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N,N′-Dichlorobis(2,4,6-trichlorophenyl)urea (CC-2) as a new reagent for the synthesis of pyrimidone and pyrimidine derivatives via Biginelli reaction

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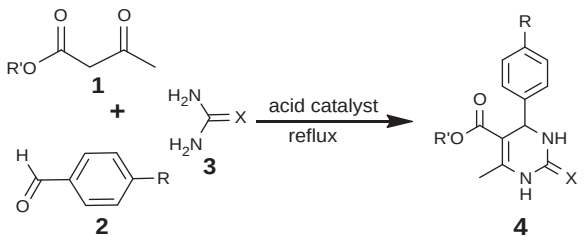
ABSTRACT

A simple and efficient method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)one and benzo[4,5]imidazo/thioazo[1,2-*a*]pyrimidine derivatives has been described using *N,N′*-dichlorobis(2,4,6-trichlorophenyl)urea (CC-2) as a new reagent. This method is found to be efficient and convenient for the synthesis of pyrimidone and pyrimidine derivatives.

Multicomponent reactions have gained increasing attention for the synthesis of new heterocycles of medicinal importance.[1–3] Medicinal chemistry relies on robust, reliable reactions, facilitating the rapid development of new chemical entities (NCE's) available for bio-evaluation. In this area, Biginelli reaction is one of the most versatile reactions for the selective construction of heterocycles. The simple and straightforward procedure reported by Biginelli[4] in 1893 involves a three component condensation reaction of β-ketoesters (**1**), arylaldehyde (**2**), and urea (**3**) to give 3,4-dihydropyrimidin-2-(1*H*)one (DHPMs, **4**) (Scheme 1) in one-pot. The DHPMs derivatives have received considerable attention in recent years essentially because of their importance in medicinal chemistry.[5–8] Due to the pharmacological importance, several protocols aimed to improve the Biginelli reaction have been reported using commercially available reagents.[9–15] However, most of reagents have been used for conventional reactants (e.g., aryl aldehyde, β-ketoesters, and urea/thiourea) only. The Biginelli reactions with alternative reactants[16–21] other than urea have gained wide interest because of pharmaceutical significance. Recently, 2-aminobenzimidazoles/2-aminobenzothioazoles derivatives as alternates to urea have been reported.[16] However, the reported methods of Biginelli reaction with these alternates suffer from several drawbacks, such as longer reaction time, harsh reaction conditions, difficulties in the isolation of products, formation of by-products, and lower yields. Therefore, development of a new reagent with a wide range of structure diversity is needed. In continuation of our work on the synthesis of biologically active compounds[15b] there was a need to synthesize a library of Biginelli products with urea and other substituents. We performed a number of reactions with various reported reagents (Table 1). However, most of the reagents were applicable only for a small range of reactants. So the development of a new reagent with wide applicability was required.

N,N′-Dichlorobis(2,4,6-trichlorophenyl)urea (CC-2),[22,23] is a mild, stable, safe reagent and has high active chlorine content (14.54%). The reagent has been used for various organic transformations.[24,25] CC-2 releases active chlorine and gets converted into an insoluble mass 1,3-bis(2,4,6-trichlorophenyl)urea. The insoluble mass can be easily separated by simple filtration and can be



Scheme 1. Biginelli reaction.

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Table 1
Comparison of CC-2 with various reagents[a,b]

