TiO_2 as a Reusable Catalyst for the One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones under Solvent-Free Conditions

by **Mohammad Zaman Kassaee***, **Hassan Masrouri**, **Farnaz Movahedi**, and **Reza Mohammadi**

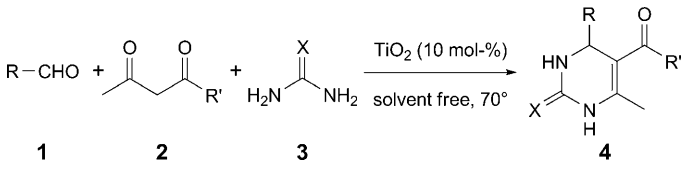
Department of Chemistry, Tarbiat Modares University, P. O. Box 14155-4838, Tehran, Iran (phone: +98-912-1000392; fax: +98-21-88006544; e-mail: kassaeem@modares.ac.ir, drkassaee@yahoo.com)

An efficient solvent-free method for the synthesis of various 3,4-dihydropyrimidin-2(1*H*)-ones using TiO_2 as a recyclable heterogeneous catalyst is described. Compared to known methods, satisfactory results are obtained with excellent yields, short reaction times, and simplicity in the experimental procedure.

Introduction. – The *Biginelli* reaction [1] offers an efficient way to access multifunctionalized 3,4-dihydropyrimidin-2(1*H*)-ones and related heterocyclic compounds.

Results and Discussions. – We wish to report an efficient and simple method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones through a three-component condensation of 1,3-dicarbonyl compounds, aldehydes, and urea, using commercially available titania (TiO_2) as an inexpensive heterogeneous and recyclable catalyst under neutral and solvent-free conditions (*Scheme*).

Scheme



In a typical general experimental procedure, we probed cyclocondensation of benzaldehyde, urea, and ethyl acetoacetate (=ethyl 3-oxobutanoate) in the presence of TiO_2 (10 mol-%) at 70° under solvent-free conditions. The mixture of reactants solidified within 20 min. It was diluted with AcOEt, and the catalyst was separated by filtration. The filtrate was washed with H_2O (two times) and dried over anhydrous $MgSO_4$. Then, it was evaporated under reduced pressure to yield the crude product, which was further purified by recrystallization from EtOH to afford pure ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate in 98% yield. A wide range of structurally varied β-dicarbonyl compounds, aldehydes, and urea are coupled by this procedure to produce the corresponding dihydropyrimidinones (*Table 1*). Both β-keto ester and β-diketone readily participated in this reaction.

Table 1. *TiO_2-Catalyzed Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones*[a])

