Copper Dipyridine Dichloride as a Mild and Efficient Catalyst for a One Pot Condensation Bigenelli Reaction

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Received January 19, 2005

The condensation reaction of aldehydes, β-ketoesters and urea/thiourea in presence of a catalytic amount of $CuPy_2Cl_2$ complex proceeded under very mild reaction conditions in high yield (80-90%).

J. Heterocyclic Chem., **42**, 1017 (2005).

Introduction.

There has been considerable interest in the development of preparative methods for the products of dihydropyrimidines-2(1*H*)-ones (DHPMS).This seems to be because of their pharmacologically importance as well as to understand the mechanism of reaction involved in what is commonly called the Biginelli condensation [1]. The DHPMS compounds have shown promising activity as calcium channel blockers, antihypertensive agents, α-1-a-antagonists, and neuropeptide Y(NPY) antagonists [2]. In addition, the dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products, including the batazelladine alkaloids, which have been found to be potent HIVgp-120-cd_4 inhibitors [3]. Many synthetic methods for the preparing DHPMS compounds under classical reflux [4a-h] (or) solvent free conditions [5-11] and microwave [12-15] (or) ultrasonic irradiation [16-17] have been reported.

Interest in the transition metal complex-catalyzed Biginelli reaction has been growing during the last few years. Copper, palladium, nickel and cobalt derivatives have proved to display good catalytic activity toward this important type of condensation reaction [18-19]. With such catalysts, the reaction is completed in a shorter time and in excellent yield, as compared with previously reported methods [20]. Now, we found that an analogous condensation reaction can be conveniently performed under neutral and mild conditions in the presence of a catalytic amount of CuPy2Cl_2 [21-22]. Catalytic improvement is apparently due to the presence of two pyridine rings, which increases the electron deficiency on the nitrogen hence it is efficiently act as a Lewis acid.

Results and Discussion.

The Biginelli condensation reaction was carried out at 40-50 °C under a nitrogen atmosphere using an aldehyde, urea and ethyl acetoacetate to $CuPy_2Cl_2$ molar ratio of 100:1. An aldehyde, β-ketoester and urea/thiourea (1:1:1.5mmol) were added into the mixture of $CuPy_2Cl_2$ (0.01 mmol) dissolved in anhydrous acetonitrile (10 mL). The homogeneous reaction mixture was stirred at 40-50 °C for 1-3 hour. The solvent was evaporated under reduced pressure. The solid thus obtained was washed with ice-cold water and recrystallized from ethanol to afford pure product in 80-90% yield.

Scheme I

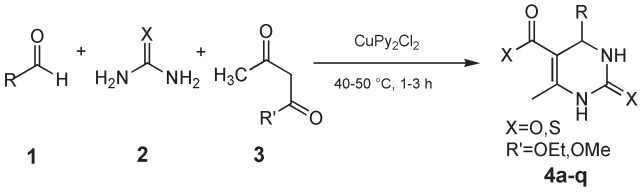

Table 1

$CuPy_2Cl_2$ Catalyzed Efficient Synthesis of Dihydropyrimidin-2(1*H*)-ones

Product	R	R^1	X	Time (h)	Yield (%) [a]	m.p. (°C)
4a [4a]	C_6H_5	OEt	O	1.0	90	200-202
4b [4a]	4-(Cl)-C_6H_4	OEt	O	3.0	82	209-211
4c [4a]	4-(NO_2)-C_6H_4	OEt	O	1.5	89	205-207
4d [4a]	3-(NO_2)-C_6H_4	OEt	O	3.0	85	225-227
4e [4d]	3-(Cl)-C_6H_4	OEt	O	2.5	88	215-217
4f [4a]	4-(OCH_3)-C_6H_4	OEt	O	2.5	82	198-200
4g [4a]	3-(NO_2)-C_6H_4	OEt	S	2.0	85	203-205
4h [4a]	4-(OH)-C_6H_4	OEt	O	2.0	88	179-181
4i [4b]	4-(OH)-C_6H_4	OEt	S	3.0	90	195-198
4j [4b]	4-(OCH_3)-C_6H_4	OEt	S	3.0	89	137-139
4k [4a]	4-(NO_2)-C_6H_4	OMe	O	2.5	90	235-236
4l [4a]	4-(OCH_3)-C_6H_4	OMe	O	3.0	84	191-193
4m [4c]	2-furyl	OEt	O	2.5	89	204-206
4n [4a]	C_6H_5	OMe	O	3.0	90	214-216
4o [4d]	3-(Cl)-C_6H_4	OMe	O	2.0	90	207-09
4p [4a]	4-(Cl)-C_6H_4	OMe	O	3.0	89	205-207
4q [4a]	4-(OH)-C_6H_4	OMe	O	3.0	88	175-177

[a] Yields refer to pure solid products, all products were characterized by comparison of their physical and spectral data with those of authentic samples.

