A New Substrate for the Biginelli Cyclocondensation: Direct Preparation of 5-Unsubstituted 3,4-Dihydropyrimidin-2(1*H*)-ones from a *β*-Keto Carboxylic Acid

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Introduction

The first reported synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using a multicomponent reaction milieu was described by Biginelli in 1893.[1] This multicomponent reaction consisting of an aromatic aldehyde, urea, and ethyl acetoacetate in an acidic ethanolic solution produced highly functionalized pyrimidones. This reaction was reported over one century ago, and yet considerable interest in this transformation has steadily increased over the past decade.[2] Much of this interest has arisen from the multifaceted pharmacological profiles of such heterocycles. These molecules have been shown to elicit calcium channel modulatory activity,[3] inhibit platelet activating factor,[4] and selectively antagonize the human α_{1A} receptors,[5] to name a few.

Dihydropyrimidones have historically housed esters at C(5) and an alkyl substituent at C(6). The ester derives from the *β*-ketoester component. This malonate-like portion of the substrate appears to be crucial in the reaction mechanism[6] as its enol tautomer captures the *N*-acyliminium ion (Figure 1, **1a** → **4a**). Therefore, the types of coupling partners used in the Biginelli cyclocondensation have been limited.[2] An interest in 5-unsubstituted dihydropyrimidones led to an exploration of unique conditions and substrates for the cyclocondensation leading directly to 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones. Researchers at Merck recently described the synthesis of certain 5-unsubstituted dihydropyrimidones. This approach and other reported literature methods[7] have typically accomplished the synthesis of 5-unsubstituted dihydropyrimidones in a multistep fashion via the saponification of the C(5) ester on the preassembled pyrimidone followed by thermal decarboxylation. These harsh and inefficient methods have resulted in low-yielding transformations and multiple side-products. Herein, the expedient synthesis of a novel series of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones using oxalacetic acid as an unprecedented substrate for the Biginelli reaction is reported. Also described herein is an effectual set of conditions used to execute this cyclocondensation.

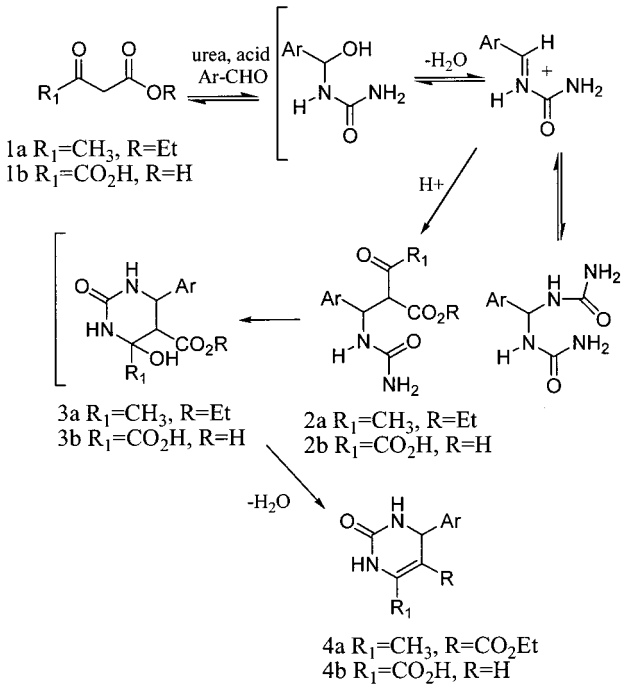

Figure 1.

Results and Discussion

Although this reaction was described over 100 years ago, the Biginelli process lacks literature precedent for the use of *β*-keto carboxylic acids as substrates. This is understandable given that under the standard acidic reaction conditions a typical *β*-keto carboxylic acid should undergo spontaneous decarboxylation to give carbon dioxide and a ketone. However, oxalacetic acid does not undergo decomposition at low pH since the residing enol forms are inactive to decarboxylation.[8] The enol forms of oxalacetic acid predominate in strongly acidic media.[9] Steinberger and Westheimerm[10] have shown that the first-order rate constants for the decarboxylation of oxalacetic acid depend on pH. Presumably the resonance

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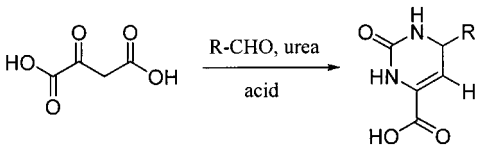
Table 1. Cyclocondensations of Oxalacetic Acid



Compound	R	Method A[a] % Yield	Method B[b] % Yield
5	3,5-diMePh	62	75
6	Ph	55	88
7	2,3-diClPh	34	96
8	3-NO_2Ph	73	99
9	cyclohexyl	50	75
10	2-thienyl	51	72

[a] Method A: cat. H_2SO_4, absolute EtOH, Δ, 12 h, avg scale: 10 mmoles. [b] Method B: cat. TFA, DCE, Δ, 12 h, avg scale: 10 mmoles.

