Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1421–1423

Propane phosphonic acid anhydride: a new promoter for the one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

Franz L. Zumpe,* Melanie Flüß, Krischan Schmitz and Andreas Lender

Bayer HealthCare AG, Chemical Development—Process Research, 42096 Wuppertal, Germany

Received 21 November 2006; accepted 15 December 2006
Available online 20 December 2006

Abstract—Propane phosphonic acid anhydride has been found to promote the Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones. The use of this agent is characterized by moderate costs, low toxicity and simple workup conditions.

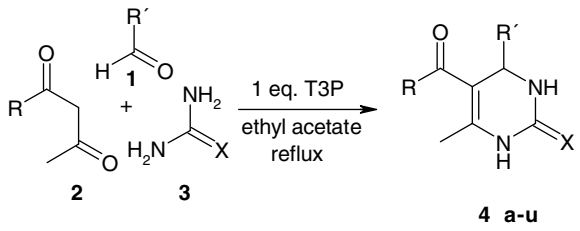
As reviewed recently[1] dihydropyrimidinones (DHPMs) have received considerable attention due to the interesting pharmacological properties associated with this heterocyclic scaffold. Dihydropyrimidinones can readily be assembled by the so called Biginelli reaction, a prominent example of a multicomponent condensation reaction.

Since Biginelli first reported the one-pot condensation of an aldehyde, a β-ketoester and urea under strongly acidic conditions,[2] a plethora of different conditions has been developed for this reaction in order to keep the simplicity of the original one-pot Biginelli protocol and to simultaneously overcome its drawbacks such as low yields, especially in the case of substituted aromatic and aliphatic aldehydes. In recent years several methods for the synthesis of dihydropyrimidinones have been reported in the literature.[3]

For several reasons, we found the method of Kappe et al.,[4] which is making use of polyphosphate ester (PPE) as a promoter for the Biginelli reaction, most suited for our needs. Firstly, the reaction and the workup conditions are very simple. In most cases the yields obtained according to the Kappe protocol are good to excellent. Furthermore, it tolerates variations in all three components and last but not least, the dihydropyrimidinones thus synthesized will not be contaminated by heavy metal residues, which is extremely important when thinking about synthesizing active pharmaceutical ingredients. Unfortunately, polyphosphate ester cannot be purchased and has to be prepared freshly prior to use. Therefore, we were looking for a commercially available alternative to the polyphosphate ester.

Kappe reasoned that the success of the PPE method may be due to both specific interactions between PPE and *N*-acyliminium ion intermediates and dehydrating properties driving the reaction along the desired pathway. Thus, we reckoned that other phosphorous containing reagents with dehydrating properties might promote the Biginelli reaction as well. In the course of our investigations we found that ®T3P[5] (propane phosphonic acid anhydride), which is used in peptide synthesis[6] and for the formation of substituted heterocycles[7] due to its water scavenging properties, can be used in the one-pot Biginelli reaction for the synthesis of dihydropyrimidinones (Scheme 1).

After some experimentation with respect to the molar ratio of the reactants, reaction temperature, reaction



Scheme 1. ®T3P Promoted Biginelli reaction.

Keywords: Biginelli reaction; Propane phosphonic acid anhydride; Multicomponent reaction; 3,4-Dihydropyrimidin-2(1*H*)-ones; Heterocycles.
* Corresponding author. Tel.: +49 202 362308; fax: +49 202 362566; e-mail: franz.zumpe@bayerhealthcare.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.12.098

time and possible solvents we found optimized conditions for benzaldehyde. These conditions utilize a 1:1.2:1.2 ratio of aldehyde **1**, β-ketoester **2** and urea **3** in a one-pot Biginelli reaction employing refluxing ethyl acetate as solvent. One equivalent of ®T3P with respect to the aldehyde suffices for complete conversion of the starting materials. After completion of the reaction water is added to the reaction mixture in order to hydrolyze the residual ®T3P and the reaction mixture is stirred for another hour, before the precipitated product is isolated by filtration.

In a typical procedure benzaldehyde (0.53 g, 5 mmol), ethyl acetoacetate (0.78 g, 6 mmol) and urea (0.36 g, 6 mmol) were dissolved in 8 ml of ethyl acetate. ®T3P (3.18 g, 5 mmol) as a 50% solution in ethyl acetate was added and the mixture was heated to reflux for 6 h. After cooling to room temperature, 10 ml of water were added and the resulting mixture was stirred for 1 h. The precipitated product was filtered, washed with water and dried in vacuum. In most cases no further purification was necessary.

All compounds obtained according to this protocol were characterized and identified by their melting points, mass spectra and NMR spectra in comparison to the analytical data reported in the literature. To study the generality of the process several aldehydes were reacted with ethyl acetoacetate or pentane-2,4-dione and urea or thiourea in the presence of ®T3P (Table 1) under the conditions mentioned above.

