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A Practical and Highly Efficient Synthesis of 1,2,4,5-Tetrasubstituted Imidazoles Using 2-Ethylhexanoic Acid as a Reusable Organocatalyst and Reaction Medium

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ABSTRACT

2-Ethylhexanoic acid has been used as a dual solvent-catalyst for the one-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles. This naturally occurring and widely produced fatty acid exhibited remarkable catalytic activity and was easily separated by extraction. The reusability of this catalytic medium was tested by recovering the catalyst and using it again in the reaction up to four times with no significant drop in activity. The catalyst is commercially available, of low cost and ecofriendly, offering short reaction times (30-90 min), very good to excellent yields (88-93) and a straightforward workup procedure.

KeyWords: *2-ethylhexanoic acid, 1,2,4,5-tetrasubstituted imidazoles, organocatalyst, multicomponent reaction*.

1. INTRODUCTION

In spite of the research advances made in green chemistry over the past 20 years and the fact that it is considered a major scientific discipline, this field of chemistry is still in a nascent stage [1,2]. For synthetic organic chemists both in academia and industry, the development of more environmentally benign processes has become one of the most fundamental challenges. The use of conventional organic solvents in synthetic procedures results in an energy-intensive processes during their recovery while their volatility makes them difficult to contain [3,4]. Latest innovations for replacing organic solvents include ionic liquids [5], supercritical carbon dioxide [6], perfluorinated solvents [7], polyethylene glycol polymers [8] and bio-based solvents [9]. However, there is widespread debate over the relative greenness of some of the mentioned reaction mediums [2]. As a result, constant attempts are still being made for discovering safer solvents.

On the other hand, development of efficient catalysts that are reusable is another foundational pillar of green chemistry. In recent years, organocatalysis has emerged as a viable tool in organic synthesis since it provides advantages such as a metal free nature, reduced toxicity, lack of sensitivity to moisture and oxygen, mildness and availability of the catalyst [10]. However, a practical procedure using organocatalysts should involve facile separation of the catalyst from reaction products as well as recovery and reuse of the catalyst since its common high

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[♠] Corresponding author, e-mail: rhekmatus@yahoo.com loading levels could make the process less atom economical [11]. Although realizing these ambitions could raise the interest for more applications of these catalysts in large-scale operations, few attempts have been made toward designing more efficient strategies. In some cases the organocatalyst was separated by tedious column chromatography [11] or solid phase extraction [12]. Recently, several investigations on the preparation of solid-supported organocatalysts were focused on more convenient separation and recycling of the catalyst including silica [13], resin [14], polystyrene [15] and poly(propyleneimine) dendrimer [16] supported organocatalysts and also a poly(*N*-heterocyclic carbene) as a self-supported organocatalyst [17]. In spite of all these alternatives, developing more feasible organocatalytic processes is still highly desirable.

2-Ethylhexanoic acid (2-EHA) is a dense, clear, colorless, high boiling liquid and is the most highly produced commercial aliphatic carboxylic acid [18] (Figure). This oily compound belongs to the family of branched fatty acids and is an endogenous compound [19] which is also found in some fruits such as grapes [20]. Its ester derivatives are located in cellular membranes that induce membrane integrity and stability [21]. Beside various acknowledged biofunctions attributed to 2-EHA, it is frequently used in industry as co-solvent, wetting agent in emulsions and as defoamer in pesticides. Moreover, it is one of the key ingredients in the preparation of paint driers, synthetic lubricants, metal soaps and PVC stabilizers. Most of these applications are accounted for by its lipophilicity due its relatively long hydrocarbon chain combined with the unique properties of the metal salts or ester derivatives [22].

Simple organic acids could be included as one of the major categories of organocatalysts. In this paper, an organocatalytic process is demonstrated using 2-EHA which presents dual solvent-catalyst functions. A combination of reduced toxicity and wider temperature range of solid acids and the motility of liquid acids is the main utility of 2-EHA which enables this organic acid could compete with the state of the art ionic liquids. Indeed, noncorrosive and green nature, low flammability, quite low cost, commercial availability and reusability are the promising advantages that give way to multi-purpose applications of this acid in organic transformations.