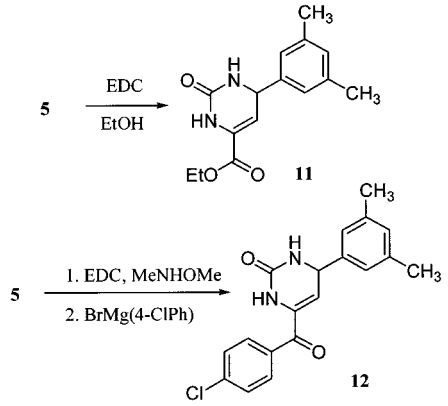
stabilization involving both acids also makes it somewhat more stable than simple enols.

Under suitable reaction conditions, oxalacetic acid proved to be an excellent substrate for the Biginelli reaction. Cyclization and in-situ decarboxylation cleanly yielded 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones.[11] As described in Table 1, using standard conditions developed by Folkers and Johnson[12] to synthesize traditional dihydropyrimidones, the targeted 5-unsubstituted adducts **5**−**10** were prepared in good to poor yields (method A). A more effective method utilized conditions more favorable for *N*-acyliminium ion formation and keto to enol equilibrium manifestation. This method employed trifluoroacetic acid as the acid catalyst and dichloroethane as the solvent (method B). Conditions in method B are advantageous for *N*-acyliminium ion formation, a transient species believed to be a key intermediate in the reaction pathway.[6c] Differences in the acidity and/or dielectric constant of the media can play a role in the relative keto−enol equilibrium.[9a] Indeed, the influence of the solvent polarity may be quite different in method A (sulfuric acid in refluxing ethanol) compared to that of method B. The pH of the media has been reported to have an inherent effect on the keto−enol population and the rate of decarboxylation.[13] In these studies, the researchers have also shown that solvent effects on 3-keto acid decarboxylations are small and somewhat variable.

In effort to determine if the decarboxylated form of oxalacetic acid was playing a role in the cyclization, the Biginelli reaction was performed on pyruvic acid. In this experiment only 5% of the product was isolated using method A. Therefore, it is believed that the decarboxylation is occurring after the initial capture of the *N*-acyliminium species by the enol of oxalacetic acid (Figure 1, **2b** → **4b**). The loss of CO_2 may be occurring on the acyclic and/or cyclic adduct in the reaction pathway. Substituent effects in the β position can cause rate enhancements for decarboxylation.[14]

The resultant product can be further transformed by activation of the free acid with EDC and esterification

Scheme 1



with a carbinol such as ethanol (Scheme 1). The acid **5** was also converted to the corresponding Weinreb amide[15] and treated with a Grignard reagent. As shown in Scheme 1, the transformation to the ketone **12** was effected by reaction with 4-chloromagnesium bromide.

In summary, a novel substrate for the Biginelli reaction has been identified and exploited to expeditiously synthesize a diverse set of 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones in high yield. Electron-rich as well as electron-deficient aldehydes proved to be excellent substrates for the cyclocondensation. The described pyrimidones were prepared using standard cyclization conditions and more effectively synthesized using a unique set of conditions (i.e., TFA in refluxing dichloroethane). The carboxylic acid appendage on C(6) offers functionality capable of a wide variety of transformations.

Experimental Section

General Methods. All unspecified reagents were from commercial sources. Reactions were routinely run in a nitrogen atmosphere. ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts are reported in ppm relative to the residual signal of the solvent. Medium-pressure liquid chromatography (MPLC) was carried out on SiO_2 (silica gel 60, particle size 0.040−0.063 mm). Drying of organic extracts during reaction workup was performed over anhydrous Na_2SO_4. Evaporation of organic solvents was achieved using a Brinkmann Rotavapor. Microanalyses were performed by Quantitative Technologies Inc., Whitehouse, NJ.

