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A Novel and Efficient One-Pot Method to Biginelli-Like Scaffolds

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A novel and efficient one-pot method for the preparation of fused ring 3,4-dihydropyrimidin-2(1*H*)-ones and thiones from cyclocondensation of aldehydes, cyclic ketones and urea or thiourea using a catalytic amount of cupric chloride under mild conditions reaction is described. This new method has the advantage to give high yields, to be completed in short reaction times and simple product isolation procedure.

Keywords: Biginelli-like scaffold, Fused ring, 3,4-Dihydropyrimidin-2(1*H*)-ones, Thiones, Cupric chloride

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 reaction was reported over one century ago, and yet considerable interest in this transformation has steadily increased [2]. Dihydropyrimidinones derivatives have attracted great attention recently in synthetic organic chemistry due to their pharmacological and therapeutic properties such as the antibacterial, antiviral, antitumor, anti-inflammatory [3] and antihypertensive activity as well as calcium channel blockers [4], α-1a-antagonists [5], and neuropeptide Y (NPY) antagonists [6].

The classical Biginelli reaction involves one-pot condensation of an aldehyde, a β-ketoester and urea under strongly acidic conditions. In recent years, interest in this reaction has increased rapidly and several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis have been reported [7]. Biginelli reaction was enlarged by the variation of the 1,3-dicarbonyl compound building blocks [8], including the use of β-keto carboxylic acid [9], cycloalkanones [10] cyclic ketones and substituted α-keto acids [11], or acyclic and cyclic ketones [12]. For example, Abelman *et al*. [11a] described the HCl-catalyzed synthesis of Biginelli-like scaffolds by the condensation of cyclic ketones, urea, and aldehydes under refluxing ethanol for 24 h.

In this connection, we have envisioned the use of cyclic ketones instead of β-ketoester to prepare corresponding Biginelli-like scaffolds. In continuation of our investigations in the Biginelli reaction [13], herein we describe a simple and efficient method for the novel Biginelli-like scaffolds three-component cyclocondensation reactions of aldehydes, cyclic ketones and urea or thiourea for the synthesis of fused ring 3,4-dihydropyrimidin-2(1*H*)-one and thione derivatives using $CuCl_2$ as catalyst under mild conditions.

EXPERIMENTAL

Melting points were determined in evacuated capillaries with a Buchi B-545 apparatus. GC/MS analysis was performed on a FISON GC 8000 series TRIO 1000 gas chromatograph equipped with a capillary column CP Sil.5 CB,

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60 M × 0.25 mm Id. ^{1}H NMR spectra were recorded on a Bruker 500 spectrometer using TMS as internal standard. Infrared (IR) spectra were recorded from KBr disks with a Bruker Vector 22 FT-IR spectrometer. Elemental analyses were performed on a ThermoFinigan Flash EA 1112 series elemental analyzer.

Typical Procedure for Fused Ring 3,4-Dihydropyrimidin-2(1*H*)-ones and Thiones Derivatives

To a solution of aldehyde **1-5** (2 mmol) and urea or thiourea (3 mmol) in CH_3CN (10 ml) was added cupric chloride (10 mol%), TMSCl (2 mmol) and α-tetralone or 1-indanone (2 mmol). The reaction mixture was heated at reflux of solvent for 8 h. After the completion of the reaction, the mixture was poured into crushed ice and after stirring, it was directly filtrated through a sintered funnel and washed by ethylacetate-hexane (1:3). For further purification, the product was purified by recrystallization from ethanol. Spectroscopic data for the compounds **6-12a-b**:

Compound 6a [11a, b, 13b] (entry 1, Table 2). m.p.: 275-277 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.77 (m, 1H, CH_2), 2.13 (m, 1H, CH_2), 2.58 (m, 1H, CH_2), 2.71 (m, 1H, CH_2), 4.93 (s, 1H, CH), 7.14-7.38 (m, 9H, 8CH arom. and NH), 7.58 (d, *J* = 7.3 Hz, 1H, CH arom.), 8.53 (s, 1H, NH); MS: m/z (%) 276 (45) (M^+), 260 (3), 248 (5), 232 (11), 199 (100), 181 (11), 114 (21), 89 (10), 77 (27); IR (KBr): ν 3331, 3232, 3088, 2939, 2362, 1681, 1487, 1429, 1340, 1290, 763 cm^{-1}; Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14%, Found: C, 77.47; H, 5.82; N, 10.05%.

