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SYNTHESIS AND CHARACTERIZATION OF FUNCTIONALIZED DIHYDROPYRIMIDINONES VIA ONE-POT ISOCYANIDE-BASED THREE-COMPONENT REACTION OF N-FORMYL UREA AND DIALKYL ACETYLENEDICARBOXYLATES

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ABSTRACT. The reactive intermediate generated by the addition of alkyl isocyanides to dialkyl acetylenedicarboxylates was trapped by N-formyl urea to produce highly functionalized dihydropyrimidinones in fairly good yields.

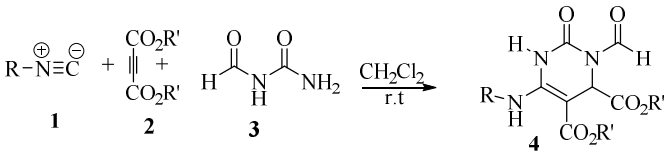
KEY WORDS: Alkyl isocyanides, Dialkyl acetylenedicarboxylate, N-Formyl urea, Three-component reaction, Dihydropyrimidinones

INTRODUCTION

The dihydropyrimidinones (DHPMs) have exhibited interesting and multifaceted pharmacological properties such as antitumor, anti-inflammatory, antiviral, antifungal and antibacterial activity [1-3]. In addition, these compounds have emerged as potential calcium channel blockers, antihypertensive, α_{1a}-adrenergic antagonists and neuropeptide antagonists [4].

As a consequence, the synthesis of dihydropyrimidinone derivatives has attracted significant attention by Pietro Biginelli [5]. In recent years, new methods for the synthesis of dihydropyrimidinones have been developed by different groups [6-15]. It is still highly valuable to develop newly direct approaches for the efficient synthesis of DHPMs due to the continued importance of these compounds core in organic and medicinal chemistry.

On the other hand, multicomponent reactions (MCRs) have attracted much attention and are particularly useful for the synthesis of chemical and biological important compounds [16-20]. Moreover isocyanide-based multicomponent reactions (IMCRs) by virtue of their synthetic potential, convergent nature and molecular diversity have attracted much attention because of the advantages that they offer in the field of combinatorial chemistry [21-23].



1

	R
a	*t*-Bu
b	*Cy*-Hexyl
c	*1,1,3,3-tetra methyl*-butyl

2

	R'
a	Me
b	Et
c	t-Bu

3

4

	R	R'	Yield of **4** (%)
a	*t*-Bu	Me	72
b	*Cy*-Hexyl	Me	69
c	*t*-Bu	Et	76
d	*Cy*-Hexyl	Et	86
e	*Cy*-Hexyl	*t*-Bu	79
f	*1,1,3,3-tetra methyl*-butyl	Me	75
g	*1,1,3,3-tetra methyl*-butyl	Et	70

Scheme 1. The preparation of substituted dihydropyrimidinones.

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Preparation of DHPMs, via multicomponent reactions (MCRs), with high facileness, efficiency and economy in organic chemistry prompted us to synthesize formyl-2-oxo-1,2,3,4-tetrahydropyrimidone derivatives. Here in we report an efficient synthetic route to dihydropyrimidinone derivatives (**4**) using alkyl isocyanides (**1**) and dialkyl acetylene-dicarboxylate (**2**) in the presence of N-formyl urea (**3**) (Scheme 1). Compounds **4a-g** are all reported for the first time.

EXPERIMENTAL

General

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Carlo Erba EA 1108 instrument. EI mass spectra (70 eV) were measured on a Finnigan-MAT- 8430 mass spectrometer. The IR spectra were measured on a Shimadzu IR-460 spectrometer. The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 Avance instrument with $CDCl_3$ as the solvent at 300 and 75 MHz, respectively. Alkyl isocyanides, dialkyl acetylenedicaboxylates and N-formyl urea were obtained from Fluka and were used without further purification.

*General procedure for the preparation of pyrimidines **4***

To a stirred solution of **3** (2 mmol) and tert-butyl isocyanide (2 mmol) in 10 mL of CH_2Cl_2, dimethyl acetylenedicarboxylate (DMAD) (2 mmol) was added dropwise and the reaction mixture was then allowed to warm to room temperature and stand for 24 h. The solvent was removed under partial vacuum reduced pressure and oily residue was purified by preparative TLC on silica gel (Merck silica gel DCFertigplatten 60/Kieselgur F_{254}) 20×20 cm glass plates using n-hexane-EtOAc (1:1) as eluent.

