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One-pot construction of dihydropyrimidinones in ionic liquids

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The use of the ionic liquid [bmim]Cl·2AlCl$_3$ for the preparation of dihydropyrimidinones is described.

In 1893, the Italian chemist Pietro Biginelli reported that the acid-catalysed one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea gave multifunctionalised dihydropyrimidones (DHPMs).[1] After nearly 100 years, a resurgence of interest occurred as evidenced by an increase in the number of publications and patents on both the synthesis[2–4] and biological activity[5–10] of these compounds. Antiviral, antitumor, antibacterial, potent calcium channel blocking and anti-inflammatory activities were ascribed to DHPMs. However, the Biginelli synthesis of DHPMs suffers from relatively low yields of products, in particular, when substituted aromatic aldehydes or thioureas are employed.[3,11–14] This has led to the recent disclosure of several improved synthetic protocols for DHPMs, which involve either modification of the Biginelli synthesis[11] or the development of novel but more complex multistep strategies.[11–14] In addition, several combinatorial solid-phase approaches have been reported that use microwave conditions.[15,16]

The Biginelli synthesis is an example of the use of less toxic chemicals. Thus, the use of catalysts that contain both Lewis acid and transition metal salts, *e.g.*, BF_3–OEt_2,[17] montmorillonite(KSF),[18] polyphosphate ester[19] and reagents such as $InCl_3$,[20] LiBr,[21] $CeCl_3 \cdot H_2O$[22] and $Mn(OAc)_3 \cdot 2H_2O$[23] gave better yields of DHPMs.

Ionic liquids are environmentally benign alternative solvents for various chemical processes. They have attracted the attention of chemists owing to their unique physical and chemical properties.[24,25] Because of their low vapour pressure, ionic

Table 1 Dihydropyrimidinones **4a–s**[a] produced according to Scheme 1.

Entry	R^1	R^2	X	*t*/min	Yield[b] (%)	Found mp[c]/°C	Reported mp/°C
4a	4-$NO_2C_6H_4$	Me	O	80	97	231–232 (decomp.)	230 (decomp.)[13]
4b	3-$NO_2C_6H_4$	Me	O	90	95	268–270 (decomp.)	267–269 (decomp.)[31]
4c	Pr	Me	O	75	94	151–152	152–154[31]
4d	Ph	Me	O	50	98	235–236	235–236[13]
4e	3-$NO_2C_6H_4$	OMe	O	60	92	239–240 (decomp.)	240–241 (decomp.)[31]
4f	4-$NO_2C_6H_4$	OMe	O	70	95	237–239	235–237[29]
4g	Ph	OMe	O	90	94	210–213	209–216[13]
4h	2-ClC_6H_4	OMe	O	80	89	226–228	226–229[32]
4i	Et	OMe	O	55	90	184–186	184–185[31]
4j	Pr	OMe	O	80	93	173–175	174–175[31]
4k	4-$MeOC_6H_4$	OMe	O	60	97	194–196	191–193[13]
4l	Ph	OEt	O	45	90	205–207	203–205[23]
4m	3-$NO_2C_6H_4$	OEt	O	60	91	227–229	227–228[23]
4n	4-$NO_2C_6H_4$	OEt	O	90	96	202–204	201–202[31]
4o	2-ClC_6H_4	OEt	O	70	88	214–216	214–215[23]
4p	Et	OEt	O	60	96	179–183	179[23]
4q	Me_2CHCH_2	OEt	O	75	87	185–186	185–186[23]
4r	4-$MeOC_6H_4$	OEt	O	80	95	209–212	207–210[13]
4s	Ph	OEt	S	90	91	209–211	208–210[32]

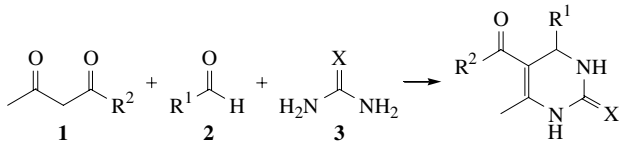
[a]All compounds are characterised by IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. [b]The optimised yield is based on the crystalline product obtained. [c]Melting points are uncorrected.