Compound 6b (entry 2, Table 2) firstly reported. m.p.: 245-246 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.86 (m, 1H, CH_2), 2.06 (m, 1H, CH_2), 2.60 (m, 1H, CH_2), 2.74 (m, 1H, CH_2), 4.98 (s, 1H, CH), 7.16-7.25 (m, 3H, CH arom.), 7.30-7.41 (m, 5H, CH arom.), 7.71 (d, *J* = 7.4 Hz, 1H, CH arom.), 9.07 (s, 1H, NH), 9.68 (s, 1H, NH); MS: m/z (%) 292 (98) (M^+), 259 (22), 215 (100), 127 (60), 114 (36), 77 (26); IR (KBr): ν 3379, 3161, 2968, 2362, 1672, 1564, 1500, 1452, 1197, 1136, 823, 767, 734, 700 cm^{-1}; Anal. Calcd. for $C_{18}H_{16}N_2S$: C, 73.94; H, 5.52; N, 9.58%, Found: C, 70.23; H, 5.33; N, 10.01%.

Compound 7a [11a, 13b] (entry 3, Table 2). m.p.: 276-278 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.80 (d, *J* = 22.6 Hz, 1H, CH_2), 3.27 (d, *J* = 22.7 Hz, 1H, CH_2), 5.46 (d, *J* = 0.7 Hz, 1H, CH), 7.14-7.17 (m, 1H, CH arom.), 7.19 (br, s, 1H, NH), 7.25-7.39 (m, 7H, CH arom.), 7.62 (d, *J* = 7.5 Hz, 1H, CH arom.), 9.34 (s, 1H, NH); MS: m/z (%) 261 (50) (M^+), 243 (3), 231 (4), 216 (17), 185 (100), 115 (22), 89 (7), 77 (28); IR (KBr): ν 3402, 3329, 3205, 3088, 2999, 2958, 2366, 1678, 1460, 1355, 773, 744 cm^{-1}; Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68%, Found: C, 77.46; H, 5.38; N, 10.60%.

Compound 8a [13b] (entry 4, Table 2). m.p.: 219-221°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.76 (m, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.59 (m, 1H, CH_2), 2.73 (m, 1H, CH_2), 5.14 (s, 1H, CH), 7.15-7.23 (m, 3H, CH arom.), 7.43 (s, 1H, NH), 7.60-7.62 (m, 3H, CH arom.), 8.25 (d, *J* = 8.7 Hz, 2H, CH arom.), 8.67 (s, 1H, NH). MS: m/z (%) 321 (31) (M^+), 320 (12), 274 (14), 305 (3), 293 (4), 277 (5), 199 (100), 181 (18), 115 (33), 89 (9), 76 (6); IR (KBr): ν 3404, 3334, 3242, 3107, 2927, 2360, 1670, 1598, 1517, 1467, 1344, 1269, 826, 812, 763, 731 cm^{-1}; Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08%, Found: C, 67.19; H, 4.55; N, 12.80%.

Compound 8b (entry 5, Table 2) firstly reported. m.p.: 199-200 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.85 (m, 1H, CH_2), 2.24 (m, 1H, CH_2), 2.62 (m, 1H, CH_2), 2.75 (m, 1H, CH_2), 5.22 (s, 1H, CH), 7.17-7.25 (m, 3H, CH arom.), 7.61 (d, *J* = 8.6 Hz, 2H, CH arom.), 7.75 (d, *J* = 6.9 Hz, 1H, CH arom.), 8.28 (d, *J* = 8.6 Hz, 2H, CH arom.), 9.30 (s, 1H, NH), 9.92 (s, 1H, NH); MS: m/z (%) 337 (57) (M^+), 336 (18), 305 (7), 290 (7), 215 (100), 127 (24), 115 (22), 76 (15); IR (KBr): ν 3186, 2972, 2935, 2366, 1674, 1566, 1500, 1346, 1195, 1018, 856, 815, 765, 734 cm^{-1}.

Compound 9a [12a] (entry 6, Table 2) firstly reported. m.p.: 229-231 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.76 (m, 1H, CH_2), 2.12 (m, 1H, CH_2), 2.59 (m, 1H, CH_2), 2.71 (m, 1H, CH_2), 4.97 (s, 1H, CH), 7.14-7.28 (m, 3H, CH arom.), 7.31 (s, 1H, NH), 7.35 (d, *J* = 8.4 Hz, 2H, CH arom.), 7.42 (d, *J* = 8.4 Hz, 2H, CH arom.), 7.58-7.64 (m, 1H, CH arom.), 8.59 (s, 1H, NH); MS: m/z (%) 312 (6) $(M+2)^+$, 310 (35) (M^+), 309 (50), 307 (17), 294 (3), 281 (7), 266 (5), 251 (3), 199 (100), 181 (12), 115 (20), 89 (15), 77 (10); IR (KBr): ν 3336, 3232, 3088, 2935, 2364, 1670, 1641, 1485, 1429, 1369, 1321, 1286, 769, 732 cm^{-1}; Anal. Calcd. for $C_{18}H_{15}ClN_2O$: C, 69.57; H, 4.86; N, 9.01%, Found: C, 68.96; H, 4.67; N, 9.08%.

