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Diketene as an alternative substrate for a new Biginelli-like multicomponent reaction: one-pot synthesis of 5-carboxamide substituted 3,4-dihydropyrimidine-2(1*H*)ones

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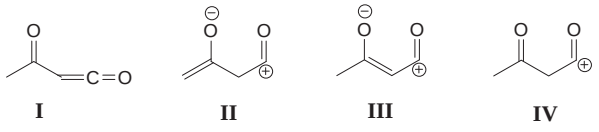
ABSTRACT

5-Carboxamide substituted 3,4-dihydropyrimidine-2(1*H*)one derivatives were synthesized in a simple and efficient method from the one-pot four-component reactions of an aliphatic or aromatic amine, diketene, an aromatic aldehyde and urea or thiourea in the presence of *p*-toluenesulfonic acid as a catalyst under mild reaction conditions at ambient temperature.

1. Introduction

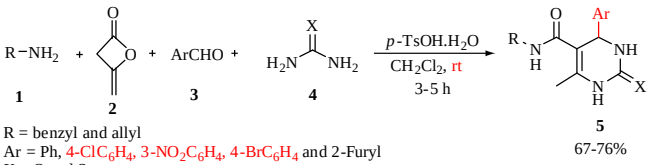
The classic version of the Biginelli[1] three-component condensation reaction, which combines an aldehyde, urea or thiourea and an open-chain β-dicarbonyl compound under acidic conditions in ethanol affords a 3,4-dihydropyrimidin-2(1*H*)one, has seen widespread use for generating large collections of molecules in combinatorial synthesis.[2] Very recently, for novel Biginelli-like scaffold synthesis, the use of the common open-chain β-dicarbonyl compounds in Biginelli reactions has been extended to the use of cyclic β-diketones,[3] β-ketolactones,[4] cyclic β-diesters[5] or β-diamides,[5,6] benzocyclic ketones[7] and α-keto acids.[7] Although the Biginelli reaction was described over 100 years ago, this process lacks literature precedent for the synthesis of 3,4-dihydropyrimidine-2(1*H*)ones using diketene as the same of the β-dicarbonyl synthon instead of the usual β-dicarbonyl compounds under the four-component reactions strategy.

Diketene is a strained molecule (E_{strain}=22.5 kcal/mol),[8] which is readily ring-opened and therefore frequently appears to react as acetylketene **I** or one of its dipolar tautomers (**II** and **III**). It is important to note that each of dipolar tautomers is equal to a β-dicarbonyl synthon. On the other hand diketene is a reagent for synthon **IV** (Scheme 1).



Scheme 1.

Due to the biological activity of 3,4-dihydropyrimidine derivatives[9–16] and in continuation of our interest in diketene-based MCRs[17–20] and Biginelli reactions,[5,21] we describe herein the synthesis of a new class of 3,4-dihydropyrimidine-2(1*H*)one derivatives **5a–f** in a one-pot process by a four-component condensation reaction of an aliphatic or aromatic amine **1**, diketene **2**, an aromatic aldehyde **3** and urea/thiourea **4** in the presence of *p*-toluenesulfonic acid (*p*-TsOH·H_2O) as a catalyst in CH_2Cl_2 at ambient temperature (Scheme 2). Since the number of possible



Scheme 2. Synthesis of dihydropyrimidine-5-carboxamides **5a–f**.

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combinations in four-component reactions is greater than the three-component reactions, the diversity of Biginelli reaction is increased under four-component reaction strategy.[22]

2. Results and discussion

In an exploratory experiment, the reaction of *N*-alkyl-3-oxobutanamide **6**, which was prepared by addition of benzylamine **1** to diketene **2**, with 4-chlorobenzaldehyde and urea **4** in the presence of *p*-TsOH·H_2O as a catalyst was performed in dry dichloromethane at ambient temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (3 h), the product, *N*-benzyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide **5a** was obtained in 73% yield.

