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REGULAR ARTICLE

Special Section on Transition Metal Catalyzed Synthesis of Medicinally Relevant Molecules

Successful utilization of β-ketonitrile in Biginelli reaction: synthesis of 5-cyanodihydropyrimidine

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Abstract. A Biginelli reaction of β-ketonitriles, aldehydes and urea in principle can yield 5-cyano substituted dihydropyrimidinones. Although potentially very useful, this substituted heterocycle is often difficult to synthesize via the three component reaction, presumably due to the lack of stability of β-ketonitriles. The present work describes the development of reaction conditions yielding the desired product. Interesting mechanistic observations have also been noted. Thirteen new compounds (derivatives) of 5-cyanodihydropyrimidin were synthesized.

Keywords. Biginelli; β-Ketonitrile; dihydropyrimidin; aldol; aldehyde; urea.

1. Introduction

Pyrimidines and their derivatives have a significant presence in many small molecule pharmaceutical compounds.[1] Some of the pharmaceutically active molecules containing substituted pyrimidine framework are Rosuvastatin (**1**), 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**2**), *etc*. (Figure 1). Rosuvastatin (**1**) drug is a member of statin family which is used to treat high cholesterol and to prevent cardiovascular disease. 6-Methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**2**) was found to induce a phenotype in cells similar to the Eg5 inhibitor Monastrol.[2] BMS-644950 (**3**), was identified for advancement into clinical development for the treatment of hypercholesterolemia (Figure 1).[3] Among the various methods adopted for the construction of these heterocycles, a particularly useful transformation is the Biginelli three-component reaction. Discovered in the 1880s, it recently witnessed a remarkable revival, and presented opportunities in drug discovery research due to its ability to produce interesting pharmacophores.[1,2,4] Insightful contributions from many chemists, particularly Kappe *et al.,* have expanded the scope of the Biginelli reaction by performing comprehensive mechanistic studies.[5]

The use of suitable building blocks namely aldehydes, urea and β-keto compounds has enabled assembly of diversely functionalized dihydropyrimidines. β-Keto components such as β-ketosulfones,[6] β-ketoacids,[7] β-ketonitro alkanes[8] and β-ketoamides[9] have been known to participate productively in this reaction.

2. Experimental

All reagents were used as received from commercial sources without further purification or were prepared as described in the literature. Reaction mixtures were stirred using Teflon coated magnetic stirring bars and mechanical stirrer. TLC plates were visualized by ultraviolet light. Chromatographic purification of products was carried out by flash column

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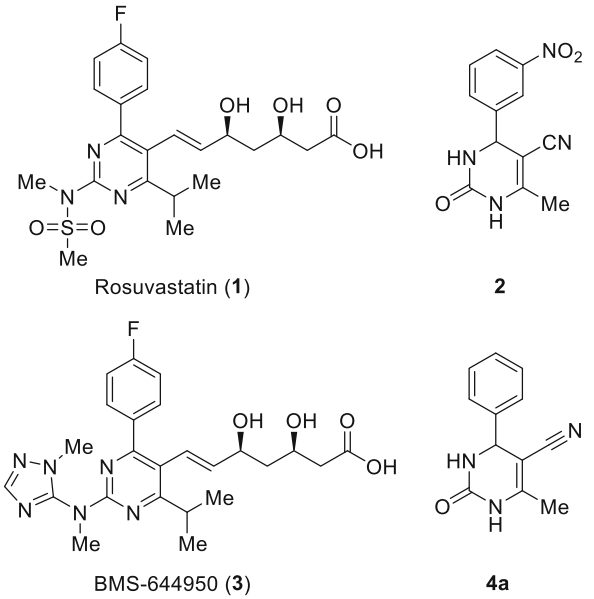


Figure 1. Some of the pharmaceutically active compounds containing substituted pyrimidine framework.

chromatography on silica gel (60–120 mesh). Melting points were determined using Mettler Toledo MP70 Melting point system. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$, DMSO-d_6, D_2O (all with TMS as internal standard) on a Bruker Avance 400 MHz NMR spectrometer FT NMR spectrometer magnetic resonance spectrometer.

2.1 *General procedure for the preparation of Biginelli compound (**11a−m**)*

A mixture of 4-methyl-3-oxopentanenitrile **10i** or **10ii** (1.5 eq), aldehyde **6(a–m)** (1.0 eq), urea (1.5 eq) and CuCl (0.01 eq) in MeOH containing concentrated H_2SO_4 (0.62 eq) was stirred at reflux temperature for 3–5 days. After the reaction was deemed complete by TLC, methanol was removed by concentration *in vacuo*. The precipitated solid was extracted in dichloromethane. The dichloromethane layer was washed with water twice so as to remove water soluble impurities. The organic layer was concentrated again to dryness *in vacuo*. The crude residue was purified by silica gel column chromatography using ethyl acetate: hexanes to give pyrimidine compound **11**(**a–m**).

