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Acyl pyruvates as synthons in the Biginelli reaction

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ABSTRACT

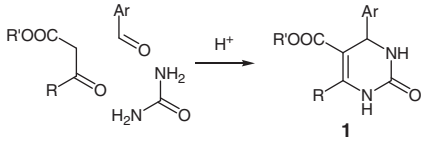
Chlorotrimethylsilane-promoted Biginelli-type reaction of ethyl 2,4-dioxo-4-phenylbutanoate, benzaldehyde, and various (thio)ureas is explored. The outcome of the reaction depends on the structure of the (thio)urea used and is strongly affected by the acceptor electronic properties of the COOEt substituent in the molecule of the starting β-dicarbonyl compound. The di- and tetrahydropyrimidine derivatives obtained possess two functional groups with orthogonal reactivity, and thus represent promising building blocks for drug discovery.

Multicomponent reactions which employ three or more reagents that are combined into a single product have attracted significant attention from chemists.[1] The main reason is the huge diversity of chemical space covered by the compounds thus produced. On the other hand, one-pot, high-yield procedures are employed in most cases which allow the multicomponent reactions to be considered as reliable synthetic methods. These features are particularly important in the early steps of drug discovery, by either high-throughput screening or fragment-based design, as well as for hit-to-lead optimization.[2] The use of three or more building blocks combined with the excellent efficacy of multicomponent reactions is important for combinatorial chemistry as structurally and functionally diverse libraries of compounds can be obtained.[3]

The Biginelli reaction is an acid-catalyzed three-component condensation of an aldehyde, a β-ketoester, and an urea leading to the formation of dihydropyrimidinones **1** (Scheme 1). The latter have been shown to exhibit manifold biological effects such as calcium channel modulator, mitotic kinesine inhibitor, adrenergic receptor antagonist, and antibacterial and antiviral activities.[4] Thus dihydropyrimidines can be considered as privileged scaffolds for drug discovery.

Since the pioneering report of Biginelli,[5] a range of modified conditions have been developed to facilitate this reaction including the use of various Lewis acids as reaction promoters,[6] as well as microwave assistance,[7] and solid- and fluorophase techniques.[8] Recently, it was demonstrated that the chlorotrimethylsilane-promoted Biginelli reaction has wide applicability and allows various (hetero)aromatic aldehydes and (thio)ureas to be used as starting materials.[9]

Despite the initial publication of Biginelli[5] reporting the use of diethyl oxaloacetate **2** as a β-dicarbonyl component, β-acylpyruvates **3** are considered to be poor substrates for the Biginelli reaction, mainly due to their high reactivity and sensitivity to acids. To the best of our knowledge, apart from oxaloacetic acid[10] and its derivatives, no examples of substrates of general formula **3** being used in the Biginelli reaction have been reported to date. 5-Acyltetrahydropyrimidine-4-carboxylates **4**, which might be obtained in the latter reaction, possess two functional groups with orthogonal



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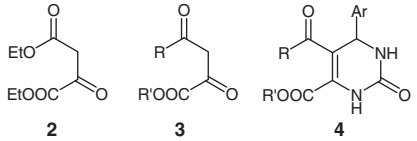
Scheme 1. Biginelli reaction.



2 3 4

Figure 1.

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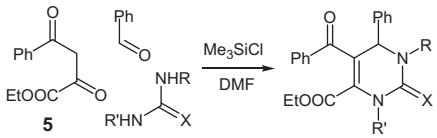
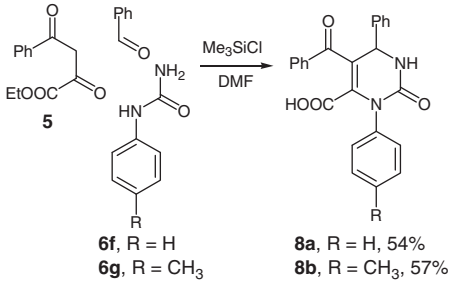
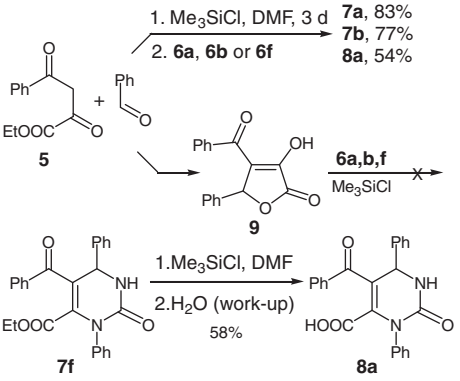