EXPERIMENTAL

General Procedure.

A solution of an appropriate β-ketoester (1 mmol), corresponding aldehyde (1 mmol), urea or thiourea (1.5 mmol), and $CuPy_2Cl_2$ (0.01 m mol) in anhydrous acetonitrile (10 mL) was stirred at 40-50 °C for a certain period of time as required to com-

plete the reaction (TLC). The solvent was removed under reduced pressure to yield a solid, which was washed thoroughly with water, filtered and recrystallized from ethanol to afford pure product. ^{1}H NMR and MS data for compounds **4a-q** are given below:

4a: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 6.82 Hz, CH_3), 2.22 (s, 3H, CH_3), 3.92 (q, 2H, *J*=6.74, OCH_2), 5.11 (d, 1H, *J*=3.05 Hz, C_4-H), 7.71 (bs, 1H, NH), 7.20-7.35 (m, 5H, Ar-H), 9.16 (bs, 1H, NH); MS: m/z=261.1 (M^+).

4b: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.07 (t, 3H, J = 6.8 Hz, CH_3), 2.20 (s, 3H, CH_3), 3.94 (q, 2H, *J*=7.2 Hz, OCH_2), 5.02 (s, 1H, C_4-H), 6.64 (d, 2H, *J*= 8.2 Hz, Ar-H), 7.02 (d, 2H, *J*=8.2 Hz, Ar-H), 7.57 (bs, 1H, NH), 9.10 (bs, 1H, NH); MS: m/z=295 (M^+), 265.

4c: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.07 (t, 3H, *J* = 6.8 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.96 (q, 2H, *J*=5.4 Hz, OCH_2), 5.25 (s, 1H, C_4-H), 7.50 (d, 2H, *J*= 7.3 Hz, Ar-H), 7.85 (bs, 1H, NH), 8.20 (d, 2H, *J*=7.2Hz, Ar-H), 9.31 (bs, 1H, NH); MS: m/z=306.29 (M^+).

4d: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.06 (t, 3H, *J* = 7. 01 Hz, CH_3), 2.26 (s, 3H, CH_3), 3.98 (q, 2H, *J*=4.6 Hz, OCH_2), 5.30 (d, 1H, *J*= 2.64 Hz, C_4-H), 7.60-7.70 (m, 2H, Ar-H), 7.95 (bs, 1H, NH), 8.11-817 (m, 2H, Ar-H), 9.38 (bs, 1H, NH); MS: m/z=306 (M^+).

4e: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.05 (t, 3H, *J* = 6.83 Hz, CH_3), 2.22 (s, 3H, CH_3), 3.96 (q, 2H, *J*=7.2 Hz, OCH_2), 5.12 (s, 1H, C_4-H), 6.65-6.92 (m, 3H, Ar-H), 7.05 (s, 1H, Ar-H), 7.61 (bs, 1H, NH), 9.13 (bs, 1H, NH); MS: m/z=295 (M^+).

4f: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.10 (t, 3H, *J* = 7.05 Hz, CH_3), 2.16 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.96 (q, 2H, *J*=7.22 Hz, OCH_2), 5.08 (d, 1H, C_4-H), 6.86 (d, 2H, *J*= 8.52 Hz, Ar-H), 7.14 (d, 2H, J=8.54 Hz, Ar-H), 7.67 (bs, 1H, NH), 9.13 (bs, 1H, NH); MS: m/z=291.3 (M^+).

4g: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.06 (t, 3H, *J* = 7. 01 Hz, CH_3), 2.25 (s, 3H, CH_3), 3.97 (q, 2H, *J*=4.6 Hz, OCH_2), 5.29 (d, 1H, *J*= 2.64 Hz, C_4-H), 7.59-7.68 (m, 2H, Ar-H), 7.93 (bs, 1H, NH), 8.10-815 (m, 2H, Ar-H), 9.36 (bs, 1H, NH); MS: m/z=322 (M^+), 292.