Synthesis Using General Method A. 6-(3,5-Dimethylphenyl)-2-oxo-1,2,3,6-tetrahydro- pyrimidine-4-carboxylic Acid (5). Sulfuric acid (0.5 mL) was added to a mixture of urea (3.5798 g, 59.5 mmol) and 3,5-dimethylbenzaldehyde (6.38 mL, 47.6 mmol) stirred in absolute ethanol (25 mL). Oxalacetic acid (5.0 g, 39.67 mmol) was added to the reaction mixture, and the reaction was heated to reflux for 12 h. The reaction mixture was cooled to room temperature and diluted with water (100 mL). The product was extracted with ethyl acetate (2 × 100 mL). The organics were washed with saturated sodium chloride solution (100 mL), dried, filtered, and concentrated. The residue was purified by MPLC by eluting with ethyl acetate and hexane (1:1, v/v). The product was isolated as a white solid (2.9058 g, 62.3% yield).

^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.26 (s, 6 H), 5.06−5.08 (m, 1 H), 5.73−5.75 (m, 1 H), 6.89−6.92 (m, 3 H), 7.25 (s, 1 H), 7.75 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.31, 152.72, 144.6, 138.05, 129.25, 127.83, 124.15, 109.45, 55.10, 21.29. Anal. Calcd for $C_{13}H_{14}N_2O_3 \times 0.5$ mol H_2O: C, 61.17%; H, 5.92%; N, 10.97%. Found: C, 61.51%; H, 5.59%; N, 11.37%.

Synthesis Using General Method B. 6-(3,5-Dimethylphenyl)-2-oxo-1,2,3,6-tetrahydro- pyrimidine-4-carboxylic Acid (5). Trifluoroacetic acid (0.5 mL) was added to a mixture of urea

(11) HMBC, COSY, and HMQC experiments were used to confirm the location of the decarboxylation of C(5) carboxy acid by determination of the location of the C(5) hydrogen for example 5. The spectra are available in the Supporting Information.

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(0.6832 g, 11.35 mmol) and 3,5-dimethylbenzaldehyde (1.12 mL, 8.33 mmol) stirred in dichloroethane (15 mL, anhydrous). Oxalacetic acid (1.00 g, 7.57 mmol) was added to the reaction mixture, and the reaction was heated to reflux for 12 h. The reaction mixture was cooled to room temperature, and a white precipitate formed upon cooling. The product was simply collected by filtration to give a white powder **5** (1.3928 g, 75.1% yield).

6-Phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic Acid (6). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.13−5.16 (m, 1 H), 5.77−5.79 (m, 1 H), 7.29−7.41 (m, 5 H), 7.79 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.30, 152.79, 144.11, 129.04, 128.06, 127.89, 126.45, 109.26, 55.08. Anal. Calcd for $C_{11}H_{10}N_2O_3 \times 0.1$ mol H_2O: C, 66.02%; H, 7.03%; N, 5.92%. Found: C, 66.11%; H, 7.47%; N, 6.26%.

6-(2,3-Dichlorophenyl)-2-oxo-l1,2,3,6-tetrahydropyrimidine-4-carboxylic Acid (7). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.52−5.54 (m, 1 H), 5.78−5.79 (m, 1 H), 7.35−7:50 (m, 3 H), 7.62 (dd, J = 7.89 and 1.44 Hz, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.03, 152.81, 143.31, 132.49, 130.01, 129.37, 129.28, 128.622, 126.99, 105.57, 53.45. Anal. Calcd for $C_{11}H_8Cl_2N_2O_3$: C, 46.02%; H, 2.81%; N, 9.76%. Found: C, 45.89%; H, 2.60%; N, 9.64%.

6-(3-Nitrophenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylic Acid (8). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.36−5.38 (m, 1 H), 5.86−5.87 (m, 1 H), 7.50 (bs, 1 H), 7.70 (dd, J = 7.63 and 7.70 Hz, 1 H). 7.80 (d, J = 7.70 Hz, 1 H), 8.01 (s, 1 H), 8.17−8.19 (m, 2 H). ^{13}C NMR (DMSO-d_6) δ: 163.11, 152.70, 148.33, 146.22, 133.27, 130.76, 128.81, 122.88, 121.05, 108.09, 54.32. Anal. Calcd for $C_{11}H_9N_3O_5$: C, 50.20%; H, 3.45%; N, 15.96%. Found: C, 49.89%; H, 3.27%; N, 15.73%.