2.1a *6-Isopropyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**11a**)*: Yield 85%, M.p. 161.63 °C; IR (KBr) 3397, 2206, 1694, 1650, 1586; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.16 (d, J = 6.0 Hz, 6H), 2.83 (m, 1H), 5.04 (d, J = 1.5 Hz, 1H), 7.28–7.43 (m, 5H), 7.83 (s, 1H), 9.4 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 31.5, 54.7, 79.1, 118, 126.4, 128.1, 128.8, 142.9, 151.2, 157.5; HRMS (ESI) calcd m/z for $C_{14}H_{16}N_3O$ $[M]^+$ 242.1281, found m/z 242.1293.

2.1b *6-Isopropyl-4-(4-methoxyphenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile (**11b**)*: Yield 82%, M.p. 211.71 °C; ^{1}H NMR, (400 Hz, DMSO-d_6), δ_H 1.17 (d, J = 2.0 Hz, 3H), 1.18 (d, J = 2.0 Hz, 3H), 2.84 (m, 1H), 3.75 (s 3H), 4.99 (d, J = 2Hz, 1H), 6.94 (d, 2H), 7.19 (d, 2H), 7.75 (s, 1H), 9.32 (s 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 31.5, 54.1, 55.1, 79.4, 114, 119, 118.0, 127.7, 135.0, 151.2, 157.2, 159.1; HRMS (ESI) calcd m/z for $C_{15}H_{18}N_3O_2$ $[M]^+$ 272.1385, found 272.1399.

2.1c *6-Isopropyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**11c**)*: Yield 65%, M.p. 221.41 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.21 (d, J = 5.2 Hz, 3H), 1.23 (d, J = 4.8 Hz, 3H), 2.52 (m, 1H), 5.27 (d, J = 2.4 Hz, 1H), 7.68–7.78 (m, 2H), 7.93 (s, 1H), 8.1–8.2 (m, 2H), 9.47 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 31.6, 53.7, 78.1, 117.7, 121.1, 123.2, 130.6, 133.2, 144.8, 147.9, 151.0, 158.5; HRMS (ESI) calcd. m/z for $C_{14}H_{15}N_4O_3$ $[M]^+$ 287.1149, found 287.1144.

2.1d *4-(3-Fluorophenyl)-6-isopropyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile (**11d**)*: Yield 82%, M.p. 203.68 °C; ^{1}NMR (400 Hz, DMSO-d_6), δ_H 1.16 (d, J = 5.4 Hz, 3H), 1.18 (d, J = 5.4 Hz, 3H,), 2.85 (m, 1H), 5.13 (d, J = 1.9 Hz, 1H), 7.08–7.21 (m, 3H), 7.45 (m, 1H), 7.90 (s, 1H), 9.43 (s 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 18.9, 31.5, 54.0, 78.5, 113.1, 113.3, 114.9, 115.1, 117.8, 122.4, 130.9, 131.1, 145.6, 145.6, 151.1, 158.0, 161.0, 163.4; HRMS (ESI) calcd m/z for $C_{14}H_{15}FN_3O$ $[M]^+$ 260.1185, found 260.1199.

2.1e *6-Isopropyl-2-oxo-4-(p-tolyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carbonitrile (**11e**)*: Yield 80%, M.p. 187.63 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.15 (m, 6H), 2.3 (s, 3H), 2.83 (m, 1H), 4.9 (d, J = 2 Hz, 1H), 7.15–7.20 (m, 4H), 7.78 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 20.6, 31.5, 54.4, 79.2, 118.0, 126.3, 129.3, 137.4, 140.0, 151.2, 157.3; HRMS (ESI) calcd m/z for $C_{15}H_{18}N_3O$ $[M]^+$ 256.1435, found 256.1450.

2.1f *4-(3-Hydroxyphenyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**11f**)*: Yield 84%, M.p. 240.67 °C^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.17 (d, J = 4.0 Hz, 3H), 1.18 (d, J = 4.0 Hz, 3H), 2.8 (m, 1H), 4.9 (s, 1H), 6.7 (m, 3H), 7.2 (t, J = 2.8 Hz, 1H), 7.78 (s, 1H), 9.3 (s 1H), 9.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 31.5, 54.6, 79.1, 113.0, 115.0, 116.9, 118.0, 129.7, 144.3, 151.2, 157.3, 157.6; HRMS (ESI) calcd m/z for $C_{14}H_{16}N_3O_2$ $[M]^+$ 258.1241, found 258.1243.

