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Note

A simple and efficient one pot synthesis of 2,4 dioxopyrimidine carbonitrile and 4-oxo-2-thioxopyrimidine carbonitrile derivatives using ammonium chloride under solvent free conditions

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Various substituted 4-oxo-2-thioxopyrimidine and 2,4-dioxo-pyrimidine derivatives have been synthesized by ternary condensation of ethyl cyanoacetate, aldehyde and thiourea/urea by using ammonium chloride. Structures of all the products are supported by their spectral data.

Keywords: Bigenelli reaction, ammonium chloride, ethyl cyanoacetate, aldehydes

In a few decades Bigenelli reaction has attracted considerable attention for synthesis of pyrimidines which have broad spectrum of biological activity[1-13] such as antiviral, antibacterial, anticancer, antifungal, antioxidant, antimalarial, anti-HIV, sedatives, anticonvulsant, anti-histamic agent, anti-hypertensive, anti-inflammatory, anti-cancer and calcium channel blockers. On account of these reasons, synthesis of substituted dihydropyrimidenes is of great interest.

Kambe *et al*.[14] in 1979 documented the synthesis of 4-oxo-6-substituted phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile by ternary condensation of aromatic aldehyde, thiourea and ethyl cyanoacetate in ethanol using potassium carbonate as a base. But it suffers from several drawbacks such as long reaction time, low yield and harsh reaction conditions. Several other important synthesis protocols have been reported such as KOH in dry methanol (12 h)[15], $Mg(OMe)_2$ (5-7 h)[16], sodium ethoxide (48 h)[17,18], microwave and ultrasonication[19], piperidine (12 h)[20] and microwave radiation[21]. Many of these methods involve long reaction time, anhydrous solvents, stiocheometric amounts, hazardous radiation, use of costly apparatus and give unsatisfactory yields. Therefore in our present work we have used the least expensive and easily available catalyst as well as mild and neutral reaction conditions for the synthesis of 2,4-dihydropyrimidine carbonitrile.

Hence we wish to report the results obtained from study of preparation of 2,4-dihydropyrimidine carbonitrile and its derivatives with NH_4Cl as easily available catalyst under neutral and solvent free conditions (Scheme I). The procedure gives product in good yield and avoids the problems such as cost, handling and safety associated with the use of the solvent.

The method has decreased reaction time because of the increase in the reactivity of the reactant in the solid state at the reaction temperature of 100°C.

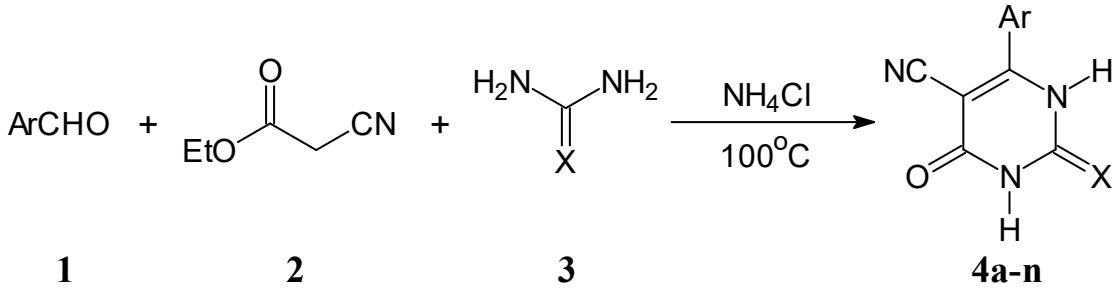
Experimental Section

All the reagents used are of research grade purchased from SD Fine and Merck. Melting points were recorded on open capillary method and are uncorrected. The melting points were compared with literature report. Synthesized products were characterized by IR and ^{1}H NMR. Infrared (IR) spectra were recorded on Shimadzu FTIR spectrometer. ^{1}H NMR spectra were recorded on Bruker Advance II (400 MHz) using DMSO-d_6 as solvent.