As can be seen from the data in Table 1 dihydropyrimidinones bearing aromatic rings with pharmacologically relevant substitution patterns can be obtained using ®T3P in the Biginelli reaction. Aldehydes with electron-withdrawing groups clearly gave the best results in terms of yield and purity. In all cases studied, the crude product was isolated in good to very good yield and no further purification processes were required (Table 1, entries 3–5, 9–11). Aldehydes with electron-donating groups behaved differently. Normally, they furnished somewhat lower yields and products required chromatographic workup for purification in some cases (Table 1, entries 6, 8, 12). For both electron-deficient and electron-rich aromatic aldehydes the *para* substituted derivatives led to a little lower yield than those bearing *ortho* or *meta* substituents (Table 1, entries 3–8). Alkyl substituted aromatic aldehydes, heterocyclic aldehydes and aliphatic aldehydes reacted smoothly and gave rise to products with a high purity albeit in moderate yield only (Table 1, entries 2, 16, 17). Nevertheless, this protocol has its limitations. Employing acid sensitive aldehydes such as furfural or aldehydes substituted with functional groups that might participate in condensation reactions was not suited for carrying out the Biginelli reaction under these conditions. They only provided low to moderate yields of the desired products. Moreover, the products had to be purified by extractive or chromatographic workup procedures (Table 1, entries 13–15). Instead of ethyl acetoacetate, pentane-2,4-dione could be used as the 1,3-dicarbonyl component without loss of efficiency (Table 1, entries 18–20). Likewise, the reaction was not negatively affected by replacing urea by thiourea (Table 1, entries 20–21).

In summary, ®T3P has been shown to be a novel promoter for the synthesis of DHPMs by the three-compo-

Table 1. ®T3P Promoted formation of dihydropyrimidinones

Entry	Product[a]	R	R′	X	Yield[b] (%)	Mp[c] (°C) found	Mp (°C) reported
1	**4a**	OEt	Ph–	O	77	206–207	206–207[4b]
2	**4b**	OEt	4-(CH_3)–C_6H_4–	O	69	215–216	214–215[8]
3	**4c**	OEt	4-(Cl)–C_6H_4–	O	69	212–213	213–215[9]
4	**4d**	OEt	3-(Cl)–C_6H_4–	O	86	195–197	192–193[10]
5	**4e**	OEt	2-(Cl)–C_6H_4–	O	86	216–219	215–218[4b]
6	**4f**	OEt	4-(OCH_3)–C_6H_4–	O	59	203–204	201–203[9]
7	**4g**	OEt	3-(OCH_3)–C_6H_4–	O	81	220–221	207–208[11]
8	**4h**	OEt	2-(OCH_3)–C_6H_4–	O	86[d] (48)[e]	257–258	259–260[12]
9	**4i**	OEt	4-(NO_2)–C_6H_4–	O	74	212–213	208–211[9]
10	**4j**	OEt	4-(CF_3)–C_6H_4–	O	73	177–178	173–175[13]
11	**4k**	OEt	3,4-$(Cl)_2$–C_6H_3–	O	77	223–224	222–223[14]
12	**4l**	OEt	3,4-$(OCH_3)_2$–C_6H_3–	O	47	177–178	174–176[14]
13	**4m**	OEt	4-(OH)–C_6H_4–	O	44[f]	209–220	225–226[15]
14	**4n**	OEt	4-(NMe_2)–C_6H_4–	O	16[e]	246–248	256–258[16]
15	**4o**	OEt	2-Furyl–	O	30[e]	201–202	206–208[14]
16	**4p**	OEt	2-Thienyl–	O	69	210–211	207–208[14]
17	**4q**	OEt	Hexyl–	O	53	238–239	237–238[14]
18	**4r**	Me	3-(OCH_3)–C_6H_4–	O	60	242–243	245–246[17]
19	**4s**	Me	3-(Cl)–C_6H_4–	O	64	269–270	284–285[17]
20	**4t**	Me	Ph–	S	72	219–222	220–222[11]
21	**4u**	OEt	Ph–	S	80	205–207	206–207[4b]

[a] All compounds were characterized by ^{1}H NMR, MS and mp.
[b] Isolated yields.
[c] Melting points are uncorrected.
[d] Yield of crude product.
[e] After chromatographic workup.
[f] After extractive workup.

nent condensation of a β-ketoester or pentane-2,4-dione, aldehyde and urea or thiourea. It is a low toxic reagent, which is commercially available at a moderate price. Reaction and workup conditions are simple and straightforward. An added benefit, which is of special importance for the synthesis of active pharmaceutical ingredients, is that the product will not be contaminated by heavy metal traces. The method described in this Letter is applicable to substituted aromatic, aliphatic and heterocyclic aldehydes.

References and notes

1. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.
2. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
3. Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1–116, and references cited therein.
4. (a) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718–720; (b) Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799–1803.
5. ®T3P is a registered trademark of Clariant and can be obtained as 50% solution in ethyl acetate, DMF or other solvents on request.
6. Escher, R.; Bünning, P. *Angew. Chem.* **1986**, *98*, 264–265.
7. Patent: Höchst WO99/37620.
8. Gohain, M.; Prajapati, D.; Sandhu, J. S. *Synlett* **2004**, 235–238.
9. Hu, E. H.; Sidler, D. R.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454–3457.
10. Lu, J.; Ma, H. *Synlett* **2000**, 63–64.
11. Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270–6272.
12. Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889–2891.
13. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864–3868.
14. Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, 1341–1345.
15. Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramalingam, T. *J. Chem. Res. (S)* **2000**, 354–355.
16. Lu, J.; Bai, Y. *Synthesis* **2002**, 466–470.
17. Yarim, M.; Sarac, S.; Ertan, M.; Babu, O. *Il Farmaco* **1999**, *54*, 359–363.