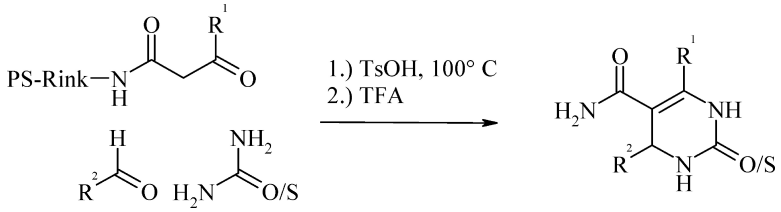
JOURNAL OF combinatorial CHEMISTRY

Report

Solid-Phase Synthesis of 4,6-Diaryl-3,4-dihydropyrimidine-2(1*H*)-one-5-carboxylic Acid Amide Derivatives: A Biginelli Three-Component Condensation Protocol Based on Immobilized β-Ketoamides

G. Alexander Gross, Hanns Wurziger, and Andreas Schober

J. Comb. Chem., **2006**, 8 (2), 153-155• DOI: 10.1021/cc050074c • Publication Date (Web): 24 December 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Solid-Phase Synthesis of 4,6-Diaryl-3,4-dihydropyrimidine-2(1*H*)-one-5-carboxylic Acid Amide Derivatives: A Biginelli Three-Component Condensation Protocol Based on Immobilized *β*-Ketoamides

G. Alexander Gross,*[,†] Hanns Wurziger,[‡] and Andreas Schober[§]

Microreaction Technology Department, Institute of Physics, Technical University of Ilmenau, Weimarerstrasse 32, D-98693 Ilmenau, Germany, Medicinal Chemistry, Merck KGaA, Frankfurterstrasse 250, D-64293 Darmstadt, Germany, and Center for Micro- and Nanotechnologies, Technical University of Ilmenau, Gustav-Kirchhoff-Strasse 7, D-98693 Ilmenau, Germany

Received June 7, 2005

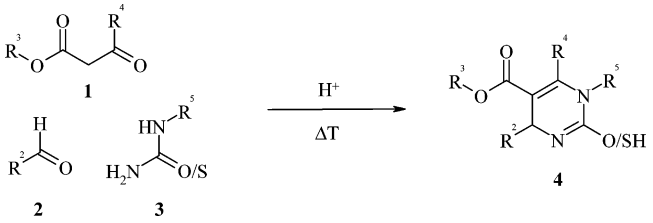
Introduction

In 1893, Pietro Biginelli discovered a multicomponent reaction which leads to partly reduced pyrimidinone derivatives (**4**).[1] Since that time, the "Biginelli reaction" has been known as an efficient one-pot reaction protocol to prepare 3,4-dihydropyrimidine-2(1*H*)-one (DHPM) derivatives (**4**).[2] DHPM derivatives are known as interesting heterocyclic scaffolds for drug research. The basic form of the Biginelli reaction is illustrated in Scheme 1. In the past decade, DHPM derivatives with different pharmacological properties were found. The DHPM core structure was found to possess Ca-channel modulating, adrenergic agonistic, mitotic kinesin inhibiting, antibacterial, fungicidal, and other pharmacological properties.[3] In addition, the dihydropyrimidine-5-carboxylate core has been found in several marine natural products.[4] DHPM derivatives are regarded as privileged structures in drug research.[5,6]

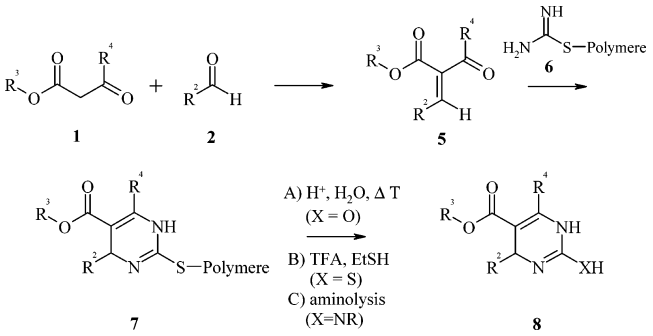
To make new DHPM derivatives available to drug discovery, appropriate synthetic protocols are needed. Here, we describe a simple and efficient procedure for the preparation of 4,6-diaryl DHPM derivatives under solid-phase Biginelli conditions. In a previous publication, we described two methods for the preparation of the *β*-ketoamide precursors.[7]

Depending on the building blocks for the three-component reaction, the immobilization strategies were chosen. At least three different strategies for the preparation of DHPM derivatives (**4**) on solid support were described in recent literature. The first one makes use of immobilized urea or thiourea moieties (**3**). The second uses an immobilized *β*-ketoester (**1**), and the third one uses an S-linked isothiouronium salt (**6**). Biginelli protocols depending on immobilized aldehydes (**2**) were not found. The following examples for immobilized ureas and isothioureas were described before.