Urea	Product	R	R′	X	Yield, %
6a	**7a**	H	H	O	84
6b	**7b**	H	CH_3	O	75
6c	**7c**	CH_3	CH_3	O	73
6d	**7d**	H	H	S	78
6e	**7e**	CH_3	CH_3	S	76

Scheme 2. One-pot synthesis of dihydropyrimidines **7a–e**.[12]



Scheme 3. One-pot synthesis of carboxylic acids **8a**,**b**.[13]



Scheme 4.

reactivity (i.e., ketone and ester functions) which can be selectively transformed into various pharmacophore units, or both used for further heterocyclizations. It should be noted that compounds of general formula **4** [Fig. 1, where R is alkyl, cycloalkyl, or (het)aryl] have not been described in the literature.

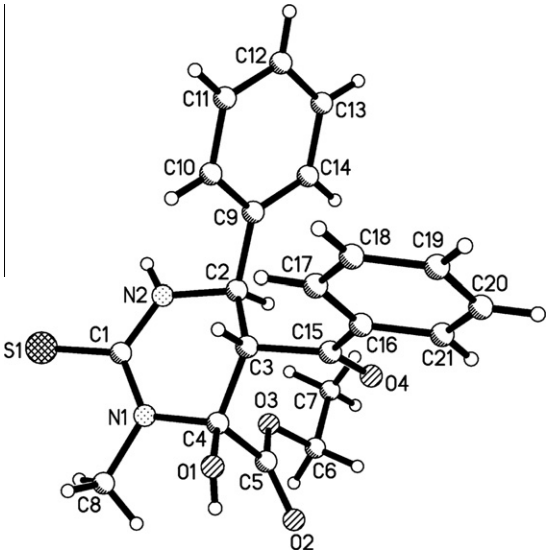


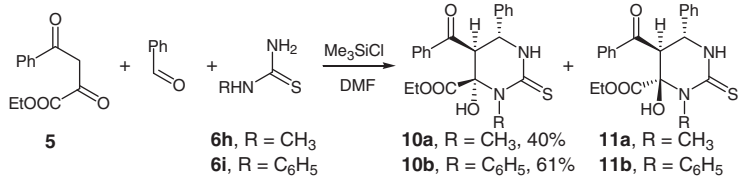
Figure 2. Molecular structure of compound **10a**.

In this Letter, we report our results on the chlorotrimethylsilane-promoted Biginelli reaction involving ethyl 2,4-dioxo-4-phenylbutanoate (**5**) as a β-dicarbonyl component. As the applicability of the method to various (hetero)aromatic aldehydes was demonstrated previously,[9b–d] benzaldehyde was selected as the aldehyde component. A set of (thio)ureas **6a–i** varying in *N*,*N*-binucleophilic reactivity was explored in this study.

Reaction of ester **5**, benzaldehyde, and (thio)ureas **6a–e** in the presence of Me_3SiCl in DMF at ambient temperature resulted in the formation of the target dihydropyrimidines **7a–e** in 73–84% yields (Scheme 2).[11] In the case of unsymmetric urea **6b**, complete regiospecificity was observed; the assignment of the structure of **7b** was followed from routine ^1H NMR spectroscopy (coupling between the 1-N*H* and 6-C*H* protons was observed) and was in accordance with our previous results.[9b–d]

When the above-mentioned conditions were applied to the reaction of ester **5**, benzaldehyde, and *N*-arylureas **6f**,**g**, carboxylic acids **8a**,**b** were obtained in 54% and 57% yields instead of the expected ester (Scheme 3). The structures of **8a**,**b** were assigned using NMR, LC–MS, and elemental analysis.