We have shown that the use of a wide diversity of substituents in amines **1** and aromatic aldehydes **3** in this multicomponent reaction makes possible the synthesis of libraries under similar circumstances. Two substituents in the products can be varied independently of each other. The results are shown in Table 1. As anticipated from our original results, these reactions proceeded very cleanly under mild conditions at room temperature and no undesirable side reactions were observed. All compounds, described in the paper, were synthesized for the first time. The structures of products **5a**–**f** are shown in Figure 1.

Table 1
Synthesis of dihydropyrimidine-5-carboxamide**s 5a**–**f**

Entry	R	Ar	X	Product	Time (h)	Yield[a] (%)
1	Benzyl	4-ClC_6H_4	O	**5a**	3	73
2	Benzyl	3-$NO_2C_6H_4$	O	**5b**	3	75
3	Benzyl	Ph	O	**5c**	4.5	69
4	Allyl	4-BrC_6H_4	S	**5d**	4	74
5	Benzyl	Furyl	O	**5e**	5	67
6	Benzyl	4-BrC_6H_4	S	**5f**	3.5	76

[a] Isolated yield.

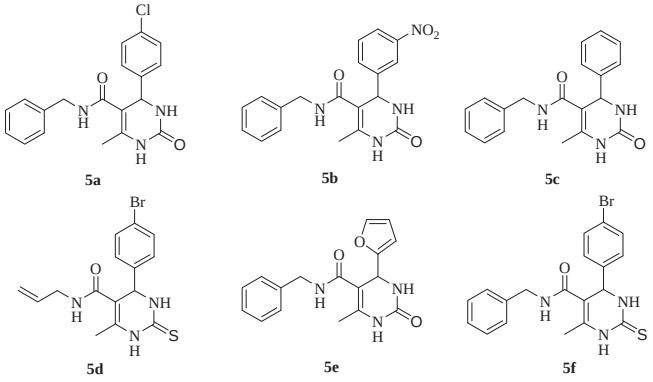
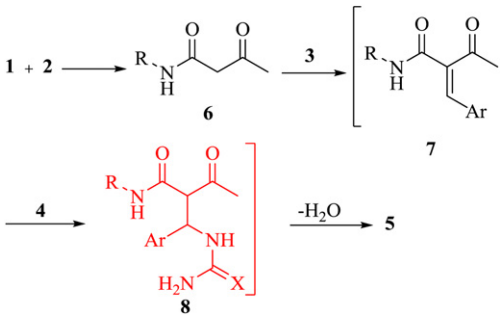


Figure 1. Structures of products **5a**–**f**.

Compounds **5a**–**f** are stable solids whose structures were established by IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectra of products **5a**–**f** displayed molecular ion peaks at appropriate values, which were consistent with the proposed products.

The possible mechanism for the formation of products **5a**–**f** is shown in Scheme 3. It is reasonable to assume that **7** results from initial addition of an aldehyde **3** to *N*-alkyl-3-oxobutanamide **6**, which derived from the addition of an amine **1** to diketene **2**. Then, the subsequent Michael-type addition of the urea/thiourea **4** to **7**, followed by an intramolecular condensation reaction of intermediate **8** to afford the corresponding products **5a**–**f** (Scheme 3).



Scheme 3. Proposed mechanism.

3. Conclusion

In summary, diketene as a new substrate for the Biginelli reaction has been identified and a diverse set of 5-carboxamide substituted 3,4-dihydropyrimidine-2(1*H*)ones has been synthesized without using any activation in high yields at room temperature. Our literature survey shows that this is the first example in which diketene as an activated β-dicarbonyl synthon is used in a Biginelli reaction.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solution in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Merck and Fluka Chemical Companies.