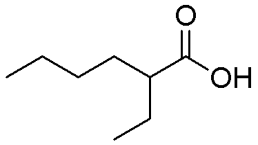
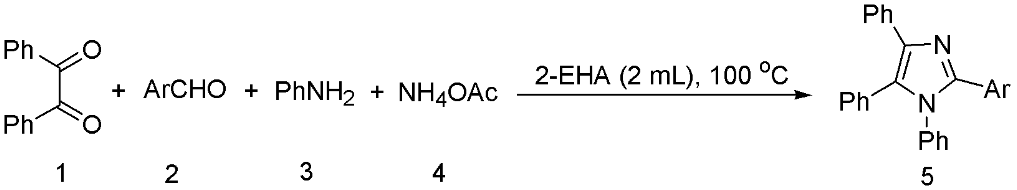


Figure 1. 2-Ethylhexanoic acid (2-EHA)

In continuation of our ongoing investigations toward novel organocatalytic multicomponent reactions for the construction of heterocycles [23,24], and optimizing reaction conditions for more facile synthesis of substituted imidazoles [25], a versatile methodology for the four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles, as a privileged structure, occurring in a wide range of pharmaceutical compounds [26] and natural products [27] is presented using 2-EHA as a green catalytic reaction medium. 2-EHA exhibited pronounced catalytic activity in terms of reaction times and yields. Pure target compounds were obtained via straightforward workup procedure and 2-EHA was easily separated by simple extraction (Scheme).



Scheme 1. One-pot, four-component synthesis of 1,2,4,5-tetrasubstituted imidazoles using 2-EHA as a catalytic reaction media.

2. EXPERIMENTAL

All the chemicals were purchased from Merck and Sigma-Aldrich companies. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}H-NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer, using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded on the FT-IR Bruker Tensor 27.

Table 1. Synthesis of various 1,2,4,5-tetrasubstituted imidazoles via a four-component reaction utilizing 2-EHA as catalytic reaction media.[a]

Entry	Ar	Product	Time(min)	Yield(%)	Mp(^oC)	
					Found	Reported
1	C_6H_5	5a	30	91	221	221[28]
2	4-MeC_6H_4	5b	60	93	188	185-188[29]
3	4-$NO_2C_6H_4$	5c	30	90	193	191-193[30]
4	3-$NO_2C_6H_4$	5d	40	93	245-246	244-246[28]
5	2-OHC_6H_4	5e	20	89	256	255-257[28]
6	4-OHC_6H_4	5f	60	90	282	280-281[28]
7	4-$OMeC_6H_4$	5g	45	92	184	180-182[31]
8	4-ClC_6H_4	5h	60	92	159-160	160-161[29]
9	4-BrC_6H_4	5i	90	88	150-153	152-154[31]

[a] Reaction Conditions: aldehyde (1 mmol), aniline (1 mmol), benzil (1 mmol), ammonium acetate (1 mmol), 2-EHA (2 mL), stirring at 100 °C

2.1. General procedure for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by 2-EHA:

To a stirred solution of aldehyde (1 mmol) in 2-EHA (2 mL), aniline (1 mmol, 93.13 g), ammonium acetate (1 mmol, 77.08 g) and benzil (1 mmol, 210.23 g) were added. The reaction mixture was heated to 100 °C for the time indicated in Table 1. After completion of the reaction as monitored by TLC, using petroleum ether: ethyl acetate (4:1) as eluent, the reaction mixture was cooled to room temperature. Next, water (5 mL) and petroleum ether (5 mL) were added and the precipitated product was filtered, washed with petroleum ether (5 mL) and recrystallized from ethanol to give the pure title compounds. All of the products were known and their physical data were compared with those of authentic samples in the literature [26-29] and found to be identical in all respects.

