Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

Efficient Synthesis of 5-Carboxanilide-Dihydropyrimidinones Using Cobalt(II) Nitrate Hexahydrate

Mehrnoush Kangan,* Nourallah Hazeri,* Afshin Yazdani-Elah-Abadi and Malek-Taher Maghsoodlou

Department of Chemistry, Faculty of Science, University of Sistan and Baluchestan, Zahedan 98135-674, Iran

(Received: December 13, 2016; Accepted: February 25, 2017; DOI: 10.1002/jccs.201600841)

5-Carboxanilide-dihydropyrimidinone derivatives were synthesized in good yield in a three-component and efficient process by the condensation reaction of acetoacetanilide, aldehyde and urea/thiourea in the presence of cobalt(II) nitrate hexahydrate as catalyst in ethanol at ambient condition.

Keywords: 5-Carboxanilide-dihydropyrimidinones; Acetoacetanilide; Cobalt(II) nitrate hexahydrate.

INTRODUCTION

Pyrimidines exhibit a broad range of biological effects including antiviral, antitumor, antibacterial, antihypertensive,[1] anti-inflammatory,[2] neuropeptide Y (NPY) antagonistic activity,[3] cardiovascular calcium,[4] and channel blocking.[5] In 1893, Biginelli reported the synthesis of dihydropyrimidinones via the reaction of benzaldehyde, ethyl acetoacetate, and urea in ethanol under strongly acidic conditions.[6] However, this method suffers from drawbacks such as low yields of the desired products, particularly in the case of substituted aldehydes, and loss of acid-sensitive functional groups during the reaction. This has led to multistep synthetic strategies that produce somewhat better yields but lack the simplicity of the original one-pot Biginelli protocol.[7] Many synthetic methods for preparing of pyrimidines have been developed to improve and modify this reaction by using Lewis acid catalysts as well as protic acids, including $TaBr_5$,[8] lanthanide triflate,[9] HCOOH,[10] VCl_3,[11] $Sr(OTf)_2$,[12] PPh_3,[13] indium(III) halides,[14] LiBr,[15] silica sulfuric acid,[16] $Mn(OAc)_3{\bullet}2H_2O$,[17] $Y(NO_3)_3{\bullet}6H_2O$,[18] $In(OTf)_3$,[19] $FeCl_3{\bullet}6H_2O$, $NiCl_2{\bullet}6H_2O$,[20] $Ce(NO_3)_3{\bullet}6H_2O$,[21] silica chloride,[22] H_3BO_3,[23] $SrCl_2{\bullet}6H_2O$–HCl,[24] $Yb(OTf)_3$,[25] $Bi(NO_3)_3{\bullet}5H_2O$,[26] tungstate sulfuric acid,[27] and $HClO_4$–SiO_2.[28] In addition, ionic liquids,[29] microwave irradiation,[30] ultrasound irradiation,[31] and etidronic acid[32] were also utilized as the catalytic agent. However, many of these methods suffer from long reaction times, expensive reagents, and strong acidic conditions. In continuation of our research on multicomponent reactions,[33–35] here we report an efficient synthesis of 5-carboxanilide-dihydropyrimidinones using cobalt(II) nitrate hexahydrate as catalyst in ethanol at ambient condition (Scheme 1).

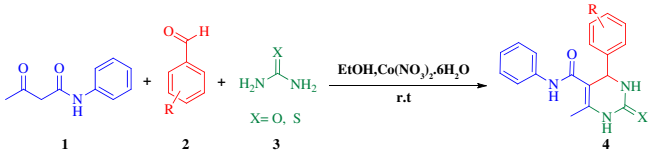
RESULTS AND DISCUSSION

Because of the biological importance of dihydropyrimidinones and to develop methods of the synthesis of new derivatives of pyrimidinones, we have chosen the reaction of acetoacetanilide (1.0 mmol), 4-nitrobenzaldehyde (1.0 mmol), and urea/thiourea (1.5 mmol) used as starting materials. The reaction was initially carried out in EtOH in the presence of different catalysts (Table 1). As seen in Table 1, cobalt(II) nitrate hexahydrate (10 mol%) was found to be the most effective catalyst for the reaction at room temperature. The reaction was performed in various solvents, and EtOH was found to be the best solvent in respect to the time and yield of the reaction (Table 2).

According to the obtained optimum conditions, we decided to synthesize new derivatives using various aromatic aldehydes in the present of urea/thiourea and a catalytic amount of cobalt(II) nitrate hexahydrate. The corresponding desired products were isolated in excellent yield, and the results are summarized in Table 3.