Scheme 1. Biginelli Three-Component Condensation



Scheme 2. The Atwal's Modification on Solid Support



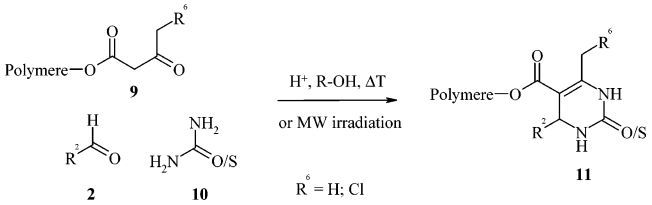
Wipf and Cunnigham first described a solid-phase Biginelli protocol which immobilizes a *γ*-butyric acid (GABA)-derived urea to Wang's resin by esterification.[8] The following condensation reaction with different arylaldehydes (**2**) and *β*-ketoesters (**1**) leads to N1-substituted DHPM (**4**) derivatives. Lusch et al. made use of (3-hydroxypropyl)-urea, which was bound by a silyl linker to the solid support.[9] After cleavage, an N-1-(3-hydroxypropyl)-substituted DHPM carboxylate ester was obtained. Kappe et al. made use of immobilized isothioureas for the DHPM synthesis.[10] In contrast to Wipf and Cunningham, the thiourea component was bound to Wang's resin by S-alkylation (**6**). The N1-unsubstituted DHPM derivative (**7**) was then formed by application of the so-called "Atwal's modification",[11] as outlined in Scheme 2. Here, the enone (**5**) is condensed with the immobilized isothiourea (**6**) under basic conditions. The enone (**5**) has to be prepared before through condensation of the aldehyde- (**2**) and *β*-ketoester- (**1**) components. Each oxy-, thio-, and amino DHPM derivatives (**8**) can be formed by application of different cleavage procedures (see Scheme 2.; way A, B, and C).[10,13]

In the recent literature, we found at least three solid-phase protocols using immobilized *β*-ketoesters (see Scheme 3). Xia and Wang prepared the immobilized 3-oxobutyric acid ester (9, $R^6 = H$) by reaction of diketene acetone adduct with a soluble HO−PEG polymer.[12] Kappe et al. immobilized 4-chloro-3-oxobutyric acid (9, $R^6 = Cl$) to Wang's resin by thermal esterfication.[13] In both cases, the corresponding DHPMs **11** were formed under standard Biginelli conditions by heating or microwave irradiation and released from the solid support by a multidirectional cyclization−cleavage approach. A synthetic route based on 1,3-dicarbonyl

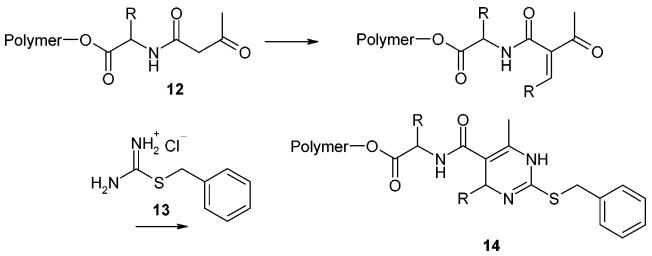
* Corresponding author. Phone: +49 3677 69-3152. E-mail: grossalexander@gmx.net.
† Institute of Physics, Technical University of Ilmenau.
‡ Merck KGaA.
§ Center for Micro- and Nanotechnologies, Technical University of Ilmenau.

