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A Practical and Convenient Protocol for the Synthesis of (*E*)-α,*β*-Unsaturated Acids[†]

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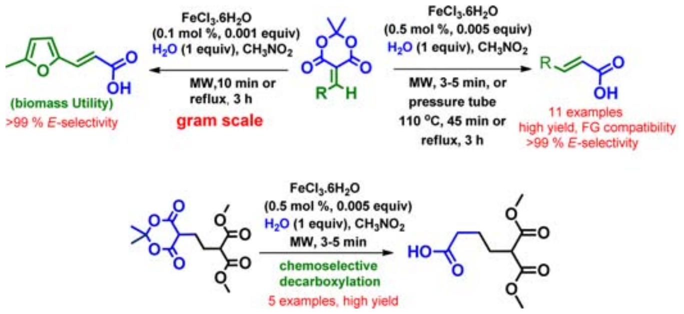
ABSTRACT



α,*β*-Unsaturated acids are very useful and versatile reagents in organic synthesis. A novel, practical, and convenient catalytic protocol comprising $FeCl_3 \cdot 6H_2O$ (0.5 mol %) and H_2O (1 equiv) in CH_3NO_2 is described for the rapid synthesis of α,*β*-unsaturated acids with high *E*-stereoselectivity under both microwave and conventional heating conditions with high TON and TOF values. This powerful approach efficiently demonstrated the utility of biomass derived aldehydes to build chemical agents used as fuel additives. The method proved to be scalable to gram scale synthesis.

The α,*β*-unsaturated acids are very important and useful reagents in organic synthesis. These are significant structural motifs in many natural products (viz. the secretion of the queen honey bee,[1a,b] caffeic acid[1c]), pheromones,[2] and bioactive compounds.[3] Owing to their wide ranging applications, α,*β*-unsaturated carboxylic acids are synthesized on a commercial scale.

Indisputably, the Doebner–Knoevenagel reaction has been one of the most extensively used protocols for the preparation of α,*β*-unsaturated carboxylic acids, but most often they need severe refluxing conditions and use of excess base.[4] The α,*β*-unsaturated acids have also been prepared from dibromoacetic acid and aldehydes with the aid of an excess amount of SmI_2.[5] The construction of carbon–carbon double bonds starting from aldehydes has been achieved via Wittig and Horner–Wadsworth–Emmons reactions.[6] However, in both reactions use of a strong base and the formation of a considerable amount of organophosphorous byproducts are unavoidable. Most of these reactions are noncatalytic and less stereoselective. In some cases eventually esters have been hydrolyzed to prepare the unsaturated acids.

To the best of our knowledge, there is no efficient catalytic method for the preparation of α,*β*-unsaturated acids other than the catalytic method reported by Breit and

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[†] Dedicated to Prof. K. N. Ganesh on the occasion of his 60th birthday.

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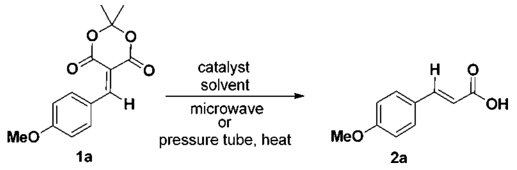
co-workers.[7] Hence there is a demand for an efficient and rapid catalytic protocol for the stereoselctive synthesis of α,β-unsaturated acids. Environmentally benign and sustainable catalytic protocols with milder conditions which can tolerate a wide variety of functionality are highly desirable. Carrying out the transformations through unconventional reagents and catalysts provide a useful and wider space for selectivity.

Herein, we report a protocol catalyzed by $FeCl_3 \cdot 6H_2O$ with the aid of H_2O (1 equiv) in CH_3NO_2 for the synthesis of α,β-unsaturated acids from the derivatives of cyclic 1,3-diesters. Moreover this catalytic protocol is very selective for cyclic 1, 3-diesters over acyclic 1,3-diesters. To the best of our knowledge methylene tethered Meldrum's acid derivatives have not been explored for the synthesis of α,β-unsaturated carboxylic acids. Earlier literature precedence reveals that reaction of alkylidene Meldrum's acids with phenol derivatives afforded 3-carboxycoumarin derivatives.[8,9] Wherein instantaneous decarboxylation was very tedious due to the presence of a double bond in conjugation with the carboxylic group. Similarly the reaction of phloroglucinol with alkylidene Meldrum's acids under alkaline conditions gave dihydrocoumarins.[10]

These earlier results encouraged us to believe that alkylidene Meldrum's acid derivatives would afford the corresponding α,β-unsaturated carboxylic acids on treatment with an appropriate Lewis acid catalyst and H_2O as a nucleophile.