To explain the formation of compounds **7f**,**g**, several assumptions can be made. As the nucleophilicity of *N*-arylureas **6f**,**g** decreases, the reaction can start with condensation of the aldehyde and β-ketoester at the first stage, resulting in the formation of compound **9**,[14] or its silylated analogues, which then react with the urea to give **7f**,**g**. This is contrary to the standard Biginelli reaction mechanism which involves the reaction between the urea and the aldehyde in the first step, followed by condensation of the formed iminium intermediate with the β-ketoester.[15] To test this hypothesis, ureas **6a**,**b**,**f** were introduced to the reaction mixture after compound **5** and benzaldehyde had been allowed to react over a three-day period. However, this modification of the experiment



Scheme 5.

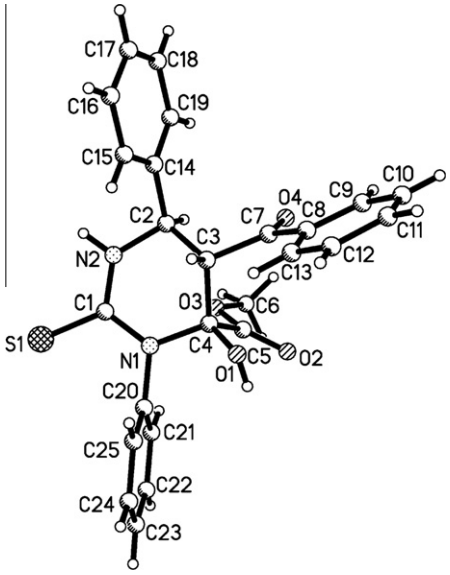


Figure 3. Molecular structure of compound **10b**.

did not lead to any changes in the reaction outcome (i.e., the products **7a**,**b** and **8a** were obtained, respectively). We also prepared compound **9**[14] and subjected it to reaction with ureas **6a,b,f** under the conditions described above. In these cases, complex mixtures were obtained. Therefore, we assumed that the formation of carboxylic acids **8a**,**b** occurs via normal hydrolysis of the corresponding esters. Indeed, ester **7f** (which was obtained from **8a** using a standard method[16]) underwent hydrolysis to **8a** upon reaction with Me_3SiCl in DMF and subsequent work-up (Scheme 4).

Reaction of ester **5**, benzaldehyde, and thioureas **6h,i** in the presence of Me_3SiCl in DMF led to the formation of tetrahydropyrimidines **10a,b** and **11a,b** in 70–80% combined yields (Scheme 5).[17] As in the previous cases, complete regioselectivity was observed. Nevertheless, the diastereoselectivity of the reaction was moderate (**10a**:**11a** = 3:1, **10b**:**11b** = 9:1). Both major isomers **10a,b** were isolated in 40% and 61% yields, respectively. The stereochemistry of products **10a,b** was assigned by X-ray diffraction (Figs. 2 and 3).[18] Whereas minor isomer **11a** (de 85%) was also isolated, compound **11b** could only be detected in the crude product by NMR and GC–MS.

The formation of compounds **10a,b** and **11a,b** is connected to our previous results on Biginelli-type reactions involving trifluoromethyl-substituted diketones.[9c] This can be rationalized from the similarity of the electronic properties of the CF_3 and COOEt substituents (σ_p = 0.54 and 0.45, respectively).[19] As the acceptor properties of the carboxyethyl group are somewhat diminished compared to the trifluoromethyl moiety, stable hydrates are formed only from monosubstituted thioureas **6h,i**. Therefore, in the light of its behavior in the Biginelli reaction, the acylpyruvate **5** occupies an intermediate position between trifluoromethyl-substituted β-diketones and common β-dicarbonyl compounds such as ethyl acetoacetate.

