International Scholarly Research Network
ISRN Organic Chemistry
Volume 2012, Article ID 474626, 4 pages
doi:10.5402/2012/474626

Research Article

Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones and Their Corresponding 2(1H)Thiones Using Trichloroacetic Acid as a Catalyst under Solvent-Free Conditions

Zahed Karimi-Jaberi and Mohammad Sadegh Moaddeli

Department of Chemistry, Firoozabad Branch, Islamic Azad University, P.O. Box 74715-117, Firoozabad, Fars, Iran

Correspondence should be addressed to Zahed Karimi-Jaberi, zahed.karimi@yahoo.com

Received 3 August 2012; Accepted 8 October 2012

Academic Editors: D.-M. Du and G. K. Patra

Trichloroacetic acid was found to be a convenient catalyst for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and their corresponding 2(1H)-thiones through a one-pot three-component reaction of aldehydes, alkyl acetoacetate, and urea or thiourea at 70°C under solvent-free conditions.

1. Introduction

Biginelli reaction is a useful three-component reaction offering versatile protocol for the production of 3,4-dihydropyrimidin-2(1H)-ones which exhibit widespread biological applications such as antihypertensive, antiviral, antitumor, antibacterial, α-1a-antagonism, antioxidant, and anti-inflammatory actions [9, 10].

Although numerous catalysts have been developed in accelerating this reaction [1–8, 11–22], it is still desirable to develop this reaction using newer reagents with greater efficiency, simpler operational procedure, and milder reaction condition, and a higher yield of products coupled with potential bioactivity is important.

With the awareness of environmental issues and importance of this reaction and keeping our interest in the development of synthetic routes to heterocyclic compounds [23–27], herein, we report a heterogeneous, solid trichloroacetic acid, as an alternative, cheap, and efficient catalyst for the Biginelli reaction (Scheme 1).

Trichloroacetic acid is a readily available and inexpensive solid reagent and it has been used by our group for the synthesis of dihydropyrano[2,3-c]pyrazoles [23] and tetrahydrobenzo[a]xanthen-11-ones and dibenzo[a,j]xanthenes [24].

2. Results and Discussion

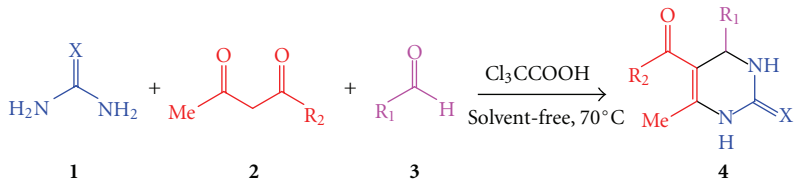
The catalytic activity of trichloroacetic acid was first investigated using three-component reaction of benzaldehyde, ethyl acetoacetate, and urea as a model reaction. After carrying out the reaction at different conditions, the best results have been obtained with 20 mol% trichloroacetic acid at 70°C after 4 min with 85% yield under solvent-free conditions. In the absence of trichloroacetic acid, only 20% yield of the product was obtained even after heating at 70°C for 12 h with recovery of starting material.

The reaction was also examined in solvents such as EtOH, H_2O, $CHCl_3$, and toluene. In the presence of solvents, reaction was sluggish and the formation of by-products was observed. The reaction temperature was also optimized, below 70°C the reaction proceeded slow giving a relatively low yield and no improvement was observed above 70°C.

Having established the reaction conditions, various 3,4-dihydropyrimidin-2(1H)-ones were synthesized in excellent yields through the reaction of different aldehydes, alkyl acetoacetate, and urea. The results are summarized in Table 1, which clearly indicates the generality and scope of the reaction with respect to various aromatic, heteroaromatic, unsaturated, and aliphatic aldehydes. It is noteworthy that acid-sensitive aldehydes such as furfural and cinnamaldehyde

Table 1: Trichloroacetic acid catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones or thiones under solvent-free conditions.