The proposed mechanism for the synthesis of 5-carboxanilide-dihydropyrimidinones in the presence of cobalt(II) nitrate hexahydrate as catalyst is shown in Scheme 2.

*Corresponding authors. Email: mehrnooshkangani@gmail.com; nhazeri@chem.usb.ac.ir



Scheme 1. Synthesis of 5-carboxanilide-dihydropyrimidinones in the presence of cobalt(II) nitrate hexahydrate as catalyst in ethanol at ambient conditions.

Table 1. Optimization of the reaction conditions for the synthesis of **4a**[1]

Entry	Catalyst (mol%)	Solvent	Time	Isolated Yield (%)
1	TiO_2	EtOH	5 h	20
2	$Zn(SO_4)_2{\cdot}7H_2O$	EtOH	24 h	45
3	$Zr(NO_3)_4$	EtOH	7 h	40
4	$ZrCl_4$	EtOH	11 h	20
5	$HClO_4$–SiO_2	EtOH	8 h	30
6	$KHSO_4$	EtOH	10 h	46
7	NH_4HSO_4	EtOH	5 h	50
8	$Co(NO_3)_2.6H_2O$ (5 mol%)	EtOH	2 h	65
9	$Co(NO_3)_2.6H_2O$ (10 mol%)	EtOH	40 min	85
10	$Co(NO_3)_2.6H_2O$ (15 mol%)	EtOH	40 min	85

[1] Amounts of material in all reactions: aldehyde (1.0 mmol), urea/thio urea (1.5 mmol), and acetoacetanilide (1.0 mmol).

Table 2. Synthesis of **4a**[1] in the presence of different solvents

Entry	Solvent	Time	Isolated Yield (%)*
1	EtOH, r.t.	40 min	85
2	MeOH, r.t.	1 h	65
3	CH_3CN, r.t.	5 h	40
4	$CHCL_3$, r.t.	10 h	50
5	H_2O, r.t.	24	Trace
6	Solvent-free	24	Trace

[1] Amounts of material in all reactions: aldehyde (1.0 mmol), urea/thio urea (1.5 mmol), acetoacetanilide (1.0 mmol), $Co(NO_3)_2.6H_2O$ (10 mol%), solvent (2 mL).

EXPERIMENTAL

Physical methods

IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points of all compounds were measured on an Electro Thermal 9100 apparatus. The ^1H and ^{13}C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE instrument using $CDCl_3$ and DMSO, with TMS as internal standard, at 300 and 75 MHz, respectively. The mass spectra were recorded on a Shimadzu GCMS-QP5050A mass spectrometer operating at an ionization potential of 70 eV. All reagents and solvents were obtained from Aldrich and Merck and used without further purification.

General procedure for the synthesis of 5-carboxanilide-dihydropyrimidinones

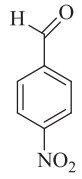
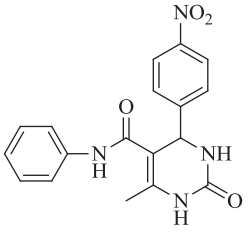
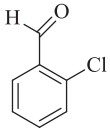
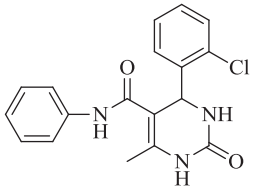
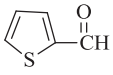
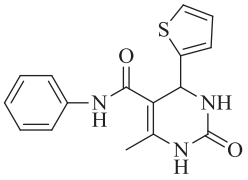
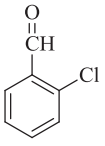
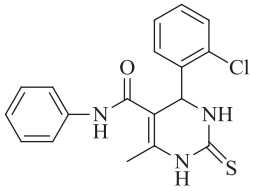
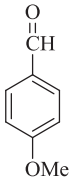
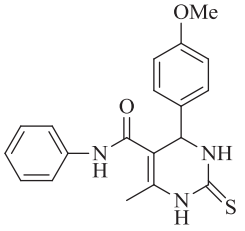
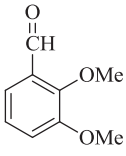
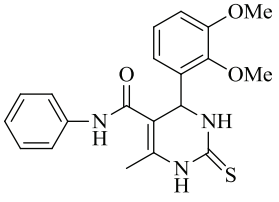
Cobalt(II) nitrate hexahydrate (10 mol%) was added to a mixture of aromatic aldehyde (1.0 mmol), acetoacetanile (1.0 mmol), and urea or thiourea (1.5 mmol) in EtOH (2 mL) at ambient temperature. The progress of reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the products were isolated by filtration and washed with EtOH (3 × 2 mL) to afford pure products in good to high yields (85–90).