Compound 9b (entry 7, Table 2) firstly reported. m.p.: 252-254 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.85 (m, 1H,

CH_2), 2.19 (m, 1H, CH_2), 2.62 (m, 1H, CH_2), 2.74 (m, 1H, CH_2), 5.01 (d, *J* = 2.1 Hz, 1H, CH), 7.16-7.25 (m, 3H, CH arom.), 7.35 (d, *J* = 8.4 Hz, 2H, CH arom.), 7.45 (d, *J* = 8.4 Hz, 2H, CH arom.), 7.71 (d, *J* = 7.4 Hz, 1H, CH arom.), 9.09 (s, 1H, NH), 9.73 (s, 1H, NH); MS: m/z (%) 328 (67) $(M+2)^+$, 326 (100) (M^+), 293 (14), 266 (27), 230 (28), 215 (98), 181 (22), 127 (38), 115 (32), 89 (73), 77 (33); IR (KBr): ν 3194, 2987, 2935, 2875, 2825, 2360, 1647, 1500, 1400, 1292, 1192, 1138, 1085, 1014, 815, 773, 736 cm^{-1}; Anal. Calcd. for $C_{18}H_{15}ClN_2S$: C, 66.15; H, 4.63; N, 8.57%, Found: C, 64.21; H, 4.61; N, 8.56%.

Compound 10b (entry 8, Table 2) firstly reported. m.p.: 223-225 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.92 (d, *J* = 23.0 Hz, 1H, CH_2), 3.34 (d, *J* = 23.1 Hz, 1H, CH_2), 5.54 (s, 1H, CH), 7.20 (t, *J* = 7.4 Hz, 1H, CH arom.), 7.27-7.32 (m, 3H, CH arom.), 7.38 (d, *J* = 7.4 Hz, 1H, CH arom.), 7.45 (d, *J* = 8.3 Hz, 2H, CH arom.), 7.85 (d, *J* = 7.6 Hz, 1H, CH arom.), 9.02 (s, 1H, NH), 10.80 (s, 1H, NH); MS: m/z (%) 312 (85) (M^+), 310 (47), 279 (13), 251 (35), 201 (100), 114 (39), 75 (51); IR (KBr): ν 3396, 3138, 2962, 2358, 1911, 1797, 1660, 1500, 1483, 1458, 1396, 1184, 1089, 1006, 831, 759, 709 cm^{-1}; Anal. Calcd. for $C_{17}H_{13}ClN_2S$: C, 65.27; H, 4.19; N, 8.96%, Found: C, 64.42; H, 4.04; N, 8.82%.

Compound 11a [13b] (entry 9, Table 2). m.p.: 258-260 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.76 (m, 1H, CH_2), 2.11 (m, 1H, CH_2), 2.59 (m, 1H, CH_2), 2.70 (m, 1H, CH_2), 4.95 (s, 1H, CH), 7.14-7.22 (m, 3H, CH arom.), 7.29 (m, 3H, CH arom. and NH), 7.57-7.59 (m, 3H, CH arom.), 8.58 (s, 1H, NH); MS: m/z (%) 355 (25) (M^+), 353 (27), 340 (3), 327 (4), 312 (4), 199 (100), 181 (12), 115 (21), 89 (9), 76 (6); IR (KBr): ν 3334, 3221, 3086, 2933, 2362, 1682, 1483, 1286, 769, 731 cm^{-1}; Anal. Calcd. for $C_{18}H_{15}BrN_2O$: C, 60.86; H, 4.26; N, 7.89%, Found: C, 60.48; H, 4.22; N, 7.97%.

