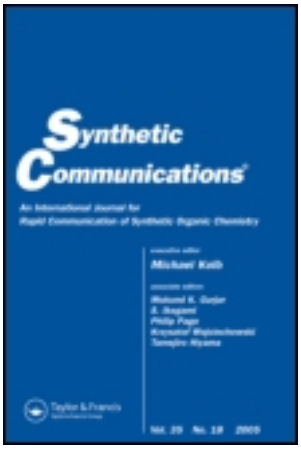


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

PEG-SO_3H as Catalyst for 3,4-Dihydropyrimidones via Biginelli Reaction Under Microwave and Solvent-Free Conditions

Xicun Wang [a], Zhengjun Quan [a], Fang Wang [a], Mangang Wang [a], Zhang Zhang [a] & Zheng Li [a]

[a] Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, China

Published online: 19 Aug 2006.

To cite this article: Xicun Wang , Zhengjun Quan , Fang Wang , Mangang Wang , Zhang Zhang & Zheng Li (2006) PEG-SO_3H as Catalyst for 3,4-Dihydropyrimidones via Biginelli Reaction Under Microwave and Solvent-Free Conditions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:4, 451-456, DOI: 10.1080/00397910500383519

To link to this article: http://dx.doi.org/10.1080/00397910500383519

Synthetic Communications®, 36: 451–456, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500383519

PEG-SO_3H as Catalyst for 3,4-Dihydropyrimidones via Biginelli Reaction Under Microwave and Solvent-Free Conditions

Xicun Wang, Zhengjun Quan, Fang Wang, Mangang Wang, Zhang Zhang, and Zheng Li

Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, China

Abstract: An efficient and environmentally friendly process for the synthesis of 3,4-dihydropyrimidones via the Biginelli-type condensation reaction using poly(ethylene glycol)-bound sulfonic acid as catalyst irradiated by microwave has been developed. The functionalized poly(ethylene glycol) acted simultaneously as catalyst and as solvent in the condensation. The workup was easy, and the products were obtained in good to excellent yields and high purities.

Keywords: Biginelli reaction, 3,4-dihydropyrimidone, microwave, poly(ethylene glycol) (PEG), polymer-supported catalyst

INTRODUCTION

In recent years, there has been rapid growth in the development of novel polymer-supported compounds,[1] such as supported catalysts, reagents, and scavengers. These species allow rapid and simplified procedures, and their

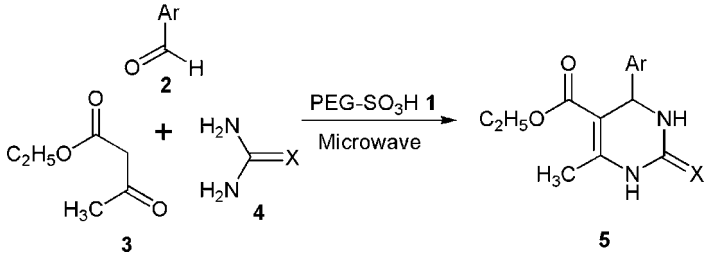
Received in Japan July 11, 2005

Address correspondence to Xicun Wang, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, China. Tel.: +86-931-7971971; Fax: 86-931-7971971; E-mail: wangxicun@nwnu.edu.cn

use has become widespread in solution-phase organic synthesis and combinatorial chemistry.[2] After reaction by filtration and multiple washing steps, reagents, excess starting materials, solvents, and by-products are removed. Then the desired products are obtained in good purity by simple operation. The polymer-supported compounds include mainly two types: the dominated insoluble polymer supported and soluble polymer supported. However, in recent years, the soluble polymer-bound compounds have received some interest in various organic reactions.[3] One could envision that in an ideal case such a functionalized polymer could act as a catalyst and at the same time as a solvent in the synthesis step. Appropriately functionalized polymeric resins could be utilized that not only mediate a specific chemical reaction but at the same time act as solvents. However, examples of such supported polymers that act simultaneously as a catalyst and as solvent are rare.[3a] Poly(ethylene glycol) (PEG) and its aqueous solutions represent interesting solvents for solvent replacement and may stand comparison to other currently favored systems, such as ionic liquids, supercritical carbon dioxide, and micellar systems.[4]

We recently reported the synthesis of 1,3,4-oxadiazoles using PEG-supported dichlorophosphate as catalyst and solvent under microwave irradiation.[5] Herein we preliminarily report the generation of libraries of Biginelli-type compounds 3,4-dihydropyrimidones (DHPMs) **5**, employing PEG-bound sulfonic acid that acts simultaneously as reaction promoter in the Biginelli-type reaction step and as reaction solvent (Scheme 1).