2.1g *4-(4-Chlorophenyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**11g**)*: Yield 85%, M.p. 159.68 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.17 (d, J = 6.0 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H), 2.84 (m, 1H), 5.1 (d, J = 2.4 Hz, 1H), 7.3 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.83 (s, 1H), 9.4 (s 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 18.9, 31.5, 53.9, 78.7, 117.8, 128.3,

128.8, 132.6, 141.7, 151.1, 157.8; HRMS (ESI) calcd m/z for $C_{14}H_{15}N_3OCl$ $[M]^+$ 276.0902, found 276.0904.

2.1h *4-(4-Fluorophenyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile*[10] ***(11h)***: Yield 81%, M.p. 175.62 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.17 (d, J = 3.4 Hz, 3H), 1.18 (d, J = 3.4 Hz, 3H), 2.83–2.90 (m, 1H), 5.1 (d, J = 2.5 Hz, 1H), 7.2–7.36 (m, 4H), 7.84 (s, 1H), 9.4 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 31.5, 54.0, 79.0, 115.50, 115.1, 117.9, 128.5, 128.6, 139.1, 139.1, 151.1, 157.6, 160.6, 163.1; HRMS (ESI) m/z calcd for $C_{14}H_{15}FN_3O$ $[M]^+$ 260.1200, found 260.1199.

2.1i *6-Isopropyl-2-oxo-4-(m-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile* ***(11i)***: Yield 79%, M.p. 187.84 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.16 (m, 6H), 2.31 (s, 3H), 2.84 (m, 1H), 4.99 (d, J = 2 Hz, 1H), 7.06–7.31 (m, 4H), 7.78 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.9, 19.0, 20.0, 31.5, 38.8, 39.0, 39.2, 39.5, 39.7, 39.9, 40.1, 54.7, 79.1, 118.0, 123.5, 126.9, 128.7, 128.7, 137.8, 142.8, 151.2, 157.4; HRMS (ESI) calcd m/z for $C_{15}H_{18}N_3O$ $[M]^+$ 256.1439, found 256.1450.

2.1j *6-(Tert-Butyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile* ***(11j)***: Yield 77%, M.p. 179.05 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.32 (s, 9H), 4.94 (d, J = 3.2 Hz, 1H), 7.29–7.41 (m, 5H), 7.94 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 28.2, 36.1, 56.0, 79.0, 119.2, 126.3, 128.1, 128.8, 142.7, 151.4, 158.5; HRMS (ESI) m/z calcd for $C_{15}H_{18}N_3O$ $[M]^+$ 256.1441, found 256.1450.

2.1k *4,6-Di-tert-butyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile* ***(11k)***: Yield 62%, M.p. 213.56 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 0.86 (s, 9H), 1.31 (s, 9H), 3.40 (d, J = 4.40 1H), 7.66 (Br s, 1H), 8.61 (Br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 25.0, 28.3, 36.1, 38.8, 39.0, 39.2, 39.5, 39.7, 39.9, 39.9, 40.1, 60.8, 75.2, 120.8, 152.6, 161.1; HRMS (ESI) m/z calcd for $C_{13}H_{22}N_3O$ $[M]^+$ 236.1769, found 236.1763.

2.1l *4-(Tert-Butyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile* ***(11l)***: Yield 67%, M.p. 259.18 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 0.85 (s, 9H), 1.13–1.17 (q, J = 7.20 6H), 2.90 (m, 1H), 3.46 (d, J = 4.0 1H), 7.53 (Br s, 1H), 9.21 (Br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 18.83, 19.46, 24.87, 31.48, 38.87, 39.08, 39.29, 39.50, 39.71, 39.92, 40.12, 59.31, 75.61, 119.66, 152.74, 160.34; HRMS (ESI) m/z calcd for $C_{12}H_{20}N_3O$ $[M]^+$ 222.1607, found 222.1606.

2.1m *6-Isopropyl-4-(naphthalen-1-yl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile* ***(11m)***: Yield 82%, M.p. 237.49 °C; ^{1}H NMR (400 Hz, DMSO-d_6), δ_H 1.21 (d, J = 6.8 Hz, 6H), 2.87 (m, 1H), 5.9 (s, 1H), 7.48–7.58 (m, 4H), 7.86 (s, 1H), 7.93–7.99 (m, 2H), 8.22 (m, 1H), 9.48 (s 1H); ^{13}C NMR (100 MHz, DMSO-d_6), δ_c 14.0, 18.8, 19.0, 20.7, 31.6, 52.4, 59.6, 79.1, 117.8, 123.3, 125.6, 125.9, 126.2, 128.8, 128.9, 130.1, 133.7, 137.8, 151.2, 157.5 170.3; HRMS (ESI) calcd m/z for $C_{18}H_{18}N_3O$ $[M]^+$ 292.1438, found 292.1450.