4h: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.07 (t, 3H, *J* = 6.9 Hz, CH_3), 2.22 (s, 3H, CH_3), 3.95 (q, 2H, *J*=7.12 Hz, OCH_2), 5.05 (d, 1H, *J*=2.78 Hz, C_4-H), 6.68 (d, 2H, *J*= 8.42 Hz, Ar-H), 7.04 (d, 2H, *J*=8.49 Hz, Ar-H), 7.65 (bs, 1H, NH), 9.13 (bs, 1H, NH), 9.33 (bs, 1H, OH); MS: m/z=277 (M^+), 247, 246.

4i: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.07 (t, 3H, *J* = 6.95 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.96 (q, 2H, *J*=7.16Hz, OCH_2), 5.13 (d, 1H, *J*=2.75 Hz, C_4-H), 6.67 (d, 2H, *J*= 8.46 Hz, Ar-H), 7.06 (d, 2H, *J*=8.47 Hz, Ar-H), 7.68 (bs, 1H, NH), 9.15 (bs, 1H, NH), 9.35 (bs, 1H, OH); MS: m/z=293 (M^+), 263, 262.

4j: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.05 (t, 3H, *J* = 7.25 Hz, CH_3), 2.08 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 3.94 (q, 2H, *J*=7.25 Hz, OCH_2), 5.02 (d, 1H, C_4-H), 6.82 (d, 2H, *J*= 8.55 Hz, Ar-H), 7.11 (d, 2H, *J*=8.57 Hz, Ar-H), 7.65(bs, 1H, NH), 9.11 (bs, 1H, NH); MS: m/z=307.39 (M^+).

4k: ^{1}H NMR (200MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.53 (s, 3H, OCH_3), 5.25 (d, 1H, *J*= 3.17 Hz, C_4-H), 7.50 (d, 2H, *J*= 7.3 Hz, Ar-H), 7.85 (bs, 1H, NH), 8.20 (d, 2H, *J*=7.2Hz, Ar-H), 9.31 (bs, 1H, NH); MS: m/z=292.08 (M^+), 274, 232, 186.

4l: ^{1}H NMR (200MHz, DMSO-d_6): δ 2.18 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.13 (d, 1H, C_4-H), 6.88 (d, 2H, *J*= 8.46 Hz, Ar-H), 7.17(d, 2H, *J*=8.49 Hz, Ar-H), 7.67 (bs, 1H, NH), 9.13 (bs, 1H, NH); MS: m/z=277.2 (M^+).

4m: ^{1}H NMR (200MHz, DMSO-d_6): δ 1.07 (t, 3H, *J* = 6.8 Hz, CH_3), 2.20 (s, 3H, CH_3), 3.94 (q, 2H, *J*=7.2 Hz, OCH_2), 5.02 (s, 1H, C_4-H), 6.64 (m, 3H, Ar-H), 7.57 (bs, 1H, NH), 9.10 (bs, 1H, NH); MS: m/z=251.2 (M^+).

4n: ^{1}H NMR (200MHz, DMSO-d_6): 2.26 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3) 5.15 (d, 1H, *J*=3.13 Hz, C_4-H), 7.24-7.36 (m, 5H, Ar-H), 7.78 (bs, 1H, NH), 9.16 (bs, 1H, NH); MS: m/z=247.09 (M^+).

4o: ^{1}H NMR (200MHz, DMSO-d_6): δ 2.32 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 5.38 (s, 1H, CH, C_4-H), 7.66 (s, 1H, Ar-H), 7.91 (bs, 1H, NH), 8.01-8.12 (m, 3H, Ar-H), 9.41 (bs, 1H, NH); MS: m/z=281.7 (M^+).

4p: ^{1}H NMR (200MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 3.63 (s, 3H, OCH_3), 5.40 (s, 1H, CH, C_4-H), 7.63-7.72 (m, 2H, Ar-H), 7.95 (bs, 1H, NH), 8.11-8.18 (m, 2H, Ar-H), 9.41 (bs, 1H, NH); MS: m/z=281.7 (M^+).

4q: ^{1}H NMR (200MHz, DMSO-d_6): δ 2.26 (s, 3H, CH_3), 3.85 (s, 3H, OCH_2), 5.26 (d, 1H, J=2.78 Hz, C_4-H), 6.71 (d, 2H, *J*= 8.38 Hz, Ar-H), 7.24 (d, 2H, *J*=8.36 Hz, Ar-H), 7.63 (bs, 1H, NH), 9.11(bs, 1H, NH), 9.32 (bs, 1H, OH); MS: m/z=263.25 (M^+).

Acknowledgement.

The authors are thankful to University Grants Commission, New Delhi for financial assistance and to the Director, IICT Hyderabad for ^{1}H NMR and mass spectral analysis.

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