*Dimethyl 6-(tert-butylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate **(4a)***. Yellow powder, (0.45 g, 72% yield) mp 157-159 ^{o}C; IR (KBr) ν_{max} 3423, 2956, 2854, 1735, 1699, 1461, 1262, 1188, 1025, 965, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.34 (1H, s, C*H*O), 8.77 (1H, brs, N*H*), 6.88 (1H, brs, N*H*), 5.91 (1H, s, C*H*), 3.77 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 1.30 (9H, s, 3CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0 (*C*HO), 167.7 (*C*=O esrer), 160.6 (*C*=O ester), 151.0 (N_2C=O), 147.0 (*C*N_2), 71.4 (C), 68.1 (*C*-N), 53.7 (O*C*H_3), 52.0 (O*C*H_3), 49.5 (*C*H), 29.6 (3*C*H_3); EI-MS *m/z* (rel. int.): 313 [M^{+}] (13), 212 (54), 195 (72), 83 (78), 57 (100). Anal. C 49.87%, H 6.10%, N 13.40%, calcd. for $C_{13}H_{19}N_3O_6$, C 49.84%, H 6.11%, N 13.41%.

*Dimethyl 6-(cyclohexylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate **(4b)***. Yellow powder, (0.46 g, 69 % yield), mp 165-167 ^{o}C; IR (KBr) ν_{max} 3421, 2932, 2855, 1739, 1693, 1436, 1262, 1165, 1026, 953, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.44 (s, 1H, C*H*O), 8.81 (1H, brs, N*H*), 8.10 (1H, brs, N*H*), 5.84 (1H, s, C*H*), 3.78 (3H, s, OCH_3), 3.78 (1H, s, C*H*), 3.74 (3H, s, OCH_3), 1.21-1.62 (10H, m, 5CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7 (*C*HO), 167.1 (*C*=O ester), 160.5 (*C*=O ester), 151.8 (N_2C=O), 149.4 (*C*N_2), 70.6 (C), 53.7 (O*C*H_3), 52.3 (O*C*H_3), 50.0 (*C*HN), 49.8 (*C*H), 33.6 (*C*H_2), 25.0 (*C*H_2), 24.3 (*C*H_2), 24.2 (*C*H_2); EI-MS *m/z* (rel. int.): 339 [M^{+}] (21), 221 (100), 212 (84), 57 (74), 41 (27). Anal. C, 52.89%, H 6.18%, N 12.47%, calcd. for $C_{15}H_{21}N_3O_6$, C 53.09%, H 6.24%, N 12.38%.

*Diethyl 6-(tert-butylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate **(4c)***. Yellow powder, (052 g, 76% yield), mp 153-155 ^{o}C; IR (KBr) ν_{max} 3411, 2938, 2855, 1737, 1686, 1440, 1199, 1141, 1023, 953, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.33 (1H, s, C*H*O), 8.78 (1H, brs, N*H*), 6.95 (1H, brs, N*H*), 5.86 (1H, s, C*H*), 4.08-4.38 (4H, m, 2OCH_2),

1.45 (9H, s. 3CH_3), 1.30 (3H, t, J = 7.1 Hz, CH_3), 1.23 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6 (*C*HO), 167.5 (*C*=O ester), 160.7 (*C*=O ester), 150.9 (N_2C=O), 150.4 (*C*N_2), 72.6 (C), 61.8 (O*C*H_2), 59.6 (O*C*H_2), 52.2 (*C*-N), 49.7 (*C*H), 30.9 (3*C*H_3); 14.55 (*C*H_3), 13.95 (*C*H_3); EI-MS *m/z* (rel. int.): 341 [M^+] (10), 241 (70), 223 (82), 83 (68), 57 (100). Anal. C, 52.82%, H 6.70%, N 12.26%, calcd. for $C_{15}H_{23}N_3O_6$. C 52.78%, H 6.79%, N 12.31%.