In conclusion, the chlorotrimethylsilane-promoted Biginelli reaction involving ethyl 2,4-dioxo-4-phenylbutanoate (**5**) as the β-dicarbonyl component is an efficient method for the synthesis of di- and tetrahydropyrimidine derivatives possessing two functional groups with orthogonal reactivity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.032.

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11. *General procedure for the Biginelli reactions*. A mixture of ester **5** (4 mmol), benzaldehyde (4 mmol), thiourea **6** (6 mmol), and dry DMF (10 mL) was sonicated for 1 h at rt to dissolve the starting materials, and then chlorotrimethylsilane (16 mmol) was added dropwise. The resulting mixture was allowed to stand for 3–4 d and then poured into water (20–30 mL). The suspension was sonicated for 1 h and the precipitate was filtered and washed with a small amount of *i*PrOH. The filtrate was evaporated under reduced pressure, and the residue was triturated with a small amount of *i*PrOH and filtered again. The combined solids were recrystallized to yield the products **7**–**9** (see Schemes 2–4).
12. *Ethyl 5-benzoyl-2-oxo-6-phenyl-1,2,3,6-tetrahydropyrimidine-4-carboxylate* (**7a**): Yield: 84%; mp 180 °C (2-propanol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.85 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 3.50–3.72 (m, 2H, CH_2CH_3), 5.33 (s, 1H, 4-H_{DHPM}), 7.23 (m, 3H, 2,4,6-H_{Ph}), 7.31 (t, $^3J_{HH}$ = 7.2 Hz, 2H, 3,5-H_{Ph}), 7.38 (t, $^3J_{HH}$ = 7.8 Hz, 2H, 3,5-$H_{Ph'}$), 7.46-7.54 (d+t, $^3J_{HH}$ = 7.8 Hz, 3H, 2,4,6-$H_{Ph'}$), 7.86 (s, 1H, NH), 9.16 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.5, 56.8, 62.3, 115.0, 126.9, 128.4, 128.9, 129.2, 133.1, 133.9, 138.6, 142.9, 152.3, 161.9, 193.6. APSI MS: M^++1 = 351. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.42; H, 5.30; N, 8.08.