3. RESULTS AND DISCUSSION

On the outset, the four-component reaction of benzaldehyde, aniline, benzil and ammonium acetate with 1:1:1:1 molar ratio was determined as the model reaction to optimize reaction conditions. In the first step, the model reaction was performed in the presence of different quantities of 2-EHA at 100 °C. As shown Table 2, 2 mL of 2-EHA was found to be the best, affording 91 percent of the desired product within 30 min. Applying higher amounts of 2-EHA resulted in lower yields, probably because of the excessive dilution of the reaction system. To further optimize reaction conditions, we decided to run the model reaction in 2 mL of 2-EHA and at various temperatures. The outcome of the reaction showed a dependence on temperature. Lower temperatures resulted in remarkable reduction of yields while temperatures higher than 100 °C had no effect on reaction profiles. Therefore, 100 °C was determined as the optimized temperature.

With these results in hand, we next examined the scope and generality of the method using a variety of substituted aromatic aldehydes. Under the optimized conditions, irrespective of the substituent present on the aromatic ring of the aldehyde moiety, corresponding products were obtained in very good to excellent yields within relatively short reaction times (Table 1). Furthermore, the reaction profiles were clean and no side products were detected.

Table 2. Optimizing reaction conditions for the model reaction of benzaldehyde, aniline, benzil and ammonium acetate.

Entry	Amount of 2-EHA(mL)	Temperature(^oC)	Time(min)	Yield(%)
1	0.5	100	30	56
2	1	100	30	78
3	2	100	30	91
4	3	100	30	87
5	2	25	120	62
6	2	80	30	77
7	2	120	30	89

After each run, the reaction mixture was cooled to room temperature and then water and petroleum ether were added. Next, the precipitated product was filtered. For investigating the reusability of 2-EHA, the organic phase in the filtrate was simply extracted and evaporated to recover 2-EHA almost quantitatively. The recycled 2-EHA promoted the model reaction in a similar manner without remarkable loss in activity (Table 3).

Table 3. Evaluating the reusability of 2-EHA

Run	1	2	3	4
Yiled(%)	91	89	90	88

In order to prove the merit of 2-EHA functioning as both catalyst and solvent in the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles, the results obtained for the model reaction in the present work have been compared with previously reported catalysts in Table 4. The outcome illustrates that the yield obtained using 2-EHA is almost comparable to other catalysts. Surprisingly, reaction time is significantly shorter than any other catalyst presented so far in the literature.

Table 4. comparison the efficiency of 2-EHA with other reagents utilized in previously reported methods for the synthesis of 1,2,4,5-tetrasubstituted imidazoles

Entry	Catalyst	Condition/Solvent	Time(h)	Yield(%)	[Ref.]
1	SiO_2	Solar Heating/CH_2Cl_2	2	88	[29]
2	Montmorilonite K10	Reflux/C_2H_5OH	1.5	75	[31]
3	Zeolite	Reflux/C_2H_5OH	1	80	[31]
4	Nano Sulfated Zirconia	Reflux/C_2H_5OH	0.75	87	[31]
5	$InCl_3.3H_2O$	RT/CH_3OH	6.4	83	[32]
6	K10 Supported Ti	120 ^oC/Solvent free	2.5	78	[33]
7	Nano $TiCl_4.SiO_2$	110 ^oC/Solvent free	0.5	82	[34]
8	37% $BF_3.SiO_2$	140 ^oC/Solvent free	2	89	[35]
9	DABCO	60-65 ^oC/t-BuOH	12-15	82	[36]
10	PEG-400	110 ^oC/PEG-400	6	86	[37]
11	2-EHA	100 ^oC/2-EHA	0.5	91	-

In conclusion, taking into account the economical, environmental and practical aspects in mind, any liquid may be used as solvent if it meets the aforementioned standards. 2-EHA a quite low-priced and widely produced and utilized fatty acid in industry, was introduced as a catalytic reaction medium for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles. The catalyst is readily recycled without significant loss in catalytic activity. Furthermore, together with its catalytic role, 2-EHA could be considered as an extension of traditional organic solvents with the advantage of being nontoxic and fully recyclable.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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