Compound 11b (entry 10, Table 2) firstly reported. m.p.: 249-250 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.85 (m, 1H, CH_2), 2.19 (m, 1H, CH_2), 2.62 (m, 1H, CH_2), 2.74 (m, 1H, CH_2), 5.00 (d, *J* = 2.1 Hz, 1H, CH), 7.17-7.25 (m, 3H, CH arom.), 7.28 (d, *J* = 8.3 Hz, 2H, CH arom.), 7.59 (d, *J* = 8.3 Hz, 2H, CH arom.), 7.71 (d, *J* = 7.2 Hz, 1H, CH arom.), 9.10 (s, 1H, NH), 9.73 (s, 1H, NH); MS: m/z (%) 373 (36) $(M+2)^+$, 371 (37) (M^+), 370 (33), 339 (6), 215 (100), 127 (65), 115 (36), 75 (58); IR (KBr): ν 3271, 3192, 2989, 2933, 1674, 1570, 1480, 1292, 1190, 1138, 1010, 831, 771, 738 cm^{-1}; Anal. Calcd. for $C_{18}H_{15}BrN_2S$: C, 58.23; H, 4.07; N, 7.54%, Found: C, 56.46; H, 4.11; N, 7.57%.

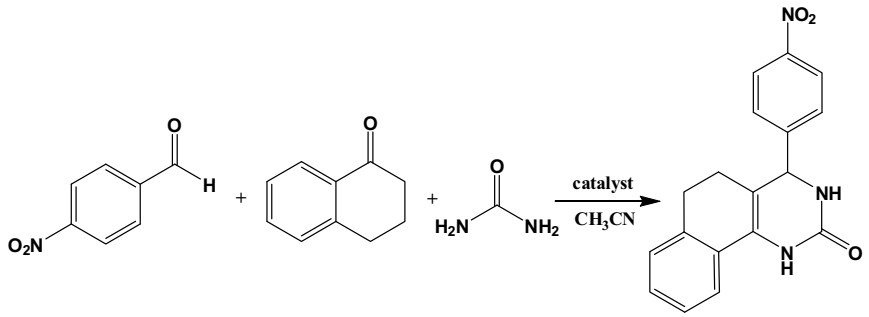
Compound 12b (entry 11, Table 2) firstly reported. m.p.: 215-217 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.85 (m, 1H, CH_2), 2.17 (m, 1H, CH_2), 2.29 (s, 3H, CH_3), 2.60 (m, 1H, CH_2), 2.72 (m, 1H, CH_2), 4.92 (s, 1H, CH), 7.16-7.24 (m, 7H, CH arom.), 7.69 (d, *J* = 7.4 Hz, 1H, CH arom.), 9.02 (s, 1H, NH), 9.64 (s, 1H, NH); MS: m/z (%) 306 (65) (M^+), 305 (54), 303 (12), 273 (16), 246 (18), 215 (100), 127 (47), 115 (63), 91 (82), 78 (28); IR (KBr): ν 3197, 2983, 2931, 2362, 1674, 1567, 1483, 1292, 1188, 1136, 815, 765, 734 cm^{-1}; Anal. Calcd. for $C_{19}H_{18}N_2S$: C, 74.47; H, 5.92; N, 9.14%, Found: C, 70.75; H, 5.75; N, 9.57%.

RESULTS AND DISCUSSION

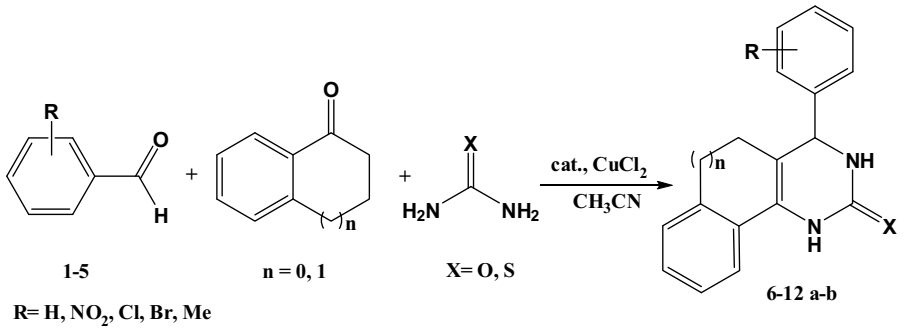
At earlier stage of our work, an equimolar quantity of 4-nitrobenzaldehyde and α-tetralone, 1.5 equimolar of urea in acetonitrile were mixed and heated under reflux of solvent for 10 h by examining different catalysts (Scheme 1). Many catalysts such as HCl, CuCl, $CuCl_2$, I_2 and $Pd(OAc)_2$ were used to explore the reaction. After 10 h, the crude products poured into crushed ice after stirring were directly filtrated through a sintered funnel and washed by ethylacetate-hexane (1:3). For further purification, the product was recrystallized from ethanol. The results are presented in Table 1 which shows that $CuCl_2$ and I_2 were the best among tested catalysts, but the yields were not so high.

