Chinese Chemical Letters Vol. 13, No. 10, pp 921 – 922, 2002
http://www.imm.ac.cn/journal/ccl.html

Indium (III) Tribromide : An Excellent Catalyst for Biginelli Reaction

Nan Yan FU, Mei Li PANG, Yao Feng YUAN, Ji Tao WANG*

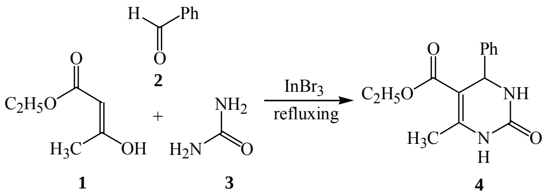
Department of Chemistry, National Key Laboratory of Elemento-organic Chemistry,
Nankai University, Tianjin 300071

Abstract: A highly efficient catalyst indium (III) tribromide is used to synthesize 5-alkoxy-carbonyl-4-hydrocarbyl-3,4-dihydropyrimidin-2(1H)-ones by a three-component coupling of β-keto ester, aldehydes and urea through improved Biginelli reaction.

Keywords: Indium (III) tribromide, dihydropyrimidinone, β-keto ester, one-pot condensation, Biginelli reaction.

Many dihydropyrimidinones and their derivatives are pharmacologically important as calcium channel blockers, antihypertensive agents, and α-1a-antagonists. Therefore, many synthetic methods for preparing such compounds have been developed. The most simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strong acidic conditions[1, 2]. However, one serious drawback of Biginelli's reaction is its low (20-50%) yields, particularly, in the case of substituted aromatic and aliphatic aldehydes, which hinders the application of this reaction.

Scheme 1



Recently, we discovered an excellent catalyst indium (III) tribromide as a mild Lewis acid which not only preserved to simplify Biginelli's one-pot reaction but also enhanced the yields of the dihydropyrimidin-2(1H)-ones to 80-90% (**Scheme 1**).

In order to optimize the reaction conditions, we have tested a variety of solvent with the model reaction using indium (III) tribromide as a catalyst. According to the control experiment, we can see that indium (III) tribromide plays a very important role in Biginelli reaction. It also seems that THF (83%), benzene (94%) and ethanol (98%) are the optimum solvents than all others. Considering the environmental concerns, we

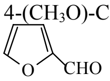
---

*E-mail: wangjitao@nankai.edu.cn

chose the ethanol as reaction solvent. Furthermore, indium (III) tribromide could be reused four times without any loss of activity.

Several aromatic and aliphatic aldehydes were examined under the optimized conditions: refluxing in ethanol with 10 mol% indium (III) tribromide for 7 hours. The results are listed in **Table 1**. In all the cases, the three-component reaction proceeded smoothly to give the corresponding dihydropyrimidinones in high yields. Compared to the classical Biginelli method, one additional important feature of the present protocol is the ability to tolerate the variation in aldehyde. Not only aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents, but also aliphatic aldehydes such as valeric aldehyde and polyformaldehyde all gave excellent yields without depolymerization; many of the pharmacological relevant substitution patterns on the 4-position of the ring can thus be introduced with high efficiency.

Table 1 Indium (III) Tribromide Catalyzed Synthesis of Dihydropyrimidinones Using Different Aldehydes

entry	aldehyde	product	refluxing time (hr)	yield(%)[a]	m.p. (°C) (lit.)
1	C_6H_5CHO	**4a**	7	98	202-204 (202-204[3])
2	3-(OH)-C_6H_4CHO	**4b**	7	90	163-165 (164-166[4])
3	4-(OH)-C_6H_4CHO	**4c**	7	93	230-232 (230-232[4])
4	2-Cl-C_6H_4CHO	**4d**	7	75	222-224
5	4-Cl-C_6H_4CHO	**4e**	7	86	212-214 (213-215[3])
6	4-(CH_3O)-C_6H_4CHO	**4f**	7	97	202-204 (201-203[3])
7		**4g**	7	95	209-211
8	3-NO_2-C_6H_4CHO	**4h**	36	95	229-231
9	4-NO_2-C_6H_4CHO	**4i**	36	86	207-209 (208-211[3])
10	$CH_3(CH_2)_3CHO$	**4j**	7	92	164-166
11	polyformaldehyde	**4k**	7	80	242-245 (dec.)

[a] Isolated yield.

General procedure

A solution of β-keto ester (**1**, 4 mmol), the appropriate aldehyde (**2**, 4 mmol), urea (**3**, 5.2 mmol), $InBr_3$ (142 mg, 0.4 mmol, 10 mol%) in ethanol (10 mL) was heated under reflux for 7 hrs. After cooling, the product was crystallized from the reaction solution. After filteration, it was washed with ethanol (3×10 mL). All the products were characterized by ^1H NMR spectral data and their melting points have been compared with that reported in literature.

Acknowledgments

Financial support was provided by the National Natural Science Foundation of China (29872018 & 29972026).

References

1. P. Biginelli, *Gazz. Chim. Ital.*, **1893**, *23*, 360.
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. B. C. Ranu, A. Hajra, U. Jana, *J. Org. Chem.*, **2000**, *65*, 6270.

Received 24 December, 2001