Entry	R_1	R_2	X	Time (min)	Yield (%)	mp (°C, obsd)	mp (°C, lit) (ref.)
1	C_6H_5	OEt	O	4	85	201–203	202–205 [1]
2	4-ClC_6H_4	OEt	O	9	92	212–216	210–212 [1]
3	4-HOC_6H_4	OEt	O	40	90	226–228	231–233 [2]
4	3-$O_2NC_6H_4$	OEt	O	20	93	225–228	227-228 [1]
5	4-$O_2NC_6H_4$	OEt	O	5	85	206–209	207–209 [1]
6	$C_6H_5CH{=}CH$	OEt	O	3	90	225–227	223–226 [1]
7	4-$MeOC_6H_4$	OEt	O	20	95	200–202	202–204 [1]
8	2,4-$(Cl)_2C_6H_3$	OEt	O	4	91	247–249	246–248 [3]
9	4-MeC_6H_4	OEt	O	5	90	213–215	214–216 [1]
10	2-$MeOC_6H_4$	OEt	O	2	94	262-263	260 [4]
11	2,6-$(Cl)_2C_6H_3$	OEt	O	3	96	226–228	226 [5]
12	2-ClC_6H_4	OEt	O	9	85	221–223	221–223 [2]
13	4-BrC_6H_4	OEt	O	11	90	212–214	215 [6]
14	CH_3	OEt	O	3	92	188–190	194-195 [7]
15	CH_3CH_2CH	OEt	O	50	88	163–165	164–166 [7]
16	3-MeC_6H_4	OEt	O	8	93	219–222	224–226 [2]
17	2-Furyl	OEt	O	19	86	202–205	202–204 [5]
18	C_6H_5	OMe	O	5	94	208–211	210–213 [1]
19	4-$MeOC_6H_4$	OMe	O	9	85	192–195	193–196 [3]
20	4-ClC_6H_4	OMe	O	8	92	204–206	203–205 [1]
21	4-$O_2NC_6H_4$	OMe	O	3	95	235–237	235-236 [5]
22	2-ClC_6H_4	OMe	O	6	84	180–182	181–183 [1]
23	3-$O_2NC_6H_4$	OMe	O	12	90	271–274	273–275 [2]
24	4-MeC_6H_4	OMe	O	14	93	206–209	210–213 [3]
25	4-HOC_6H_4	OMe	O	7	87	235–237	231–233 [2]
26	2-$MeOC_6H_4$	OMe	O	2	95	284–286	285–287 [2]
27	3-MeC_6H_4	OMe	O	4	96	214–217	216–218 [2]
28	3-ClC_6H_4	OMe	O	9	92	208–211	209-210 [2]
29	2,4-$(Cl)_2C_6H_3$	OMe	O	3	94	252–255	252-253 [3]
30	2-Furyl	OMe	O	11	88	216–218	214–216 [8]
31	C_6H_5	OEt	S	25	90	210–212	210–212 [1]
32	4-ClC_6H_4	OEt	S	18	86	181–183	184-185 [3]
33	4-$MeOC_6H_4$	OEt	S	20	85	136–138	137–139 [3]
34	3-$O_2NC_6H_4$	OEt	S	15	87	205–208	205-206 [8]
35	C_6H_5	OMe	S	13	92	220–222	221-222 [3]



Scheme 1

that (Table 1) worked well gave the corresponding products. The reaction can also proceed with methyl acetoacetate (Table 1, entries 18–30). In all cases, dihydropyrimidinones were the sole products and no by-product was observed.

The reaction of aldehydes with alkyl acetoacetate and thiourea under similar reaction conditions also provided the corresponding 3,4-dihydropyrimidin-2(1H)-thiones in high yields (Table 1, entries 31–35), which are also of interest with respect to their biological activities [21].