Entry	Urea/alternate	Reagent	Time (h)	Yield (%)[c,ref]
1	Urea	$CaCl_2$	2	98[15a]
2	Urea	$SiOCl_2$	3	90[15b]
3	Urea	Ph_3P	10	58[15c]
4	Urea	$Yb(OTf)_3$	6	96[15d]
5	Urea	$Bi(NO_3)_3$	6	80[15e]
6	Urea	CC-2	3	98
7	2-Aminobenzimidazole	$CaCl_2$	10	35
8	2-Aminobenzimidazole	$SiOCl_2$	9	15
9	2-Aminobenzimidazole	Ph_3P	12	45
10	2-Aminobenzimidazole	$Yb(OTf)_3$	15	65
11	2-Aminobenzimidazole	$Bi(NO_3)_3$	15	60
12	2-Aminobenzimidazole	CC-2	5	82
13	2-Aminobenzothioazole	$CaCl_2$	12	28
14	2-Aminobenzothioazole	$SiOCl_2$	11	30
15	2-Aminobenzothioazole	Ph_3P	14	30
16	2-Aminobenzothioazole	$Yb(OTf)_3$	16	45
17	2-Aminobenzothioazole	$Bi(NO_3)_3$	16.5	40
18	2-Aminobenzothioazole	CC-2	6.5	75

[a] Reaction conditions: 4-methoxy benzaldehyde (1.0 equiv), ethyl acetoacetate (1.0 equiv), urea/alternate (1.2 equiv) and CC-2 (0.3 equiv) in ethanol as solvent under reflux conditions.
[b] Reaction conditions for other reagents was same as in literature.[15a–e]
[c] Isolated yield.

converted back to CC-2 by the reaction with $AcOH/Cl_2/NaOH$.[26] Due to these advantages, we attempted the use of this reagent for the Biginelli reaction with urea and other alternatives. Herein, we describe *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea (CC-2) as a versatile reagent for Biginelli and modified Biginelli reactions.

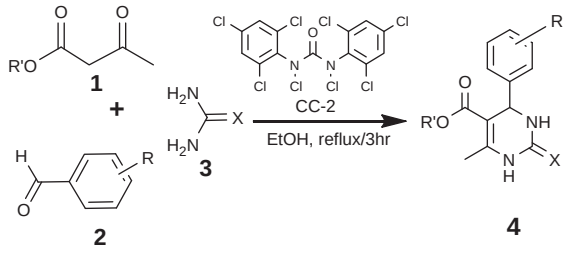
In order to optimize the reaction conditions, 4-methoxy benzaldehyde, ethyl acetoacetate and urea were taken as model reactants in ethanol under reflux conditions (Table 1, entry 6). It was observed that when aryl aldehydes, acetoacetate, urea, and CC-2 were used in the ratio of 1:1:1.2:0.3 in ethanol, it gave the best result. Additionally, we found that CC-2 was also compatible to carry out Biginelli reaction with other alternatives (**5**) to urea (Table 1, entries 12 and 18). The CC-2 was further compared with other reported reagents of the Biginelli reaction (Table 1) and it was revealed that only CC-2 gave the best results with urea and other substituents with respect to reaction time and yield.

The optimized reaction conditions were further extended to a wide range of reactants and the results have been summarized (Table 2). In addition, various pyrimidine derivatives were also synthesized using 2-aminobenzimidazole/ 2-aminobenzothioazole as alternatives to urea using CC-2 in a Biginelli like reaction (Table 3). The conversion was found to be modest with 2-aminobenzimidazole/benzothioazole. This might be due to lower conversion to the imine intermediate. The rate of formation of desired product was also found to be modest with substituted benzaldehydes especially at position 3 (Table 3, entries 7 and 10) and with higher aryl aldehydes (Table 3, entries 13 and 14). The modest yield might be because of steric hindrance in the formation of Schiff's base.

On the basis of the above observations and the literature reports, a plausible mechanism for the Biginelli reaction with CC-2 is depicted (Scheme 2). The first step of the reaction involves the electrophilic attack of positive chlorine on the imine formed by the reaction of urea and aldehyde.[13c] The activated imine (2) attacks on alkyl acetoacetate to give final product DHPMs. The nitronium ion formed on CC-2 after release of active chlorine picks up the proton from water and results in the formation of 1,3-bis(2,4,6-trichlorophenyl)urea.[22]

In conclusion, we have demonstrated the application of CC-2 for the synthesis of diversified pyrimidones and pyrimidines by three component coupling in one-pot. According to the conversion and reaction work-up, CC-2 was found to be an efficient and convenient reagent. The important advantages of this method are a simple work-up procedure, wide applicability and recyclability of the by-product formed during the reaction.

