Organocatalytic Decarboxylative Doebner–Knoevenagel Reactions between Arylaldehydes and Monoethyl Malonate Mediated by a Bifunctional Polymeric Catalyst

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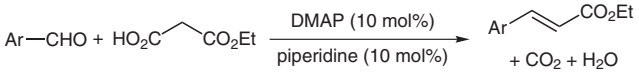
Abstract: A bifunctional polystyrene bearing both DMAP and piperidine groups has been prepared and used as an organocatalyst for decarboxylative Doebner–Knoevenagel reactions of arylaldehydes and monoethyl malonate. Isolated yields of the resulting cinnamates were very high, and in all cases only the *E*-isomer was detected. When a polystyrene catalyst functionalized with only DMAP or piperidine groups was used in these reactions, catalysis was much less efficient. Furthermore, catalysis using a combination of the monofunctional polymers was also less efficient than with the bifunctional polystyrene. Thus, it appears that there is a synergistic effect obtained by co-locating the two different catalytic amine groups on the same polymer backbone.

Key words: Doebner–Knoevenagel reaction, organocatalysis, polystyrene, DMAP, cinnamates

The Doebner–Knoevenagel reaction is a venerable and versatile process that has received renewed interest in recent years.[1] For example, when malonic acid is used as the pronucleophile, it has been demonstrated to be useful for the conversion of 2- or 4-hydroxyarylaldehydes into the corresponding styrenes,[2] and has been used in conjunction with a hydroformylation reaction in a one-pot procedure for stereoselectively synthesizing (*E*)-α,β-unsaturated carboxylic acids.[3] Alternatively, it has been demonstrated by List and co-workers[4] that monoesters of malonic acid[5] can also be used in a variation of this reaction for the stereoselective synthesis of (*E*)-cinnamates from arylaldehydes (Scheme 1).[6–8] These later reactions are efficiently catalyzed by a combination of piperidine and DMAP, and thus this process represents an attractive organocatalytic alternative to the Wittig reaction for cinnamate synthesis since only CO_2 and water are produced as byproducts rather than Ph_3PO.



Scheme 1 The Doebner–Knoevenagel reaction in cinnamate synthesis

We have been interested in both the development of polymers for use in organic synthesis[9] and polymer-supported organocatalysts,[10,11] and have recently described the use of immobilized DMAP catalysts in Morita–Baylis–Hillman reactions[12] and CO_2 addition to epoxide processes.[13] Furthermore, we have reported a bifunctional polymeric phosphine-phenol organocatalyst for alkyne isomerization reactions,[14,15] and a related amine-phosphine bifunctional polymer-supported reagent for a wide range of Wittig reactions.[16] Thus, we wanted to see if our strategy of immobilizing two different catalyst or reagent groups onto the same polystyrene[17] backbone would be applicable for the generation of a bifunctional DMAP-piperidine polymeric organocatalyst. Herein we report the synthesis of such a polymer and its application in a series of Doebner–Knoevenagel reactions that result in the stereoselective synthesis of a range of (*E*)-cinnamates from the corresponding arylaldehydes.

Since it was reported that the combination of DMAP and piperidine catalyzed the reaction between nonenolizable arylaldehydes and monoethyl malonate to form the corresponding (*E*)-cinnamates, we co-polymerized monomers **1**[12] and **2**[18] with styrene in a 1:1:10 ratio. After deprotection and basification of the resulting polymer **3**, bearing both electron-rich 4-dialkylaminopyridine and cyclic secondary amine groups, was obtained in moderate overall yield (Scheme 2).[18] It should be noted that styrene was incorporated into **3** so that it could be isolated as a dry, free-flowing powder. When no styrene was used, the resulting polymer was a tacky, amorphous material that was difficult to handle. For comparison, monofunctional polymers **4** and **5** were prepared similarly by the omission of **2** or **1**, respectively, from the polymerization reaction. The monomer incorporation ratios of **3**–**5**, and thus the loading levels, were determined by ^{1}H NMR analysis, and were found to be similar to the theoretical values based on the monomer input ratios. It should be noted that polymers **3**–**5** were found to be soluble in DMF, and thus they could function as homogeneous catalysts.

