

Notes

Envirocat EPZ10: A Recyclable Solid Acid Catalyst for the Synthesis of Biginelli-type 3,4-Dihydropyrimidin-2(1H)-ones

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Recently, 3,4-dihydropyrimidin-2(1H)-ones (**4**, Scheme 1) and their sulfur analogs (DHPMs) have attracted considerable interest due to their pharmaceutical properties such as antitumoral, antiviral and antihypertensive activities.¹ The original method for the synthesis of DHPMs reported by Biginelli in 1893, involves the HCl-catalyzed condensation reaction of ethyl acetoacetate, aldehydes, and urea or thiourea in ethanol.² One major drawback of this so-called Biginelli reaction, however, is the low to moderate yield that is often encountered when substituted aromatic (20-60%) or aliphatic aldehydes (10%) is used.³ To circumvent this problem, a variety of new reagents has been introduced in the literature. Recent examples involve the use of LiClO₄,^{4a} Lewis acids such as ytterbium triflate,^{4b} cupric chloride,^{4c} manganese(III) acetate,^{4d} bismuth triflate,^{4e} cerium(III) chloride,^{4f} copper(II) triflate,^{4g} ferric chloride,^{4h} nickel chloride,^{4h} BF₃ etherate/copper(II) acetate,⁴ⁱ zirconium(IV) chloride,^{4j} and polymer-supported ytterbium(III) reagent^{4k} as well as Brønsted acids such as *p*-toluenesulfonic acid,^{4l} silica sulfuric acid^{4m} and KHSO₄.⁴ⁿ Also, Montmorillonite KSF was claimed to act as solid acid catalyst in the Biginelli reaction.^{4o}

Due to the ever-mounting environmental concern in the fields of chemistry, it is advisable to easily recover and recycle catalysts, especially expensive or toxic metallic ones for the next use.⁵ In this respect, few of the catalysts mentioned above meet this criterion of green chemistry.⁶ Therefore, there is still room for further search for recyclable catalysts that can convert a variety of aldehydes in high

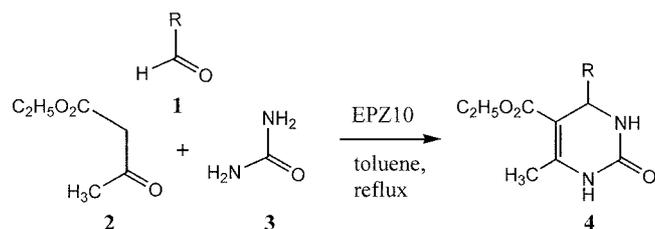


Table 1. Envirocats-catalyzed Synthesis of DHPMs^a

Entry	Catalysts ^b	Solvent	Time (h)	Yield (%) ^c
1a	EPZ10 (10 mol%)	Toluene	6	84
1b		CH ₂ Cl ₂	36	36
1c		EtOH	48	45
1d		THF	48	44
1e		CH ₃ CN	48	55
1f		Solvent-free ^d	6	80
2	EPZG (10 mol%)	Toluene	15	78
3	EPIC (10 mol%)	Toluene	20	75

^aReaction temperature: refluxing temperature. Molar ratio of aldehyde : ethyl acetoacetate : urea = 1 : 1 : 1.5. ^bComposition of the active substance in Envirocats EPZ10, EPZG and EPIC is 12, 20, 22% by weight, respectively. ^cYield refers to the isolated yield. ^dReaction temperature: 110 °C.

yields under mild reaction conditions.

