione (4h) : mp 245-247°C (lit.,[1] mp 255°C); IR (KBr) *v*: 3315 (NH), 2274 (CN), 1726, 1702 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.08 (s, 1 H, NH), 7.20-6.92(m, 4 H, ArH), 4.73-4.69 (m, 2 H, CH), 4.34-4.28 (m, 1 H, CH); Anal. Calcd for $C_{13}H_8FN_3O_2$: C, 60.70; H, 3.13; N, 16.33. Found: C, 60.45; H, 3.15; N, 16.20.

4-(4-Methoxyphenyl)-3,5-dicyano-2,6-piperidinedione (4i) : mp 317-318°C (lit.,[1] mp 325°C); IR (KBr) *v*: 3294 (NH), 2256 (CN), 1736, 1698 (C=O), 1282, 1088 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.02 (s, 1 H, NH), 7.40-6.95(m, 4 H, ArH), 4.82-4.76 (m, 2 H, CH), 4.22-4.16 (m, 1 H, CH), 3.74 (s, 3 H, CH_3); Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.22; H, 4.15; N, 15.52.

4-Methyl-4-phenyl-3,5-dicyano-2,6-piperidinedione (4j) : mp 290-291°C; IR (KBr) *v*: 3304 (NH), 2238 (CN), 1746, 1706 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ: 12.15 (s, 1 H, NH), 7.44-7.20(m, 5 H, ArH), 4.82 (s, 2 H, CH), 1.46 (s, 3 H, CH_3); Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.20; H, 4.27; N, 16.40.

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