10.1021/cc050074c CCC: $33.50
Published on Web 12/24/2005

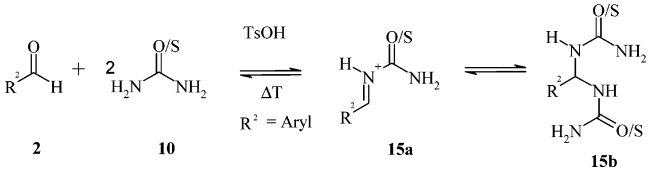
Scheme 3. DHPM Synthesis with Immobilized β-Ketoesters



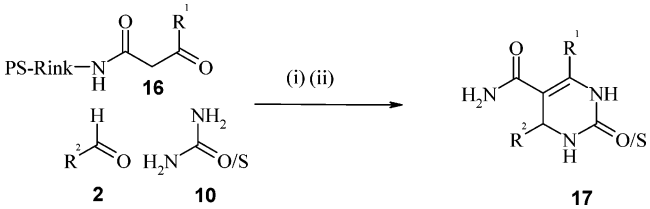
Scheme 4. DHPM Synthesis with Immobilized β-Ketoamides Using Atwal's Route



Scheme 5. *N*-Acyliminium Ion, the Essential Reaction Intermediate



Scheme 6



Reagents and conditions: (i) (1) 10 equiv of aldehyde (**2**), 15 equiv of urea/thiourea, 2 equiv of TsOH, 2-propanol/1,4-dioxane, 3/4, 1 h, 95 °C; (2) polymer **16**, 12 h, 95 °C; (ii) TFA/DCM 1/1, 1 h.

compounds with enhanced molecular diversity on solid support has not yet been described.

Zhang et al. described a synthesis of DHPM derivatives starting with immobilized diketene-derived amino acids of type **12**.[14] After condensation of *p*-tolualdehyde (2, R = $-C_6H_4CH_3$) and cyclization with S-benzylated isothiourea (**13**) under typical Atwal's conditions, DHPM derivatives of type **14** are obtained. The idea of the authors was to add greater diversity to the DHPM scaffold. More details for the Biginelli reactions in heterogeneous systems is given in the literature.[6]

Results and Discussion

We have developed a synthetic protocol based on immobilized β-ketoamides to increase the diversity of DHPM

Table 1. Selected Building Blocks and Received Purities[a]

	R1:	A		B		C		D	
	R2:								
	purity (yield)[a]	urea	thiourea	Urea	thiourea	urea	thiourea	urea	thiourea
1		94 (>95)	87 (>95)	87 (>95)	95 (>95)	96 (>95)	96 (>95)	82 (>95)	90 (>95)
2		82 (>95)	94 (>95)	97 (>95)	93 (>95)	93 (>95)	>93 (>95)	91 (>95)	90 (>95)
3		- (-)[b]	- (-)[b]	- (-)[b]	- (-)[b]	- (-)[b]	- (-)[b]	- (-)[b]	- ()[b]
4		89 (>95)	85 (>95)	92 (>95)	96 (>95)	95 (>95)	94 (>95)	91 (>95)	83 (>95)

[a] Purity and yield of crude products. HPLC purity at 220 nm. [b] In the HPLC analysis, product mixtures were found. The expected product masses were found in most peaks in the LC/MS analysis.

derivatives by varying the substituents in position 4 in a simple manner. In a previous publication, we described the preparation of immobilized 3-aryl-3-oxopropanamide derivatives (**16**) on Rink's amide resin.[7] Here, we describe the synthesis of DHPM derivatives (**17**) starting from these β-ketoamides (**16**). The reaction conditions were optimized by using 4-ethoxybenzaldehyde, urea, and polymer-bound 3-(4-methoxyphenyl)-3-oxopropionic acid amide. Under classical solution-phase Biginelli conditions, polar solvents, such as EtOH or CH_3CN, were used. For solid-phase chemistry on polystyrene resins, such solvents are unfavorable. The low polymer swelling causes a low reaction rate and product yield. We found that a mixture of 3 parts 2-propanol and 4 parts 1,4-dioxane gave the best results. Different acids, such as acetic acid, 30% aqueous HCl, and toluene-4-sulfonic acid (TsOH), were tried as catalysts. With acetic acid and aqueous HCl, the desired product was formed only in low yield. The unreacted β-ketoamide precursor was recovered predominantly after cleavage. The best results were obtained using 2 equiv of toluene-4-sulfonic acid in combination with 10 equiv of arylaldehyde and 15 equiv of urea. To prevent precipitation, the urea/thiourea and the acidic catalyst were separately dissolved in 2-propanol and the aryl aldehydes, in 1,4-dioxane. When the clear solutions are combined, the mixture becomes cloudy, probably due to the precipitation of urea/thiourea and the condensation products formed. After this mixture was heated to 95 °C for 1 h, we observed a clear solution with darker color. No reprecipitation was observed after it was cooled to ambient temperature. After addition of the polymer, the suspension was heated to 95 °C for 12 h. The expected DHPM derivatives were found in high purity and yield after washing and cleavage.