3. Conclusion

In conclusion, a novel approach to explore the use of trichloroacetic acid for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and their corresponding 2(1H)thione has been described through the Biginelli reaction at 70°C under solvent-free conditions. This method offers several advantages including high yields, short reaction times, solvent-free condition, a simple work-up procedure without using any chromatographic methods, and it also has the ability to tolerate a wide variety of substitutions in all three components.

4. Experimental

All chemicals were commercially available and used without further purification. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The NMR spectra were recorded on a Bruker 250 MHz spectrometer.

4.1. General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones/Thiones. A mixture of aldehyde (1 mmol), alkyl acetoacetate (1 mmol), urea/thiourea (1 mmol), and trichloroacetic acid (0.032 g, 20 mol%) was stirred at 70°C for the appropriate time indicated in Table 1. The progress of reactions was monitored by TLC (ethyl acetate/n-hexane). After completion of the reaction, a solid was obtained. It was allowed to cool to room temperature, and ethanol (5 mL) was added, and the catalyst was recovered by filtration. The filtrate was concentrated and allowed to crystallize the desired product.

4.2. Selected Characterization Data

Ethyl-6-Methyl-2-Oxo-4-Phenyl-1,2,3,4-Tetrahydropyrimidine-5-Carboxylate. IR (KBr): 3240, 3110, 1725, 1700, 1645; ^{1}H NMR (DMSO-*d*6): δ 1.12 (t, J = 7.5 Hz, 3H), 2.28 (s, 3H), 4.03 (q, J = 7.5 Hz, 2H), 5.17 (d, J = 3.0 Hz, 1H), 7.22–7.41 (m, 5H), 7.78 (br s, 1H), 9.22 (br s, 1H).

Ethyl-6-Methyl-4-(4-Nitrophenyl)-2-Oxo-1,2,3,4-Tetrahydropyrimidine-5-Carboxylate. IR (KBr): 3230, 3120, 1730, 1710, 1650; ^{1}H NMR (DMSO-*d*6): δ 1.11 (t, J = 7.5 Hz, 3H), 2.29 (s, 3H), 4.00 (q, J = 7.5 Hz, 2H), 5.29 (d, J = 3.0 Hz, 1H), 7.51 (d, J = 10 Hz, 2 H), 7.91 (br s, 1H), 8.23 (d, J = 10.0 Hz, 2H), 9.37 (br s, 1H).

Ethyl-6-Methyl-4-(4-Methoxyphenyl)-3,4-Dihydropyrimidin-2(1H)-One-5-Carboxylate. IR (KBr): 3390, 3243, 3106, 2958, 1706, 1651,1278, 1088. ^{1}H NMR (DMSO-*d*6): δ 1.01–1.20 (t, 3H, J = 7 Hz, CH_2CH_3), 2.30 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 3.90–4.20 (q, 2H, J = 7 Hz, CH_2CH_3), 5.60 (s, 1H, C4-H), 6.80–6.90 (d,2H, J = 7.2 Hz, ArH), 7.15–7.25 (d, 2H, J = 7.2 Hz, ArH), 7.65 (bs, 1H, NH), 9.17 (bs, 1H, NH).

6-Methyl-4-Phenyl-3, 4-Dihydropyrimidin-2(1H)-Thione-5-Carboxylate. IR (KBr): 3412, 3312, 3174, 3096, 2967, 1667, 1610, 1575. ^{1}H NMR (DMSO-*d*6): δ 1.02–1.18 (t, 3H, J = 7.1 Hz, CH_2CH_3), 2.32 (s, 3H, CH_3), 4.02–4.21 (q, 2H, J = 7.1 Hz,CH_2CH_3), 5.50 (s, 1H, C4-H), 7.15–7.35 (m, 5H, ArH), 8.90 (bs, 1H, NH), 9.95 (bs, 1H, NH).

References

[1] G. H. Mahdavinia and H. Sepehrian, "MCM-41 anchored sulfonic acid (MCM-41-R-SO_3H): a mild, reusable and highly efficient heterogeneous catalyst for the Biginelli reaction," *Chinese Chemical Letters*, vol. 19, no. 12, pp. 1435–1439, 2008.

