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Soluble polymer-supported synthesis of Biginelli compounds

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Abstract—An efficient and general liquid-phase synthesis of Biginelli compounds has been developed. Polyethylene glycol (PEG) bound acetoacetate reacted with urea and aldehydes under reflux or solvent-free microwave irradiation conditions to afford PEG-supported 3,4-dihydropyrimidin-2(1*H*)-ones. The desired 3,4-dihydropyrimidin-2(1*H*)-ones were cleaved from the polymer support under mild conditions in high yields and high purity.

3,4-Dihydropyrimidin-2(1*H*)-ones, named Biginelli compounds, represent a heterocyclic system of remarkable pharmacological interest. In the past decades, a broad range of biological effects including antiviral, antitumor, antibacterial and anti-inflammatory activities have been described for these compounds.[1] More recently, appropriately functionalized 3,4-dihydropyrimidin-2(1*H*)-ones have emerged as potent calcium channel blockers,[2] antihypertensive agents,[3] α_{1a} adrenergic antagonists[4] and neuropeptide Y antagonists.[5] The Biginelli reaction is the most straightforward and simple protocol for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones, and involves a one-pot, but low yielding (25–60%) condensation of β-dicarbonyl compounds with aldehydes and urea in the presence of a strong acid.[6] Although there have been complex multistep strategies that produce somewhat higher overall yields, they lack the simplicity of the one-pot protocol.[7]

Generally, in order to drive the reaction to completion, an excess of two of the three components has to be used for solution-phase synthesis. However, a troublesome workup involving crystallization or chromatography is inevitable, and the resultant loss of products cannot be neglected in some cases. Although the solid-phase strategy on insoluble polymers appeared to solve the problem of separation and purification,[8] the drawbacks of solid-phase synthesis include the possibility of lower reactivity at the polymer–solvent interface and difficulty of characterization of intermediate products still attached to the polymer. Fortunately, some of these problems can be alleviated by the use of a soluble polymer support. In recent years, the synthesis of small molecular compound libraries on soluble polymers has increasingly become an attractive field.[9] It couples the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without following the cleavage-and-check technique) with those of solid-phase chemistry (use of excess reagents and easy isolation and purification of products). Moreover, owning to the homogeneity of liquid-phase reactions, the reaction conditions can be readily shifted from solution-phase systems without large changes, and the amount of the excess reagents is less than that in solid-phase reactions. Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising. Previously, we have

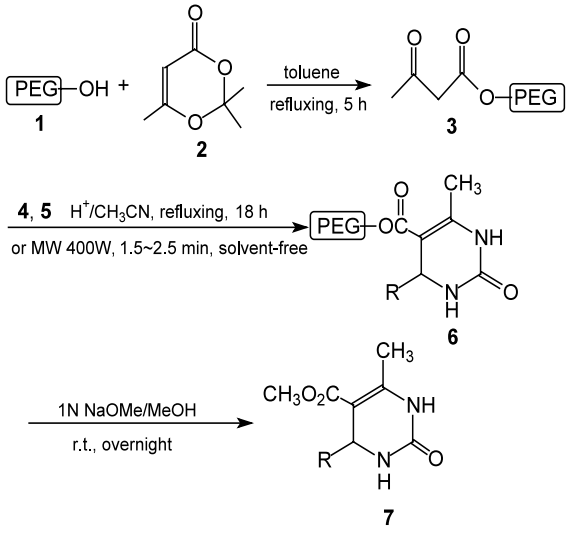

Figure 1. Liquid-phase synthesis of 3,4-dihydropyrimidinones.

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reported the PEG-supported synthesis of isoxazoles through a 1,3-dipolar cycloaddition.[10] Herein we disclose a novel liquid-phase synthesis of Biginelli compounds that offers 3,4-dihydropyrimidinone derivatives in high yields and high purity, maintaining the advantage of the one-pot procedure. To the best of our knowledge, this is the first report on the liquid-phase synthesis of Biginelli compounds.

As shown in Fig. 1, the PEG 4000 **1** linked acetoacetate **3** was prepared by reacting PEG 4000 with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **2** (i.e. diketene acetone adduct, TKD)[11] in anhydrous toluene under reflux for 5 h. The conversion of terminal hydroxyl groups on PEG 4000 was determined by ^{1}H NMR analysis to be quantitative. The liquid-phase synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones took place as follows: To the mixture of PEG 4000 linked acetoacetate **3** (1 mmol), urea **4** (4 mmol) and the corresponding aldehyde **5** (4 mmol) in CH_3CN was added 2–3 drops of concentrated HCl as catalyst. The resulting mixture was refluxed for 18 h and the solvent was removed. The residue was dissolved in a small volume of CH_2Cl_2 and then ether was added with stirring. The precipitate was washed with ether and ethyl acetate several times. The target compounds **7** were released from the PEG by treatment of the polymer bound products **6** with 1N NaOMe in MeOH.[12] Complete cleavage of the products was determined by the observation of the downfield shift of the α-methylene protons at the polymer attached site from δ 4.4 ppm to δ 3.6 ppm in the ^{1}H NMR. If the peak of the α-methylene protons was still present after NMR checking, the recovered PEG bound products could be resubmitted to the same reaction conditions until a complete scission was achieved. Normally, cleavage was complete after stirring in 1N NaOMe/MeOH overnight.