species do not contribute to volatile organic compound emission. They have also been referred to as 'designer solvents'[26] since their properties can be altered by the fine tuning of parameters such as the choice of the organic cation, inorganic anion and alkyl chain attached to the organic cation. These structural variations provide an opportunity to devise the most idealised solvent needed for a particular chemical process. Several reactions have been carried out in ionic liquids[27] including the Biginelli, Diels–Alder, Wittig and Pechman reactions, the benzoin condensation, catalytic hydrogenation and several enzyme catalysed reactions.[28]

Chloroaluminate ionic liquids have been used in Friedel–Crafts and other reactions where they play the dual role of both the Lewis acid catalyst and the solvent.[27] Thus, we decided to investigate the Biginelli synthesis under these conditions. Here we report a new synthesis of DHPMs in the presence of the Lewis acid [bmim]Cl·2$AlCl_3$ ionic liquid.

The composition of ionic liquids is expressed as the apparent mole fraction of $AlCl_3$, *N*. Accordingly, they are classified as basic, neutral and acidic liquids when *N* is 0–0.5, 0.5 and 0.5–0.67, respectively. The reaction of (thio)ureas, aldehydes and α-ketoesters was carried out in liquids with $N = 0.33$, 0.5 and 0.67, respectively. Positive results were obtained only in case of acidic ionic liquids as expected.

In order to study the effect of substituents on the reactivity of the reactants, a variety of aliphatic and aromaic aldehydes were used. The results are given in Table 1.† In comparison with reported procedures,[29] the reaction time for the complete



Scheme 1

† The purity of compounds was checked by TLC. The IR spectra were recorded on a JASCO spectrophotometer (Japan) using KBr pellets. The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were measured on a FT-NMR spectrophotometer model Ac-300 F (Bruker, Germany) at 300 MHz using TMS as an internal standard. Satisfactory microanalysis data (±0.4% of calculated values) were obtained for all the compounds.

Typical experimental procedure. To a stirred mixture of urea or thiourea (2.6 mmol), an appropriate α-ketoester (2 mmol) and an aldehyde (2 mmol), the ionic liquid [bmim]Cl·2$AlCl_3$ (11 mmol) was added, and the reaction mixture was stirred for an appropriate time at room temperature. The reaction mixture was quenched with cold 6 M HCl (15 ml). The precipitate was filtered off, and the solid was purified by column chromatography (ethyl acetate–hexane) and characterised by IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

*5-Aceto-4-propyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4c**: mp 151–152 °C. ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 8.94 (s, 1H, NH), 7.42 (s, 1H, NH), 4.09 (t, 1H, H-4, *J* 3.2 Hz), 2.18 (s, 3H, COMe), 2.16 [s, 3H, C(6)–Me], 1.20 (m, 4H, CH_2CH_2Me), 0.82 (t, 3H, CH_2CH_2*Me*, *J* 7.0 Hz). ^{13}C NMR, δ: 194.5, 153.3, 147.8, 111.1, 50.5, 30.6, 19.3, 17.6, 14.2. IR (KBr, ν/cm^{-1}): 3247, 3113, 2956, 1723, 1625. MS (70 eV, EI), *m*/*z*: 196 (M^+, 1.27%).

*5-Methoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4e**: mp 239–240 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 9.31 (s, 1H, NH), 8.09–8.13 (m, 2H, Ar–H), 7.85 (s, 1H, NH), 7.63–7.70 (m, 2H, Ar–H), 5.31 (d, 1H, H-4, *J* 3.0 Hz), 3.35 (s, 3H, COOMe, *J* 3.0 Hz), 2.28 [s, 3H, C(6)–*Me*]. ^{13}C NMR, δ: 165.5, 151.7, 149.6, 147.8, 146.6, 132.8, 130.1, 122.3, 120.8, 98.0, 53.3, 50.8, 17.8. IR (KBr, ν/cm^{-1}): 3358, 3244, 3102, 2957, 1701, 1641. MS (70 eV, EI), *m*/*z*: 291 (M^+, 5.86%).

*5-Methoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4h**: mp 226–228 °C. ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 9.21 (s, 1H, NH), 7.59 (s, 1H, NH), 7.25–7.40 (m, 4H, Ar–H), 5.62 (d, 1H, H-4, *J* 2.5 Hz), 3.45 (s, 3H, COOMe), 2.30 [s, 3H, C(6)–Me]. ^{13}C NMR, δ: 165.4, 151.3, 149.3, 141.4, 131.6, 129.4, 129.0, 128.6, 127.6, 97.6, 51.3, 50.6, 17.6. IR (KBr, ν/cm^{-1}): 3367, 3221, 3103, 2948, 1714, 1698. MS (70 eV, EI), *m*/*z*: 280 (M^+, 5.13%).

