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Dowex-promoted general synthesis of N,N′-disubstituted-4-aryl-3,4-dihydropyrimidinones using a solvent-free Biginelli condensation protocol

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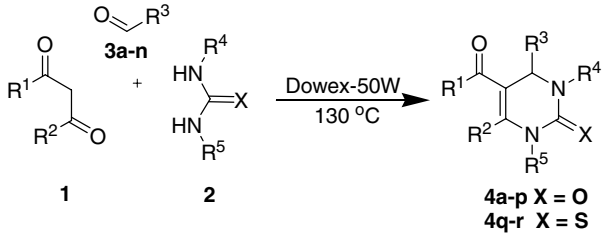
Abstract—Dowex-50W ion exchange resin-promoted solvent-free heating of an intimate mixture of an aldehyde, an active methylene compound and *N*,*N*′-dimethylurea furnished the title compounds in moderate to good yields.

The demand for structure diversification to prepare compound libraries for screening in drug discovery is the driving force behind the development of new methodologies and structural motifs. 4-Aryl-3,4-dihydropyrimidinones (Biginelli compounds, DHPMs) of the type **4** represent a heterocyclic system of remarkable pharmacological profile.[1] In the area of calcium channel modulators, appropriately functionalized DHPMs occupy a place of prominence and more recently these have emerged as potent antihypertensive agents, α_{1a}-adrenergic antagonists and mitotic kinesin inhibitors.[1] A number of improved variants of the classical Biginelli condensation[2] employing new reagents, catalysts, methodologies and techniques have been reported.[3] In addition, several combinatorial approaches towards DHPMs have been advanced, using, for example, solid phase[4a] or fluorous phase reaction conditions.[4b] N,N′-Disubstituted DHPMs are important on account of the fact that N,N′-disubstitution enhances lipophilicity and facilitates chemoenzymatic synthesis of enantiopure DHPMs in organic solvents. In our programme aimed at the functionalization[5] of DHPMs to synthesize 'drug-like' molecules, the title compounds were required. To access the title DHPMs, the straightforward three component condensation involving *N*,*N*′-dimethylurea, alkyl acetoacetate and a carbonyl substrate often fails or provides a multitude of products with the desired DHPMs only in trace amounts. Solvent-free heating conditions without catalyst also failed to furnish these compounds.[6] Recently, a high-pressure synthesis has been explored but is confined to only one such DHPM.[7] To date, the direct synthesis of N,N′-disubstituted DHPMs remains a challenge for synthetic chemists.

In this letter, we report a novel and highly efficient method that allows the rapid synthesis of N,N′-disubstituted DHPMs **4** and does not rely on the use of traditional complex catalysts or reagents. Instead, our procedure involves heating a solvent-free mixture of an aldehyde, an active methylene compound, *N*,*N*′-dimethylurea and Dowex-50W ion exchange resin (Scheme 1). Dowex-50W is used here for the first time in DHPM condensations, and this catalyst has shown considerable advantages as it is heterogeneous and can be recovered at the end of the reaction by simple filtration of the solvent diluted residue. Thus, an aldehyde, a β-ketoester and



Scheme 1. Dowex-50W catalyzed preparation of *N*,*N*′-dimethyl-4-substituted DHPMs.

Keywords: Biginelli compounds; Solvent-free synthesis; Dowex; DHPMs; Calcium channel modulators.
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N,*N*′-dimethylurea upon heating, in the presence of a catalytic amount of Dowex-50W resin, gave N,N′-disubstituted DHPMs.[8] The method also allowed the preparation of *N*-1 methyl DHPMs, when *N*-methylurea is condensed with a β-ketoester and an aldehyde.

In order to be able to carry out such a Biginelli condensation in a more efficient way minimizing the time, temperature and amount of catalyst, a series of reactions were run using *p*-nitrobenzaldehyde, ethyl acetoacetate and *N*,*N*′-dimethylurea in equimolar ratios. The amount of Dowex resin does not appear to be critical, as we have run successful experiments with 100–300 mg of Dowex per mole of the aldehyde. However, for optimum conversion, the amount of catalyst could be reduced to 100 mg for 20 mmol of aldehyde. The results are summarized in Table 1. The best conversion was obtained when the reaction was run at 130 °C for 90 min. An increase in the reaction temperature and time did not improve the yields significantly.

Table 1. Dowex-50W catalyzed condensation of *p*-nitrobenzaldehyde, ethyl acetoacetate and *N*,*N*′-dimethylurea under different reaction conditions

Entry	Reaction temperature (°C)	Reaction time (min)	Conversion to **4g** (%)[a,b,c]
1	95	90	38
2	120	90	74
3	130	90	81
4	130	10	30
5	130	30	52
6	130	45	64
7	130	60	66

[a] Conversion was deduced from the relative intensity of the aldehydic-H and C-4H signals of the reactants and products in the ^{1}H NMR spectra of crude reaction mixtures.
[b] Aldehyde decomposes at temperatures above 130 °C.
[c] Under traditional Biginelli condensation conditions (solvent, acid), very little product formation is observed and only in some cases after prolonged reflux.