13. *5-Benzoyl-3,6-diphenyl-2-oxo-6-1,2,3,6-tetrahydropyrimidine-4-carboxylic acid* (**8a**): Yield: 54%; mp >250 °C, dec. (MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.97 (s, 1H, 4-H$_{DHPM}$), 7.08 (t, $^3J_{HH}$ = 7.0 Hz, 1H, 4-H$_{Ph}$), 7.19 (t, $^3J_{HH}$ = 7.4 Hz, 1H, 4-H$_{Ph}$), 7.26 (t, $^3J_{HH}$ = 7.0 Hz, 2H, 3,5-H$_{Ph}$), 7.32 (t, $^3J_{HH}$ = 7.4 Hz, 2H, 3,5-H$_{Ph}$), 7.39 (d, $^3J_{HH}$ = 7.0 Hz, 2H, 2,6-H$_{Ph}$), 7.47 (m, 4H, 2,3,5,6-H$_{Ph}$), 7.58 (t, $^3J_{HH}$ = 7.0 Hz, 1H, 4-H$_{Ph}$), 7.71 (t, $^3J_{HH}$ = 7.8 Hz, 2H, 2,6-H$_{Ph}$), 10.25 (s, 1H, NH), 12.00 (br s, 1H, COOH) ^{13}C NMR (125 MHz, DMSO-d_6): δ 60.5, 120.1, 124.4, 127.7, 128.2, 128.7, 128.8, 129.3, 129.5, 133.5, 137.4, 137.8, 138.0, 148.2, 148.5, 168.1, 189.6. APSI MS: M$^+$+1 = 399, M$^-$−1 = 397. Anal. Calcd for $C_{24}H_{18}N_2O_4$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.62; H, 4.28; N, 6.97.
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17. *Ethyl [rel-(4S,5S,6R)-5-benzoyl-4-hydroxy-3-methyl-6-phenyl-2-thioxohexahydropyrimidine-4-carboxylate* (**10a**) *and ethyl [rel-(4S,5S,6S)-5-benzoyl-4-hydroxy-3-methyl-6-phenyl-2-thioxohexahydropyrimidine-4-carboxylate* (**11a**): A sample of the mixture of isomers **10a** and **11a** obtained in 74% total yield via the general procedure was subjected to flash chromatography (460 mm × 36 mm silica gel column, 5–6 bar, detection at 254 nm, $CHCl_3$–EtOAc (95:5) as eluent) to give **10a** (0.54 g, 40%) and **11a** (0.16 g, 12%, 85% de). Major isomer **10a**: mp 170 °C (2-propanol). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.96 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 3.11 (s, 3H, NCH_3), 3.57 (m, 2H, CH_2CH_3), 4.63 (d, $^3J_{HH}$ = 11.2 Hz, 1H, 5-H$_{THPM}$), 4.95 (d, $^3J_{HH}$ = 11.2 Hz, 1H, 4-H$_{THPM}$), 7.18 (t, $^3J_{HH}$ = 7.4 Hz, 1H, 4-H$_{Ph}$), 7.25 (t, $^3J_{HH}$ = 7.4 Hz, 2H, 3,5-H$_{Ph}$), 7.34 (s, 1H, OH), 7.40 (t, $^3J_{HH}$ = 8.0 Hz, 2H, 3,5-H$_{Ph'}$), 7.44 (d, $^3J_{HH}$ = 7.4 Hz, 2H, 2,6-H$_{Ph}$), 7.55 (t, $^3J_{HH}$ = 8.0 Hz, 1H, 4-H$_{Ph'}$), 7.66 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2,6-H$_{Ph'}$), 8.80 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 13.9, 37.0, 53.0, 54.2, 62.6, 85.6, 128.5, 128.6, 128.7, 128.9, 129.0, 133.9, 137.6, 138.7, 168.8, 178.8, 195.2. APSI MS: M$^+$+1 = 399. Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03; S, 8.05. Found: C, 63.48; H, 5.44; N, 6.92; S, 8.20. Minor isomer **11a**: ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.33 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 3.15 (s, 3H, NCH_3), 4.33 (m, 2H, CH_2CH_3), 4.58 (d, $^3J_{HH}$ = 11.0 Hz, 1H, 5-H$_{THPM}$), 4.88 (d, $^3J_{HH}$ = 11.0 Hz, 1H, 4-H$_{THPM}$), 7.11 (t, $^3J_{HH}$ = 7.4 Hz, 1H, 4-H$_{Ph}$), 7.18 (t, $^3J_{HH}$ = 7.4 Hz, 2H, 3,5-H$_{Ph}$), 7.24 (d, $^3J_{HH}$ = 7.4 Hz, 2H, 2,6-H$_{Ph}$), 7.28 (s, 1H, OH), 7.34 (t, $^3J_{HH}$ = 8.0 Hz, 2H, 3,5-H$_{Ph'}$), 7.51 (t, $^3J_{HH}$ = 8.0 Hz, 1H, 4-H$_{Ph'}$), 7.70 (d, $^3J_{HH}$ = 8.0 Hz, 2H, 2,6-H$_{Ph}$), 8.74 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.7, 37.3, 52.9, 55.6, 63.6, 85.3, 127.5, 128.2, 128.5, 129.0, 129.2, 134.1, 136.4, 136.7, 169.0, 180.1, 197.7. APSI MS: M$^+$+1 = 399.
18. Final atomic coordinates, geometrical parameters, and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 759878 (**10a**) and CCDC 759879 (**10b**).
19. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.