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A novel synthesis of pyrimidins from an efficient one-pot multicomponent reaction of isocyanides and dialkyl-acetylene dicarboxlate in the presence of urea derivatives

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Abstract: An efficient method for the synthesis of highly substituted oxopyrimidine derivatives has been developed via one-pot reaction of isocyanides and dialkylacetylenedicarboxylate in the presence of urea derivatives. The reaction stoichiometric amounts of DMAD, isocyanide and urea derivatives afforded highly substituted oxopyrimidine derivatives in moderate to good yield.

Keywords: Pyrimidin; Urea; Acetylenicester; Cyclohexylisocyanide.

Introduction

One-pot reactions in which three or more starting materials react sequentially and lead to product(s) that retain all or most of the atoms of the starting materials are called multicomponent reactions (MCRs). These reactions are characterized by their convergence, ease of execution, high yields, efficiency, and atom economy [1]. The advent of Passerini [2] and Ugi [3] reactions established the special propensity of isocyanides to take part in MCRs.

Many dihydropyrimidinones (DHPMs) are pharmacologically important as calcium channel blockers [4], antihypertensive agents [5], α-adrenergic antagonists [6] and neuropeptide Y (NPY) antagonisrs [7]. Several recently isolated marine alkaloids with interesting biological activities also contain the dihydropyrimidinone-5-carboxylate core [8]. Most notably among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors [9].

The original Biginelli condensation [10] involving the reaction of aldehydes, urea and *β*-ketoesters under strong acidic conditions to give 3,4-dihydropyrimidin-2-ones often suffers from low yields for aliphatic and substituted aromatic aldehydes. Several modifications and improvements have resulted in milder and more efficient procedures and catalysts [11].

An efficient synthesis of 3,4-dihydropyrimidin-2(1*H*)-one derivatives has been described by Tu and co-workers [12,13] using potassium hydrogen sulfate as the promoter in glycol solution for the Biginelli reaction. It can be applied not only to open-chained 1,3-dicarbonyl compounds, but also to cyclic 1,3-dicarbonyl compounds. Salehi and Guo [14] have reported a magnesium bromide-catalyzed facile and efficient one-pot synthesis of dihydropyrimidines under solvent-free conditions. An efficient niobium (V) chloride-catalyzed synthesis of 3, 4-dihydropyrimidines has been described by Yadav and co-workers [15] *via* the condensation reaction of an aldehyde, a *β*-keto ester and urea or thiorea under ambient conditions. The study of this reaction using other Lewis acids such as indium (III) chloride, cerium (III) chloride, gadolinium (III) chloride, tantalium (V) chloride and yttrium (III) chloride revealed that niobium (V) chloride was found to be superior in terms of conversion and reaction time [16]. Li *et al.* [17, 18] have reported a zinc-chloride, catalyzed, solvent-free protocol for preparation of 3, 4-dihydropyrimidin-2-(1*H*)-ones by the condensation of an aldehyde, α-1,3-dicarbonyl compound and urea or thiourea at 80ºC with shorter reaction times.

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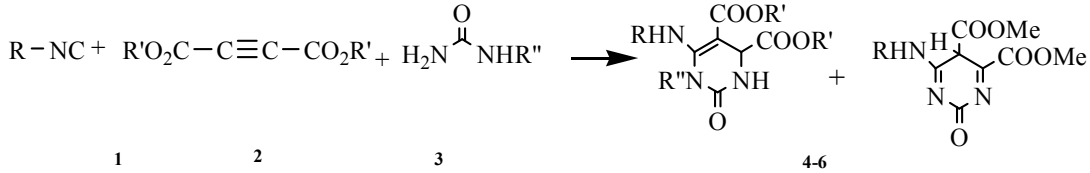
In view of our general interest in multicomponent reactions (MCRs), we wish to report the synthesis of several highly substituted dihydro or tetrahydro-oxopyrimidine derivatives, such as dimethyl-6-(cyclohexylamino)-2,5-dihydro-2-oxopyrimidine-4,5-dicarboxylate **4**, dimethyl-6-(*tert*-butylamino)-2,5-dihydro-2-oxopyrimidine-4,5-dicarboxylate **5** and dimethyl-6-(*tert*-butylamino)-1,2,3,4-tetrahydro-1-methyl-2-oxopyrimidine-4,5-dicarboxylate **6** from the reaction of isocyanides and dialkylacetylene dicarboxylate in the presence of urea derivatives (Scheme **1)**.