For the benchmark Doebner–Knoevenagel reaction used to assess the utility of bifunctional catalyst **3**, we arbitrarily chose 4-methoxybenzldehyde (**6a**) as the reaction partner with monoethyl malonate (**7**) to form cinnamate **8a**, using 5 mol% of the catalyst(s) (Table 1).[18,19] As can be seen from entries 1 and 2, when either monofunctional polymeric catalyst **4** or **5**, with only DMAP or piperidine groups, respectively, was used (5 mol% in DMF at 50 °C) only low yield of desired product **8a** was obtained. This is

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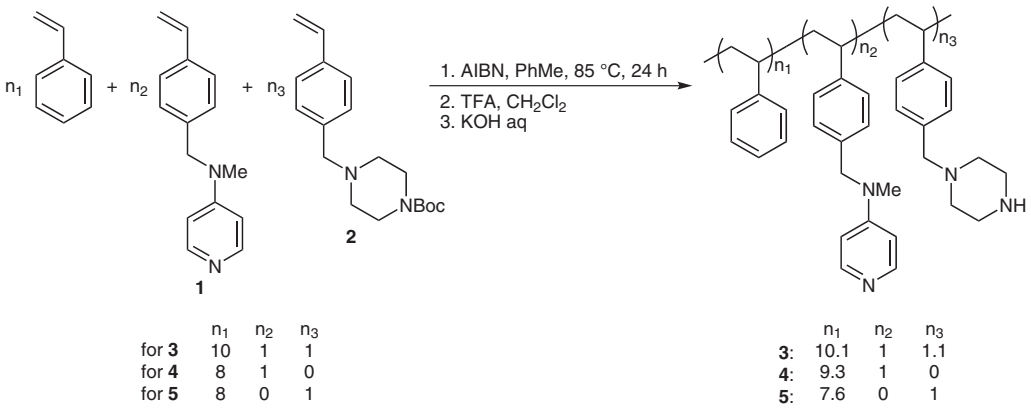
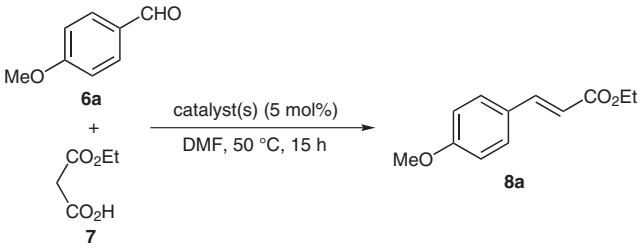


Scheme 2 Synthesis of polymers **3–5**

similar to what was previously reported.[4] However, when a combination of **4** and **5** were used together, the isolated yield of **8a** was dramatically higher (Table 1, entry 3). Significantly, when bifunctional catalyst **3** was used to catalyze the reaction, nearly quantitative yield of **8a** was obtained (Table 1, entry 4), which is the same result observed when the combination of actual DMAP and piperidine was used (Table 1, entry 5). Thus, it appears that there is an advantage to using a single bifunctional polymer over using a combination of monofunctional polymers, and that **3** is a good replacement for the pair of DMAP and piperidine catalysts in decarboxylative Doebner–Knoevenagel reactions.

Table 1 Catalyst Screening for the Reaction between **6a** and **7**



Entry	Catalyst(s)	Isolated yield of **8a** (%)[a]	*E*/*Z*[b]
1	**4**	10	>99:1
2	**5**	21	>99:1
3	**4** + **5**	78	>99:1
4	**3**	97	>99:1
5	DMAP + piperidine	97	>99:1

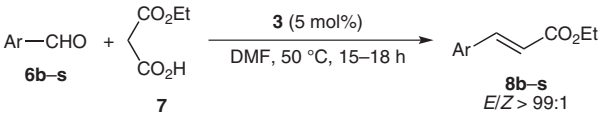
[a] Yield of reactions using **6a** (0.5 mmol), **7** (0.75 mmol), and catalyst(s) (0.025 mmol) at 50 °C in DMF (0.5 mL) for 15 h.
[b] Determined by ^{1}H NMR analysis.

After demonstrating the utility of **3** for catalyzing the formation of **8a**, we then studied the scope of aryl aldehydes applicable in this reaction (Table 2).[20] When **6b**, bearing an electron-donating 4-hydroxy group, was used as the starting material, the reaction was more sluggish than with other substrates, and required a longer time to proceed to completion (Table 2, entry 1). Of the other benzldehyde derivaties **6c–p** studied, only very sterically hindered **6o** failed to react to completion, even after a prolonged reaction time (Table 2, entry 14), and it was clear that none of the substitutents studied exerted either a strong activating or deactivating effect. We also examined heteroaromatic aldehyde substrates **6q–s** and found that the corresponding (*E*)-α,β-unsaturated esters **8q–s** could also be obtained in essentially quantitative yield (Table 2, entries 16–18). In all cases formation of products **8b–s** was highly stereoselective, and only the *E*-isomer was detected by ^{1}H NMR spectroscopy. Furthermore, isolation of pure **8b–s** was simplified by the polar and macromolecular nature of **3**, since it did not elute during chromatographic purification of the desired product. Additionally, since only a small quantity of solvent was used in these reactions, it too was separated from the desired product directly by chromatography. Thus, **3** appears to be a general catalyst for these reactions, and its use as a replacement for DMAP and piperidine is advantageous. Unfortunately, attempts to recover and reuse **3** were not successful due to difficulty in precipitating it from the reaction mixtures and obtaining it in a pure state.

