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ARTICLE

Triethylamine: A Potential *N*-Base Surrogate for Pyridine in Knoevenagel Condensation of Aromatic Aldehyde and Malonic Acid

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Hitesh. S. Pawar[a], Adhirath. S. Wagh[a] and Arvind. M. Lali[a, b*]

Cinnamic acids are intermediates with significant potential for synthesis of several industrially important chemicals. Classically,cinnamic acids are produced through Knoevenagel condensation of aromatic aldehydes and malonic acid in presence of an organocatalyst and large presence of carcinogenic pyridine.An alternative pyridine free reaction scheme for Knoevenagel condensation of malonic acid and aromatic aldehydes was investigated replacing pyridine with an aliphatic tertiary amine surrogate in toluene as reaction medium. Of the three aliphatic tertiary amines used namely, triethyl amine (TEA), trioctyl amine (TOA) and tributyl amine (TBA), only TEA afforded pyridine comparable yields of cinnamic acids. Validation thourgh a computational analysis is attempted to provide an explanation for the observed role of TEA as aliphatic *N*-base instead of TBA and TOA. The use of TEA as a mild base in place of pyridine can be seen as playing a dual role of a base catalyst as well as a phase transfer agent evidenced by the in-process ATR-FITR spectroscopy. Use of TEA-toluene system in place of pyridine can be seen resulting in a process that affords ease of handling, separation and recycling of the solvent and the catalyst.

Introduction

Carbon-carbon double bond synthesis of α, β-unsaturated carbonyl compounds by employing Knoevenagel condensation is a widely used method in organic synthesis and allows production of variety of cinnamic acids [1]. Synthesis of cinnamic acids via Knoevenagel condensation has received significant attention in both academia and industry on account of the broad spectrum of applications in cosmetics, flavors, perfumery products, pharmaceuticals, agrochemicals, and pharmaceuticals intermediates production sectors[2]-[6]. Several ester derivatives of cinnamic acids have proven significant for their antitumor, anti-inflammatory, and sunscreen actions [7] (Fig.1). Conventionally, cinnamic acids and their derivatives are synthesized by condensation of aromatic aldehydes and active methylene compounds in the presence of organic and/or inorganic base [8],[9]. The condensation of aromatic aldehyde and malonic acid in the presence of a base is the well-known Knoevenagel condensation reaction [10]. Usually, ammonia, primary or secondary amines and their salts are employed as base [11]. Use of piperidine as organo-catalyst with pyridine doubling as a solvent as well as a base is the most frequently used process strategy in conducting the Knoevenagel condensation [12].

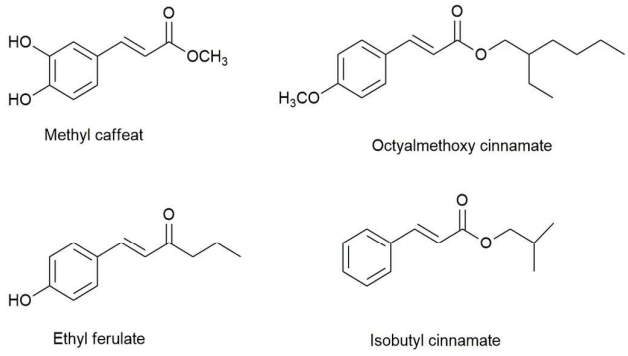


Fig.1 Several significant pharmaceutically active cinnamic acid esters derivatives

Reports however continue to be published as chemists attempt to improve the strategy to render it less energy intensive, green, safe and rapid. Mcnulty et al [13] compared condensation of malonic acid and aromatic aldehydes in the presence of pyridine and piperidine using ultrasound and conventional heating. Kappe et al [14] reported use of silicon carbide vessel for microwave assisted condensation of malonic acid and aromatic aldehyde. In another report Kappe et al [15] suggested use of microwave reactors as well as silicon carbide autoclave for synthesis of cinnamic acids in presence of

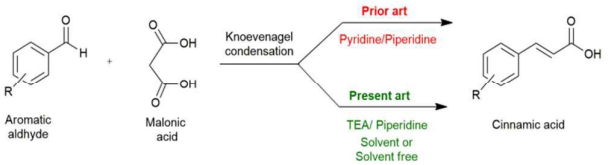
[a] DBT-ICT Centre for Energy Biosciences, Institute of Chemical Technology, N.P.Marg Matunga (w) Mumbai 400 019.
[b] Department of Chemical Engineering, Institute of Chemical Technology, N.P.Marg Matunga (w), Mumbai 400 019.