The considerable interest in DHPM-type products stems from their wide range of biological activities as calcium channel blockers, antihypertensive agents, α_{1a} adrenergic antagonists, and neuropeptide Y antagonists.[6] DHPMs are generally referred to as Biginelli compounds because in 1893 P. Biginelli reported the synthesis of DHPMs by cyclocondensation of ethyl acetoacetate, aldehyde, and urea. Because of the strongly acidic conditions, low yields, and difficult isolation in the original Biginelli conditions, improved procedures using different types of catalysts and conditions have been reported with the aim of overcoming the main drawbacks of the Biginelli reaction.[7]



Scheme 1. Synthesis of 3,4-dihydropyrimidones using PEG-SO_3H as catalyst.

As described in Scheme 1, the PEG-bound sulfonic acid **1** was prepared by reacting PEG with excess chlorosulfonic acid at 0°C to room temperature. The conversion of terminal hydroxyl groups on PEG was determinated by ^{1}H NMR analysis to be quantitative, and the appearance of singlets at δ12.85 and δ4.23 ppm due to the proton of SO_3H and the α-methylene protons at the polymer attached site, respectively. Biginelli-type condensation took place by subjecting a mixture of an equivalent of aldehyde **2** and ethyl acetoacetate **3** and an excess of urea/thiourea **4** (1.2 equiv) to microwave irradiation in the presence of a catalytic amount of PEG-SO_3H under open-vessel conditions to facilitate the removal of water formed during the reaction. Finally, by adding hot water, filtration, and multiple washing with hot water and diethyl ether, reagents, excess starting materials, and by-products were removed and the desired products obtained in good purities and good yields. PEG was readily recovered from the aqueous solution by extraction. The results are listed in Table 1.

In the initial studies of screening of catalysts, we found the application of PEG-6000–bound sulfonic acid as catalyst in the Biginelli reaction of **5a** resulted in excellent yield: 91% (Table 1, entry 1). Various solvents were tested including toluene, MeCN, and C_2H_5OH under microwave irradiation using an equivalent of aldehyde and dicarbonyl compound, a catalytic amount of PEG-6000–bound sulfonic acid, and an excess of urea, affording the product **5a** in yields of 71%, 82%, and 86%, respectively. On the other

Table 1. Synthesis of 3,4-dihydropyrimidones using PEG-SO_3H as catalyst

Entry	Ar	X	Product	Yield (%)[a]	Purity (%)[b]
1	C_6H_5	O	**5a**	91	90
2	4-HOC_6H_4	O	**5b**	85	85
3	4-$CH_3OC_6H_4$	O	**5c**	89	85
4	4-$NO_2C_6H_4$	O	**5d**	78	85
5	2-ClC_6H_4	O	**5e**	79	85
6	4-ClC_6H_4	O	**5f**	83	88
7	2,4-$Cl_2C_6H_3$	O	**5g**	82	89
8	C_6H_5	S	**5h**	88	90
9	4-HOC_6H_4	S	**5i**	83	89
10	4-$CH_3OC_6H_4$	S	**5j**	89	85
11	4-$NO_2C_6H_4$	S	**5k**	77	83
12	2-ClC_6H_4	S	**5l**	79	85
13	4-ClC_6H_4	S	**5m**	82	85
14	2,4-$Cl_2C_6H_3$	S	**5n**	88	85
15	2-$CH_3OC_6H_4$	S	**5o**	90	88

[a]Determined based on weight of isolated sample.
[b]Determined by HPLC analysis of crude products.

hand, when conducting the reaction under solvent-free conditions by microwave irradiation, the yield of **5a** was 91%. Here, the PEG-bound sulfonic acid acts as an acidic mediator to facilitate the Biginelli-type condensation and at the same time as reaction solvent. This approach was used to prepare 3,4-dihydropyrimidone in good purities and good yield. This clearly demonstrates the success of the PEG-bound sulfonic acid simultaneously acting as catalyst and as solvent in the Biginelli-type condensation. Not only is the product easily isolated, this method also does not need any organic solvents. This method presents a remarkable technique toward an environmentally clean synthesis of DHPMs. Unfortunately, the use of recycled PEG-SO_3H resulted in a substantial loss of its activity as the yield of **5a** dropped to a low value (50%).

CONCLUSION

In summary, we have developed a simple, efficient, and environmentally friendly process for the synthesis of 3,4-dihydropyrimidones via a Biginelli-type condensation reaction using PEG-SO_3H as catalyst in which the functionalized PEG acts simultaneously as catalyst and as solvent. The procedure afforded 3,4-dihydropyrimidones within a shorter period in high purities and improved yields compared with the classical solution-phase reaction. Furthermore, the solvent-free preparation of DHPMs is an environmentally benign method.