*5-Methoxycarbonyl-4-ethyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4i**: mp 184–186 °C. ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 8.96 (s, 1H, NH), 7.30 (s, 1H, NH), 4.01 (m, 1H, H-4), 3.59 (s, 3H, COOMe), 2.16 [s, 3H, C(6)–Me], 1.39 (q, 2H, CH_2Me, *J* 7.5 Hz), 0.77 (t, 3H, CH_2*Me*, *J* 7.5 Hz). ^{13}C NMR, δ: 165.9, 152.7, 148.6, 98.5, 51.3, 50.7, 29.5, 17.7, 8.4. IR (KBr, ν/cm^{-1}): 3249, 3118, 2961, 1728, 1708, 1680. MS (70 eV, EI), *m*/*z*: 198 (M^+, 0.59%).

*5-Methoxycarbonyl-4-propyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4j**: mp 173–175 °C. ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 8.94 (s, 1H, NH), 7.31 (s, 1H, NH), 4.03 (t, 1H, H-4, *J* 3.2 Hz), 3.59 (s, 3H, COOMe), 2.15 [s, 3H, C(6)–Me], 1.19–1.40 (m, 4H, CH_2CH_2Me), 0.82 (t, 3H, CH_2CH_2*Me*, *J* 6.7 Hz). ^{13}C NMR, δ: 165.8, 152.6, 148.3, 99.1, 50.6, 49.8, 17.6, 16.9, 13.6. IR (KBr, ν/cm^{-1}): 3442, 3252, 3123, 2957, 1726, 1708, 1653. MS (70 eV, EI), *m*/*z*: 212 (M^+, 0.43%).

*5-Ethoxycarbonyl-4-ethyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4p**: mp 185–186 °C. ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 8.82 (s, 1H, NH), 7.18 (s, 1H, NH), 4.03–4.09 (m, 3H, H-4 and OCH_2Me), 2.16 [s, 3H, C(6)–*Me*], 1.41 (m, 2H, CH_2Me), 1.17 (t, 3H, OCH_2*Me*, *J* 6.0 Hz), 0.78 (t, 3H, CH_2*Me*, *J* 7.5 Hz). ^{13}C NMR, δ: 165.3, 152.6, 148.1, 98.7, 58.8, 51.2, 29.4, 17.5, 14.0 and 8.31. IR (KBr, ν/cm^{-1}): 3250, 3123, 2962, 1723, 1703, 1675. MS (70 eV, EI), *m*/*z*: 212 (M^+, 0.43%).

*5-Ethoxycarbonyl-4-isobutyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one* **4q**: mp 185–186 °C. ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 8.86 (s, 1H, NH), 7.32 (s, 1H, NH), 4.01–4.10 (m, 3H, H-4 and OCH_2Me), 2.16 [s, 3H, C(6)–Me], 1.69 (m, 1H, CH_2C*H*Me_2), 1.35 (m, 1H, CH_2C*H*Me_2), 1.17 (t, 3H, OCH_2*Me*, *J* 7.0 Hz), 1.10 (m, 1H, CH_2C*H*Me_2), 0.85 (d, 6H, CH_2CHMe_2, *J* 6.5 Hz). ^{13}C NMR, δ: 165.1, 152.6, 147.9, 100.2, 58.8, 48.1, 45.8, 23.5, 22.7, 21.3, 17.4, 14.0. IR (KBr, ν/cm^{-1}): 3447, 3244, 3112, 2951, 1701, 1652. MS (70 eV, EI), *m*/*z*: 241 (M^+ + 1, 1.08%).

conversion of starting materials **1**, **2** and **3** into products **4** is considerably reduced and the yields of the products are higher. The method works equally well for urea, thiourea and aliphatic or aromatic aldehydes. Compounds containing electron-withdrawing or electron-releasing groups give the best yield and the highest purity. Furthermore, the ionic system used acted as both a Lewis acid catalyst and a solvent, which is important in reactions where stoichiometric amounts are used.

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