In order to verify this we prepared various methylene tethered Meldrum's acid derivatives by condensing different aldehydes with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in water following the reported procedure.[11] Having obtained the alkylidene derivatives, we selected a *p*-methoxybenzylidene derivative of Meldrum's acid (**1a**) as a model substrate and screened various Lewis acids as catalysts in order to achieve the efficient catalytic decarboxylation for a one-pot synthesis of α,β-unsaturated carboxylic acids (Table 1). The reactions were screened under both conventional heating conditions and microwave irradiation (2.5 GHz). We observed that under both conditions $FeCl_3 \cdot 6H_2O$ (0.8 mol %) and H_2O (1 equiv) in the CH_3NO_2 catalyst system worked efficiently in a relatively short time. Heating conditions afforded **2a** in 87% yield in 45 min (entry 6); however, **2a** was obtained in 86% yield in a very short time (4 min) under microwave irradiation (entry 6). Different solvents were also screened as described in Table 1, and we observed that nitromethane and water (1 equiv) proved to be very crucial to bring about the desired transformation.[12] Interestingly, when water alone was used as solvent the reaction led to decomposition (entry 5). It is very significant to mention that the reaction worked very efficiently with 0.0038 mmol (0.005 equiv, 0.5 mol %) of $FeCl_3 \cdot 6H_2O$ as the catalyst, under both microwave and heating conditions to afford **2a** (TON 17660, TOF 44/min, microwave and TON 17459, TOF 3.9/min, heating) (entry 10).

Table 1. Reactivity of Catalyst on Decarboxylation



entry	catalyst (mmol %)	solvent[a]	T (°C)/ t (h)	Y^b (%)	MW[c] (%)
1	$CeCl_3 \cdot 7H_2O$ (0.03)	CH_3NO_2	110/3	0	0
2	$MgSO_4$ (0.023)	CH_3NO_2	110/3	0	0
3	LiBr (0.015)	CH_3NO_2	110/3	0	0
4	$FeCl_3 \cdot 6H_2O$ (0.0063)	CH_3NO_2	110/3	5	6
5	$FeCl_3 \cdot 6H_2O$ (0.0063)	H_2O	100/2	dec[d]	dec[d]
6	$FeCl_3 \cdot 6H_2O$ (0.0063)	CH_3NO_2[e]	110/45 m	87	86
7	$FeCl_3 \cdot 6H_2O$ (0.0063)	EtOAc	77/2	0	0
8	$FeCl_3 \cdot 6H_2O$ (0.0063)	MeOH	65/2	0	0
9	$FeCl_3 \cdot 6H_2O$ (0.0063)	CH_3CN[e]	82/2	0	0
10	$FeCl_3 \cdot 6H_2O$ (0.0038)	CH_3NO_2[e]	110/45 m	87	88
11	$B(C_6F_5)_3$ (0.0076)	CH_3NO_2[e]	110/3	39	39
12	$CeCl_3 \cdot 7H_2O$/NaI (0.076)	CH_3NO_2[e]	110/3	0	0
13	$SnCl_2$ (0.0076)	CH_3NO_2[e]	110/3	65	65
14	no catalyst	CH_3NO_2[e]	110/3	0	0

[a] Solvents were used. [b] Yield of isolated product. [c] Microwaved for 3–5 min (2.5 GHz, 250 W). [d] Decomposition. [e] 1 equiv of H_2O used; T, temperature; t, time in hours (h) or min (m); Y, yield in %; reactions were carried out using 0.2 g of **1a**.

Encouraged by this initial success we explored this catalytic protocol using the $FeCl_3 \cdot 6H_2O$ (0.005 equiv)–H_2O (1 equiv) in CH_3NO_2 for synthesizing various α,β-unsaturated carboxylic acids (**2a**–**2k**) in good yields (66–91%) (Scheme 1).