[2] C. Jiang and Q. D. You, "An efficient and solvent-free one-pot synthesis of dihydropyrimidinones under microwave irradiation," *Chinese Chemical Letters*, vol. 18, no. 6, pp. 647–650, 2007.

[3] Y. Yu, D. Liu, C. Liu, and G. Luo, "2007One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using chloroacetic acid as catalyst," *Bioorganic & Medicinal Chemistry Letters*, vol. 17, no. 12, pp. 3508–3510, 2007.

[4] S. Ghassamipour and A. R. Sardarian, "One-pot synthesis of dihydropyrimidinones by dodecylphosphonic acid as solid Bronsted acid catalyst under solvent-free conditions via Biginelli condensation," *Journal of the Iranian Chemical Society*, vol. 7, pp. 237–242, 2010.

[5] J. K. Joseph, S. L. Jain, and B. Sain, "Ion exchange resins as recyclable and heterogeneous solid acid catalysts for the Biginelli condensation: an improved protocol for the synthesis of 3,4-dihydropyrimidin-2-ones," *Journal of Molecular Catalysis A*, vol. 247, no. 1-2, pp. 99–102, 2006.

[6] M. M. Heravi, F. Derikvand, and F. F. Bamoharram, "A catalytic method for synthesis of Biginelli-type 3,4-dihydropyrimidin-2 (1H)-one using 12-tungstophosphoric acid," *Journal of Molecular Catalysis A*, vol. 242, no. 1-2, pp. 173–175, 2005.

[7] N. Y. Fu, Y. F. Yuan, Z. Cao, S. W. Wang, J. T. Wang, and C. Peppe, "Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction," *Tetrahedron*, vol. 58, no. 24, pp. 4801–4807, 2002.

[8] N. S. Nandurkar, M. J. Bhanushali, M. D. Bhor, and B. M. Bhanage, "$Y(NO_3)_3.6H_2O$: a novel and reusable catalyst for one pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions," *Journal of Molecular Catalysis A*, vol. 271, no. 1-2, pp. 14–17, 2007.

[9] C. O. Kappe, "Biologically active dihydropyrimidones of the Biginelli-type—a literature survey," *European Journal of Medicinal Chemistry*, vol. 35, no. 12, pp. 1043–1052, 2000.

[10] J. P. Wan and Y. Liu, "Synthesis of dihydropyrimidinones and thiones by multicomponent reactions: strategies beyond the classical Biginelli reaction," *Synthesis*, vol. 23, pp. 3943–3953, 2010.

[11] H. Adibi, H. A. Samimi, and M. Beygzadeh, "Iron(III) trifluoroacetate and trifluoromethanesulfonate: recyclable Lewis acid catalysts for one-pot synthesis of 3,4-dihydropyrimidinones or their sulfur analogues and 1,4-dihydropyridines via solvent-free Biginelli and Hantzsch condensation protocols," *Catalysis Communications*, vol. 8, no. 12, pp. 2119–2124, 2007.

[12] S. D. Salim and K. G. Akamanchi, "Sulfated tungstate: an alternative, eco-friendly catalyst for Biginelli reaction," *Catalysis Communications*, vol. 12, no. 12, pp. 1153–1156, 2011.

[13] M. Litvic, I. Vecenaj, Z. M. Ladisic, M. Lovric, V. Vinkovic, and M. F. Litvic, "First application of hexaaquaaluminium(III) tetrafluoroborate as a mild, recyclable, non-hygroscopic acid

catalyst in organic synthesis: a simple and efficient protocol for the multigram scale synthesis of 3,4-dihydropyrimidinones by Biginelli reaction," *Tetrahedron*, vol. 66, no. 19, pp. 3463–3471, 2010.

[14] M. A. Bigdeli, G. Gholami, and E. Sheikhhosseini, "*P*-Dodecylbenzenesulfonic acid (DBSA), a Brønsted acid-surfactant catalyst for Biginelli reaction in water and under solvent free conditions," *Chinese Chemical Letters*, vol. 22, no. 8, pp. 903–906, 2011.