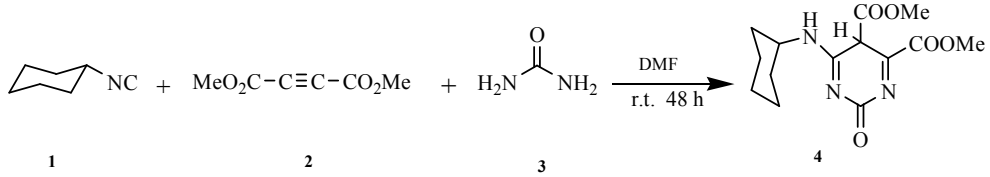
1 **2** **3** **4-6**

	R	R'	R"
4	Cyclohexyl	Me	H
5	*tert*-but	Me	H
6	*tert*-but	Me	Me

Scheme 1:

Results and discussion

Our investigations were initiated with cyclohexylisocyanide, which on treatment with dimethylacetylene dicarboxylate (DMAD) in presence of stoichiometric amount of urea in room temperature and in presence of DMF afforded a product characterized as dimethyl-6-(cyclohexylamino)-2, 5-dihydro-2-oxopyrimidine-4, 5-dicarboxylate **4** (Scheme **2**).



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

Scheme 2:

The IR spectrum of compound **4**, showed strong absorption at 3283 cm^{-1} indicating the presence of amine functionality. The sharp bands at 1734 and 1671 cm^{-1} were assigned to the two ester carbonyls. In the ^1H NMR spectrum, the signals due to methoxy groups were observed at δ 3.78 and 3.84 as two singlets and the amine hydrogen atom resonated as a doublet at 6.73 (exchangeable by D_2O). The signal due to CH was observed at δ 5.30 as a singlet. In the ^{13}C NMR spectrum, the two ester carbonyls were observed at δ 167.7 and 167.9. The amide carbonyl was observed at δ 167.7.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate between cyclohexyl isocyanide and DMAD, which react with urea. Cyclization leads to the dimethyl-6-(cyclohexylamino)-1, 2-dihydro-2-oxopyrimidine-4, 5-dicarboxylate. Subsequently, it undergoes a [1,3] hydrogen shift to yield the dimethyl-6-(cyclohexylamino)-2, 5-dihydro-2-oxopyrimidine-4, 5-dicarboxylate **4** (Scheme **3**).

Similar reaction was observed with urea, which underwent facile reaction with DMAD and *tert-but*-isocyanide yielding the corresponding dimethyl-6-(*tert*-butylamino)-2,5-dihydro-2-oxopyrimidine-4,5-dicarboxylate **5** in good yield (Scheme **4**).

Also, the intermediate react with methylurea and yielding the corresponding dimethyl-6-(*tert*-butylamino)-1,2,3,4-tetrahydro-1-methyl-2-oxo-pyrimidine-4,5-dicarboxylate **6** in good yield (Scheme **5**).

Conclusion

In conclusion, we have devised some novel and efficient three component condensation reactions for the synthesis of fully substituted dihydro or tetrahydro-oxopyrimidine derivatives. It may be mentioned that, recently 3, 4-dihydropyrimidine derivatives have been

found to undergo the reaction of urea, and aldehydes or ketones under strong acidic condition in low yield [10]. Its advantages are, the reactions are carried out with high efficient, without catalyst, high yield and at room temperature.

