Pergamon

Tetrahedron Letters 42 (2001) 7975–7978

TETRAHEDRON LETTERS

Parallel synthesis of dihydropyrimidinones using Yb(III)-resin and polymer-supported scavengers under solvent-free conditions. A green chemistry approach to the Biginelli reaction

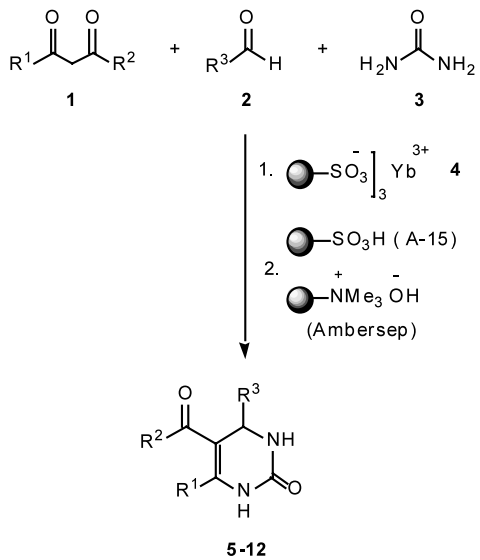
Alessandro Dondoni* and Alessandro Massi

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università di Ferrara, Via L. Borsari 46, I-44100 Ferrara, Italy

Received 25 July 2001; accepted 14 September 2001

Abstract—An efficient synthesis of an array of 3,4-dihydropyrimidin-2-(1*H*)-ones using solid-supported ytterbium(III) reagent from aldehydes, 1,3-dicarbonyl compounds and urea (Biginelli reaction) under solvent-free conditions is described. Purification of each member of the library was carried out using a cocktail of acid and basic polymer-supported scavengers © 2001 Elsevier Science Ltd. All rights reserved.

In the last two decades, automated solid-phase organic synthesis (SPOS) of drug-like molecules via parallel combinatorial approach has been an efficient tool for the rapid generation of diverse compound collections.[1] However, the difficult analysis of intermediates by conventional methodologies and the time consuming process of adjusting solution-phase chemistry on a polymer-supported substrate have stimulated several research groups to introduce alternatives to SPOS. Fluorous synthesis,[2] soluble polymer-supported organic synthesis,[3] and phase-tags organic synthesis[4] have been used in several combinatorial programs. Nevertheless, during the last few years, polymer-assisted solution-phase (PASP) synthesis has become the prevalent method for the parallel synthesis of chemical libraries as confirmed by the increasing number of publications in this area.[5] The true potential of any combinatorial approach is exploited when maximum diversity is achieved. The use of multicomponent reactions (MCRs),[6] and multi-step syntheses allow to reach this goal. While many papers report on the use of SPOS and PASP synthesis in multi-step synthetic programs,[5b,7] the use of MCRs in conjunction with polymer-supported reagents is still rather rare in the literature.[8] Following our interest[9] in the three-component Biginelli reaction,[10] we initiated a study to revisit this reaction in a parallel combinatorial fashion using the PASP synthesis approach. The Biginelli reaction is a one-pot acid-catalyzed condensation of an aldehyde, a 1,3-dicarbonyl compound and urea leading to 3,4-dihydropyrimidin-2-(1*H*)-one (DHPM) (Scheme 1). The considerable interest in building up libraries of DHPMs relies on their activities as calcium channel blockers and antihypertensive agents.[11] Solid-phase[12] and fluorous synthesis[13] approaches suitable for DHPMs libraries generation have been described. The use of clay catalysis has also been reported.[14]



Scheme 1. Synthesis–purification procedure for DHPMs library generation.

Keywords: Biginelli reaction; dihydropyrimidinones; polymer-supported reagents; multicomponent reaction.

* Corresponding author. Fax: +39-0532 291167; e-mail: adn@dns.unife.it

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)01728-2

Given the high efficiency of lanthanide(III) Lewis acids to catalyze solution-phase Biginelli condensation,[15] we envisaged to using an equivalent polymer-bound lanthanide(III) reagent to exploit the advantages of both lanthanide catalyst and solid support. Therefore, we prepared the Yb(III) reagent **4** (Yb(III)-resin) supported on Amberlyst 15 resin[16] according to the procedure described by Wang and coworkers.[17] Then, we considered as a model reaction the condensation of ethyl acetoacetate (R^1 = Me, R^2 = OEt), benzaldehyde ($R^3 = C_6H_5$) and urea promoted by Yb(III)-resin **4** (Scheme 1). Firstly, various temperatures, molar ratios of the reagents, and reaction times were tested using toluene as a solvent. All comparative reactions were conducted under optimized conditions and, after filtration of the resin, the dihydropyrimidinone **5a** was isolated as a pure compound by crystallization. The best yield of **5a** (55%) was obtained by carrying out the reaction in refluxing toluene for 48 h using equivalent amounts of aldehyde, dicarbonyl compound, Yb(III)-resin **4** and excess of urea.[18] Secondly, other solvents were tested including THF, MeCN, H_2O. In all cases the reaction afforded the product **5a** in moderate yield (20–35%). On the other hand, conducting the reaction under solvent-free conditions at 120°C for 48 h, the yield of **5a** raised to a good value (82%). Due to the increasing demand in modern organic processes avoiding expensive purification techniques and large amount of solvents as well as contamination of products with heavy metals, the use of polymer-bound Yb(III) reagent **4** in combination with solventless conditions presented itself as a remarkable technique toward an environmentally clean synthesis of DHPMs. Unfortunately, the use of recycled Yb(III)-resin **4**, resulted in a substantial loss of its activity as the yield of **5a** dropped to a very low value (25%).