Entry	Product	R	R′	X	Time [min]	Yield [%][b])	M.p. [°] (lit. m.p.)
1	**4a**	Ph	EtO	O	20	98	203–204 (201–203) [2]
2	**4b**	Ph	Me	O	20	96	235–237 (233–236) [2]
3	**4c**	Ph	MeO	O	30	98	209–211 (207–210) [2]
4	**4d**	Ph	MeO	S	20	91	228–230 (221–222) [3]
5	**4e**	Ph	EtO	S	30	92	204–205 (202–204) [3]
6	**4f**	4-Br–C_6H_4	Me	O	20	89	216–219
7	**4g**	4-Br–C_6H_4	MeO	O	25	91	221–223
8	**4h**	4-Br–C_6H_4	EtO	O	20	92	220–222
9	**4i**	4-Me–C_6H_4	Me	O	20	96	228–230
10	**4j**	4-Me–C_6H_4	MeO	O	35	97	212–214 (204–206) [4]
11	**4k**	4-Me–C_6H_4	EtO	O	30	97	213–215 (213–216) [3]
12	**4l**	4-Me–C_6H_4	EtO	S	40	93	184–187 (192–194) [4]
13	**4m**	3-Me–C_6H_4	MeO	O	25	94	210–212 (209–211) [5]
14	**4n**	4-MeO–C_6H_4	MeO	O	25	92	193–195 (191–193) [2]
15	**4o**	4-MeO–C_6H_4	EtO	O	25	93	201–203 (199–201) [2]
16	**4p**	4-MeO–C_6H_4	EtO	S	35	90	150–152 (150–152) [4]
17	**4q**	4-Cl–C_6H_4	MeO	O	35	93	205–208 (207–208) [3]
18	**4r**	4-Cl–C_6H_4	EtO	O	30	95	210–212 (210–212) [2]
19	**4s**	3-Cl–C_6H_4	Me	O	25	89	205–208
20	**4t**	3-Cl–C_6H_4	MeO	O	35	91	224–225
21	**4u**	3-Cl–C_6H_4	EtO	O	35	92	194–196 (193–195) [4]
22	**4v**	2-Cl–C_6H_4	MeO	O	40	88	235–237
23	**4w**	2-Cl–C_6H_4	EtO	O	40	90	221–223 (222–224) [4]
24	**4x**	4-OH–C_6H_4	MeO	O	30	93	247–249 (245–246) [6]
25	**4y**	4-OH–C_6H_4	EtO	O	30	95	230–233 (230–232) [4]
26	**4z**	Ph–CH=CH	MeO	O	45	90	230–232
27	**4aa**	Ph–CH=CH	EtO	O	45	92	234–237 (232–235) [2]
28	**4ab**	Thien-2-yl	MeO	O	60	87	184–186
29	**4ac**	Thien-2-yl	EtO	O	60	89	209–211 (207–208) [7]
30	**4ad**	Furan-2-yl	EtO	O	50	91	228–230
31	**4ae**	3-NO_2, 4-Cl–C_6H_4	EtO	O	55	86	245–247
32	**4af**	Bu	EtO	O	60	83	157–158 (157–158) [2]
33	**4ag**	^{i}Pr	EtO	O	50	86	194–195 (194–195) [2]
34	**4ah**	H	EtO	O	60	82	242–244 (242–244) [4]

[a]) Reaction conditions: aldehyde (1.5 mmol), urea/thiourea (2 mmol), β-dicarbonyl compound (1.5 mmol), catalyst (10 mol-%), at 70° under solvent-free conditions. [b]) Yield of isolated material.

The reaction can tolerate a wide range of heterocyclic, aliphatic, or aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents in *ortho*, *meta*, or *para* position. Acid sensitive aldehydes such as furfuraldehyde (= furan-2-carbaldehyde) worked well without the formation of any side products and gave the 3,4-dihydropyrimidin-2(1*H*)-one derivative in 91% yield (*Table 1*, *Entry 30*). Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1*H*)-thiones which are also of interest with regard to their biological activity. Thus, variations in all three components have been accommodated very comfortably. All products were characterized on the basis of their spectroscopic data such as ^{1}H- and ^{13}C-NMR, and physical data.

To investigate the effects of media, we carried out the condensation of benzaldehyde, urea, and ethyl acetoacetate in various organic solvents under refluxing condition while using 10 mol-% of TiO_2 as the catalyst (*Table 2*). The use of solvents such as MeCN, THF, EtOH, or H_2O decreased the product yields (*Table 2*, *Entries 1–4*). In evaluating the effects of catalyst concentration, we found the use of 10 mol-% of TiO_2 sufficient to push the reaction forward. A higher amount of TiO_2 (20 mol-%) did not improve the result to an appreciable extent (*Table 2*, *Entry 9*).

Table 2. *Optimization of the TiO_2-Catalyzed Model Reaction for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones*[a])

Entry	Solvent	Catalyst	Time [min]	Yield [%][b])
1	MeCN	TiO_2 (10 mol-%)	120	68
2	THF	TiO_2 (10 mol-%)	90	86
3	H_2O	TiO_2 (10 mol-%)	180	45
4	EtOH	TiO_2 (10 mol-%)	120	80
5	neat	No catalyst	180	0
6	neat	TiO_2 (5 mol-%)	50	78
7	neat	TiO_2 (10 mol-%)	240	30[c])
8	neat	TiO_2 (10 mol-%)	20	98
9	neat	TiO_2 (20 mol-%)	20	98

[a]) Reaction conditions: aldehyde (1.5 mmol), urea/thiourea (2 mmol), β-dicarbonyl compound (1.5 mmol), catalyst (10 mol-%) under reflux or solvent-free conditions at 70°. [b]) Yield of isolated material. [c]) Reaction carried out at room temperature.