Diethyl 6-(cyclohexylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate ***(4d)***. Yellow powder (0.63 g, 86 % yield), mp 150-152 °C; IR (KBr) ν_{max} 33430, 2944, 2856, 1738, 1698, 1449, 1370, 1199, 1025, 954, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.35 (1H, s, C*H*O), 8.75 (1H, brs, N*H*), 8.00 (1H, brs, N*H*), 5.87 (1H, s, C*H*), 4.03-4.32 (4H, m, 2OCH_2), 3.42-3.49 (1H, m, C*H*), 1.32 (3H, t, J = 7.1 Hz, CH_3), 1.25 (3H, t, J = 7.1 Hz, CH_3), 1.15-1.46, (10H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9 (*C*HO), 167.5 (*C*=O ester), 160.7 (*C*=O ester), 151.8 (N_2C=O), 149.8 (*C*N_2), 70.7 (C), 61.8 (O*C*H_2), 59.4 (O*C*H_2), 50.2 (*C*HN), 49.8 (*C*H), 33.6 (*C*H_2), 29.7 (*C*H_2), 25.0 (*C*H_2), 24.3 (*C*H_2), 24.2 (*C*H_2), 14.5 (*C*H_3), 13.9 (*C*H_3); EI-MS *m/z* (rel. int.): 367 [M^+] (5), 241 (67), 223 (82), 57 (100), 41 (68). Anal. C 55.67%, H 6.79%, N 11.40%, calcd. for $C_{17}H_{25}N_3O_6$, C 55.58%, H 6.86%, N 11.44%.

Di-tert-butyl 6-(cyclohexylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate ***(4e)***. Yellow powder (0.67 g, 79% yield), mp 167-169 °C; IR (KBr) ν_{max} 3419, 2934, 2856, 1733, 1698, 1437, 1255, 1150, 1022, 953, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.32 (s, 1H, C*H*O), 8.64 (1H, brs, N*H*), 7.64 (1H, brs, N*H*), 5.65 (1H, s, C*H*), 3.30-3.36 (1H, m, C*H*), 1.51 (9H, s, 3CH_3), 1.43 (9H, s, 3CH_3), 1.23-1.32 (10H, m, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2 (*C*HO), 167.3 (*C*=O ester), 160.8 (*C*=O ester), 151.9 (N_2C=O), 149.4 (*C*N_2), 82.3 (*C*-O), 79.8 (*C*-O), 72.4 (C), 50.8 (*C*HN), 50.4 (*C*H), 27.9 (3*C*H_3), 27.7 (3*C*H_3); EI-MS *m/z* (rel. int.): 423 [M^+] (9), 325 (67) 296 (76), 57 (88), 41 (45). Anal. C 59.46%, H 7.78%, N 9.83%, $C_{21}H_{33}N_3O_6$, calcd. for C 59.56%, H 7.85%, N 9.92%.

Dimethyl 6-(2,4,4-trimethylpentan-2-ylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate ***(4f)***. Yellow powder, (0.55 g, 75% yield), mp 166-168 °C; IR (KBr) ν_{max} 3423, 2954, 2854, 1742, 1703, 1436, 1217, 1149, 1023, 953, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.32 (1H, s, C*H*O), 8.84 (1H, brs, N*H*), 8.70 (1H, brs, N*H*), 5.74 (1H, s, C*H*), 3.74 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 1.75-1.60 (2H, m, CH_2), 1.52 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.00 (9H, s, 3CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0 (*C*HO), 167.9 (*C*=O ester), 160.6 (*C*=O ester), 151.1 (N_2C=O), 150.3 (*C*N_2), 71.8 (C), 55.9 (*C*N), 53.4 (O*C*H_3), 53.2 (O*C*H_3), 51.0 (*C*H_2), 49.4 (*C*H), 34.6 (*C*H_3), 31.8 (C), 31.4 (3*C*H_3), 31.3 (*C*H_3); EI-MS *m/z* (rel. int.): 369 [M^+] (17), 251 (83), 211 (43), 128 (69), 57 (96). Anal. C 55.20%, H 7.40%, N 11.29%, calcd. for $C_{17}H_{27}N_3O_6$, C 55.27%, H 7.37%, N 11.37%.

