Iodine Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones and Thiones: A Simple and Efficient Procedure for the Biginelli Reaction[1]

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Abstract: Iodine efficiently catalyzes the Biginelli reaction. This procedure involves a one-pot three-component cyclocondensation of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones or thiones in high yields.

Keywords: iodine, aldehydes, 1,3-dicarbonyl compounds, urea, thiourea, one-pot condensation, dihydropyrimidin-ones and thiones, Biginelli reaction

Dihydropyrimidinones and their sulfur analogues have attracted considerable interest recently because of their wide range of biological activities such as antiviral, antibacterial, antitumour, and anti-inflammatory properties.[2] Many of these compounds act as antihypertensive agents as well as calcium channel blockers, α-1a-antagonists and neuropeptide Y (NPY) antagonists.[3] The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the molecules.[4] Most importantly among them are batzeladine alkaloids which have been found to be potent HIVgp-120-CD4 inhibitors.[5] Hence, synthesis of these dihydropyrimidinones and thiones has gained much importance in recent years.

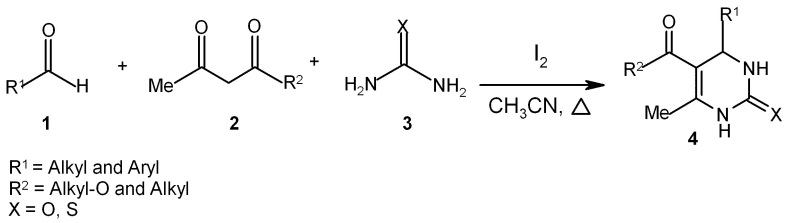
A simple and direct method for the synthesis of dihydropyrimidinones, reported first by Biginelli in 1893, involves the one-pot condensation of an aldehyde, a β-ketoester and urea under strongly acidic conditions.[6] However, it suffers from low yields of the products particularly in the cases of substituted aromatic and aliphatic aldehydes. Subsequently development of more complex multistep synthesis afforded somewhat higher yields but these methods do not have the simplicity of the original one-pot Biginelli reaction.[7] Recently several methods have been reported for preparing dihydropyrimidinones using different Lewis acids such as $BF_3{\cdot}OEt_2$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, $InCl_3$, $InBr_3$, $ZrCl_4$, $BiCl_3$, $Bi(OTf)_3$, LiBr, $LiClO_4$, $Mn(OAc)_3$, CAN, $FeCl_3{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$ etc.[8] as well as protic acids such as H_2SO_4, HOAc, concd HCl etc.[9] as promoters. Many other methods including microwave irradiation, ionic liquids, and clays[10] are also reported. However, many of these methods are associated with expensive and toxic reagents, stoichiometric amounts of catalysts, strongly acidic conditions, long reaction times, unsatisfactory yields, incompatibility with other functional groups and involve difficult product isolation procedures. Moreover, some of the methods are only practical for aromatic aldehydes.[8a,k,10c] Thus there is still a need for a simple and general procedure for one-pot synthesis of dihydropyrimidinones and thiones under mild conditions.

We now show that iodine is an inexpensive, mild and efficient catalyst for Biginelli three-component one-pot synthesis of dihydropyrimidinones and thiones.

The three components, aldehyde, 1,3-dicarbonyl compound and urea or thiourea were refluxed under N_2 in the presence of iodine as catalyst using CH_3CN as a solvent (Scheme 1). We found that CH_3CN is most effective solvent in terms of yields than other tested solvents such as $CHCl_3$, THF and EtOH.

The minimum amount of iodine required to get maximum yields of the products is 39.5 mmol% with respect to the aldehydes (0.79 mmol of iodine is necessary for 2 mmol of an aldehyde along with 2 mmol of an 1,3-dicarbonyl compound and 2.5 mmol of urea or thiourea).

Most importantly aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents react-



Scheme 1

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ed very well to give the desired products in excellent yields (Table 1). We verified the yields of some products by repeating some experiments for two to three times. Even aliphatic aldehydes, which normally show poor yields in the Biginelli reaction afforded the products with high yields.[11] Thiourea also reacted in a similar manner like urea. Another important feature of this procedure is the survival of a variety of functional groups such as ether, nitro, hydroxyl, halides etc., under the reaction conditions.

