A Convenient Synthesis of N1-Substituted 3,4-Dihydropyrimidin-2(1*H*)-ones by Cyclocondensation of α-Chlorobenzyl Isocyanates with Ethyl *N*-alkyl(aryl)-β-aminocrotonates

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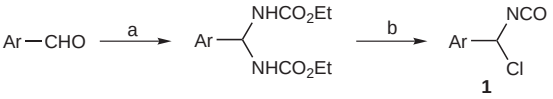
Abstract: A new convenient approach to the synthesis of N1-substituted 3,4-dihydropyrimidin-2(1*H*)-ones was developed using the regioselective cyclocondensation of α-chlorobenzyl isocyanates with ethyl *N*-alkyl(aryl)-β-aminocrotonates. A number of N1-aryl and N1-alkyl substituted Biginelli compounds difficult to obtain by other methods were prepared with high yields.

Key words: cyclocondensation, regioselectivity, α-chloroalkyl isocyanates, dihydropyrimidones, β-aminocrotonic esters

Functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs, Biginelli compounds) represent a heterocyclic system that has aroused considerable interest of specialists on biologically active materials, drug design and research, etc.[1] A wide diversity of pharmacological properties displayed by this class of compounds, along with their relatively simple constitution, accessibility, and modifiability of substituent structure, make them extremely advantageous objects for large-scale biological screening (a recent vivid example is offered by the discovery of monastrol).[2]

A conventional synthesis of DHPMs first performed by P. Biginelli in 1893 involves a three-component condensation of 1,3-dicarbonyl compounds, aldehydes, and urea under acidic conditions.[3] In the last two decades, more efficient conditions have been found for the Biginelli reaction using soft Lewis acids as catalysts.[4] Microwave exposure[5] as well as solid-phase and fluoro-phase techniques[6] facilitating this synthesis have also become increasingly widespread. Some modifications of the reaction have been reported which depart from the initial multicomponent reaction scheme and provide notable conveniences in the synthesis of biologically active 3-acyl substituted DHPMs and their 4-alkyl substituted derivatives.[7] Overman et al. conducted the full synthesis of a number of natural products, e.g., alkaloid batzelladine B exhibiting anti-HIV activity, by the reaction between acetoacetic ester and the analogues of hydroxyalkyl urea; this approach enabled convenient stereoselective construction of the condensed 3,4-dihydropyrimidine nucleus.[8] Alternatively, Kishi et al. reacted acetaldehyde, isocyanic acid, and a cyclic derivative of the β-aminoacrylic ester in a three-component condensation to obtain a previously inaccessible condensed DHPM constituting the main structural moiety of saxitoxin.[9] Thus, great progress has been made in the chemistry of these partially unsaturated pyrimidine systems and a great manifold of their derivatives have been obtained. However, the simplest 1-aryl substituted DHPMs are represented in the literature very scantily.[10] This may be attributed to the fact that *N*-arylureas involved in the Biginelli reaction lead to a complex mixture of products containing a negligible amount of the corresponding dihydropyrimidones.[1a,11] *N*-Alkylureas provide higher yields of the target compounds but they are more conveniently obtained by an alternative method based on selective alkylation of N1-unsubstituted analogues.[12]



Scheme 1 *Reagents and conditions*: (a) H_2NCO_2Et, H_2SO_4 (cat.), 150–160 °C, 15 min (94–98%); (b) PCl_5, benzene, reflux, 4 h.

Table 1 Preparation of α-Chlorobenzyl Isocyanates **1**

1	Ar	Bp (°C, torr)	Yield (%)[a]
a	Ph	125–128 (10)	68[a]
b	2-FC_6H_4	119–123 (10)	69
c	3-BrC_6H_4	141–145 (0.2)	81
d	3-$(NO_2)C_6H_4$	161–164 (0.2)	82
e	4-ClC_6H_4	126–130 (0.2)	77
f	4-BrC_6H_4	140–143 (0.2)	80[a]
g	4-$(NO_2)C_6H_4$	152–156 (0.2)	75[a]
h	3,4-$Cl_2C_6H_3$	148–152 (0.2)	73

[a] For literature data see ref. 16.