4.2. Typical procedure for the synthesis of *N*-benzyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (5a)

A solution of benzylamine (0.107 g, 1.0 mmol) and diketene (0.084 g, 1.0 mmol) was magnetically stirred in 5 mL of dry CH_2Cl_2 for 2 h. Then, 4-chlorobenzaldehyde (0.140 g, 1.0 mmol), urea (0.060 g, 1.0 mmol) and *p*-TsOH·H_2O (0.019 g, 0.1 mmol) were added simultaneously. The reaction mixture was allowed to stir for 1 h until a precipitate appeared. After completion of the reaction, as indicated by TLC (EtOAc/*n*-hexane, 1:2), the reaction mixture was filtered and the residue was washed with water and then with ethanol and dried in vacuo to give **5a** as pure product. White powder (0.26 g, yield 73%). Mp 234–236 °C. IR (KBr) (ν_{max}/cm^{-1}): 3437, 3397, 3105, 2929, 1673, 1619, 1536, 1457, 1454. MS, *m*/*z* (%): 355 (M^+, 22), 342 (22), 340 (76), 264 (12), 247 (21), 221 (48), 137 (20), 91 (100), 65 (20). ^1H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 2.01 (3H, s, CH_3), 4.14–4.32 (2H, m, CH_2), 5.44 (1H, br s, CH), 6.92–7.40 (9H, m, H–Ar), 7.54 (1H, br s, NH), 8.12 (1H, br s, NH), 8.64 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 17.4 (CH_3), 42.5 (CH_2), 55.0 (CH), 104.8, 126.9, 127.3, 128.4, 128.8, 129.0, 138.2, 140.1, 141.8, 143.6 (C–Ar and C=C), 152.8, 166.6 (CO). Anal. Calcd for $C_{19}H_{18}ClN_3O_2$: C, 64.13; H, 5.10; N, 11.81%. Found C, 64.23; H, 5.16; N, 11.75%.

*4.2.1. N-Benzyl-1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxamid (**5b**).* White powder (0.27 g, yield 75%). Mp 206–207 °C. IR (KBr) (ν_{max}/cm^{-1}): 3437, 3385, 3282, 3086, 2925, 1720, 1641, 1522, 1422. MS, *m*/*z* (%): 349 (M^+−17, 100), 318 (32), 261 (10), 232 (15), 202 (27), 176 (63), 137 (30), 106 (100), 91 (78), 43 (62). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 2.07 (3H, s, CH_3), 3.96–4.29 (2H, m, CH_2), 5.34–5.44 (1H, m, CH), 6.62–7.76 (10H, m, H–Ar, NH), 8.16 (1H, br s, NH), 8.75 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 17.2 (CH_3), 42.4 (CH_2), 53.4 (CH), 106.3, 122.6, 127.1, 127.3, 128.4, 129.1, 129.9, 134.8, 139.0, 140.3, 144.1, 147.9 (C–Ar and C=C), 165.7, 166.4 (CO). Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29%. Found C, 62.23; H, 4.91; N, 15.39%.

*4.2.2. N-Benzyl-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxamide (**5c**).* White powder (0.23 g, yield 69%). Mp 202–204 °C. IR (KBr) (ν_{max}/cm^{-1}): 3293, 3064, 2925, 1727, 1681, 1617, 1535, 1491. MS, *m*/*z* (%): 321 (M^+, 27), 306 (100), 275 (10), 230 (20), 214 (65), 137 (18), 91 (100), 42 (35). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 2.02 (3H, s, CH_3), 4.20–4.24 (2H, m, CH_2), 5.31 (1H, br s, CH), 6.93–7.36 (10H, m, H–Ar), 7.57–7.66 (1H, m, NH), 8.07–8.16 (1H, t, $^3J_{HH}$=5.6 Hz, NH), 8.59 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 17.4 (CH_3), 42.5 (CH_2), 55.5 (CH), 105.3, 126.9, 127.3, 128.5, 128.8, 129.0, 138.0, 140.1, 141.9, 144.7 (C–Ar and C=C), 153.1, 166.8 (CO). Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08%. Found C, 71.23; H, 5.76; N, 13.15%.