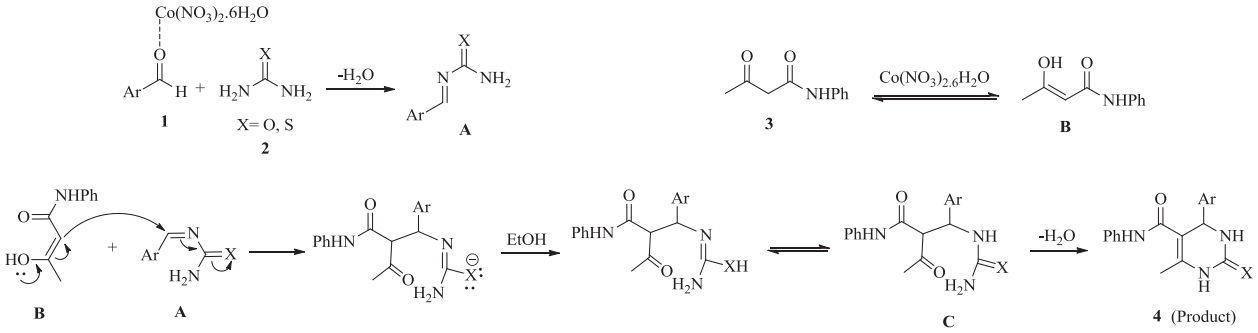
Characterization of compounds

1,2,3,4-Tetrahydro-6-methyl-4-(4-nitrophenyl)-2-oxo-*N*-phenyl-pyrimidine-5-carboxamide (4a) IR (KBr, cm^{-1}): 3375, 3268, 3106, 2931, 1723, 1667. ^1H NMR (300 MHz, DMSO) δ (ppm): 2.07 (s, 3H,CH_3), 5.51(s, 1H, CH), 7.01 (t, J = 6.0 Hz, 1H), 7.26 (t, J = 6.0 Hz, 2H), 7.54 (d, J = 6.0 Hz, 2H), 7.756 (d, J = 6.0 Hz, 2H), 7.77 (s, br, 1H, NH), 8.23 (d, J = 6.0 Hz, 2H), 8.91 (s, 1H, NH), 9.65 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO) δ (ppm) : 17.54, 55.06, 104.84, 120.03, 123.72, 124.35, 128.05, 129.03, 139.39, 139.49, 139.72, 139.82, 147.24, 151.90, 152.73, 152.79, 152.84, 165.41, MS (EI, 70 eV) *m/z* (%): 352 (M+, 16), 324 (10), 307 (14), 283 (16), 262 (100), 234 (25), 214 (8), 199 (5), 179 (16), 163 (16), 135 (50), 91 (53), 69 (50), 41 (80).

1,2,3,4-Tetrahydro-6-methyl-4-(2-chlorophenyl)-2-oxo-*N*-phenylpyrimidine-5-carboxamide (4b) IR (KBr, cm^{-1}): 3409, 3225, 3102, 2966, 1698, 1662. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.38 (s, 3H, CH_3), 5.86 (s, 1H, CH), 5.88 (s, 1H, NH), 6.98–7.51 (m, 10H, Ar, NH), 8.34 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 18.05, 52.98, 102.74, 120.12 (2C), 124.41, 126.71, 128.28 (2C), 128.95, 130.32, 132.45, 137.61, 138.03, 142.95, 153.17, 164.16. MS (EI, 70 eV) *m/z* (%): 343 (M + 2, 16), 341 (M+, 33), 306 (25), 249 (100),

Table 3. Synthesis of 5-carboxanilide-dihydropyrimidinones

Entry	Ar	Product	Time (min)	Isolated yields (%)	M.p. (°C)
1		**4a** 	40	85	287–288
2		**4b** 	60	80	185–186
3		**4c** 	60	90	230–233
4		**4d** 	60	80	223–225
5		**4e** 	40	90	183–184
6		**4f** 	40	90	215–218



Scheme 2. Proposed mechanism for the synthesis of 5-carboxanilide-dihydropyrimidinones in the presence of cobalt(II) nitrate hexahydrate as catalyst.

223 (9), 206 (45), 185 (16), 166 (25), 137 (19), 111(9), 93 (50),65 (30), 42 (45).