Notably, we observed that (*E*)-stereoisomers were formed as major products (>99%) using this protocol; however, compound **2h** was obtained in an E/Z = 87:13 ratio. *E*-Stereochemistry of the C=C double bond of α,β-unsaturated carboxylic acids was assigned on the basis of ^1H NMR coupling constants. Moreover, to study the reactivity of the ketone derived cyclic 1,3-diester toward the catalyst system we prepared the alkylidene derivative (**1i**) from the corresponding acetophenone. When subjected to the optimized reaction conditions using $FeCl_3 \cdot 6H_2O$ (0.005 equiv)–H_2O (1 equiv) in CH_3NO_2 under microwave irradiation, the alkylidine Meldrum's acid derivative (**1i**)

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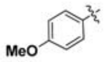
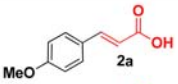
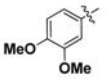
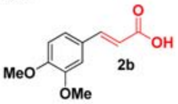
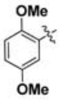
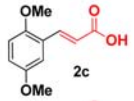
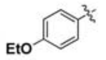
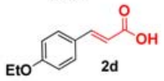
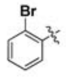
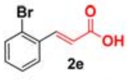
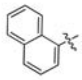
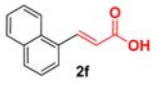
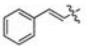
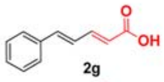
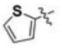
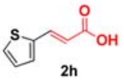
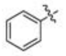
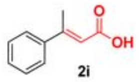
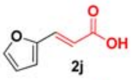
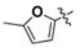
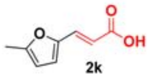
(12) It is very interesting to note that the reactivity of alkylidene derivatives of Meldrum acid with Lewis acid in CH_3NO_2 is significantly different from the result that we observed with a Lewis acid and H_2O in CH_3NO_2. An excess amount of water leads to a mixture of products. Please see: Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440–454.

Scheme 1. Decarboxylation of Methylene Tethered Cyclic 1,3-Diesters with $FeCl_3 \cdot 6H_2O$ and H_2O (1 equiv) in CH_3NO_2

entry	R^1	R	1 yield (%)	2	MW yield (%)	heating yield (%)
1		H	1a (87)	 2a	88	87
2		H	1b (67)	 2b	67	77
3		H	1c (84)	 2c	84	87
4		H	1d (90)	 2d	90	87
5		H	1e (90)	 2e	90	87
6		H	1f (71)	 2f	76	83
7		H	1g (79)	 2g	79	87
8		H	1h (84)	 2h	84	87
9		Me	1i (91)[e]	 2i	91	87
10		H	1j (82)	 2j	82	81
11		H	1k (66)	 2k	66	76

[a] 1 equiv of H_2O. [b] CH_3NO_2 as solvent. [c] Microwave irradiation (2.5 GHz, 250 W). [d] We observed more than 99% *E*-selectivity in (**2a**–**2g**, **2i**–**2k**); however **2h** gave an $E/Z = 87{:}13$ ratio. [e] **1i** was synthesized using $TiCl_4 \cdot THF$ complex, pyridine.

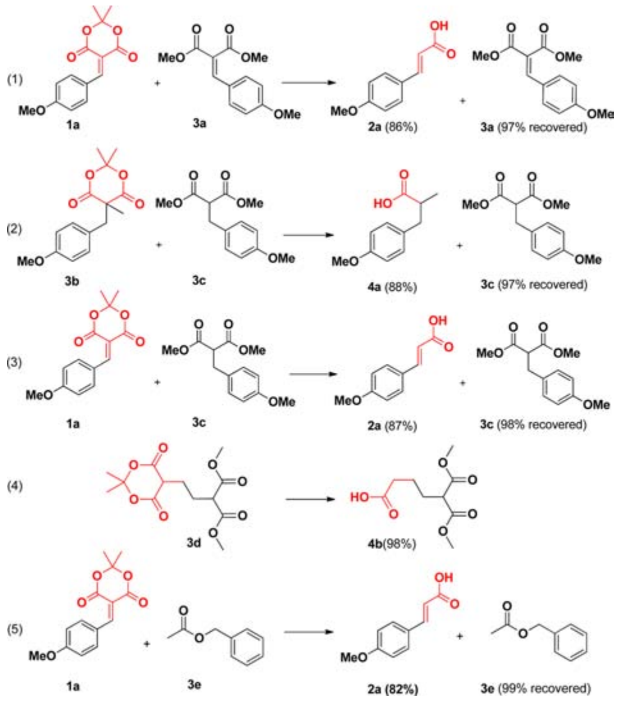
furnished the corresponding α,*β*-unsaturated acid (**2i**) in just 3 min in very good yield (91%). To our knowledge this is the first protocol which effectively demonstrated the synthesis of α,*β*-unsaturated carboxylic acids from the corresponding ketones. Further we demonstrated the gram scale synthesis of **2a** (80% yield) starting from **1a** (53 g) using this catalytic protocol under refluxing conditions (110 °C, 6.5 h) in a round bottomed flask at ambient pressure.