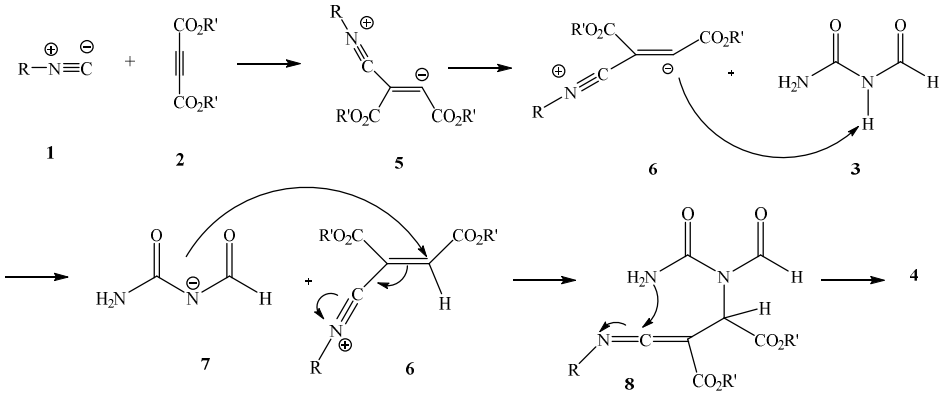
Diethyl 6-(2,4,4-trimethylpentan-2-ylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate ***(4g)***. Yellow powder, (0.55 g, 70% yield), mp 172-174 °C; IR (KBr) ν_{max} 3421, 2957, 2857, 1746, 1698, 1473, 1254, 1162, 1026, 690, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (1H, s, C*H*O), 9.34 (1H, brs, N*H*), 9.31 (1H, brs, N*H*), 5.70 (1H, s, C*H*), 4.14-4.38 (4H, m, 2OCH_2), 1.78-1.72 (2H, m, CH_2), 1.54 (3H, s, CH_3), 1.51 (3H, s, CH_3), 1.01 (9H, s, 3CH_3), 0.91 (3H, t, J = 7.1 Hz, CH_3), 0.86 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2 (*C*HO), 167.6 (*C*=O ester), 160.5 (*C*=O ester), 150.8 (N_2C=O), 150.3 (*C*N_2), 71.7 (*C*H), 61.2 (O*C*H_2), 56.2 (*C*N), 59.5 (O*C*H_2), 53.3 (*C*H_2), 49.9 (*C*H), 31.7 (*C*H_3), 31.6 (C), 31.3 (3*C*H_3), 31.0 (*C*H_3), 14.7 (*C*H_3), 14.4 (*C*H_3); EI-MS *m/z* (rel. int.): 397 [M^+] (7), 269 (39), 251 (52), 83 (96), 57 (94). Anal. C 57.33%, H 7.78%, N 10.64%, calcd. for $C_{19}H_{31}N_3O_6$, C 57.41%, H 7.86%, N 10.57%.

RESULTS AND DISCUSSION

Herein, a number of new 3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine derivatives **4** were prepared at room temperature reaching completion in 24 hours. The structural assignments of the desired dialkyl 6-(alkylamino)-3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4,5-dicarboxylate derivatives **4a-g** were made on the basis of their ^{1}H and ^{13}C NMR spectra which are supported by their IR and mass spectrometry as well as elemental analysis.

The ^{1}H NMR spectrum of **4a** exhibited five sharp singlets for tert-butyl (δ = 1.30 ppm), methoxy (δ = 3.68 and 3.77ppm), methine (δ = 5.91 ppm) and aldehyde proton (9.34 ppm) respectively. The NHs proton resonance at (δ = 6.88, 8.77 ppm) disappeared after addition of D_2O to the $CDCl_3$ solution of **4a**. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed eleven distinct resonances in agreement with the proposed structure. The presence of amido and amino groups at one end of the double bond leads to polarization of the olefinic system. The α-carbon atom of this polarized system appears at δ = 147.0, while and the β-carbon at δ = 71.4 ppm. Partial assignments of these resonances are given in the experimental section. The ^{1}H NMR spectra of compounds **4b–4g** are similar to that of compound **4a**, except for the signals of the alkyl and ester moiety. TLC results of reaction mixture and also ^{1}H and ^{13}C NMR spectra of compound **4a-g** showed that only one steroisomer is produced.

A possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides [24, 25], nucleophilic addition of alkyl isocyanide **1** to dialkyl acetylenedicarboxylate **2** leads to zwitterion **5** which is protonated by NH acid to give **6**. This intermediate is attacked by anion **7** to produce ketenimine **8**. 1, 3-Proton transfer and subsequent cyclization forms products **4** (Scheme 2). The reaction of alkyl isocyanides (**1**) and N-formyl urea (**3**) did not lead to a remarkable product via TLC monitoring.



Scheme 2. Proposed mechanism.

CONCLUSION

In conclusion, a new method for the preparation of highly functionalized dihydropyrimidinone has been demonstrated. The present method carries the advantage of performing under neutral conditions and also the starting materials can be mixed without any activation or modification.

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