Experimental

All compounds in these reactions were obtained from Merck co. and were used without further purification. Mp: Thomas-Hoover capillary. FT-IR spectra: Bruker VERTEX-70. ^{1}H and ^{13}CNMR spectra: Bruker DRX-500Avance instrument; in $CDCl_3$ or DMSO at 500.1 and 125.7 MHz, respectively; δ in part per million, J in hertz.

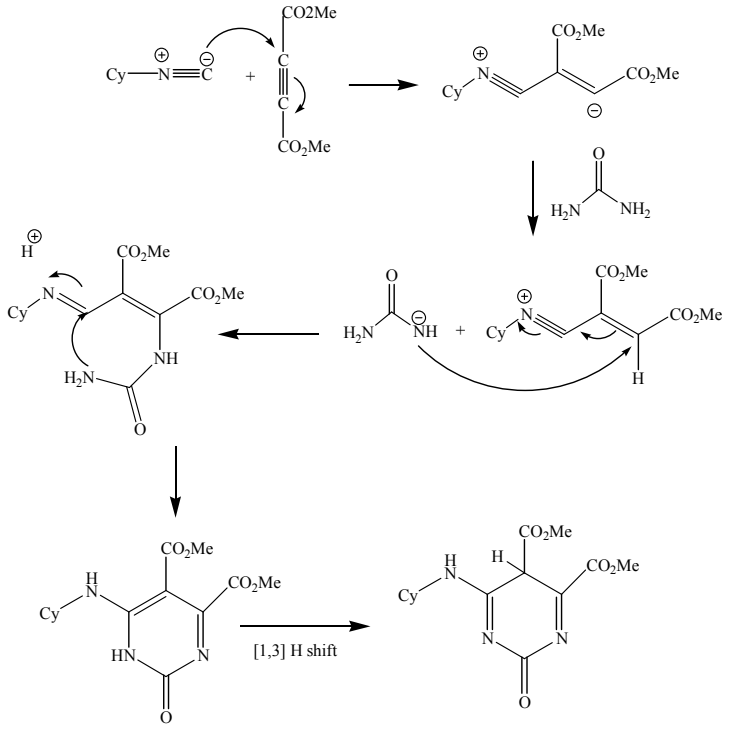
Typical experimental procedure

To a stirred solution of *tert-but-* isocyanide **1** (2 mmol), dimethylacetylene dicarboxylate **2** (2 mmol), in CH_3COCH_3 (10 ml) was added Urea (2 mmol) at room temperature. The resulting mixture was stirred for 24 h. The solvent was removed under vacuum and product was crystallized from $CHCl_3$ and n-hexane. Mp=129-132 ºC.

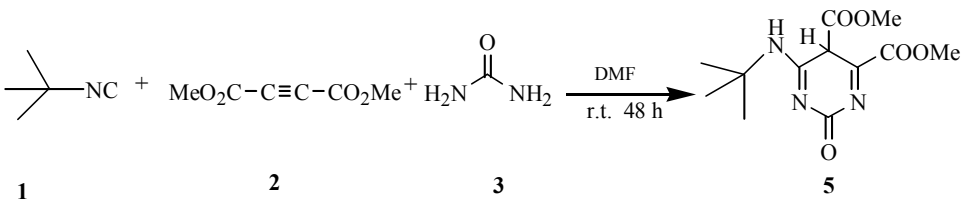
*Dimethyl-6-(cyclohexylamino)-2,5-dihydro-2-oxo-pyrimidine-4,5-dicarboxylate **4**:*

White crystals; yield: 60%; mp 129-132ºC recrystallized from ethylacetate-hexane), IR (KBr) ν_{max}: 3283 (NH), 2927 (CH aliphatic), 1734 (C=O ester), 1671 (HNC=O), 1585 and 1550 (2 C=N) cm^{-1}.