Preheating of the educts **2** and **10** in solution before adding to the β-ketoamide polymer (**16**) was found to be advantageous in terms of purity and yield. This is due to the likely initial formation of the bisureide **15b** of the aldehyde **2** in equilibrium with the *N*-acyliminium ion **15a**, the essential reactive intermediate under these conditions.[15] Equimolar amounts of aldehyde and TsOH decrease the reaction yield due to the cleavage of the Rink amide linker.

On the basis of this protocol, a library of different DHPM derivatives was prepared. Among others, a set of 4 × 4 different aryl β-ketoamides and aromatic aldehydes with both urea and thiourea was used, as outlined in Table 1. In all cases, the expected products were found in high yield and purity. The aliphatic aldehydes as exemplified by 2-methylpropionaldehyde lead to an isomeric mixture. In LC/MS analysis, a plurality of peaks with the expected mass of the expected DHPM product was found. ^{1}H NMR analysis, however, shows signals of different molecules. Only some characteristic signals of DHPM tautomers were found.

Conclusion

Starting from immobilized β-ketoamides, a solid-phase protocol for the preparation of 4,6-diaryldihydropyrimidine-2(1*H*)-one-5-carboxylic acid amides was optimized. The resulting synthetic protocol proved to be suitable for the preparation of a small library using different building blocks. We found that the expected DHPM derivatives were formed in high purity and yield if aromatic aldehyde- and β-ketoamide building blocks were used. The usage of an aliphatic aldehyde leads to an isomeric DHPM mixture. Purities and yields were not affected if thiourea was used instead of urea.

Acknowledgment. The authors thank Dr. Holger Deppe (Santhera Pharmaceuticals AG, Germany) and Jörg Wagner and Michael Gebinoga (TU-Ilmenau) for helpful discussion and practical assistance. The present work was supported by Grants from the BMBF (FKZ 0311766) and Merck KGaA (FKZ 0311767) during the NanoSynTest project.

Supporting Information Available. Experimental details for the synthesis of DHPMs **17** are given. Analytical data for a library subset is given. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360−413.
(2) For a review, see: (a) Kappe, C. O. *Acc. Chem. Res.* **2003**, *33*, 869−888. (b) Kappe, C. O.; Stadler, A. **2004**, *63*, 1−116. (c) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937−6963.
(3) (a) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043−1052. (b) Dallinger, D.; Stadler, A.; Kappe C. O. *Pure Appl. Chem.* **2004**, *76*, 1017−1024.
(4) (a) Heys, L.; Moore, C. G.; Murphy, P. *Chem. Soc. Rev.* **2000**, *29*, 57−67. (b) Aron, Z. D.; Overman, L. E. *Chem. Commun.* **2004**, *3*, 253−265.
(5) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.
(6) Examples and references for solution-phase, polymer-supported, fluoros, and soluble polymer DHPM synthese is given in: Kappe, C. O. *QSAR Combi. Sci.* **2003**, *22*, 630−645. Soluble vs insoluble polymer-assisted synthesis is discussed in: Eynde, J. J. V.; Watte, O. *Arkivoc* **2003**, *4*, 93−101. Solution-phase conditions are given in: Shanmugam, P.; Annie, G.; Perumal, P. T. *J. Heterocycl. Chem.* **2003**, *40* (5), 879−884.
(7) Gross, A. G.; Deppe, H.; Schober, A. *Tetrahedron Lett.* **2003**, *44*, 3939−3942.
(8) Wipf, P.; Cunnigham, A. *Tetrahedron Lett.* **1995**, *36*, 7819−7822.
(9) Lusch, M. J.; Tallarico, J. A. *Org. Lett.* **2004**, *6*, 3237−3240.
(10) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49−51.
(11) (a) O'Reilly, B. C.; Atwal, K. S. *Heterocyles* **1987**, *26*, 1185−1188. (b) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898−5907.
(12) Xia, M.; Wang, Y. *Synthesis* **2003**, *2*, 262−266.
(13) Perez, R.; Beryozkina, T.; Zbruyev, O. I.; Haas, W.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 501−510.
(14) Zhang, L.; Rana T. M. *J. Comb. Chem.* **2004**, *6*, 457−459.
(15) Kappe, O. C. *J. Org. Chem.* **1997**, *62*, 7201−7204.

CC050074C