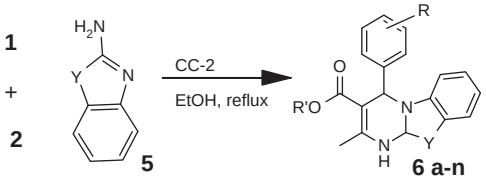
Table 2
Preparation of dihydropyrimidinones[a]



Entry	R	R′	X	Yield[b] (%)	Mp (°C)	
					Observed	Reported[ref]
1	H	C_2H_5	O	93	200–202	202–204[15a]
2	4-OCH_3	C_2H_5	O	98	196–198	200–201[15a]
3	4-OH	C_2H_5	O	88	200–202	199–200[15a]
4	4-F	C_2H_5	O	85	180–182	182–184[15b]
5	4-$N(CH_3)_2$	C_2H_5	O	91	228–230	230–232[15a]
6	4-CH_3	C_2H_5	S	82	194–196	192–194[15c]
7	4-OH	CH_3	O	84	242–244	245–246[13a]
8	4-OCH_3	CH_3	S	80	152–154	150–152[13b]
9	4-NO_2	CH_3	O	90	233–235	235–237[15a]
10	4-F	CH_3	O	85	193–195	192–194[13c]
11	4-OCH_3	CH_3	O	86	194–196	192–194[15a]
12	3-OCH_3	CH_3	O	80	204–206	207–208[13d]
13	H	C_2H_5	S	90	202–204	206–207[15c]

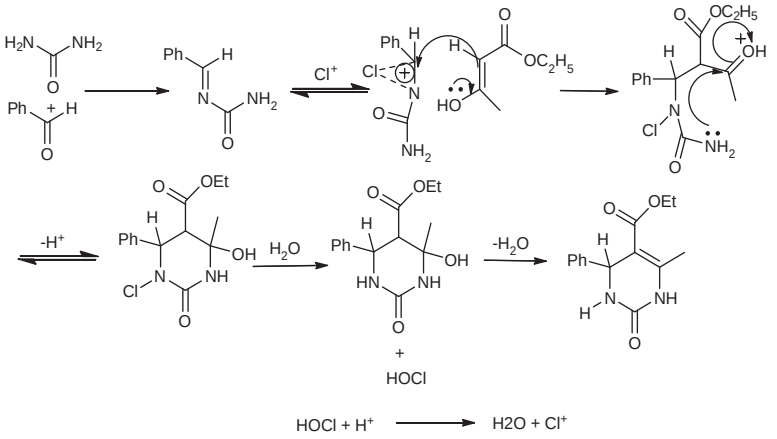
See Ref. 27 for general procedure.
[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), **3** (1.2 equiv) and CC-2 (0.3 equiv) in refluxed ethanol for 3 h.
[b] Isolated yield.

Table 3
Biginelli reaction with 2-aminobenzimidazole/2-aminobenzothioazole[a]



Entry	R	R′	Y	Product	Time (h)	Yield[b,ref] (%)
1	4-OCH_3	C_2H_5	N	**6a**	5	82[16]
2	4-OC_2H_5–	C_2H_5	N	**6b**	5	78
3	4-C_2H_5–	C_2H_5	N	**6c**	5.5	76[16]
4	4-Me_2CH–	C_2H_5	N	**6d**	6.5	72[16]
5	4-F–	C_2H_5	N	**6e**	6	68[16]
6	4-NO_2–	C_2H_5	N	**6f**	6	70[16]
7	3-NO_2–	CH_3	N	**6g**	7	68
8	4-OH–	C_2H_5	N	**6h**	6	71
9	4-OCH_3	C_2H_5	S	**6i**	6.5	75[16]
10	3-OH–	C_2H_5	S	**6j**	6.5	66
11	4-Me_2N–	C_2H_5	S	**6k**	6.5	65
12	4-CF_3–	C_2H_5	S	**6l**	8	58[16]
13	3,4,5-$(OMe)_3$–	CH_3	N	**6m**	8	55
14	Indol-	CH_3	N	**6n**	10	55

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), **5** (1.2 equiv) and CC-2 (0.3 equiv) using EtOH as solvent under reflux condition.
[b] Isolated yield.