To increase the yield, the reaction was performed by using varied stoichiometric ratio of reagents. Excellent results were obtained with 0.5:1:1:1.5 ratio of ammonium chloride, aldehyde, ethyl cyanoacetate and urea/thiourea. From Table I, aldehyde, ethyl cyanoacetate, urea/thiourea, in presence of NH_4Cl gave corresponding 2,4-dioxopyrimidine carbonitrile and 4-oxo-2-thioxopyrimidine carbonitrile under neutral conditions in good yield after 3 h. Futhermore, aromatic aldehydes carrying either electron donating or electron withdrawing substituents react well giving moderate to excellent yield.

General procedure for synthesis of 2,4-dioxo-pyrimidine carbonitrile and 4-oxo-2-thioxopyrimidine carbonitrile

A mixture of benzaldehyde (0.30 g, 2 mmol), ethyl cyanoacetate (0.26 g, 2 mmole), thiourea (0.18 g, 3 mmole) and NH_4Cl (0.05 g, 0.8 mmol) was heated under stirring at 100°C for 3 h. After cooling, solid



1 **2** **3** **4a-n**

Ar = C_6H_5, 4-(Cl)-C_6H_4, 4-(OH)-C_6H_4, 2-Furyl

X = O,S

Scheme I

Table I — Synthesis of 2,4-dioxopyrimidine carbonitrile and 4-oxo-2-thioxopyrimidine carbonitrile under solvent free condition using ammonium chloride

Compd	Ar	X	Yield (%)	m.p. (°C)
4a	-C_6H_5	O	70	240-42
4b	4-(Cl)-C_6H_4	S	85	260-62
4c	4-(OH)-C_6H_4	S	80	235-37
4d	C_6H_5	S	75	296-98
4e	2-furyl	O	74	186-88
4f	4-(Cl)-C_6H_4	O	82	238-40
4g	3-(Cl)-C_6H_4	S	87	220-22
4h	4-(OH)-C_6H_4	O	84	210-12
4i	2-furyl	S	85	200-202
4j	3-(Cl)-C_6H_4	O	71	201-203
4k	3-(NO_2)-C_6H_4	O	77	250-52
4l	4-(OCH_3)-C_6H_4	S	90	272-74
4m	3-(NO_2)-C_6H_4	S	72	275-78
4n	4-(OCH_3)-C_6H_4	O	73	223-26

product obtained was filtered and washed with cold water. It was purified by recrystallization from ethanol or ethyl acetate:*n*-hexane (1:3) to obtain the analytical sample for spectral analysis.

Spectral data of synthesized compounds:

1,2,3,4-Tetrahydro-4-oxo-6-(4-chlorophenyl)-2-thioxopyrimidine-5-carbonitrile, 4b: m.p.260-62°C (Lit m.p.260°C). IR: 3375, 3271, 3167, 2685, 2337, 2234, 1609, 1470, 1408, 1180, 1083 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.38 (s, 1H, -NH), 8.23 (s, 1H, -NH), 8.07 (d, 1 H, ArH), 8.05 (d, 1 H, ArH), 7.63 (d, 1 H, ArH), 7.61 (d, 1 H, ArH).

1,2,3,4-Tetrahydro-4-oxo-6-phenyl-2-thioxo-pyrimidine- 5-carbonitrile, 4d: m.p.296-98°C (Lit m.p.296°C). IR: 3372, 3055, 2241, 1964, 1613, 1474, 1431 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.1 (s, 1H, -NH), 7.6-8.0 (m, 5 H, ArH).

1,2,3,4-Tetrahydro-2,4-dioxo-6-(4-chlorophenyl)-pyrimidine-5-carbonitrile, 4f: m.p.238-40°C (Lit m.p.240°C). IR: 3372, 3267, 3163, 2684, 2230, 2110, 1605, 1466, 1404, 1177, 1084 cm^{-1}; ^1H NMR (DMSO-d_6 400 MHz): δ 8.36 (s, 1H, -NH), 8.17 (s, 1 H -NH), 8.05 (d, 1 H, ArH), 8.04 (d, 1 H, ArH), 7.60 (d, 1 H, ArH), 7.58 (d, 1 H, ArH).

Conclusion

In summary, we have developed an economic and environment friendly procedure for the synthesis of 2,4-dioxopyrimidine carbonitrile and 4-oxo-2-thioxopyrimidine carbonitrile with short reaction time, inexpensive with easily available catalyst under neutral and solvent free conditions.

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