To establish the scope and usefulness of this methodology, a number of reactions (Table 2) were conducted and the products isolated. The yields given in Table 2 refer to the purified products from the reactions run at 20 mmol scale. It was also found that in scaling-up the reaction the amount of Dowex did not need to be increased proportionally. Further, apart from the simplicity of the procedure, an important feature is the ability to tolerate functional group variations in all three building blocks. The aryl aldehyde **2**, for example, can be varied to include many pharmaceutically relevant substitution patterns (NO_2, Br, OH) on the aryl ring. Similarly, variation of the β-ketoester as well as the urea was employed. Replacing substituted urea derivatives with urea/thiourea furnish the corresponding N,N′-unsubstituted DHPMs **4o**–**r** in near quantitative yields[9] (Table 2). In view of the simplicity of the process and the importance of parallel synthesis, we have carried out the synthesis of a number of DHPM analogues **4** in a parallel fashion. At least 10 experiments were run simultaneously by taking appropriate mixtures of β-ketoesters, aldehydes and urea and Dowex-50W, and after usual work-up the individual DHPMs were obtained. In analogy with microwave aided synthesis,[10] this solvent-free protocol is applicable to the parallel synthesis of DHPM libraries.

In conclusion, we have described a highly efficient Dowex-50W catalyzed solvent-free method for obtaining a category of DHPMs for which a general synthetic methodology was not available. The method is environmentally benign, amenable to parallel synthesis and offers operational advantages, such as clean reaction profiles and simple experimental/product isolation procedures,

Table 2. Scope of the Dowex-50W promoted solvent-free Biginelli condensation

Entry	**4**					Mp (°C)	Isolated yields[a,b] (%)
	R^1	R^2	R^3	R^4	R^5		
4a	OEt	Me	Ph	Me	Me	54–56	59
4b	OEt	Me	3,4,5-$(MeO)_3C_6H_2$	Me	Me	93–95	48
4c	OEt	Me	4-$MeOC_6H_4$	Me	Me	84–86	56
4d	OEt	Me	4-BrC_6H_4	Me	Me	65–67	42
4e	OEt	Me	2-$NO_2C_6H_4$	Me	Me	134–136	62
4f	OEt	Me	3-$NO_2C_6H_4$	Me	Me	125–127	58
4g	OEt	Me	4-$NO_2C_6H_4$	Me	Me	105–107	65
4h	OEt	Me	3-HOC_6H_4	Me	Me	162–164	38
4i	OEt	Me	4-$Me_2NC_6H_4$	Me	Me	85–87	27
4j	OEt	Ph	4-$NO_2C_6H_4$	Me	Me	164–165	55
4k	Ph	Me	4-$NO_2C_6H_4$	Me	Me	159–160	50
4l	OMe	Me	4-$NO_2C_6H_4$	Me	Me	140–142	62
4m	OEt	Me	4-$NO_2C_6H_4$	H	Me	106–107	69
4n	OEt	Me	3-$NO_2C_6H_4$	H	Me	130–131	63
4o	OEt	Me	Ph	H	H	210–211	92
4p	OEt	Me	3-$NO_2C_6H_4$	H	H	238–239	95
4q	OEt	Me	Ph	H	H	223–224	90
4r	OEt	Me	3-$NO_2C_6H_4$	H	H	205–206	93

[a] Use of HCl as a catalyst in place of Dowex-50W did not lead to any noticeable improvement in yields.
[b] Yields based on recovered aldehyde (**4a**–**n**); **4o**–**r** were compared with authentic samples.[9]

which make it a useful and attractive strategy for the preparation of DHPMs of synthetic importance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.061.

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8. Typical procedure: A mixture of *p*-nitrobenzaldehyde (3.02 g, 20.0 mmol), ethyl acetoacetate (2.60 g, 20 mmol), *N*,*N*′-dimethylurea (1.76 g, 20 mmol) and Dowex-50W (Aldrich Chemical Company) (100 mg) in a glass test tube was heated for 3 h at 130 °C, in an oil bath. After cooling to room temperature, the reaction was dissolved in ethyl acetate and Dowex-50W was removed by filtration. The filtrate was concentrated under reduced pressure. Recrystallization from dichloromethane gave pure **4g**. For 50 mmol reactions, the quantity of Dowex-50W was increased to 200 mg. All compounds exhibited satisfactory spectral and microanalytical data (kindly see Supplementary data).
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