[15] P. G. Mandhane, R. S. Joshi, D. R. Nagargoje, and C. H. Gill, "An efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by thiamine hydrochloride in water under ultrasound irradiation," *Tetrahedron Letters*, vol. 51, no. 23, pp. 3138–3140, 2010.

[16] Y. Y. Wu, Z. Chai, X. Y. Liu, G. Zhao, and S. W. Wang, "Synthesis of substituted 5-(Pyrrolidin-2-yl)tetrazoles and their application in the asymmetric Biginelli reaction," *European Journal of Organic Chemistry*, vol. 2009, no. 6, pp. 904–911, 2009.

[17] X. H. Chen, X. Y. Xu, H. Liu, L. F. Cun, and L. Z. Gong, "Highly enantioselective organocatalytic Biginelli reaction," *Journal of the American Chemical Society*, vol. 128, no. 46, pp. 14802–14803, 2006.

[18] D. S. Bose, L. Fatima, and H. B. Mereyala, "Green chemistry approaches to the synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones by a three-component coupling of one-pot condensation reaction: comparison of ethanol, water, and solvent-free conditions," *Organic Chemistry*, vol. 68, no. 2, pp. 587–590, 2003.

[19] J. Wannberg, D. Dallinger, C. O. Kappe, and M. Larhed, "Microwave-enhanced and metal-catalyzed functionalizations of the 4-aryl-dihydropyrimidone template," *Journal of Combinatorial Chemistry*, vol. 7, no. 4, pp. 574–583, 2005.

[20] K. V. N. S. Srinivas and B. Das, "Iodine catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones: a simple and efficient procedure for the Biginelli reaction," *Synthesis*, no. 13, pp. 2091–2093, 2004.

[21] I. S. Zorkun, S. Sarac, S. C. Elebi, and K. Erol, "Synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-thione derivatives as potential calcium channel blockers," *Bioorganic & Medicinal Chemistry*, vol. 14, no. 24, pp. 8582–8589, 2006.

[22] Y. Zhu, Y. Pan, and S. Huang, "Trimethylsilyl chloride: a facile and efficient reagent for one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones," *Synthetic Communications*, vol. 34, pp. 3167–3174, 2004.

[23] Z. Karimi-Jaberi and M. M. ReyazoShams, "Trichloroacetic acid as a solid heterogeneous catalyst for the rapid synthesis of dihydropyrano[2,3- c]pyrazoles under solvent-free conditions," *Heterocyclic Communications*, vol. 17, p. 177, 2011.

[24] Z. Karimi-Jaberi, S. Z. Abbasi, B. Pooladian, and M. Jokar, "Efficient, one-pot synthesis of tetrahydrobenzo[a]xanthen-11-ones and dibenzo[a,j]xanthenes using trichloroacetic acid as a solid heterogeneous catalyst under solvent-free conditions," *E-Journal of Chemistry*, vol. 8, p. 1895, 2011.

[25] Z. Karimi-Jaberi and L. Zarei, "Tris(hydrogensulfato)boron catalysed rapid synthesis of 2-substituted-2,3-dihydroquinazolin-4(1H)-ones under solvent-free conditions," *Journal of Chemical Research*, vol. 36, pp. 194–196, 2012.

[26] Z. Karimi-Jaberi and B. Pooladian, "A facile synthesis of α, α'-bis(substituted benzylidene) cycloalkanones catalyzed by p-TSA under solvent-free conditions," *Green Chemistry Letters and Reviews*, vol. 5, pp. 187–193, 2012.

[27] Z. Karimi-Jaberi, M. Mardani, and M. Amiri, "Green, one-pot synthesis of α-aminophosphonates catalyzed by ZnI2 at room temperature," *Green Processing and Synthesis*, vol. 1, pp. 191–193, 2012.