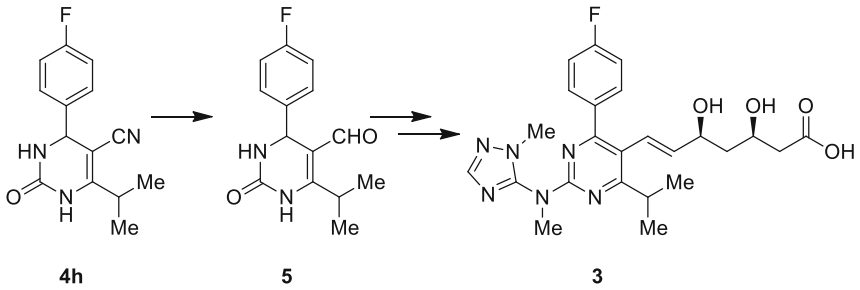
2.1n *Preparation of 4-methyl-3-oxopentanenitrile* ***(10i)***[17]: Acetonitrile (1.5 eq) was charged to a flask containing NaOMe (1.5 eq) and ethyl isobutyrate (1.0 eq) under nitrogen atmosphere at room temperature (30 °C). The mixture was heated to reflux for 5–7 h at 80−85 °C. After the completion of the reaction, toluene was added at 80 − 85 °C. The mixture was cooled to room temperature (30 °C). Water was then added to the mixture. Toluene layer was separated and kept aside. The aqueous layer was acidified to pH 6–7 with 1N HCl and extracted with toluene. The toluene layers were washed with $NaHCO_3$ solution and dried over anhydrous Na_2SO_4, and concentrated *in vacuo* on rotary evaporator to yield orange oil (compound 10i). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H = 1.19 (d, J = 5.6 Hz, 6H), 2.81 (m, 1H), 3.57 (s, 2H). These data indicate the existence of compound 10i in exclusively the keto form.

2.1o *Preparation of (E)-2-benzylidene-4-methyl-3-oxopentanenitrile* ***(14)***: A mixture of 4-methyl-3-oxopentanenitrile 10i (1.5 eq), benzaldehyde 6a (1.0 eq), CuCl (0.01eq), and MeOH containing concentrated H_2SO_4 (0.62 eq) was stirred at reflux temperature. After stirring at reflux temperature for 20 h, the precipitated solid was filtered at 2 °C to yield compound **14**. The geometric *E* isomer was confirmed by ^{1}H NMR studies including 1D-NOESY experiments. M.p. 53.04 °C; IR (KBr) 2206, 1693, 1650, 1587; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.13 (d, J = 6.8 Hz), 3.41–3.59 (m, 1H), 7.59–7.70 (m, 3H), 8.08 (d, J = 6.8 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR (DMSO-d_6), δ_c 18.4, 35.6, 109.7, 116.7, 129.3, 130.8, 131.8, 133.2, 153.4, 198.1; HRMS (ESI) calcd m/z for $C_{13}H_{14}NO$ $[M]^+$ 200.1069, found m/z 200.1075.

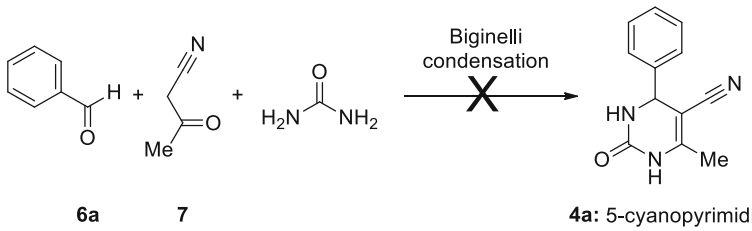
3. Results and Discussion

In this communication, we report a finding that has stayed relatively unexplored: β-ketonitrile as the reactive methylene coupling partner in Biginelli reaction.[10,11] 5-Carbonitrile pyrimidine (**4a**) renders the opportunity for further diversification by the manipulation of nitrile functional group. At the same time, nitrile group can also survive many synthetic transformations staying inherently 'protected' and often obviating the need for redundant oxidation–reduction manipulation steps.[12] 5-Carbonitrile pyrimidine (**4h**) can serve as as precursor to the synthesis of statin drugs (Scheme 1) using the literature methods.[3,10]