In conclusion, we have developed a simple and general method for the synthesis of dihydropyriminones and thiones by applying Biginelli reaction using iodine as catalyst. The present procedure is equally effective for both urea and thiourea and also for aromatic and aliphatic alde-

Table 1 Iodine Catalyzed One-Pot Synthesis of Dihydropyrimidinones and Thiones[a]

Entry	Product	R^1	R^2	X	Time (h)	Yield[b] (%)	Ref.
1	**4a**	4-$(CH_3)C_6H_4$	OEt	O	7	86	8e
2	**4b**	4-$(CH_3O)C_6H_4$	OEt	O	6.5	87	8e
3	**4c**	4-ClC_6H_4	OEt	O	8	91	8e
4	**4d**	4-$NO_2C_6H_4$	OEt	O	7.5	89	8e
5	**4e**	3,4-$(CH_3O)_2C_6H_3$	OEt	O	6	87	8j
6	**4f**	C_6H_5CH=CH	OEt	O	7	82	8e
7	**4g**	2-$(OH)C_6H_4$	OEt	O	8	71	8m
8	**4h**	3,4-$(OCH_2O)C_6H_3$	OEt	O	7	84	8m
9	**4i**	3-(CH_3O)-4$(OH)C_6H_3$	OEt	O	8	90	8m
10	**4j**	C_6H_5	OEt	S	6.5	92	8e
11	**4k**	4-ClC_6H_4	OEt	S	7	88	8e
12	**4l**	4-$NO_2C_6H_4$	OEt	S	7	90	8e
13	**4m**	4-$(CH_3O)C_6H_4$	OEt	S	6	87	8e
14	**4n**	3-$(OH)C_6H_4$	OEt	S	8	76	8n
15	**4o**	3-(CH_3O)4$(OH)C_6H_3$	OEt	S	7.5	88	
16	**4p**	C_6H_5	OMe	O	6.5	93	8e
17	**4q**	C_6H_5	OMe	S	6	91	8o
18	**4r**	4-ClC_6H_4	OMe	O	7	89	8e
19	**4s**	4-$NO_2C_6H_4$	OMe	O	7	90	8e
20	**4t**	4-$(CH_3O)C_6H_4$	OMe	O	6.5	88	8e
21	**4u**	C_6H_5	Me	O	6	85	8j
22	**4v**	C_6H_5	Me	S	6	86	8d
23	**4w**	4-$(CH_3O)C_6H_4$	Me	O	7	83	8c
24	**4x**	4-$NO_2C_6H_4$	Me	O	8	85	8c
25	**4y**	2-Furyl	OEt	O	7.5	72	8e
26	**4z**	$(CH_3)_2CH$	OEt	O	7	79	8m
27	**4a′**	$(CH_3)_2CH$	OMe	S	6.5	82	
28	**4b′**	C_5H_{11}	OEt	O	7	80	8e
29	**4c′**	C_5H_{11}	OEt	S	7	83	

[a] The structures of the products were confirmed from their spectral (IR, ^1H NMR and MS) data.
[b] The yields of some products were verified by repeating some experiments for two to three times and their average yields are presented here.

hydes. The compatibility with various functional groups, mild reaction conditions, high yields and application of inexpensive, mild, readily and easily available iodine as catalyst are the advantages of the present procedure.

All the aldehydes, 1,3-dicarbonyl compounds and urea or thiourea were available commercially. I_2 was obtained from LOBA Chemicals, India. Melting points were determined in a capillary tube and are not corrected. The spectra were run on the following instruments: IR, Perkin-Elmer (RX1 FT-IR), ^{1}H NMR: Varian Gemini 200 MHz and EI-MS: VG Micromass 7070 H (70 eV).

Typical Experimental Procedure

A mixture of an aldehyde (2 mmol), 1,3-dicarbonyl compound (2 mmol), urea or thiourea (2.5 mmol) and iodine (100 mg, 0.79 mmol) in CH_3CN (10 mL) was heated under reflux for 6–8 h under N_2 atmosphere. The reaction was monitored by TLC. After completion of the reaction the solvent was removed under reduced pressure and the residue was extracted with EtOAc. The EtOAc extract was washed with a solution of sodium thiosulfate (2 × 10 mL) and subsequently with water (3 × 10 mL) and dried over anhyd Na_2SO_4. Evaporation of the solvent under reduced pressure yielded the solid, which was crystallized from EtOH to afford the pure compound.

All the products were characterized from their spectral (IR, ^{1}H NMR, and MS) data. The spectral data of the unknown compounds are given below.

5-Ethoxycarbonyl-6-methyl-4-(3-methoxy,4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-thione (4o, Entry 15)

Solid; mp 241–242 °C.

