Tetrahedron Letters 53 (2012) 2537–2539

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic enamines from dialkylamide-dialkylacetals

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ARTICLE INFO

Article history:
Received 8 February 2012
Revised 23 February 2012
Accepted 7 March 2012
Available online 16 March 2012

Keywords:
Organocatalyst
Enamine
Carbonyl
Hann–Lapworth reaction
Reaction mechanism

ABSTRACT

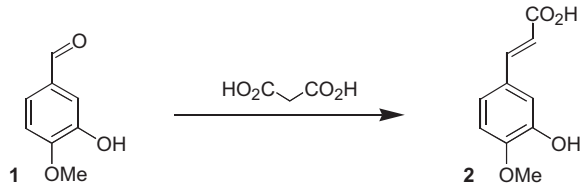
The formation of a transient enamine derived from DMF-DMA provides an effective alternative to the harsh conditions normally required for the nucleophilic addition of base-activated methylene compounds to a carbonyl group. Organocatalysts formed from dialkylamide-dialkylacetals in this manner may provide extensive synthetic utility for a number of well-established reactions in which the formation of enolates and enamines has been employed.

A great deal of effort has been devoted to explore general and efficient routes for carbonyl olefination. One interesting approach involves the dehydrative decarboxylation of β-hydroxy carboxylic acids into olefins, in the presence of *N*,*N*-dimethylformamide dimethylacetal (DMF-DMA) in synthetically useful yields.[1] Following on from our recent work,[2] it was considered that just such a route might provide a novel extension to the Hann–Lapworth reaction[3] whereby the β-hydroxy carboxylic acid intermediate generated might be redirected towards the synthesis of novel alkenes. Unfortunately, when utilising isovanillin (**1**) under standard Hann–Lapworth conditions, the addition of DMF-DMA furnished a less than 5% yield (by ^{1}H NMR spectroscopy) of the desired styrene.

Whilst investigating methods to improve this yield, it was discovered that DMF-DMA seemed able to enhance the rate of the Hann–Lapworth reaction itself (Scheme 1). Further analysis revealed that the reaction gave the corresponding *trans*-cinnamic acid **2** in quantitative yield within 4 h (Table 1). Under otherwise identical conditions, and in the absence of DMF-DMA, isovanillin remained largely unreacted within this time frame suggesting that triethylamine alone is not a strong enough base to promote effectively the Hann–Lapworth reaction. Although not recorded here, the stronger base DBU was required to achieve significant conversions in the absence of DMF-DMA. Additional experiments demonstrated that DMF-DMA is truly catalytic for the reaction and that the presence of a strong base seemed unnecessary for the reaction to proceed. Furthermore, when methylmalonic acid was utilised instead of malonic acid, DMF-DMA was similarly able to catalyse the reaction, albeit at an evidently slower rate (Table 1).

An enamine intermediate

When using dimethyl malonate as the substrate and an excess of DMF-DMA (Table 2) none of the expected dimethyl ester product was observed to accumulate. However, flash column chromatography of the crude product mixture afforded isovanillin (**1**) and an enamine **3** in high yield. In all the reactions monitored by ^{1}H NMR spectroscopy in which DMF-DMA was present and dimethyl malonate was used, formation of an enamine (Scheme 2) was observed.[6] Indeed, this enamine can be synthesised and comparison of the ^{1}H NMR spectrum of the isolated material (consistent with the literature[7]) with spectra recorded for the reaction confirmed the presence of this enamine in these reactions. The enamine was also isolated from the reactions.



Scheme 1. Reagents and condition: DMF-DMA, Et_3N, PhMe, reflux, 4 h.

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0040-4039/$ - see front matter
http://dx.doi.org/10.1016/j.tetlet.2012.03.028

Table 1

Reagent (equiv)	DMF-DMA (equiv)	Et_3N (equiv)	Time (h)	Conversion[a](%)
Malonic acid				
4	0	5	4	3.6
4	1.5	5	4	100[b]
4	0.2	5	4	88.5
4	1.5	0	4	95.2
2.5	0.2	0	16	100
Methylmalonic acid				
2.5	0	1	16	0
2.5	0.1	1	16	40.2
2.5	1.0	1	16	90.1

[a] The corresponding *trans*-cinnamic acid was the only product observed by ^{1}H NMR spectroscopy in these reactions.[4]
[b] No remaining starting material was observed by ^{1}H NMR analysis of the reaction. Typical experimental procedures are given.[5]