We have recently demonstrated an efficient application of a novel synthetic methodology for constructing a pyrimidine ring via the synthon scheme $[–C=C–N–]^{2–}$+ $[–C=N–C=O]^{2+}$. The bis-electrophilic synthon $[–C=N–C=O]^{2+}$ is furnished by α-chloroalkyl isocyanates.[13] By systematically studying the heterocyclocondensation of 1-aryl-

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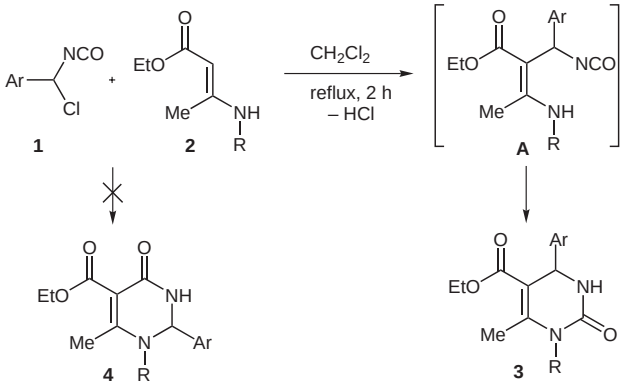
2,2,2-trifluoro-1-chloroethyl isocyanates with various C,N- and C,O-binucleophiles, we have found regioselective reactions yielding condensed dihydropyrimidine systems.[14] In particular, 1-aryl-2,2,2-trifluoro-1-chloroethyl isocyanates proved to produce 2,3-dihydropyrimidin-4(1*H*)-ones by the reaction with ethyl *N*-methyl-β-aminocrotonate in the presence of triethylamine.[15] α-Chlorobenzyl isocyanates **1**, however, have hitherto been unapplied in heterocyclic syntheses, though one of us previously developed a facile synthetic access to them starting from aromatic aldehydes, ethylurethane, and phosphorus pentachloride.[16] To gain a better insight into the synthetic potential of α-chlorobenzyl isocyanates **1**, we synthesized a number of new compounds of this class using the slightly modified procedure (see Scheme 1 and Table 1).[17] We studied their reaction with ethyl *N*-alkyl(aryl)-β-aminocrotonates with the aim to develop a general method for the preparation of N1-substituted dihydropyrimidone derivatives.

As found, α-chlorobenzyl isocyanate **1a** reacts with ethyl *N*-methyl-β-aminocrotonate in a methylene chloride solution to smoothly furnish DHPM **3a** in good yield. The compound obtained is described in the literature[18] and its structure is unquestionable. To determine the synthetic applicability limits for the conversion discovered, we have synthesized and reacted various *N*-alkyl and *N*-aryl substituted enamines of type **2**.[19] It has been shown that *N*-aryl-β-aminocrotonic esters also enter readily into the reaction with isocyanates **1** to give the corresponding DHPMs of type **3** in 67–81% yields (see Scheme 2 and Table 2).[20] Structural determination of the compounds synthesized was carried out reliably using IR, ^{1}H NMR and ^{13}C NMR spectroscopy.[21] The most plausible scheme for the reaction between **1** and **2** involves initial isocyanatoalkylation of the nucleophilic carbon atom in enamine **2** to generate intermediates A which rapidly cyclize into **3**.



Scheme 2

Isomeric 2,3-dihydropyrimidin-4(1*H*)-ones of type **4** are not detected in the reaction mixture thus suggesting complete heterocyclization regioselectivity, with the reaction course depending on the structure of an initial α-chloroalkyl isocyanate. The method developed was employed to obtain a variety of hitherto unknown N1-substituted Biginelli compounds **3a**–**e**,**g**–**p**.