In this paper, we describe an one-pot method for the Biginelli reaction using Envirocat EPZ10 as a recyclable solid acid catalyst (Scheme 1).⁷ EPZ10, which is prepared by supporting ZnCl₂ on clay, is known to contain predominantly strong Lewis acid sites as well as weak Brønsted acid sites.⁸ EPZ10 has been used as a catalyst for Friedel-Crafts alkylation, aromatic bromination and benzylation.⁷

Initially we studied a model reaction employing benzaldehyde, ethyl acetoacetate and urea in the presence of three types of Envirocats, namely EPZ10 (clay-supported ZnCl₂), EPZG (clay-supported FeCl₃) and EPIC (clay-supported polyphosphoric acid), as shown in Table 1. All Envirocats catalysts were activated via azeotropic drying with toluene to remove loosely bound water in clay support.⁷ In refluxing toluene, EPZ10 was found to be the most reactive among three catalysts, giving the product in 84% isolated yield within 6 h. In contrast, the classical Biginelli condition (cat. HCl in EtOH, reflux, 18 h) gave 80% yield. The solvent effect was studied in the case of EPZ10-catalyzed reaction (Table 1). Clearly, toluene was a much better solvent than other solvents tested in terms of yields. Lower boiling solvent (dichloromethane), protic solvent (EtOH) and Lewis basic solvents (THF, CH₃CN) retarded the reaction. Also, the solvent-free reaction gave a

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Table 2. Envirocat EPZ10-catalyzed Synthesis of DHPMs^a

Entry	R in 4	Time (h)	Yield (%) ^b	mp (°C)	mp (°C) (lit.)
1	Ph	6	84	202-204	200-202 ^{4j}
2	2-furyl	6	83	201-203	203-205 ^{4j}
3	4-(OMe)-C ₆ H ₄	10	72	198-200	199-201 ^{4b}
4	4-(NO ₂)-C ₆ H ₄	10	81	205-208	206-208 ^{4j}
5	3-(NO ₂)-C ₆ H ₄	8	83	225-227	227-229 ^{4l}
6	2-ClC ₆ H ₄	6	88	214-215	215-217 ^{4m}
7	4-OHC ₆ H ₄	11	72	225-227	227-228 ^{4d}
8	PhCH=CH-	12	56	230-232	229-232 ^{4j}
9	<i>n</i> -pentyl	10	68	158-160	161-162 ^{4a}
10	<i>n</i> -hexyl	11	64	152-154	152-154 ^{4l}
11	isopropyl	10	60	192-194	194-195 ^{4b}
12a ^c	Ph	12	80		
12b ^d	Ph	24	42		
12c ^e	Ph	6	78		
12d ^f	Ph	12	75		

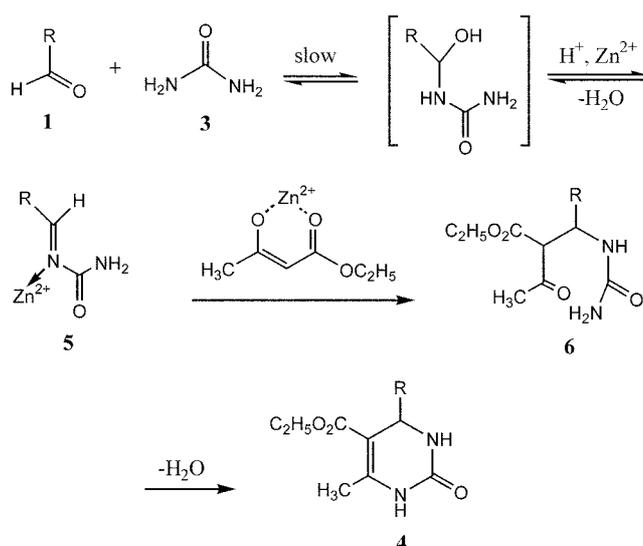
^aReaction conditions: 10 mol% catalyst, toluene, reflux. Molar ratio of aldehyde : ethyl acetoacetate : urea = 1 : 1 : 1.5. ^bYield refers to the isolated yield. ^cThe catalyst from the first run (entry 1) was dried in air at room temperature and used in the second run. ^dThe catalyst from the second run (entry 12a) was dried in air at room temperature and used in this third run. ^eThe catalyst from the third run (entry 12b) was dried in air at 110 °C for 3 h and used in this fourth run. ^fUnactivated catalyst was used as received.

good yield of product (entry 1f).