A key-step in the parallel combinatorial synthesis of compound collections involves the purification of each member of the library. The possibility of avoiding aqueous work up, crystallization and chromatographic procedures makes the whole process more suitable for automation and enhances its efficiency from economic and ecological viewpoints. Therefore, to isolate the pure dihydropyrimidinone **5a**, sequestering conditions were developed. A mixed-resin bed containing the strongly acidic resin Amberlyst 15[16] (A-15) and the strongly basic resin Ambersep 900 OH[16] was used to scavenge excess urea and by-products derived from side condensation reactions of the 1,3-dicarbonyl component

Table 1. Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones using polymer supported reagents. Yields and purities[a]

Entry	R^1	R^2	R^3	Product	Yield (%)	Purity (%)[b]	MS[c]
1	Me	OEt	C_6H_5	**5a**	80	>95	261.2
2	Me	OMe	C_6H_5	**5b**	71	>95	247.3
3	Me	O*i*-Pr	C_6H_5	**5c**	78	95	275.2
4	Me	OBn	C_6H_5	**5d**	80	90	323.4
5	Me	Me	C_6H_5	**5e**	71	95	231.3
6	Me	OEt	4-(F)-C_6H_4	**6a**	68	>95	279.2
7	Me	OMe	4-(F)-C_6H_4	**6b**	70	95	265.3
8	Me	O*i*-Pr	4-(F)-C_6H_4	**6c**	71	90	293.5
9	Me	OBn	4-(F)-C_6H_4	**6d**	73	90	341.4
10	Me	Me	4-(F)-C_6H_4	**6e**	70	>95	249.5
11	Me	OEt	4-(MeO)-C_6H_4	**7a**	72	95	291.3
12	Me	OMe	4-(MeO)-C_6H_4	**7b**	71	95	277.2
13	Me	O*i*-Pr	4-(MeO)-C_6H_4	**7c**	75	>95	305.4
14	Me	OBn	4-(MeO)-C_6H_4	**7d**	75	85	353.2
15	Me	Me	4-(MeO)-C_6H_4	**7e**	71	95	261.3
16	Me	OEt	3-(MeO)-C_6H_4	**8a**	68	95	291.6
17	Me	OMe	3-(MeO)-C_6H_4	**8b**	71	>95	277.3
18	Me	O*i*-Pr	3-(MeO)-C_6H_4	**8c**	73	95	305.7
19	Me	OBn	3-(MeO)-C_6H_4	**8d**	70	90	353.2
20	Me	Me	3-(MeO)-C_6H_4	**8e**	65	90	261.5
21	Me	OEt	2-(Br)-C_6H_4	**9a**	63	95	339.1
22	Me	OMe	2-(Br)-C_6H_4	**9b**	68	90	325.7
23	Me	O*i*-Pr	2-(Br)-C_6H_4	**9c**	70	85	353.9
24	Me	OEt	4-(NO_2)-C_6H_4	**10a**	72	95	306.4
25	Me	OMe	4-(NO_2)-C_6H_4	**10b**	61	95	292.5
26	Me	O*i*-Pr	4-(NO_2)-C_6H_4	**10c**	73	80	320.8
27	Me	OEt	4-(Cl)-C_6H_4	**11a**	65	90	295.9
28	Me	OMe	4-(Cl)-C_6H_4	**11b**	71	85	282.0
29	Me	O*i*-Pr	4-(Cl)-C_6H_4	**11c**	64	90	309.5
30	Me	OEt	4-(CF_3)-C_6H_4	**12a**	70	85	329.4
31	Me	OMe	4-(CF_3)-C_6H_4	**12b**	65	95	315.8
32	Me	O*i*-Pr	4-(CF_3)-C_6H_4	**12c**	68	90	343.3

[a] Conditions reported in Scheme 1 and Ref. 20.
[b] Purities were determined by ^{1}H NMR analysis.
[c] Mass ions are generally (M+H), (M+Na), or (M+K).

(Scheme 1).[19] The whole synthesis–purification procedure[20] was tested with the above model reaction (Table 1, entry 1) which in fact afforded **5a** in good yield and high purity. A wide range of β-dicarbonyl compounds **1**[21] and aromatic aldehydes **2**[21] were coupled with urea by the optimized protocol to produce the corresponding dihydropyrimidinones **5**–**12** in good yield and purity.[22] The results are listed in Table 1. All compounds were characterized by MS analysis and their structures confirmed by ^{1}H and ^{13}C analysis.