The catalyst system showed good functional group compatibility, as many functional moieties were tolerated under these reaction conditions.

There is a huge demand to develop methods that can be utilized for the conversion of biomass derived molecules into more useful and renewable products. A practical C–C bonding approach to make mildly oxygenated hydrocarbons (C_8–C_{15}) from biomass derived molecules would be very useful in generating gasoline and diesel fuels.[13] Biomass derived molecules such as furfural and 5-hydroxymethylfurfural (HMF) have been converted into useful molecules such as α,*β*-unsaturated carboxylic acids for potential use in fuels.[14]

To date, there is an emphasis on converting biomass into useful chemical building blocks that may also be pivotal to chemical manufacturing. It is known that some of α,*β*-unsaturated carboxylic acid derivatives obtained from biomass derived aldehydes are subsequently converted into fuel additives in the gasoline range C_8–C_9. Owing to this importance, we demonstrated the utility of biomass derived aldehydes such as furfural and 5-methylfurfural for the efficient preparation of corresponding α,*β*-unsaturated acids (**2j**, **2k**) in good yields (81–82%, TON 16 400, TOF 40.5/min; 66–76% TON 13 200, TOF 26.4/min) using the optimized protocol under both microwave and conventional heating. Owing to the industrial importance of such molecules, the utility of the method is further demonstrated by synthesizing **2j** in gram scale (1.5 g) starting from **1j** using a catalytic protocol under refluxing conditions (110 °C, 3 h) in a round bottomed flask at ambient pressure resulting in **2j** in 85% yield (TON 85 000;

Scheme 2. Chemoselective Decarboxylation of Cyclic 1,3-Diesters with Other Substrates[a,b]



[a] Substrates were treated in equimolar ratio (1:1). [b] Reactions were carried out using $FeCl_3 \cdot 6H_2O$ (0.005 equiv)–H_2O (1 equiv) in CH_3NO_2 under microwave condition (2.5 GHz) for 3–5 min.

TOF 283/h). It is important to note that the catalyst ($FeCl_3 \cdot 6H_2O$) loading was reduced to 0.1 mol % in this reaction

In order to verify the efficiency of this protocol, we further embarked on the study of selective decarboxylation of various substituted cyclic 1,3-diesters with varied substrates.

Competitive experiments were carried out with alkylidine acyclic 1,3-diesters (eq 1), substituted acyclic 1,3-diesters (eqs 2–4), and an ester (eq 5) under optimized reaction conditions to demonstrate the selectivity of the catalyst system for cyclic 1,3-diesters (Scheme 2).

Initially for the competitive experiments we subjected derivatives of acyclic 1,3-diesters (**3a**, **3c**) and cyclic 1,3-diesters (**1a**, **3b**) using the optimized catalytic protocol $FeCl_3 \cdot 6H_2O$ (0.005 equiv, 0.5 mol %)–H_2O (1 equiv) in CH_3NO_2 under microwave irradiation for 3–5 min. It is quite remarkable that a catalyst system reacted exclusively with substituted cyclic 1,3-diesters (**1a**, **3b**) and competitive substrates were significantly unreactive. Unreacted substrates were recovered in almost quantitative yields (eqs 1–3). Also when compound **3d** containing both cyclic and acyclic 1,3-diester moieties (eq 4) was treated with the catalyst system, the cyclic 1,3-diester underwent selective decarboxylation to afford compound **4b** in 98% yield (Scheme 2).

Unlike previously reported protocols this one-pot catalytic approach is certainly very convenient, practical, cost-effective, and environmentally friendly. Moreover, this method proved to be reproducible on gram scale (1.5–53 g), as exemplified by the synthesis of compounds (**2j**, **2a**) of industrial importance.[15]

In summary, a methodology to achieve α,β-unsaturated carboxylic acids from derivatives of cyclic 1,3-diesters (Meldrum's ester) using a highly efficient catalytic protocol containing an inexpensive $FeCl_3 \cdot 6H_2O$ has been described. The methodology reported herein is very rapid, with volatile byproduct formation, and is reliably selective. This selective decarboxylation route enables a gram-scale synthesis, using a very low catalyst loading (0.001 equiv). This simple approach gives easy access to a variety of α,β-unsaturated acids in good to excellent yields. The approach opens an avenue for a whole range of new chemical entities and molecules of high industrial value. It effectively augments the biomass derived aldehydes into precursors for fuel additives.

Supporting Information Available. Experimental procedures and ^1H, ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Provisional Patent filed in India, App No.: 2437/MUM/2013.

The authors declare no competing financial interest.