^{1}H NMR (500.1 MHz, $CDCl_3$): δ= 1.25-2.09 (10 H, *m*, 5 CH_2), 3.39 (1 H, *m*, NHC*H*), 3.78 (3 H, *s*, OCH_3), 3.84 (3 H, *s*, OCH_3), 5.30 (1 H, *s*, CH), 6.73 (1 H, *d*, *J*=10.1, N*H*CH), (D_2O exchangeable) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=167.9 (C=O), 167.7 (C=O), 160.2 (N-C=O), 134.4 (C=N), 128.0 (C=N), 74.2 (CH), 58.5 (NH*C*H), 52.2 (OCH_3), 50.9 (OCH_3), 33.9, 30.7, 29.6, 26.9 and 25.4 (5 CH_2) ppm.

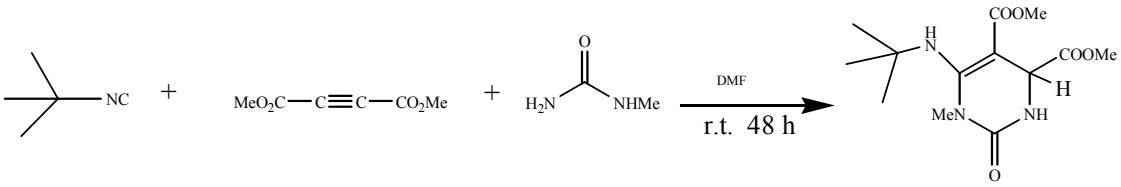


Scheme 3:



1 **2** **3** **5**

Scheme 4:



1 **2** **3** **6**

Scheme 5:

*Dimethyl-6-(tert-butylamino)-2,5-dihydro-2-oxopyrimidine-4,5-dicarboxylate **5**:*

Yellow crystals, yield: 66%; mp 100-103ºC, (recrystallized from diethylether-EtOH), IR (KBr) ν_{max}: 3283 (NH), 2980 and 2882 (CH aliphatic), 1756 (C=O ester), 1692 (HNC=O), 1624 and 1537 (C=C) cm^{-1}.
^{1}H NMR (500.1 MHz, $CDCl_3$): δ= 1.45 (9 H, *s*, 3 CH_3), 2.19 (3 H, *s*, CH_3), 3.71 (3 H, *s*, OCH_3), 3.76 (3 H, *s*, OCH_3), 4.62 (1 H, *s*, NH) (D_2O exchangeable), 5.16 (1 H, *d*, *J*=8.4 Hz, C*H*NH), 5.65 (1 H, d, J=8.4 Hz, *HN*C=O) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=171.6 (C=O), 170.0 (C=O), 167.4 (HN-C=O), 157.6 (C=C), 143.9 (C=C), 64.1 (CH), 62.5 [*C* (CH_3)], 52.7 (OCH_3), 51.6 (OCH_3), 51.0 (N-*C*H_3), 30.2 (3 CH_3) ppm.

*Dimethyl-6-(tert-butylamino)-1,2,3,4-tetrahydro-1-methyl-2-oxopyrimidine-4,5-dicarboxylate **6**:*

White Powder; yield: 69%; mp 170-173 ºC; IR (KBr) ν_{max}: 3354 (NH), , 2927 (CH aliphatic), 1734 (C=O ester), 1671 (HNC=O), 1585 and 1550 (C=C), 1438 (C=N) cm^{-1}.
^{1}H NMR (500.1 MHz, $CDCl_3$): δ= 2.18 (9 H, *s*, 3 CH_3), 3.65 (3 H, *s*, OCH_3), 3.93 (3 H, *s*, OCH_3), 4.75 (1 H, *s*, CH), 6.73 (1 H, *s br*, N*H*), (D_2O exchangeable) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=168.3 (C=O), 167.4 (C=O), 161.9 (HN-C=O), 155.4 (C=N), 143.1 (C=N), 82.6 (CH), 56.9 [*C* (CH_3)], 53.6 (OCH_3), 53.3 (OCH_3), 26.3 (3 CH_3) ppm.

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