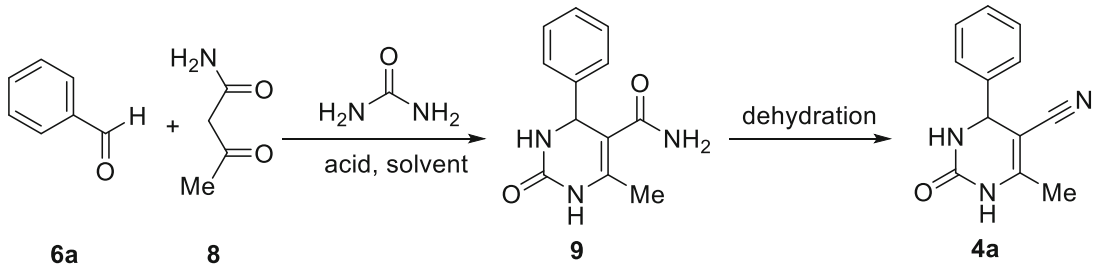
Hence, employing a β-ketonitrile as a coupling partner in the Biginelli reaction can be a useful proposition. However, as per the report by Kappe *et al.*, β-ketonitrile **7** was found to be unstable and did not yield the desired



Scheme 1. Statin drugs from 5-carbonitrile pyrimidines.



Scheme 2. Biginelli reaction with β-ketonitrile **7** using standard conditions.



Scheme 3. Synthesis of 5-Cyanodihydropyrimidine (**4a**) *via* a two-step approach.

Biginelli product **4a** when stirred with benzaldehyde **6a** and urea (Scheme 2).[13]

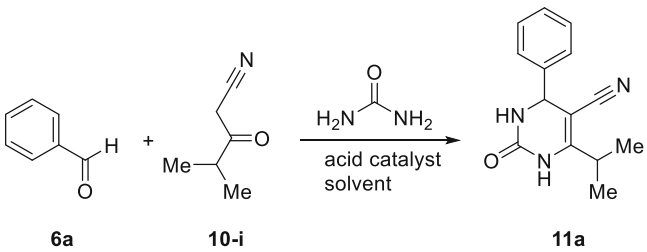
Instability thus precluded participation of β-ketonitrile **7** in a direct three-component Biginelli reaction, thus preventing the synthesis of compound 6-methyl-2-oxo-4-phenyl-1,2,3-4-tetrahydropyrimidine-5-carbonitrile (**4a**). Compound **4a** was therefore synthesized by an alternative two-step approach: i) preparation of Biginelli amide product **9** from β-ketoamide **8** and ii) amide dehydration (Scheme 3). Later, a one-pot version of the same transformation was also reported by Schmidt *et al.,* to prepare 5-cyanodihydropyrimidones using polyphosphate ester (PPE).[14]

Despite the reported instability and failure of a β-ketonitrile to form Biginelli product **4a**, we were nevertheless interested in understanding its behavior and fate under these conditions. A β-ketonitrile differs from a conventional β-ketoester in certain structural aspects. For example, the cyano group has linear geometry. Typically, β-ketoesters can be perceived as enolized, intramolecularly hydrogen bonded six-membered systems.[15] β-Ketonitriles cannot be seen the same way since intramolecular hydrogen bonding seems difficult owing to the linearity of the cyano group.[16] This communication describes an interesting variant of the Biginelli condensation supported by some mechanistic observations.

β-Ketonitrile **10i** was selected as model substrate for further exploration (Scheme 4). Preliminary experimentation on the Biginelli reaction began on the basis of reaction conditions reported in the literature.[17] Standard conditions initially attempted were: stirring unsubstituted benzaldehyde **6a** (1.0 eq), ketonitrile **10i** (1.0 eq) and urea (1.0 eq) with catalytic HCl in MeOH at room temperature for 3 days.[18]

No product **11a** was observed, while a product arising from a side-reaction was detected. It was later identified as 'dimer-like' as indicated by a mass of 292.37 which corresponds to structure **12** as shown below (Figure 2).

The formation of compound **12** can be rationalized by an aldol condensation of the aldehyde **6a** with ketonitrile **10i** in the presence of catalytic HCl to form an isomeric mix of enone and its further reaction with the ketonitrile (**10i**). Next we resorted to the use of catalytic



Scheme 4. Cyano substituted dihydropyrimidone (**11a**) synthesis by catalytic acid.