1,2,3,4-Tetrahydro-6-methyl-4-(thiophen-2-yl)-2-oxo-*N*-phenyl-pyrimidine-5-carboxamide (4c) IR (KBr, cm^{-1}): 3406, 3278, 3121, 2959, 1715, 1674. ^1H NMR (300 MHz, DMSO) δ (ppm): 2.072 (s, 3H, CH_3), 5.68 (s, 1H, CH), 6.93–7.59 (m, 8H, Ar), 7.82 (s, 1H, NH), 8.88 (s, 1H, NH), 9.59 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ (ppm): 17.54, 50.91, 105.77, 120.09, 123.58, 124.04, 125.44, 127.18, 128.99 (2C), 139.61, 139.85, 139.95, 149.12, 152.85, 165.30. MS (EI, 70 eV) *m/z* (%): 313 (M+, 9), 299 (50), 278 (9), 252 (60), 221 (100), 186 (33), 161 (9), 138 (65), 121 (20), 93 (65), 65 (50), 45 (80).

1,2,3,4-Tetrahydro-6-methyl-4-(2-chlorophenyl)-2-thio-oxo-*N*-phenylpyrimidine-5-carboxamide (4d) IR (KBr, cm^{-1}): 3403, 3205, 3212, 3020, 1717, 1678. ^1H NMR (300 MHz, DMSO) δ (ppm): 2.07 (s, 3H, CH_3), 5.39 (s, 1H, CH), 7.012–7.56 (m, 9H, Ar), 9.49 (s, 1H, NH), 9.77 (s, 1H, NH), 10.09 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ (ppm): 16.93, 54.82, 107.22, 120.05, 120.15, 123.89, 128.76, 129.08 (2C), 129.12, 132.80, 136.19, 136.29, 139.23, 139.34, 142.35, 165.18, 174.53. MS (EI, 70 eV) *m/z* (%): 359 (M + 2, 25), 357 (M+, 83), 334 (4), 291 (6), 265 (100), 237 (25), 206 (50), 165 (70), 137 (20), 120 (18), 93 (75), 65 (45), 42 (50).

1,2,3,4-Tetrahydro-6-methyl-4-(4-methoxyphenyl)-2-thio-oxo-*N*-phenylpyrimidine-5-carboxamide (4e) IR (KBr, cm^{-1}): 3383, 3278, 3190, 2836, 1737, 1677. ^1H NMR (300 MHz, DMSO) δ (ppm): 2.07 (s, 1H, CH_3), 3.72 (s, 3H, OCH_3), 5.35 (s, 1H, C, H), 6.90–7.56 (m, 9H, Ar), 9.40 (s, 1H, NH), 9.71 (s, 1H, NH), 9.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ (ppm): 16.88, 54.92, 55.57, 107.84, 114.41 (2C), 119.98, 120.08 (2C), 123.79, 128.19 (2C), 129.04 (2C), 135.67, 139.35, 159.27, 165.44, 174.08. MS (EI, 70 eV) *m/z* (%): 353(M+, 66), 335 (6), 261 (100), 233 (29), 202 (33), 178 (37), 161 (54), 133 (8), 115 (8), 94 (4), 77 (29), 59 (4), 42 (29).

1,2,3,4-Tetrahydro-6-methyl-4-(2,3-methoxyphenyl)-2-thio-oxo-*N*-phenylpyrimidine-5-carboxamide (4f) IR (KBr, cm^{-1}): 3444, 3374, 3231, 2333, 1700, 1671. ^1H NMR (300 MHz, DMSO) δ (ppm): 2.05 (s, 3H, CH_3), 3.71 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.69 (s, 1H, CH), 6.85–7.59 (m, 8H, Ar), 9.22 (s, 1H, NH), 9.72 (s, 1H, NH), 9.95 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO): δ (ppm): 16.83, 50.77, 56.11, 60.85, 107.71, 112.74, 119.92, 120.23 (2C), 123.62, 124.55, 129.01 (2C), 135.57, 136.94, 139.64, 145.89, 152.72, 165.23, 174.73. MS (EI, 70 eV) *m/z* (%): 383(M+, 58), 352 (33), 291 (100), 263 (33), 232 (29), 208 (20), 191 (8), 173 (33), 155 (16), 137 (16), 120 (15), 93 (45), 65 (37), 42 (45).

CONCLUSIONS

In this study, an efficient synthesis method for the preparation of 5-carboxanilide-dihydropyrimidinones at ambient conditions was described. The high yields of products, easy work-up, and short reaction times are the advantages of this method.

ACKNOWLEDGMENTS

This work was supported financially by the University of Sistan and Baluchestan.

Supporting information

Additional supporting information is available in the online version of this article.