IR (KBr): 3245, 2927, 1700, 1645, 1515 cm^{-1}.

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ = 8.84 (br s, 1 H), 8.30 (br s, 1 H), 7.18 (br s, 1 H), 6.88–6.62 (m, 3 H), 5.12 (d, *J* = 2.5 Hz, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 3.80 (s, 3 H), 2.21 (s, 3 H), 1.08 (t, *J* = 7.0 Hz, 3 H).

FAB–MS: *m*/*z* = 323 [M$^+$ + 1].

5-Methoxycarbonyl-6-methyl-4-(isopropyl)-3,4-dihydropyrimidin-2(1*H*)-thione (4a′, Entry 27)

Solid; mp 176–177 °C.

IR (KBr): 3236, 3108, 1702, 1647 cm^{-1}.

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ = 8.68 (br s, 1 H), 6.76 (br s, 1 H), 4.18 (d, *J* = 3.0 Hz, 1 H), 3.62 (s, 3 H), 2.27 (s, 3 H), 1.78 (m, 1 H), 0.90 (d, *J* = 6.0 Hz, 3 H), 0.80 (d, *J* = 6.0 Hz, 3 H).

FAB–MS: *m*/*z* = 229 [M$^+$ + 1].

5-Ethoxycarbonyl-6-methyl-4-(pentyl)-3,4-dihydropyrimidin-2(1*H*)-thione (entry 4c′, Entry 29)

Solid; mp 167–168 °C.

IR (KBr): 3272, 3060, 1685, 1623 cm^{-1}.

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ = 8.18 (br s, 1 H), 5.72 (br s, 1 H), 4.08–4.38 (m, 3 H), 2.30 (s, 3 H), 1.18–1.62 (m, 11 H), 0.94 (t, *J* = 7.0 Hz, 3 H).

FAB–MS: *m*/*z* = 271 [M$^+$ + 1].

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References

(1) Part 35 in the series, 'Studies on Novel Synthetic Methodologies'. For part 34 see: Das, B.; Banerjee, J.; Ravindranath, N.; Venkataih, B. *Tetrahedron Lett.* **2004**, *45*, 2425.

(2) (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Kappe, C. O.; Fabian, W. M. F. *Tetrahedron* **1997**, *53*, 2803. (c) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

(3) (a) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smille, K. M.; Mallary, M. F. *J. Med. Chem.* **1990**, *33*, 2629. (b) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hodberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806.

(4) (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828; and references cited therein. (b) Overman, L. E.; Robinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2657; and references cited therein. (c) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.

(5) (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, J.; De Brosse, C.; Mai, C.; Trunch, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. *J. Org. Chem.* **1995**, *60*, 1182. (b) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J. *Tetrahedron Lett.* **1996**, *37*, 6977.

(6) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.

(7) (a) Atwal, K. S.; Rovnyak, G. C.; O', R. e. i. l. l. y. B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898; and references cited therein. (b) Gupta, R.; Gupta, A. K.; Paul, S.; Kachroo, P. L. *Indian J. Chem.: Sect. B* **1995**, *34*, 151.

(8) (a) Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454. (b) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett.* **2000**, *41*, 9075. (c) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864. (d) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270. (e) Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.; Peppe, C. *Tetrahedron* **2002**, *58*, 4801. (f) Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657. (g) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, 863. (h) Varala, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, 67. (i) Gourhari, M.; Pradip, K.; Chandrani, G. *Tetrahedron Lett.* **2003**, *44*, 2757. (j) Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341. (k) Kumar, K. A.; Kasthuraiah, M.; Reddy, C. S.; Reddy, C. D. *Tetrahedron Lett.* **2001**, *42*, 7873. (l) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Raj, K. S.; Prasad, A. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1939. (m) Jun, L.; Yinjuan, B. *Synthesis* **2002**, 466. (n) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889. (o) Sabitha, G.; Kiran Kumar Reddy, G. S.; Bhaskar Reddy, K.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 6497.

(9) (a) Bussolari, J. C.; McDonnell, P. A. *J. Org. Chem.* **2000**, *65*, 6777. (b) Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramalingam, T. *J. Chem. Res., Synop.* **2000**, 354. (c) Atwal, K. S.; O'Reilly, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189. (d) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1985**, *54*, 5898. (e) Lu, J.; Ma, H. R. *Synlett* **2000**, 63.

(10) (a) Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 5917. (b) Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465. (c) Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799.

(11) Van den Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Van Haverbeke, Y.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.