Table 2 3,4-Dihydropyrimidin-2(1*H*)-ones **3**

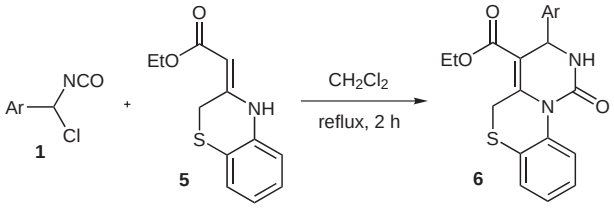
3	Ar	R	Mp (°C)	Yield (%)[a]
a	Ph	Me	176–178[b]	64
b	Ph	4-ClC_6H_4	148–150	63
c	2-FC_6H_4	Bn	145–147	55
d	2-FC_6H_4	4-$F_2HCSC_6H_4$	151–153	72
e	3-BrC_6H_4	4-$MeOC_6H_4$	157–159	73
f	3-$(NO_2)C_6H_4$	Ph	165–167[c]	70
g	3-$(NO_2)C_6H_4$	4-ClC_6H_4	208–209	75
h	4-ClC_6H_4	Bn	163–165	61
k	4-ClC_6H_4	4-$(CN)C_6H_4$	196–198	81
l	4-BrC_6H_4	Me	172–174	59
m	4-BrC_6H_4	4-$MeOC_6H_4$	180–182	72
n	4-$(NO_2)C_6H_4$	Ph	194–196	74
o	3,4-$Cl_2C_6H_3$	4-Me-3-FC_6H_3	159–161	78
p	3,4-$Cl_2C_6H_3$	2-Naph	156–158	67

[a] Yields of pure isolated products.
[b] Lit.: mp 178–180 °C.[18]
[c] Lit.: mp 168 °C.[10]

Among the limitations of the new synthetic approach is the impossibility to produce α-chlorobenzyl isocyanates (and hence the corresponding dihydropyrimidines) containing electron-donor groups on the aromatic ring as well as the groups sensitive to the action of phosphorus pentachloride and phosphorus oxychloride. In addition, β-aminocrotonates bearing bulky substituents [R = $PhCH(CH_3)$, 2-MeC_6H_4] lead to the mixture of products and do not furnish the preparative yields of the target derivatives **3**. Nevertheless, the method makes easily available a great diversity of N1-substituted DHPMs starting from amines, acetoacetic ester, aromatic aldehydes, ethyl carbamate, and phosphorus pentachloride. The new strategy of constructing the dihydropyrimidine cycle allows the synthesis of previously inaccessible hydrogenated condensed nuclei. For instance, ethyl (2*H*)-3,4-dihydro-1,4-benzothiazin-3-ylidenacetate (**5**)[22] was used to obtain 2,3-dihydropyrimido[6,1-*c*][1,4]benzothiazin-1(1*H*)-ones **6** (see Table 3).[23,24]

In conclusion, we have elaborated a convenient synthetic pathway to N1-substituted 3,4-dihydropyrimidin-2(1*H*)-ones based on a novel regioselective cyclocondensation of α-chlorobenzyl isocyanates with *N*-alkyl(aryl)-β-aminocrotonates. The method provides evident advantages in the synthesis of hardly obtainable N1-aryl-substituted Biginelli compounds and hydrogenated pyrimidobenzothiazine derivatives.

Table 3 Synthesis of 2,3-Dihydropyrimido[6,1-*c*][1,4]benzothiazin-1(1*H*)-ones **6** by Cyclocondensation of α-Chlorobenzyl Isocyanates **1** with Ethyl (2*H*)-3,4-Dihydro-1,4-benzothiazin-3-ylidenacetate (**5**)



6	Ar	Mp (°C)	Yield (%)[a]
a	Ph	205–207	70
b	4-BrC_6H_4	201–203	73
c	3-BrC_6H_4	182–184	71
d	2-FC_6H_4	195–197	76

[a] Yields of pure isolated products.

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(1) For reviews see: (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (c) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

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(17) **Improved Protocol for Preparation of α-Chlorobenzyl Isocyanates 1.**
The mixture of aromatic aldehyde (1 mol, 1 equiv) and ethylcarbamate (2.2 mol, 2.2 equiv) was heated to 140–160 °C and then few drops of concd H_2SO_4 was added. The reaction mixture was heated at this temperature for 15 min and then cooled. A solidified mass was quenched by H_2O, product(benzylidenebiscarbamate) was collected by filtration, washed with H_2O, dried and used without further purification. The suspension of obtained benzylidenebiscarbamate (0.5 mol, 0.5 equiv) and PCl_5 (1.1 mol, 2.2 equiv) in 500 mL of dry benzene was refluxed until no gas evolution observed (usually 3–4 h). The homogeneous solution was cooled, solvent and volatile substances were distilled off and the residue fractioned at reduced pressure.