In summary, we have developed a soluble, bifunctional polystyrene DMAP-piperidine material that is effective as a catalyst in decarboxylative Doebner–Knoevenagel condensation reactions between arylaldehydes and monoethyl malonate which result in the stereoselective formation of (*E*)-cinnamates that are easily isolated in nearly quantitative yield. Control reactions indicate that the DMAP and piperidine groups attached to the polymer cooperate together to more efficiently catalyze the reactions than when only one of the functional groups is present, and that colocating the two catalyst groups on the same polymer backbone enhances this synergy compared to when a combination of two monofunctional polymers is used. To our knowledge this is the first example of such an observation with organic polymers, and thus the performance of **3** compared to the combination of **4** and **5** in other organocatalytic applications, as well as the activity of other bifunctional polymeric organocatalysts, is currently under

investigation. The results of these studies will be reported in due course.

Table 2 Doebner–Knoevenagel Condensation Reactions Catalyzed by **3**



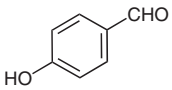
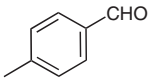
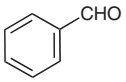
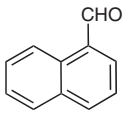
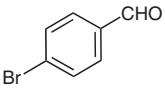
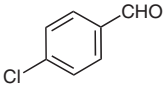
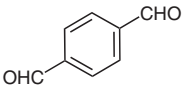
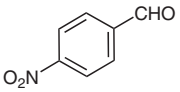
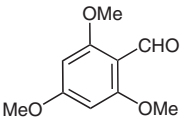
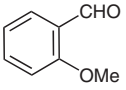
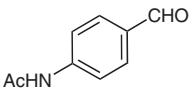
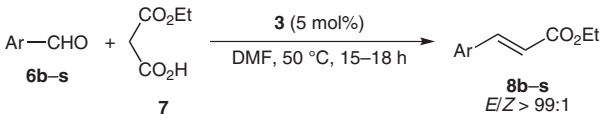
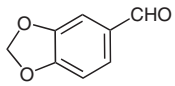
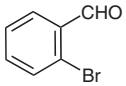
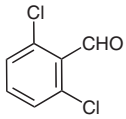
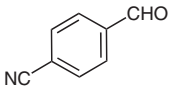
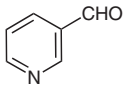
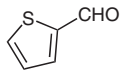
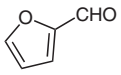
Entry	Aldehyde	Product	Isolated yield (%)[a]
1	 **6b**	**8b**	91[b]
2	 **6c**	**8c**	92
3	 **6d**	**8d**	96
4	 **6e**	**8e**	96
5	 **6f**	**8f**	99
6	 **6g**	**8g**	98
7	 **6h**	**8h**	89[c]
8	 **6i**	**8i**	89
9	 **6j**	**8j**	85
10	 **6k**	**8k**	99
11	 **6l**	**8l**	98

Table 2 Doebner–Knoevenagel Condensation Reactions Catalyzed by **3** (continued)



Entry	Aldehyde	Product	Isolated yield (%)[a]
12	 **6m**	**8m**	99
13	 **6n**	**8n**	90
14	 **6o**	**8o**	59[d]
15	 **6p**	**8p**	95
16	 **6q**	**8q**	99
17	 **6r**	**8r**	99
18	 **6s**	**8s**	91

[a] Reactions using **6b–s** (0.5 mmol), **7** (0.75 mmol), and **3** (0.025 mmol) at 50 °C in DMF (0.5 mL) for 15–18 h.
[b] This reaction required 62 h to complete.
[c] Since **6h** bears 2 aldehyde groups, 1.50 mmol of **7** and 0.05 mmol of **3** were used. The product obtained was the corresponding (*E*,*E*)-bis-enoate.
[d] This reaction was stopped after 48 h.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) See Supporting Information for details.
(19) Increasing the catalyst loading did not significantly affect the isolated yield or stereoselectivity of the reaction.
(20) **General Procedure for Doebner–Knoevenagel Reactions** Commercially available arylaldehydes **6a–s** (0.5 mmol), **7** (0.75 mmol), and catalyst **3** (0.025 mmol) were dissolved in DMF (0.5 mL). The mixture was stirred at 50 °C for 15–18 h, and then the reaction mixture was purified directly by column chromatography (EtOAc–hexane) to afford the desired product **8a–s**. In all cases only the *E*-stereoisomer was observed by ^{1}H NMR spectroscopy.