Further reactions of aromatic and aliphatic aldehydes were carried out using EPZ10 in refluxing toluene for convenience of following the reaction progress with TLC. The result of these reactions is summarized in Table 2. Substituted or conjugated aromatic aldehydes and heteroaromatic aldehydes reacted readily within 6-12 h, giving good yields of products (entries 2-8): aromatic aldehydes having either electron-withdrawing or electron-donating groups reacted in good yields. Also, aliphatic aldehydes reacted within 11 h, providing 60-68% yield (entries 9-11).

Next, the recyclability of EPZ10 was studied. The second run using the recovered catalyst that was dried in air at room temperature was slower, as one can see by comparing the reaction times (entry 1 vs. 12a in Table 2). The third run (entry 12b) employing the catalyst from the second run gave poor yield, despite longer reaction time. Fortunately, when the recovered catalyst that was dried in 110 °C for 3 h was used, the original activity was restored (entry 12c). It is probable that the decrease in activity is due to the fact that two moles of water is generated for each mole of product and ever-increasing amount of water becomes absorbed in clay as the recycling of the catalyst is repeated. As an evidence, the catalyst recovered from the first run was similar in activity to the unactivated catalyst that is known to have loosely bound water (entry 12a vs. 12d), implying the detrimental effect of water on catalysis.

Recently, Kappe proposed that the first step of the Biginelli reaction, the acid-catalyzed formation of acyl imine intermediate **5** formed by the reaction of the aldehyde



with urea, is the rate-determining step.⁹ Further reaction of the iminium ion by acetoacetate gives an ureido **6**, which subsequently cyclizes to DHPMs **4** with expulsion of water. The catalytic effect of EPZ10 probably arises from the acidity of EPZ10 catalyzing the slow step as well as the activation of **5** with coordination with zinc metal, thus facilitating the addition of acetoacetate onto the more electrophilic iminium carbon center.¹⁰

The following is a representative example: A solution of benzaldehyde (212 mg, 2.0 mmol), ethyl acetoacetate (260 mg, 2.0 mmol) and urea (180 mg, 3.0 mmol) in toluene (15 mL) was treated with EPZ10 (225 mg, ZnCl₂ content 12%, 10 mol%) under N₂ atmosphere. The whole mixture was heated at refluxing temperature and the progress of the reaction was monitored by TLC. After 6 h, the reaction mixture was concentrated *in vacuo* and the residue was treated with hot EtOH (30 mL). The resulting suspension was filtered through a Büchner funnel and the filtrate was poured into cold water (30 mL). The resulting precipitate was collected and recrystallized in EtOH, to give 435 mg (84%) of a white crystal, mp 202-204 °C (in lit.^{4j} mp 200-202 °C).

In conclusion, we have found that Envirocat EPZ10 can serve as an environmentally friendly solid acid catalyst for the Biginelli reaction. ZnCl₂, the active component of EPZ10 is non-toxic and cheap. The catalyst can be easily recovered by simple filtration and reused after activation by drying at 110 °C in air.

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6. For example, the recovery of Yb(OTf)₃ from water seems cumbersome since water must be removed through heating and then drying under vacuum at 100 °C for 2 h.^{4b} In the case of polymer-derived Yb(III) resin, the activity of recycled resin is much lower than that of the original one, thus limiting the recyclability.^{4k}
7. Envirocats catalysts are available from Contract Chemicals, England (www.contract-chemicals.com).
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10. It should be noted that the Biginelli reaction employing benzaldehyde in boiling toluene in the presence of 10 mol% ZnCl₂ did not go to completion within 6 h, giving poor yield (~10%) of product. This fact thus implies that clay plays an important role of enhancing catalytic activity of Lewis acid, probably by tying up water. On the other hand, the Biginelli reaction over Montmorillonite KSF (toluene, 100 °C, 10 h) is reported to give 35% yield of product.⁴ⁿ
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