Scheme 2. Proposed mechanism with urea.

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27. *General procedure*: A 25 ml R.B flask was charged with urea (2.4 mmol) and aromatic aldehyde (2 mmol). The mixture was stirred for ½ h. The β-ketoester (2 mmol) and CC-2 in protic solvent (ethanol) was added to the above mixture. The reaction mixture was refluxed at 70 °C with stirring till the reaction was complete. The reaction mixture was then filtered and the solvent was evaporated under reduced pressure. The solid mass was washed with cold diethylether (15 ml × 3) and dried. The product was obtained in 55–98% yield. The spectral data for some compounds are given below.
4-(4-Ethoxyphenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2,a]-3-ethylcarboxylate **6b**: mp = 290–291 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 6.8 Hz, 3H), 2.73 (s, 3H), 3.97 (q, J = 6.8 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 6.40 (s, 1H), 6.77 (d, J = 6.0 Hz, 2H), 7.02–7.06 (m, 1H), 7.13–7.17 (m, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 6.0 Hz, 2H), 7.53 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 14.75, 19.02, 55.33, 61.02, 63.85, 98.96, 110.03, 114.29, 119.78, 122.52, 128.36, 128.56, 133.31, 140.92, 145.51, 146.42, 158.15, 165.70. ESI-MS: m/z = 378. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13; O, 12.72. Found: C, 70.08; H, 6.07; N, 11.18; O, 12.67.
4-(3-Nitrophenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2,a]-3-methylcarboxylate **6g**: mp ⩾ 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.49 (s, 3H), 3.58 (s, 3H), 6.66 (s, 1H), 6.93–6.97 (m, 1H), 7.03–7.07 (m, 1H), 7.29 (d, J = 8.0, 1H), 7.37 (d, J = 8.0, 1H), 7.55–7.59 (m, 1H), 7.78 (d, J = 8.0, 1H), 8.06 (d, J = 8.0, 1H), 8.21 (s, 1H), 10.98 (s, 1H). ^{13}C NMR (DMSO-d_6) δ = 18.77, 50.86, 55.07, 97.04, 109.80, 116.96, 120.52, 121.45, 122.06, 122.84, 130.17, 131.26, 133.43, 142.18, 144.09, 145.33, 147.56, 147.76, 165.45. ESI-MS: m/z = 365.41. Anal. Calcd for $C_{19}H_{16}N_4O_4$: C, 62.63; H, 4.43; N, 15.38; O, 17.56. Found: C, 62.68; H, 4.38; N, 15.45; O, 17.49.
4-(4-Hydroxyphenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2,a]-3-ethylcarboxylate **6h**: mp ⩾ 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (t, J = 6.8 Hz, 3H), 2.43 (s, 3H), 4.01 (q, J = 6.8 Hz, 2H), 6.30 (s, 1H), 6.63 (d, J = 8.4 Hz, 2H), 6.92–6.96 (m, 1H), 7.00–7.04 (m, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.0, 1H), 7.33 (d, J = 8.0, 1H), 9.35 (s, 1H), 10.68 (s,1H). ^{13}C NMR(DMSO-d_6) δ = 18.52, 56.07, 75.39, 79.82, 83.90, 98.33, 113.67, 114.50, 114.99, 119.66, 127.73, 128.65, 131.13, 132.50, 145.91, 156.84, 165.29. ESI-MS: m/z = 304.63. Anal. Calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03; O, 13.74. Found: C, 68.72; H, 5.46; N, 12.07; O, 13.75.
4-(3-Hydroxyphenyl)-2-methyl-1,4-dihydro benzo[4,5]thioazo[1,2,a]-3-ethyl-carboxylate **6j**: mp = 210–212 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 (t, J = 7.2 Hz, 3H), 2.44 (s, 3H), 4.03 (q, J = 7.2 Hz, 2H), 5.81 (s,1H), 6.33 (s, 1H), 6.66–6.67 (m, 1H), 6.95 (s, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.06 (s, 1H), 7.21 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 9.34 (s, 1H), 10.74 (s, 1H). ^{13}C NMR (DMSO-d_6) δ = 14.13, 14.72, 56.42, 59.37, 80.13, 97.98, 113.14, 116.34, 117.17, 117.94, 128.58, 129.77, 131.58, 142.30, 143.31, 146.21, 157.34, 165.23. ESI-MS: m/z = 369. Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.16; H, 5.72; N, 7.95; O, 12.08; S, 9.09%. Found: C, 65.14; H, 5.73; N, 7.96; O, 12.11; S, 9.06%.
4-(4-Dimethylaminophenyl)-2-methyl-1,4-dihydro-benzo[4,5]thioazo[1,2,a]-3-ethylcarboxylate **6k**: M.P = 232–234 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 2.72 (s, 3H), 2.87 (s, 6H), 4.16 (q, J = 7.2 Hz, 2H), 5.81 (s, 1H), 6.37 (s, 1H), 6.59 (d, J = 8.0 Hz, 2H), 7.17–7.20 (m, 1H), 7.24–7.26 (m, 3H), 7.51 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.32, 14.96, 56.00, 59.23, 98.46, 109.57, 111.34, 112.24, 120.57, 120.87, 127.10, 128.22, 129.42, 131.58, 142.32, 145.59, 149.71, 165.30. ESI-MS: m/z = 396.42. Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88; O, 8.50. Found: C, 70.22; H, 6.38; N, 14.93; O, 8.47.
4-(3,4,5-Trimethoxyphenyl)-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2,a]-3-methylcarboxylate **6m**: mp ⩾ 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.45 (s,