REFERENCES

1. G. C. Rovnyak, K. S. Atwal, A. Hedberg, S. D. Kimball, S. Moreland, J. Z. Gougoutas, B. C. O'Reilly, J. Schwartz, M. F. Malley, *J. Med. Chem.* **1992**, *35*, 3254.
2. C. O. Kappe, *Tetrahedron* **1993**, *49*, 6937.
3. E. H. Hu, D. R. Sidler, U. H. Dolling, *J. Org. Chem.* **1998**, *63*, 3454.
4. E. L. Khania, G. O. Sillinietse, O. Ya, G. Dabur, A. A. Yakimenis, *Khim. Pharm. Chem. J.* **1978**, *12*, 1321.
5. H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, *J. Med. Chem.* **1989**, *32*, 2399.
6. P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360.
7. G. C. Rovnyak, S. D. Kimbal, B. Beyer, G. Cucinotta, J. D. Dimarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. Macarthy, R. S. Zhang, *J. Med. Chem.* **1995**, *38*, 119.
8. N. Ahmed, J. E. V. Lier, *Tetrahedron Lett.* **2007**, *48*, 5407.
9. Y. Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.* **2000**, *65*, 3864.
10. J. Cheng, D. Y. Qi, *Chem. Lett.* **2007**, *18*, 647.
11. G. Sabitha, G. S. K. K. Reddy, K. B. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2003**, *44*, 6497.
12. W. K. Su, J. J. Li, Z. G. Zheng, Y. C. Shen, *Tetrahedron Lett.* **2005**, *46*, 6037.
13. A. Debache, M. Amimour, A. Belfaitah, S. Rhouati, B. Carboni, *Tetrahedron Lett.* **2008**, *49*, 6119.
14. N. Y. Fu, Y. F. Yuan, M. L. Pang, J. T. Wang, C. Peppe, *J. Organomet. Chem.* **2003**, *672*, 52.
15. G. Maiti, P. Kundu, C. Guin, *Tetrahedron Lett.* **2003**, *44*, 2757.
16. P. Salehi, M. Dabiri, M. A. Zolfigol, M. A. B. Fard, *Tetrahedron Lett.* **2003**, *44*, 2889.
17. K. A. Kumar, M. Kasthuraiah, C. S. Reddy, C. D. Reddy, *Tetrahedron Lett.* **2001**, *42*, 7873.
18. N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor, B. M. Bhanage, *J. Mol. Catal. A: Chem.* **2007**, *271*, 14.
19. R. Ghosh, S. Maiti, A. Chakraborty, *J. Mol. Catal. A: Chem.* **2004**, *217*, 47.
20. J. Lu, Y. Bai, *Synthesis* **2002**, *4*, 466.
21. M. Adib, K. Ghanbary, M. Mostofi, M. R. Ganjali, *Molecules* **2006**, *11*, 649.
22. H. N. Karade, M. Sathe, M. P. Kaushik, *Molecules* **2007**, *12*, 1341.
23. S. J. Tu, F. Fang, C. B. Miao, H. Jiang, Y. J. Feng, D. Q. Shi, X. S. Wang, *Tetrahedron Lett.* **2003**, *44*, 6153.
24. M. Nasr-Esfahani, A. R. Khosropour, *Bull. Korean Chem. Soc.* **2005**, *26*, 1331.
25. Y. Huang, F. Yang, C. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386.
26. M. M. Khodaei, A. R. Khosropour, M. Beygzadeh, *Synth. Commun.* **2004**, *34*, 1551.
27. M. Nasr-Esfahani, B. Karami, M. Montazerozohori, K. Abdi, *J. Heterocycl. Chem.* **2008**, *45*, 1183.
28. M. Maheswara, S. H. Oh, K. Kim, J. Y. Do, *Bull. Korean Chem. Soc.* **2008**, *29*, 1752.
29. J. J. Peng, Y. Q. Deng, *Tetrahedron Lett.* **2001**, *42*, 5917.
30. B. K. Banik, A. T. Reddy, A. Datta, C. Mukhopadhyay, *Tetrahedron Lett.* **2007**, *48*, 7392.
31. J. T. Li, J. F. Han, J. H. Yang, T. S. Li, *Ultrason. Sonochem.* **2003**, *10*, 119.
32. A. M. Pansuriya, M. M. Savant, C. V. Bhuva, J. Singh, Y. T. Naliapara, *Arkivoc* **2009**, *7*, 79.
33. M. Kangani, M. T. Maghsoodlou, N. Hazeri, *Chin. Chem. Lett.* **2016**, *27*, 66.
34. Z. Vafajoo, N. Hazeri, M. T. Maghsoodlou, H. Veisi, *Chin. Chem. Lett.* **2015**, *26*, 973.
35. P. Dastoorani, M. T. Maghsoodlou, M. A. Khalilzadeh, E. Sarina, *Tetrahedron Lett.* **2016**, *57*, 314.