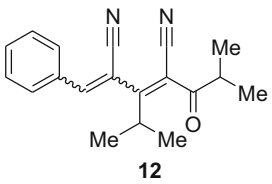


Figure 2. Dimer-like Impurity.

copper (I) chloride (CuCl) and catalytic concentrated sulfuric acid in methanol instead of catalytic HCl.[19] Interestingly, product **11a** was isolated exclusively and no formation of compound **12** was observed. Encouraged by this result, several conditions were screened to search for the best conversion, in line with literature reports of high yielding Biginelli reaction of ketoesters.

Number of conditions involving Lewis as well as protic acids were screened. For example, boric acid (cat.) in AcOH,[20] tungstate sulfuric acid,[21] $(EtO)_4Si$ with $FeCl_3$,[22] NBS, EtOH, microwave,[23] $Yb(OTf)_3$ in THF,[24] L-proline with TFA in CH_3CN,[25] PPE,[26] phenylphosphonic acid,[27] LiBr (cat.) in CH_3CN,[28] TMSCl in DMF,[29] and $BF_3.OEt_2$, CuCl[30] and AcOH.[4b] Unfortunately, all the above conditions suffered from predominant formation of undesired side-product (**12**).[31] Formation of expected product **11a** was not observed in appreciable amounts. Among the multitude of reaction conditions looked into, the use of stoichiometric $(EtO)_4Si$ with catalytic anhydrous $FeCl_3$ showed promise yielding significant amount of desired product **11a**. However, the isolated yield was not more than 25%, the rest being the side-product **12**, thus offering little improvement.

Thus, each of the above conditions show side-product **12** with the exception of catalytic CuCl with concentrated H_2SO_4 in MeOH at reflux temperature. We decided to extend the reaction time to understand the impact of time on the reaction conversion. Extending the reaction time resulted in an increase in conversion to the desired product without any side-product formation. The best conversion and isolated yield was observed under the following reaction conditions: mixture of ketonitrile **10i** (1.5 eq), benzaldehyde **6a** (1.0 eq), urea (1.5 eq), CuCl (0.01 eq) and MeOH containing concentrated H_2SO_4 (0.62 eq) stirred at reflux temperature for 3–5 days. Although the reaction time is rather long by practical considerations, clean product **11a** was obtained in consistently high yields on multi-gram scale. This reaction is very robust and there is no degradation of product even though reaction is rather long (Figure 3).

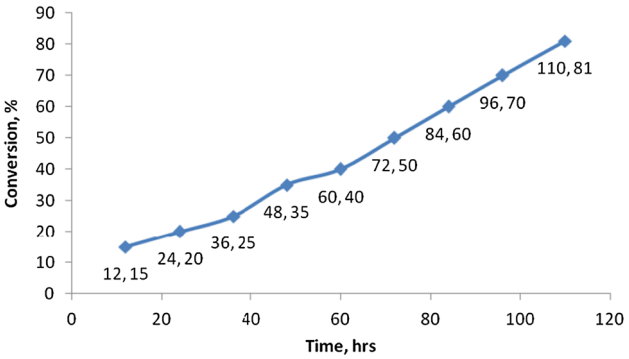


Figure 3. Formation of product (**11a**) under reflux temp with respect to time.

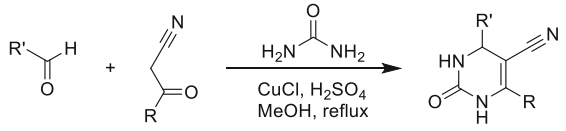
Substrate scope of this transformation with a variety of aldehydes (**6a–m**) and ketonitriles **10i** (R = ^{i}Pr) and **10ii** (R = *tert*-Bu) have been studied (Table 1). The reaction behavior was consistent irrespective of the electronic propensities of substituents on the aromatic ring. The work of Kappe and co-workers,[31] as referred to earlier, comprised a thorough mechanistic study on the Biginelli reaction of the β-ketoesters, where an iminium species **13** was shown to set off the reaction forming the corresponding dihydropyrimidone **11**. Assuming that such would also be the case with a β-ketonitrile, an attempt was made to generate the iminium species by sequential addition of urea and aldehyde, as reported earlier, stirring and then adding ketonitrile **10i**, no detectable amount of product **11a** was observed (Scheme 5). However, stirring aldehyde **6a** first with the ketonitrile **10i** for 20 h with CuCl (cat.) and H_2SO_4 (cat.) followed by the addition of urea led to the desired product **11a.**

This interesting observation indicated the possibility of an aldol mechanism suggested by Sweet and Fissekis[32] instead of iminium ion species. The product of the condensation of aldehyde and ketonitrile (compound **14**, Scheme 5) in the presence of CuCl (cat.) and H_2SO_4 (cat.) in MeOH was isolated and characterized.