3H), 3.56 (s, 3H), 3.61 (s, 3H), 3.68 (s, 6H), 6.39 (s, 1H), 6.63 (s, 2H), 6.96–7.00 (m, 1H), 7.03–7.07 (m, 1H), 7.34–7.39 (m, 2H), 10.76 (s, 1H). ^{13}C NMR (DMSO-d_6) δ = 18.5, 50.7, 55.8, 59.8, 97.7, 104.3, 110.0, 116.7, 120.2, 121.7, 131.5, 137.5, 142.2, 145.6, 152.7, 165.7. ESI-MS: m/z = 409. Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26; O, 19.54. Found: C, 64.39; H, 5.63; N, 10.31; O, 19.57.

4-Indol-2-methyl-1,4-dihydro-benzo[4,5]imidazo[1,2,a]-3-methylcarboxylate **6n**: mp $\geqslant$ 300 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.43 (s, 3H), 3.55 (s, 3H), 6.75 (s, 1H), 6.86–6.90 (m, 2H), 6.95–6.99 (m, 2H), 7.21 (d, J = 8 Hz, 1H), 7.26–7.29 (m, 3H), 7.58 (s, H), 10.83 (s, 1H), 11.00 (s, 1H). ^{13}C NMR (DMSO-d_6) δ = 18.51, 49.14, 61.20, 97.40, 97.44, 109.26, 114.83, 119.62, 120.80, 120.92, 121.38, 124.46, 131.75, 134.81, 136.32, 142.27, 145.23, 145.94, 166.00. ESI-MS: m/z = 359.59. Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63; O, 8.93. Found: C, 70.42; H, 5.01; N, 15.69; O, 8.88.