To bypass this difficulty of low yield in the next step we used trimethylchlorosilane (TMSCl) for activation of used ketone. As previously, to a stirred mixture of 4-nitro-benzaldehyde, α-tetralone, urea and a different catalyst in acetonitrile, an amount of TMSCl (1 equimolar) was added. With the TMSCl, the yields were higher and the time of reaction decreased to 8 h. The results are presented in Table 1.

The addition of TMSCl accelerated the Biginelli-like reaction and gave good results. Although the role of TMSCl is not completely clear, it may be explainable in terms of Lewis acid which activates the carbonyl group and the softness of this reagent [14]. In the presence of TMSCl the yield increased from 71 to 95% by using $CuCl_2$ and from 78 to 93% by using I_2 as catalyst (Entry 4 and 5, Table 1). However, the purification was not very simple by using I_2 as a catalyst.



Scheme 1



Scheme 2

Table 1. Effects on the Type of the Catalysts on the Formation of Fused-Ring Pyrimidin-2(1*H*)-ones

Entry	Catalyst	Amount of catalyst	Yield (%)[a, b]
1	Free		39 (60)[c]
2	HCl	1 ml	44 (48)[c]
3	CuCl	10 mol%	63 (81)[c]
4	$CuCl_2$	10 mol%	71 (95)[c]
5	I_2	10 mol%	78 (93)[c]
6	$Pd(OAc)_2$	10 mol%	30

[a]Reaction conditions: 4-nitro benzaldehyde (2 mmol), α-tetralone (2 mmol), urea (3 mmol), 10 ml CH_3CN. [b]Isolated yield. [c]The number in parentheses indicates the isolated yield of product by using the catalyst in the presence of 2 mmol TMSCl.

Furthermore, in the previous work, we synthesized the product **8a** using $LiClO_4$ [13b] and NH_4Cl [13b] in 70 and 65% yield, respectively, using the same conditions. Thus, we can conclude that $CuCl_2$ is the best catalyst for this reaction.

Based on the above optimized results and in order to examine the scope of this Biginelli-like scaffolds reaction, various aromatic aldehydes **1-5** with α-tetralone or 1-indanone, urea or thiourea in the presence of TMSCl and 10 mol% of $CuCl_2$ as catalyst were used (Scheme 2). The results are shown in the Table 2.

In all cases, the three component one-pot reaction proceeded smoothly to afford the corresponding fused ring pyrimidin-2(1*H*)-ones **6-11a** derivatives in high yields and the fused ring pyrimidin-2(1*H*)-thiones **6-12b** derivatives in moderate yields.

CONCLUSIONS

In conclusion, a mild and efficient method is proposed for the three-component Biginelli-like reactions of aldehyde with cyclic ketones and urea or thiourea using $CuCl_2$ catalyst and TMSCl for synthesis of fused ring pyrimidin-2(1*H*)-ones and thiones. The inexpensive and ready availability of the catalyst, the high yields and the simplicity of the procedure render this methodology advantageous. This new method for the synthesis of Biginelli-like scaffolds make this fused ring system

Table 2. Cupric Chloride Catalyzed Preparation of Fused Ring Pyrimidin-2(1*H*)-ones and Thiones Derivatives in the Presence of TMSCl[a, b]

Entry	Aldehyde	Ketone	X	Products	Yield (%)[c]	m.p. (°C)
1	C_7H_6O	α-Tetralone	O	**6a** [11a, b, 13b]	85	275-277
2	C_7H_6O	α-Tetralone	S	**6b**	51	245-246
3	C_7H_6O	1-Indanone	O	**7a** [11a, 13b]	84	276-278
4	4-NO_2-C_7H_5O	α-Tetralone	O	**8a** [13b]	95	219-221
5	4-NO_2-C_7H_5O	α-Tetralone	S	**8b**	50	199-200
6	4-Cl-C_7H_5O	α-Tetralone	O	**9a** [12a]	91	229-231
7	4-Cl-C_7H_5O	α-Tetralone	S	**9b**	40	252-254
8	4-Cl-C_7H_5O	1-Indanone	S	**10b**	51	223-225
9	4-Br-C_7H_5O	α-Tetralone	O	**11a** [13b]	95	258-260
10	4-Br-C_7H_5O	α-Tetralone	S	**11b**	50	249-250
11	4-Me-C_7H_5O	α-Tetralone	S	**12b**	40	215-217

[a]Reaction conditions: aldehyde (2 mmol), α-tetralone (2 mmol), urea (3 mmol), 10 ml CH_3CN, reflux 8 h. [b]All products were characterized by ^{1}H NMR, IR, mass spectra and elemental analysis. [c]Isolated yields.

accessible for inclusion into pharmacologically important agents. Further investigations on the synthesis of analog molecules using new methods are currently in progress.

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