Treatment of isolated intermediate **14** with urea in the presence of CuCl (cat.) and H_2SO_4 (cat.) in MeOH as a separate step led to the formation of Biginelli product **11a**.

It is possible that the formation of aldol product **14** in case of β-ketonitrile **10i** during the three-component

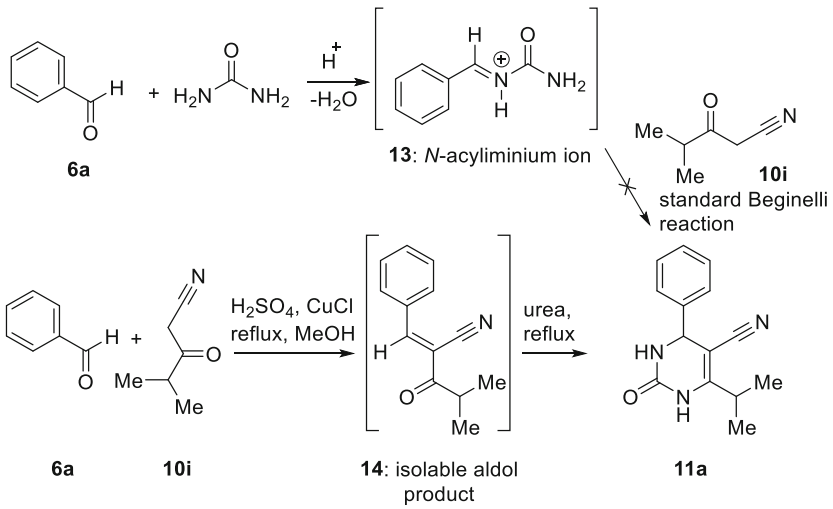
Table 1. Biginelli reaction of aldehydes (**6a–m**) with β-ketonitriles **10i-ii** to yield products**11a–m**.



6a-m (R' = aryl or ^{t}Bu) 10i (R = ^{i}Pr) 10ii (R = ^{t}Bu) 11a-m

Sl. No.	Aldehyde 6a–m (R′ = aryl or ^{t}Bu)	Ketonitrile	Product 11a–m	Time (h)	Yield (%)[a]
1	6a, R′ = Ph	10i, R = ^{i}Pr	11a	100	85
2	6b, R′ = 4-OMe-C_6H_4	10i, R = ^{i}Pr	11b	110	82
3	6c, R′ = 3-NO_2-C_6H_4	10i, R = ^{i}Pr	11c	115	65
4	6d, R′ = 3-F-C_6H_4	10i, R = ^{i}Pr	11d	105	82
5	6e, R′ = 4-Me-C_6H_4	10i, R = ^{i}Pr	11e	105	80
6	6f, R′ = 3-OH-C_6H_4	10i, R = ^{i}Pr	11f	111	84
7	6g, R′ = 4-Cl-C_6H_4	10i, R = ^{i}Pr	11g	105	85
8	6h, R′ = 4-F-C_6H_4	10i, R = ^{i}Pr	11h	110	81*
9	6i, R′ = 3-Me-C_6H_4	10i, R = ^{i}Pr	11i	105	79
10	6j, R′ = Ph	10ii, R = ^{t}Bu	11j	109	77
11	6k, R′ = ^{t}Bu	10ii, R = ^{t}Bu	11k	90	62
12	6l, R′ = ^{t}Bu	10i, R = ^{i}Pr	11l	72	67
13	6m, R′ = 1-napth	10i, R = ^{i}Pr	11m	110	82

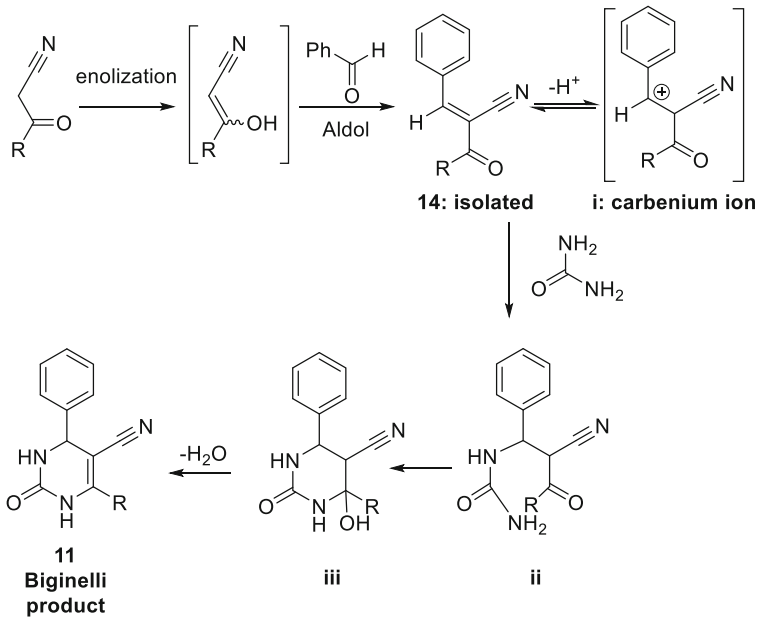
[a]Isolated yield mentioned after chromatography. *Compound 11h was synthesized on multi Kg scale.