In conclusion, we have developed an environmentally friendly procedure for the synthesis of DHPMs. This involved the use of polymer-bound Yb(III) reagent under solvent-free conditions in combination with suitable polymer-supported scavengers. A collection of DHPMs has been generated by a parallel synthesis approach. While we have not used robotic systems in this study, we believe that this route will be of great value for the generation of larger DHPMs libraries in automated parallel synthesis operations. Work is currently underway to decorate the DHPM scaffold with polymer supported reagents for the synthesis of more sophisticated DHPM derivatives.

Acknowledgements

We gratefully thank the University of Ferrara for financial support.

References

1. For reviews see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643; (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev*. **1996**, *96*, 555; (c) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 17.
2. (a) Curran, D. P. *Angew. Chem. Int. Ed*. **1998**, *37*, 1174; (b) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823.
3. Toy, P. H.; Janda, K. D. *Acc. Chem. Res*. **2000**, *33*, 546.
4. Ley, S. V.; Massi, A.; Rodriguez, F.; Horwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem. Int. Ed*. **2001**, *40*, 1053.
5. For recent reviews, see: (a) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed*. **2001**, *40*, 650; (b) 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**, 3815.
6. (a) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J*. **2000**, *6*, 3321; (b) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed*. **2000**, *39*, 3168.
7. Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon: New York, 1998.
8. (a) Ault-Justus, S. E.; Hodges, J. C.; Wilson, M. W. *Biotech. Bioeng. (Comb. Chem.)* **1998**, *61*, 17; (b) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc*. **1996**, *118*, 8977.
9. Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett*. **2001**, *42*, 4495.
10. (a) Biginelli, P. *Gazz. Chim. Ital*. **1893**, *23*, 360; (b) For a recent review see: Kappe, C. O. *Acc. Chem. Res*. **2000**, *33*, 879.
11. (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem*. **1991**, *34*, 806 and references cited therein; (b) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem*. **1990**, *33*, 2629.
12. (a) Valverde, M. G.; Dallinger, D.; Kappe, C. O. *Synlett* **2001**, *6*, 741; (b) Kappe, C. O. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 49; (c) Wipf, P.; Cunningham, A. *Tetrahedron Lett*. **1995**, *36*, 7819.
13. Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem*. **1997**, *62*, 2917.
14. Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett*. **1999**, *40*, 3465.
15. (a) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem*. **2000**, *65*, 3864; (b) Lu, J.; Bai, Y.; Wang, Z.; Yang, B.; Ma, H. *Tetrahedron Lett*. **2000**, *41*, 9075.
16. Amberlyst 15 and Ambersep 900 OH were purchased from Aldrich and Fluka, respectively. These resins were washed with methanol and dried in vacuo before use.
17. Yu, L.; Chen, D.; Li, J.; Wang, P. G. *J. Org. Chem*. **1997**, *62*, 3575.
18. The content of Yb(III) on resin **4** was determined according to the procedure described in Ref. 17 and was around 1.5 mmol/g. Urea is partially absorbed onto **4** and it is released by washing the polymer with a 2 M solution of ammonia in methanol.
19. Under these conditions the contaminants, i.e. excess urea and by-products, were selectively extracted. On the other hand a control experiment showed that on treating pure **5a** with A-15 and Ambersep 900 OH (MeOH, 2h) and filtration of the resins, the starting material was totally recovered.
20. General procedure for the preparation of dihydropyrimidinones **5**–**12**: a screw-capped vial, containing a magnetic stirring bar, was charged first with 160 mg of Yb(III)-resin **4** then with urea **3** (1.5 mmol), aldehyde **2** (0.5 mmol), and β-dicarbonyl compound (0.5 mmol) **3** and heated at 120°C for 5 min. Then 170 mg of Yb(III)-resin **4** were added. The reaction mixture was heated at 120°C under gentle stirring for 48 h. After cooling to 60°C, methanol (1 mL) was added. The suspension was stirred for an additional 30 min then the resin was filtered off and washed thoroughly with EtOAc. Amberlyst 15 (400 mg) and Ambersep 900 OH (400 mg) were added to the combined filtrates. The suspension was shaken for 2 h then the resins were filtered off and washed thoroughly with methanol. The combined filtrates were concentrated to give dihydropy-

rimidinones **5**–**12**. Data for **5c**: mp 202–203°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.18 (s, 1H, NH), 7.78 (s, 1H, NH), 7.40–7.00 (m, 5H, Ph), 5.13 (d, 1H, $J=2.5$ Hz, CH), 4.88–4.75 (m, 1H, OCH), 2.22 (s, 3H, Me), 1.18 (d, 3H, $J=6.0$ Hz, CHCH_3), 0.98 (d, 3H, $J=6.0$ Hz, CHCH_3). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 164.8, 152.1, 148.1, 145.0, 128.3, 127.2, 126.3, 99.5, 66.3, 54.1, 21.8, 21.4, 17.7.

21. Aldehydes, β-dicarbonyl compounds, and urea were all commercial materials. All liquid reagents were distilled before use.
22. Control experiments have shown a good relationship between purity versus yield (e.g. **5c**: yield of 95% pure material: 78%; yield of purified material: 74%).