Table 2

Reagent (equiv)	Solvent	Acid (equiv)	DMF-DMA (equiv)	Conversion[4] (%)
Malonic acid				
2.5	PhMe	—	0.1	91.7[a]
Dimethylmalonate				
2.5	PhMe	—	0.1	0[a]
2.5	PhMe	—	1.5	0[b]
2.5	THF	—	1.5	0[b]
2.5	MeCN	—	1.5	30[b]
2.5	$CHCl_3$	—	1.5	41.0[b]
		TFA		
2.5	$CDCl_3$	—	1.5	61.2[b]
2.5	$CDCl_3$	0.1	1.5	63.0[b]
2.5	$CDCl_3$	0.375	1.5	67.5[b]
2.5	$CDCl_3$	0.5	1.5	71.1[b]
2.5	$CDCl_3$	0.75	1.5	54.3[b]
2.5	$CDCl_3$	1	1.5	28.6[b]
2.5	$CDCl_3$	1.5	1.5	2.0[b]
2.5	$CDCl_3$	2.5	1.5	0[b]
2.5	$CDCl_3$	0.05	0.15	67.7[b]
		TsOH		
2.5	PhMe	—	1.5	0[c]
2.5	PhMe	0.5	1.5	86.8[c]

[a] Reactions were performed for 24 h at reflux.
[b] Reactions were performed for 16 h at 60 °C.
[c] Reactions were performed for 16 h at reflux.

Scheme 2.

Acid catalysis

The initial failure of the reaction to proceed when using dimethyl malonate as the substrate and an excess of DMF-DMA was surprising given the success when malonic acid was used. It was thought that the carboxylic acid groups of malonic acid might be of consequence. That is, that some degree of acid catalysis is required to drive the reaction catalysed by DMF-DMA.

Investigation of the reaction in various solvents demonstrated that THF afforded a similar result to toluene, whilst acidic solvents such as acetonitrile and chloroform were required to afford any product. These observations further support the idea that acid catalysis is required for the reaction.

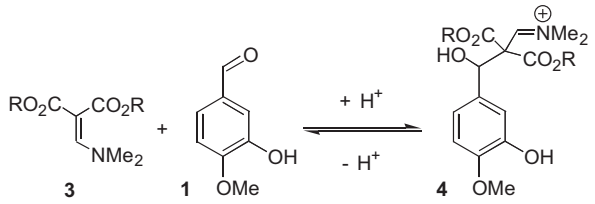
A series of ^{1}H NMR experiments in $CDCl_3$ were therefore undertaken to gauge the effect of acid catalysis on the reaction of dimethyl malonate and isovanillin (**1**) (Table 2). This study clearly demonstrated that the formation of the expected dimethyl ester increased with increasing molar equivalents of TFA. Optimum conversion was achieved at 0.5 equiv of TFA, which, notably, is also the molar excess of DMF-DMA used. However, this trend was reversed when TFA was present at quantities greater than 0.5 equiv, and no product was formed when TFA was present in greater quantity than DMF-DMA. This observation implies that acid was required to drive the reaction, but at high relative concentration also impedes the action of DMF-DMA. Therefore, the quantities of DMF-DMA and the acid used must be carefully balanced to ensure optimum rate enhancement. Indeed, this necessity is exemplified by the observation that similar results were obtained using only a catalytic quantity of DMF-DMA.

The formation of the enamine in this study was shown also to be enhanced by acid catalysis, and followed a similar trend to that of the expected product of the reaction. Notably, it was discovered that the enamine was formed in toluene in significant quantity, yet none of the expected dimethyl ester was formed under those conditions. This suggests that the addition of an acid catalyst is not strictly necessary for enamine formation, but is required for end

Table 3

Enamine (equiv)	TFA (equiv)	MeOH (equiv)	Time (h)	Conversion[a] (%)
1.5	0.5	5.0	16	58.0
1.5	0.5	0	16	0

[a] Reactions were performed in $CDCl_3$ for 16 h at 60 °C.[4]



Scheme 3.

product formation. This idea was confirmed by conducting the reaction in toluene at reflux in the presence of *p*-toluenesulfonic acid (Table 2).

Catalyst recovery

Formation of the enamine from DMF-DMA and dimethyl malonate involves the loss of two moles of methanol (Scheme 2). To probe whether this methanol is required for the DMF-DMA-catalysed reaction to proceed, the enamine (isolated in pure form from a previous reaction) was reacted with isovanillin both in the presence and absence of methanol (Table 3).

