

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

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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

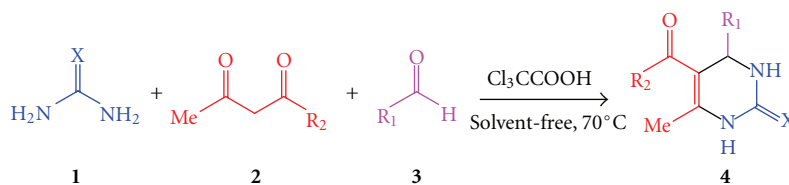
The catalytic activity of trichloroacetic acid was first investigated using three-component reaction of benzaldehyde, ethyl acetoacetate, and urea as a model reaction. After carrying out the reaction at different conditions, the best results have been obtained with 20 mol% trichloroacetic acid at 70°C 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, H₂O, CHCl₃, 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 ₆ H ₅ | OEt | O | 4 | 85 | 201–203 | 202–205 [1] |
| 2 | 4-ClC ₆ H ₄ | OEt | O | 9 | 92 | 212–216 | 210–212 [1] |
| 3 | 4-HOC ₆ H ₄ | OEt | O | 40 | 90 | 226–228 | 231–233 [2] |
| 4 | 3-O ₂ NC ₆ H ₄ | OEt | O | 20 | 93 | 225–228 | 227–228 [1] |
| 5 | 4-O ₂ NC ₆ H ₄ | OEt | O | 5 | 85 | 206–209 | 207–209 [1] |
| 6 | C ₆ H ₅ CH=CH | OEt | O | 3 | 90 | 225–227 | 223–226 [1] |
| 7 | 4-MeOC ₆ H ₄ | OEt | O | 20 | 95 | 200–202 | 202–204 [1] |
| 8 | 2,4-(Cl) ₂ C ₆ H ₃ | OEt | O | 4 | 91 | 247–249 | 246–248 [3] |
| 9 | 4-MeC ₆ H ₄ | OEt | O | 5 | 90 | 213–215 | 214–216 [1] |
| 10 | 2-MeOC ₆ H ₄ | OEt | O | 2 | 94 | 262–263 | 260 [4] |
| 11 | 2,6-(Cl) ₂ C ₆ H ₃ | OEt | O | 3 | 96 | 226–228 | 226 [5] |
| 12 | 2-ClC ₆ H ₄ | OEt | O | 9 | 85 | 221–223 | 221–223 [2] |
| 13 | 4-BrC ₆ H ₄ | OEt | O | 11 | 90 | 212–214 | 215 [6] |
| 14 | CH ₃ | OEt | O | 3 | 92 | 188–190 | 194–195 [7] |
| 15 | CH ₃ CH ₂ CH | OEt | O | 50 | 88 | 163–165 | 164–166 [7] |
| 16 | 3-MeC ₆ H ₄ | OEt | O | 8 | 93 | 219–222 | 224–226 [2] |
| 17 | 2-Furyl | OEt | O | 19 | 86 | 202–205 | 202–204 [5] |
| 18 | C ₆ H ₅ | OMe | O | 5 | 94 | 208–211 | 210–213 [1] |
| 19 | 4-MeOC ₆ H ₄ | OMe | O | 9 | 85 | 192–195 | 193–196 [3] |
| 20 | 4-ClC ₆ H ₄ | OMe | O | 8 | 92 | 204–206 | 203–205 [1] |
| 21 | 4-O ₂ NC ₆ H ₄ | OMe | O | 3 | 95 | 235–237 | 235–236 [5] |
| 22 | 2-ClC ₆ H ₄ | OMe | O | 6 | 84 | 180–182 | 181–183 [1] |
| 23 | 3-O ₂ NC ₆ H ₄ | OMe | O | 12 | 90 | 271–274 | 273–275 [2] |
| 24 | 4-MeC ₆ H ₄ | OMe | O | 14 | 93 | 206–209 | 210–213 [3] |
| 25 | 4-HOC ₆ H ₄ | OMe | O | 7 | 87 | 235–237 | 231–233 [2] |
| 26 | 2-MeOC ₆ H ₄ | OMe | O | 2 | 95 | 284–286 | 285–287 [2] |
| 27 | 3-MeC ₆ H ₄ | OMe | O | 4 | 96 | 214–217 | 216–218 [2] |
| 28 | 3-ClC ₆ H ₄ | OMe | O | 9 | 92 | 208–211 | 209–210 [2] |
| 29 | 2,4-(Cl) ₂ C ₆ H ₃ | OMe | O | 3 | 94 | 252–255 | 252–253 [3] |
| 30 | 2-Furyl | OMe | O | 11 | 88 | 216–218 | 214–216 [8] |
| 31 | C ₆ H ₅ | OEt | S | 25 | 90 | 210–212 | 210–212 [1] |
| 32 | 4-ClC ₆ H ₄ | OEt | S | 18 | 86 | 181–183 | 184–185 [3] |
| 33 | 4-MeOC ₆ H ₄ | OEt | S | 20 | 85 | 136–138 | 137–139 [3] |
| 34 | 3-O ₂ NC ₆ H ₄ | OEt | S | 15 | 87 | 205–208 | 205–206 [8] |
| 35 | C ₆ H 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; ¹H 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; ¹H 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, 2H), 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. ¹H NMR (DMSO-*d*₆): δ 1.01–1.20 (t, 3H, *J* = 7 Hz, CH₂CH₃), 2.30 (s, 3H, CH₃), 3.80 (s, 3H, OCH₃), 3.90–4.20 (q, 2H, *J* = 7 Hz, CH₂CH₃), 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. ¹H NMR (DMSO-*d*₆): δ 1.02–1.18 (t, 3H, *J* = 7.1 Hz, CH₂CH₃), 2.32 (s, 3H, CH₃), 4.02–4.21 (q, 2H, *J* = 7.1 Hz, CH₂CH₃), 5.50 (s, 1H, C4-H), 7.15–7.35 (m, 5H, ArH), 8.90 (bs, 1H, NH), 9.95 (bs, 1H, NH).

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