Scheme 5. Biginelli reaction with β-ketonitrile *via* aldol pathway.

reaction may be specific to ketonitriles due to their instability and high reactivity with the aldehyde. Compound **14** is formed as a single geometric isomer. The first event occurring rapidly is the formation of aldol product **14**,[33] after which the cyclization proceeds to yield Biginelli product **11a**. This observation seems to suggest that while typical stable β-ketoesters may react with the intermediate iminium species **13**, a β-ketonitrile such as **10i** being relatively unstable proceeds through the intermediacy of aldol product **14** and then forming corresponding Biginelli product **11a**. Based on these observations, a mechanism although speculative, along the lines of that proposed by Sweet and Fissekis proceeding through the enolic form of the ketonitrile has been shown in Scheme 6.

It is important to point out that among the reaction conditions screened, only a combination of catalytic CuCl in presence of H_2SO_4 led to the formation of Biginelli product without the formation of dimer-like compound **12**. Both events, namely the aldol and the cyclization seem to individually require this combination (Figure 4).



Scheme 6. Proposed mechanism for β-ketonitrile induced Biginelli reaction.

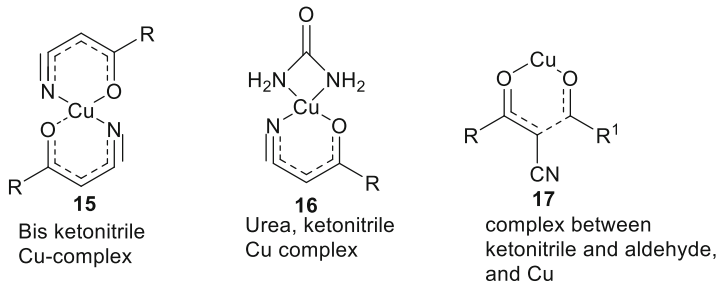


Figure 4. Proposed Copper complexes for β-ketonitrile induced Biginelli reaction.

The formation of bis ketonitrile copper complex **15**, or copper, ketonitrile, urea complex **16** or copper complex **17** formed by interaction of aldehyde ketonitrile and copper are the probable copper catalytic pathway the reaction can proceed to. Considering the planar nature of cyanide functionality in ketonitrile, bis ketonitrile copper complex formation, as well as ketonitrile urea complex formation can be ruled out. Thus the formation of aldol adduct **14** can be attributed to the formation copper complex **17**,[34] which further reacts with urea leads to Beginelli product **11**. It is possible that this catalyst combination prevents the aldol adduct **14** to form dimer-like product **12** and/or favorably impacts the nucleophilicity of urea. The reaction does not proceed in the absence of either CuCl or H_2SO_4 nor does it take place in the presence of Cu (II) Cl, $Cu(OTf)_2$, $Cu(OAc)_2$, $ZnCl_2$, $ZnBr_2$ and ZnI_2. The minimal formation of Beginelli products in absence of copper indirectly proves that formation of co-ordinate complex between aldehyde, ketonitrile and copper is essential to accelerate the aldol adduct, and minimization of other unwanted side reactions.[35] During the entire course of the reaction, the reaction colour does not change to blue, which in a way indirectly proves the reaction proceeding *via* Cu(I), and not through copper (II). Copper(I) activates the ketonitrile, and preventing its self-dimmerization, in turn facilitates the intermolecular aldol condensation to the required product 5-cyanodihydropyrimidin.

4. Conclusions

We have developed and utilized a simple and efficient multicomponent Biginelli reaction employing β-ketonitrile as one of the coupling partners with aromatic or non-enolizable aliphatic aldehydes and urea in the presence of CuCl. The reaction has been observed to yield the desired cyano substituted dihydropyrimidones. The procedure has been consistently demonstrated to furnish the products with good yields.

Supplementary Information (SI)

Full experimental details, spectral data, ^{1}H and ^{13}C NMR spectra are available at www.ias.ac.in/chemsci.

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