6-Cyclohexyl-2-oxo-1,2,3,6-tetrahydropyrimidine-4-earboxylic Acid (9). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.95−2.51 (m, 11 H), 3.87 (s, 1 H), 5.65−5.67 (m, 1 H), 6.81 (s, 1 H), 7.46 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.15, 153.55, 129.55, 107.79, 56.37, 44.85, 27.68, 27.41, 26.03, 25.98. Anal. Calcd for $C_{26}H_{31}N_2O_3 \times 1.0$ H_2O: C, 66.02%; H, 7.03%; N, 5.92%. Found: C, 66.1 1%; H, 7.47%; N, 6.26%.

6-(2-Thienyl)-2-oxo-l,2,3,6-tetrahydropyrimidine-4-carboxylic Acid (10). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.44−5.46 (m, 2 H), 5.80−5.82 (s, 1 H), 6.99 (d, J = 3.09 Hz, 1 H), 7.46−7:50 (m, 2 H), 7.94 (s, 1 H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.25, 160.03, 152.29, 148.37, 128.52, 127.34, 125.84, 124.38, 108.51, 50.50. Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21%; H, 3.60%; N, 12.49%. Found: C, 48.01%; H, 3.68%; N, 12.41%.

Ethyl 6-(3,5-Dimethylphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidine-4-carboxylate (11). To a solution of acid **5** (0.5217 g, 2.12 mmol) in dimethylformamide (DMF, 7 mL, anhydrous) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.4465 g, 2.33 mmol), 1-hydroxy-7-azabenzotriazole (HOAT, 0.3172 g, 2.33 mmol), and *N*-methylmorpholine (NMM, 0.47 mL, 4.24 mmol). Ethanol (1 mL, absolute) was added to the reaction, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (2 × 50 mL), dried, filtered, and concentrated. The residue was purified by MPLC eluting with ethyl acetate and hexane (3:7, v/v). The product was isolated as a colorless solid (0.5322 g, 91.0% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.37 (t, J = 2.79 Hz, 3 H), 2.37 (s, 6 H), 4.38 (q, J = 7 Hz, 2 H), 7.23 (bs, 1 H), 7.68 (bd, J = 7 Hz, 1 H), 7.69−7.73 (m, 3 H). Anal. Calcd for $C_{26}H_{31}N_2O_3$: C, 66.02%; H, 7.03%; N, 5.92%. Found: C, 66.11%; H, 7.47%; N, 6.26%.

6-(3,5-Dimethylphenyl)-2-oxo-1,2,3,6-tetrahydropyrimidin-4-yl-(4-chlorophenyl)methanone (12). To solution of acid **5** (0.5217 g, 2.12 mmol) in DMF (7 mL, anhydrous) were added EDC (0.4465 g, 2.33 mmol), NMM (0.47 mL, 4.24 mmol), HOAT (0.3172 g, 2.33 mmol), and *N*,*O*-dimethylhydroxylamine hydrochloride (0.2275 g, 2.33 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was diluted with water (50 mL), extracted with ethyl acetate (2 × 50 mL), dried, filtered, and concentrated. The crude residue was solubilized in THF (10 mL, anhydrous) and cooled to 0 °C with an external ice-bath. 4-Chlorophenylmagnesium bromide was slowly added, and the reaction was warmed to room temperature. After stirring for 5 h, the reaction was quenched with brine (50 mL), extracted with ethyl acetate (2 × 50 mL), dried, filtered, and concentrated. The residue was purified by MPLC by eluting with ethyl acetate and hexane (4:1, v/v). The ketone **12** was isolated as a pale yellow solid (0.2713 g, 37% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 6 H), 6.89−6.86 (m, 1 H), 7.26−7.40 (m, 1 H), 7.51 (d, J = 8.54 Hz, 2 H), 7.56 (s, 1 H), 8.06 (d, J = 8.52 Hz, 2 H). Anal. Calcd for $C_{19}H_{17}N_2O_2$: C, 66.96%; H, 5.03%; N, 8.22%. Found: C, 66.83%; H, 5.34%; N, 8.12%.

Supporting Information Available: Proton and/or carbon NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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