*4.2.3. N-Allyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxamide (**5d**).* White powder (0.27 g, yield 74%). Mp 182–183 °C. IR (KBr) (ν_{max}/cm^{-1}): 3446, 3325, 3201, 3058, 2925, 1710, 1660, 1619, 1547, 1489, 1425. MS, *m*/*z* (%): 366 (M^++1, 10), 365 (M^+, 10), 352 (50), 326 (40), 309 (53), 281 (40), 153 (30), 115 (27), 67 (25), 41 (100). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 2.03 (3H, s, CH_3), 3.57–3.67 (2H, m, CH_2), 4.82–5.28 (3H, m, H_2C=CH), 5.62–5.75 (1H, m, CH), 6.92–7.40 (9H, m, H–Ar), 7.91–7.98 (1H, t, $^3J_{HH}$=5.4 Hz, NH), 9.36 (1H, br s, NH), 9.90 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 16.8 (CH_3), 41.5 (CH_2), 54.8 (CH), 106.7, 115.3, 121.3, 129.2, 131.9, 135.5, 135.6, 142.7 (C–Ar and C=C), 166.1, 174.4 (CO). Anal. Calcd for $C_{15}H_{16}BrN_3OS$: C, 49.19; H, 4.40; N, 11.47%. Found C, 49.31; H, 4.53; N, 11.58%.

*4.2.4. N-Benzyl-4-(furan-2-yl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxamide (**5e**).* White powder (0.21 g, yield 67%). Mp 232–234 °C. IR (KBr) (ν_{max}/cm^{-1}): 3334, 3279, 3090, 2925, 1724, 1665, 1626, 1553, 1499, 1456. MS, *m*/*z* (%): 310 (M^+−1, 8), 308 (100), 264 (10), 228 (8), 201 (47), 175 (50), 106 (25), 91 (100), 65 (25). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 1.19 (3H, s, CH_3), 4.26–4.30 (2H, m, CH_2), 4.96 (1H, br s, CH), 6.96–7.23 (9H, m, H–Ar), 7.53 (1H, br s, NH), 8.23 (1H, br s, NH), 8.56 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 28.8 (CH_3), 42.3 (CH_2), 60.3 (CH), 107.7, 110.6, 126.9, 127.2, 127.5, 128.5, 128.6, 139.1, 139.6, 142.4 (C–Ar and C=C), 154.1, 167.6 (CO). Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50%. Found 65.63; H, 5.59; N, 13.65%.

*4.2.5. N-Benzyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxopyrimidine-5-carboxamide (**5f**).* White powder (0.31 g, yield 76%). Mp 126–128 °C. IR (KBr) (ν_{max}/cm^{-1}): 3492, 3399, 3070, 2819, 1671, 1612, 1535, 1457, 1365. MS, *m*/*z* (%): 416 (M^++1, 3), 415 (M^+, 8), 400 (15), 326 (28), 310 (30), 263 (27), 209 (74), 107 (26), 91 (100), 65 (35), 39 (29). ^{1}H NMR (300.13 MHz, DMSO-d_6): δ_H (ppm) 2.03 (3H, s, CH_3), 4.12–4.32 (2H, m, CH_2), 5.29 (1H, br s, CH), 6.90–7.54 (9H, m, H–Ar), 8.30–8.34 (1H, m, NH), 9.35 (1H, br s, NH), 9.91 (1H, br s, NH). ^{13}C NMR (75.47 MHz, DMSO-d_6): δ_C (ppm) 16.9 (CH_3), 42.6 (CH_2), 55.1 (CH), 106.7, 126.0, 127.4, 128.5, 128.8, 129.5, 138.9, 140.2, 142.7, 145.0 (C–Ar and C=C), 166.4, 174.2 (CO). Anal. Calcd for $C_{19}H_{18}BrN_3OS$: C, 54.81; H, 4.36; N, 10.09%. Found C, 54.92; H, 4.54; N, 10.18%.

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