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(20) **General Procedure for Preparation of 3,4-Dihydropyrimidin-2(1*H*)-ones 3.**
To the solution of appropriate ethyl β-aminocrotonate **2** (5 mmol, 1 equiv) in 20 mL of CH_2Cl_2 the solution of isocyanate **1** (5.5 mmol, 1.1 equiv) in 10 mL of CH_2Cl_2 was added dropwise. The reaction mixture was refluxed for 2 h, cooled and the solvent was evaporated. The crude product was treated with hot 70–80% aq EtOH, allowed to stand overnight at 9 °C and then collected by filtration, washed with small amount of EtOH and dried in air.

(21) **Selected Data.**
1-(4′-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (3b).
IR (KBr pellets): 3250, 3130, 1710, 1700, 1650 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2SO$–CCl_4, 2:1]: δ = 1.14 (t, *J* = 6.5 Hz, 3 H), 2.04 (s, 3 H), 4.06 (q, *J* = 6.5 Hz, 2 H), 5.27 (d, *J* = 1.0 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.35 (m, 5 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 8.14 (d, *J* = 1.0 Hz, 1 H). ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$]: δ = 14.50, 18.54, 53.65, 60.28, 104.48, 126.78, 128.03, 129.13, 129.37, 132.23, 133.13, 137.10, 144.35, 148.91, 152.36, 165.86.
1-Benzyl-4-(4′-chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (3h).
IR (KBr pellets): 3260, 3120, 1730, 1700, 1640 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2SO$–CCl_4, 2:1]: δ = 1.14 (t, *J* = 6.6 Hz, 3 H), 2.40 (s, 3 H), 4.03 (q, *J* = Hz, 2 H), 4.85 (d, *J* = 18.9 Hz, 1 H), 5.09 (d, *J* = 18.9 Hz, 1 H), 5.22 (d, *J* = 3.3 Hz, 1 H), 7.07 (d, *J* = 6.3 Hz, 2 H), 7.26 (m, 7 H), 8.15 (d, *J* = 3.3 Hz, 1 H). ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$]: δ = 14.47, 16.50, 45.43, 52.44, 60.22, 103.65, 126.62, 127.35, 128.62, 128.85, 128.95, 132.47, 139.06, 143.38, 150.30, 153.34, 165.91.

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(24) Prepared from **5** according to the general procedure for preparation of **3**.
Selected Data.
4-Ethoxycarbonyl-3-phenyl-2,3-dihydropyrimido[6,1-*c*][1,4]benzothiazin-1(1*H*)-one (6a).
IR (KBr pellets): 3240, 3140, 1710, 1650 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2SO$–CCl_4, 2:1]: δ = 1.17 (t, *J* = 6.8 Hz, 3 H), 3.54 (d, *J* = 16.5 Hz, 1 H), 4.11 (q, *J* = 6.8 Hz, 2 H), 5.17 (d, *J* = 16.5 Hz, 1 H), 5.37 (d, *J* = 4.2 Hz, 1 H), 7.29 (m, 2 H), 7.36 (m, 7 H), 8.62 (d, *J* = 4.2 Hz, 1 H). ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$]: δ = 14.46, 30.59, 53.06, 53.07, 60.97, 103.73, 126.03, 126.53, 126.70, 128.00, 128.20, 129.13, 129.25, 130.63, 135.20, 143.15, 149.59, 152.08, 165.36.
3-(3′-Bromophenyl)-4-ethoxycarbonyl-2,3-dihydropyrimido[6,1-*c*][1,4]benzothiazin-1(1*H*)-one (6c).
IR (KBr pellets): 3250, 3130, 1710, 1650 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2SO$–CCl_4, 2:1]: δ = 1.21 (t, *J* = 6.8 Hz, 3 H), 3.52 (d, *J* = 16.5 Hz, 1 H), 4.15 (m, 2 H), 5.19 (d, *J* = 16.5 Hz, 1 H), 5.35 (d, *J* = 5.1 Hz, 1 H), 7.33 (m, 8 H), 8.61 (d, *J* = 5.1 Hz, 1 H). ^{13}C NMR [75.5 MHz, $(CD_3)_2SO$]: δ = 14.45, 30.46, 52.62, 61.05, 102.91, 122.35, 125.51, 126.14, 126.73, 127.92, 129.17, 129.63, 130.68, 131.11, 131.60, 135.04, 145.78, 150.24, 151.86, 165.17.