Although there were reports that Lewis acids could promote the Biginelli reaction with improved yields and shortened times,[13] these methods were unsuitable for the PEG-supported reaction since the strong coordination between Lewis acids and the oxygen atoms on the PEG chain would result in a loss of the catalytical effects. However, due to the strategy of polymer-supported synthesis, the reagents could be used in excess to increase yields. As shown in Table 1, the yields for this liquid-phase reaction were much improved as compared with the classical solution-phase Biginelli reactions. All aryl aldehydes, with electron-withdrawing or electron-donating groups, gave good yields. In addition to the aryl aldehydes, heterocyclic and α,β-unsaturated aldehydes were also effective. Importantly, the purity of the products cleaved from the PEG support was high enough for NMR, IR and mass spectrometric characterization (>91%, determined by HPLC),[14] and no further purification was necessary. It is worth noting that, in contrast to the various restrictions on the analysis of reaction progression in solid-phase synthesis, the liquid-phase protocol allows the use of routine analytical techniques (UV, NMR, TLC, etc.) to monitor reaction progress without the need for the cleavage-and-check procedure.

Table 1. Liquid-phase synthesis of 3,4-dihydropyrimidinone derivatives on PEG support

Compd.	RCHO	Yield (%)		Purity (%)[d]
		a	b	
7a	PhCHO	91	42[13b]	99.4
7b	*p*-HOC_6H_4CHO	82	67[21c]	99.8
7c	*p*-$CH_3OC_6H_4CHO$	88	28[13b]	99.2
7d	*o*-ClC_6H_4CHO	85	51[22c]	91.9
7e	*m*-$O_2NC_6H_4CHO$	94	51[23c]	99.5
7f	PhCH=CHCHO	89	–	98.1
7g	*o*-HOC_6H_4CHO	70	19[21c]	95.3
7h	(2-Furyl)CHO	72	36[21c]	91.6
7i	*p*-$NO_2C_6H_4CHO$	83	41[13b]	93.5

[a] PEG supported conditions in liquid-phase reactions; yields refer to product cleaved from PEG.
[b] Classical Biginelli conditions in solution-phase reactions.
[c] Yields refer to ethyl 3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylates.
[d] Determined by HPLC analysis.

Classical solution-phase Biginelli reactions require prolonged reaction times (18–36 h), even for Lewis acids catalyzed reactions (8–18 h). Recently, the application of microwave irradiation in organic synthesis has been the focus of considerable attention and is becoming an increasingly popular technology.[15] The prominent features of the microwave approach are rapid reaction rates, clean reaction conditions and ease of manipulation. Reactions in 'dry media' or under solvent-free conditions are especially appealing as they provide an opportunity to work with open vessels, thus avoiding the risk of the development of high pressure and with the possibility of scaling up the reactions. Stefani and co-workers[16] have reported a microwave-promoted Biginelli reaction, but their protocol only offered low to moderate yields. As part of our continuing work on the microwave-assisted liquid-phase reaction,[17] we examined the possibility of a microwave-promoted Biginelli cyclocondensation on PEG 4000 support (Fig. 1).

Kappe et al. have reported[18] that polyphosphoric acid (PPA) is an effective catalyst in the solution-phase Biginelli reaction because it favors the formation of an *N*-acyliminium ion intermediate, which is the key intermediate in the synthesis according to its mechanism.[19] Therefore, we chose the non-volatile, high boiling point and non-oxidizing PPA as the catalyst, and found that 400 W irradiation power was a suitable energy for the MW assisted reaction on PEG support. The reaction time was varied according to the property of the corresponding aldehydes. During MW heating the PEG linked acetoacetate melted into a liquid, which ensured that the substrates reacted with each other in homogeneity, especially in the cases of solid aldehydes. In our reaction, PEG 4000 acted simultaneously as polymeric support and as solvent,[20] transporting energy and making the reaction system homogenous. As shown in Table 2, the MW-promoted protocol significantly improved yields as compared with traditional Biginelli reaction conditions. At the same time, the reaction time was decreased from 18 h to a few minutes.

Table 2. PEG supported Biginelli reaction under MW irradiation

Compd.	RCHO	Time (min)	Yield (%)[a]
7a	PhCHO	1.5	83
7c	*p*-$CH_3OC_6H_4CHO$	1.5	80
7e	*m*-$O_2NC_6H_4CHO$	2.0	88
7d	*o*-ClC_6H_4CHO	2.0	74
7f	PhCH=CHCHO	1.5	81
7h	(2-Furyl)CHO	2.5	70

[a] Yields refer to products cleaved from PEG.

In conclusion, we have developed a novel and efficient liquid-phase synthetic method for 3,4-dihydropyrimidin-2(1*H*)-ones via a Biginelli cyclocondensation reaction on a soluble polymer support. The procedure afforded 3,4-dihydropyrimidin-2(1*H*)-one derivatives in high purity and improved yields compared with the classical solution-phase reaction. Furthermore, the MW-promoted protocol provided the rapid and solvent-free preparation of 3,4-dihydropyrimidin-2(1*H*)-ones in an environmentally benign and safe manner. These versatile methods produce compounds with known pharmacophoric scaffolds and are thus suitable for the generation of a combinatorial library. Further applications of liquid-phase multicomponent synthesis of heterocycles will be reported in due course.

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