The fact that these experiments clearly show that the reaction requires methanol to proceed suggests that, in the absence of methanol the enamine adds to the aldehyde to give an iminium intermediate **4**, which being unable to proceed down any further reaction pathway, presumably decomposes to regenerate the enamine **3** and isovanillin (**1**) (Scheme 3). This experiment also suggests that an alternative mechanism whereby DMF-DMA is a source of dimethylamine (formed by H^+-catalysed elimination) which might catalyse the reaction, as demonstrated earlier with the stronger base DBU, is unlikely.

Catalytic efficiency

Finally, the operational efficiency of DMF-DMA, determined using a kinetic study[8] analysed by ^1H NMR spectroscopy in $CDCl_3$, revealed that, under these conditions, the catalyst initially functioned at above 8 turnovers per hour and on average exceeded 420 turnovers prior to catalyst deactivation. Under identical conditions in the absence of catalyst, no product accumulation was observed.

We believe that this is the first instance in which a catalytic enamine is generated in this way within a reaction in order to promote a nucleophilic attack of this nature. Moreover, we have demonstrated that these reactions, which are typically achieved under harsh, basic conditions, can now be performed under very mild conditions. Additionally, we are certain that a variety of organocatalysts of this type might be employed in a wide array of not dissimilar synthetically useful reactions. For example, the importance of enolate anions as synthetic intermediates is well-established and the use of enamines as enolate anion surrogates has been extensively utilised in synthetic organic chemistry.[9] Technology in which catalytic enamines are formed from dialkylamide-dialkylacetals as demonstrated here may therefore provide the first step towards a more expansive synthetic utility for a number of well-established reactions in which the formation of enolates and enamines has been employed.

Acknowledgment

The authors gratefully acknowledge the support of the Organic Synthesis Centre, University of Sydney, for enabling the work described in this paper.

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4. Analyses of reactions were carried out using the ^1H NMR spectra of crude products. Determination of conversions were obtained from comparative integration of either the aldehyde peak of the starting material and the protons furthest downfield in the exocyclic double bonds of the product or the methoxy protons of the starting material and products.
5. To a suspension of isovanillin (**1**) (152 mg, 1.00 mmol) and malonic acid (416 mg, 4.00 mmol) in toluene (5 mL) were added Et_3N (0.70 mL, 5.00 mmol) and DMF-DMA (0.20 mL, 1.50 mmol). The resulting mixture was heated at reflux for 4 h, then allowed to cool to room temperature, and concentrated on a rotary evaporator. The residue was dissolved in 1 M NaOH solution (20 mL), and the resulting solution washed with CH_2Cl_2 (3×20 mL). The aqueous phase was then acidified to pH 1 by addition of 3 M HCl. The creamy precipitate was collected in a Hirsch funnel, washed with dilute HCl and allowed to air dry. The precipitate was then recrystallised (MeOH–H_2O) and dried in a vacuum desiccator over P_2O_5 to afford *trans*-isoferulic acid (164 mg, 85%) as a cream-coloured crystalline solid. The ^1H NMR data were consistent with the literature (McCorkindale, N. J.; McCulloch, A. W.; Magrill, D. S.; Caddy, B.; Martin-Smith, M.; Smith, S. J.; Stenlake, J. B. *Tetrahedron* **1969**, *25*, 5475).
6. For the conversion of methylmalonic acid (Table 1) the intermediate enamine cannot be formed without undergoing a decarboxylation during enamine formation. It seems reasonable that the reaction product (iminium intermediate) formed from methylmalonic acid and DMF-DMA can eliminate MeOH and CO_2 in either an E1 or antiperiplanar E2-type mechanism. Indeed, this same mechanism could equally apply for the case of malonic acid, although this was not observed.
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8. To two solutions of isovanillin (9.99×10^{-5} mol) and malonic acid (25.38×10^{-5} mol) in $CDCl_3$ (0.5 mL) at 30 °C was added either DMF-DMA (8.27×10^{-8} mol) or an equivalent volume of $CDCl_3$. The reaction solutions were maintained at 30 °C and ^1H NMR analysis was performed at 30 °C at appropriate time intervals over 3 days. Determinations of conversions were obtained from comparative integration of the methoxy protons of the starting material and the protons of the exocyclic double bond of the product.
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