EXPERIMENTAL

Preparation of PEG-Bound Sulfonic Acid 1

At 0°C, chlorosulfonic acid (10 mmol) was added to a solution of PEG-6000 (1 mmol) in CH_2Cl_2 (10 mL). Then the resulting solution was stirred at room temperature overnight, and the solution was concentrated under vacuum. Appropriate ether was added, and the precipitate filtered and washed with ether three times to afford the PEG-SO_3H. ^1H NMR (400 MHz, $CDCl_3$): δ 12.85 (s, 1H, SO_3H), 4.23 (s, 2H, CH_2SO_3H), 3.49–3.66 (m, PEG).

General Procedure for Compound 5

A mixture of aldehyde **2** (1 mmol), ethyl acetoacetate **3** (1 mmol), urea (1.2 mmol), and PEG-bound sulfonic acid **1** (0.05 mmol) was heated at 100°C for 6 min in a microwave oven under open-vessel conditions. After reaction hot water (10 mL) was added and the suspension was filtered. The residue was washed with hot water and diethyl ether and recrystallized from ethanol to give pure dihydropyrimidone **5**. All the compounds were

characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR. For compound **5a:** mp 206–207°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, 3H, $J = 7.2$ Hz, CH_3CH_2O), 2.34 (s, 3H, CH_3), 4.06 (q, 2H, $J = 7.2$ Hz, CH_3CH_2O), 5.37 (s, 1H, CH), 7.24–7.31 (m, 5H, ArH), 7.16 (s, NH), 7.76 (s, NH). ^{13}C NMR (100 MHz, $CDCI_3$): δ14.70, 17.85, 54.72, 60.27, 94.70, 101.40, 127.06, 128.35, 129.24, 144.17, 145.69, 165.80, 174.92. IR (KBr) (cm^{-1}): v 3320, 3160, 3100, 2980, 1665, 1570, 1460, 1365, 1320, 1280, 1190, 1170, 1115, 1020, 755. **5o:** mp 190–192°C. ^{1}H NMR (400 MHz, $CDCI_3$) δ1.07 (t, 3H, $J = 7.2$ Hz CH_3CH_2O), 2.42 (s, 3H, CH_3), 3.88 (s, 3H, CH_3O), 4.06 (q, 2H, $J = 7.2$ Hz, CH_3CH_2O), 5.75 (s, 1H, CH), 6.87–7.28 (m, 4H, ArH), 7.37 (s, NH), 8.01 (s, NH); ^{13}C NMR (100 MHz, $CDCI_3$): δ14.03, 18.24, 50.68, 55.46, 60.24, 99.95, 110.65, 120.65, 126.79, 128.39, 129.53, 144.40, 156.62, 165.36, 174.58. IR (KBr) (cm^{-1}): v 3320, 3172, 3108, 3068, 1682, 1606, 1526, 1492, 1464, 1374, 1320, 1284, 1268, 1244, 1172, 1108, 1016, 840.

ACKNOWLEDGMENTS

We are thankful for the financial support from the Natural Science Foundation of Gansu Province (ZS021-A25-006-Z), the Scientific and Technological Innovation Engineering of Northwest Normal University (NWNU-KJCXGC-02-08), and the Youth Foundation of Northwest Normal University (NWNU-QN-04-28).

REFERENCES

1. (a) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637–4662; (b) Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213–1224; (c) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97–148.
2. (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, *23*, 3815–4186; (b) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem.* **2001**, *113*, 670–701; *Angew. Chem., Int. Ed.* **2001**, *40*, 65–679; (c) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem.* **2002**, *114*, 4136–4173; *Angew. Chem. Int. Ed.* **2002**, *41*, 3964–4000.
3. (a) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 821–824; (b) Zhao, X. Y.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433–8436; (c) Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932–6939; (d) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509; (e) Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917–1924; (f) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554.
4. Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64–82, and references cited therein.
5. Li, Z.; Yu, J. L.; Ding, R. B.; Wang, Z. Y.; Wang, X. C. *Synth. Commun.* **2004**, *34*, 2981–2986.

6. (a) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1–116; (b) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630–645; (c) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888; (d) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052; (e) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
7. (a) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979–6994, and references cited therein; (b) Saxena, I.; Borah, D. C.; Sarma, J. C. *Tetrahedron Lett.* **2005**, *46*, 1159–1160, and references cited therein.