To appraise the effect of the temperature, the reaction of benzaldehyde, urea, and ethyl acetoacetate in the presence of a catalytic amount of TiO_2 was carried out at different temperatures under similar experimental conditions. The reaction rate was very slow at ambient temperature, but improved with increasing the temperature. The optimum temperature was found to be 70° and no improvement was realized at higher temperatures. *Biginelli* reaction of benzaldehyde, ethyl acetoacetate, and urea under the described reaction conditions did not proceed in the absence of catalyst. No additive or protic/*Lewis* acid is necessary in this method. Another important aspect of this procedure is the survival of a variety of functional groups such as Br, Cl, NO_2, OH, MeO, and a conjugated C=C bond under the reaction conditions.

The possibility to recycle and reuse TiO_2 has also been studied (*Table 3*). The catalyst was separated by filtration from the mixture after dilution with AcOEt, and was reused as such for subsequent experiments under similar reaction conditions. The yields of **4a** only decreased a little after the fifth reuse of TiO_2.

Conclusion. – In conclusion, the present three-component, one-pot condensation for the synthesis of dihydropyrimidin-2(1*H*)-ones/thiones by TiO_2 catalysis provides an efficient, facile, and environmentally acceptable modification of *Biginelli*'s reaction. This method offers several advantages including high yields, short reaction times, a simple work-up procedure under solvent-free conditions, ease of separation, and recyclability of the catalyst, as well as the ability to tolerate a wide variety of substituents in all the three components.

Table 3. *Reusability of the TiO_2 Catalyst*[a])

Number of use	Yield [%]	Recovery of TiO_2 [%]
1	98	99
2	98	98
3	96	98
4	93	96
5	89	95

[a]) Formation of **4e** under the standard conditions.

Experimental Part

General. The reagents and solvents used in this work were obtained from *Fluka* (Buchs, Switzerland) and used without further purification. M.p.: *Electrothermal 9100* apparatus. ^{1}H- and ^{13}C-NMR spectra: at 500.1, and 125.7 MHz, resp., on a *Bruker DRX 500-Avance* FT-NMR instrument with (D_6)DMSO as the solvent.

*General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones* (exemplified for **4a**). To a stirred mixture of benzaldehyde (1.5 mmol, 159.2 mg), urea (2 mmol, 120.1 mg), and ethyl acetoacetate (=ethyl 3-oxobutanoate; 1.5 mmol, 195.2 mg) was added the TiO_2 catalyst (10 mol-%, 8 mg) at 70°. Solidification occurred within 20 min. The resulting solid was diluted with AcOEt (2 ml), and the catalyst was separated by filtration through a *Büchner* funnel. The filtrate obtained was washed with H_2O (two times) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure yielded a crude product which was purified by recrystallization from EtOH to afford pure ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (**4a**) in 98% yield, M.p. 203–204°. Similarly, other aldehydes were reacted with urea/thiourea and β-dicarbonyl compounds to obtain the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (*Table 1*).

REFERENCES

[1] P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360.
[2] Y. Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.* **2000**, *65*, 3864.
[3] Y. Yu, D. Liu, C. Liu, G. Luo, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3508.
[4] N.-Y. Fu, Y.-F. Yuan, Z. Cao, S.-W. Wang, J.-T. Wang, C. Peppe, *Tetrahedron* **2002**, *58*, 4801.
[5] C. O. Kappe, W. M. F. Fabian, M. A. Semones, *Tetrahedron* **1997**, *53*, 2803.
[6] A. Kumar, R. A. Maurya, *Tetrahedron Lett.* **2007**, *48*, 4569.
[7] G. Sabitha, G. S. K. K. Reddy, C. S. Reddy, J. S. Yadav, *Synlett* **2003**, 858.

Received May 27, 2009