Electronic Supplementary Information (ESI) available: [details of product characterization ATR-FTIR, HR LCMS, NMR and HPLC analysis]. See DOI: 10.1039/x0xx00000x

piperidine in ethanol. In spite of these advancements replace of pyridine is of crucial importance due to its unpleasant effects.

Use of pyridine is not convenient from many angles like environmental and safety due to its carcinogenic effect, hazardous nature and complexity in handling at bulk scale [16], [17],[18]. Thus, attempts have also been directed towards devising pyridine free protocols for synthesis of cinnamic acids. Several metal salts as base catalysts have been explored for this purpose. Kumar et al [19] reported use of ammonium acetate as a base for microwave assisted synthesis of cinnamic acids, and later, the same group [20] reported bismuth chloride as an efficient non-toxic catalyst for production of cinnamic acids under solvent free and microwave heating conditions. Valizadeh et al [21] reported ammonium chloride as a base catalyst under microwave assisted heating. Gupta et al [22] reported tetrabutylammoniumbromide (TBAB) and K_2CO_3 under microwave irradiation. However, while use of heavy metals for synthesis of pharmaceuticals, food and cosmetic products is not encouraged [23],[24] and use of metal free bases continue to attract attention, use of microwave for synthesis continues to face scalability issues. Zhang et al [25] reported β-alanine and 1, 8-diazabicyclo [5.4.0] Andes-7-ENE (DBU) as an efficient catalytic system for Knoevenagel condensation of benzaldehyde and malonic acid. The use of non-complex, non-expensive and metal free base catalyst would be adding a significant contribution for development of techno-commercial and eco-friendly process for production of cinnamic acids.

In the present work an attempt is made to conduct pyridine free Knoevenagel condensation reaction of aromatic aldehydes and malonic acid using TEA in toluene instead of pyridine as the base (Scheme 1). Replacement of pyridine with TEA is proposed as advantageous because of three reasons (a) pyridine has one of the lowest known LD_{Lo} at 500 ppm; (b) pyridine has a narcotic and carcinogenic effect its vapors concentrations of above 3600 ppm pose a health risk; and (c) it has several toxic effects with a maximum allowable concentration in air being 5ppm. TEA was considered as relatively safer base as compared to pyridine especially in higher boiling solvent like toluene besides expected to behave as a phase transfer agent aiding dissolution of malonic acid in toluene, and also as a base in the presence of catalytic amount of piperidine. The condensation of benzaldehyde and malonic acid was studied as a model reaction for process optimization and then extended to other derivatives of benzaldehyde to obtain respective cinnamic acids.



Scheme 1. General reaction scheme for pyridine free synthesis of cinnamic acid

Results and discussion

Dual role of Triethylamine

Knoevenagel condensation traditionally uses pyridine as a solvent as well as a base in presence of catalytic amounts of piperidine [26],[27]. In addition, use of pyridine in Knoevenagel reaction as a base as well as a neat solvent has been reported to facilitate*in situ* decarboxylation of the dicarboxylic acid [28].Sakai et al[29] have recently reported incomplete decarboxylation of dicarboxylic acid in presence of In (III) catalyst. In present study we have explored use of TEA as potential *N*-base surrogate for pyridine free formation of cinnamic acid. Thus, pyridine free model reaction using benzaldehyde and malonic acid was conducted in toluene as reaction medium using three different tertiary amines (TEA, TOA and TBA) in presence of catalytic amounts of piperidine. The results are shown in Table 1.

Table1. Influence of different tertiary amines on yield.

Sr.No	Reaction system	Yield[a] (%)	Time (h)	Reference
1	TEA: Piperidine	90	3	This work
2	TOA: Piperidine	n.d.	5	This work
3	TBA: Piperidine	n.d.	5	This work
4[b]	Pyridine: Piperidine	99	3	13
5[c]	Pyridine: Piperidine	97	0.03	26
6	Pyridine: Piperidine	75-85	24	37

Reaction conditions: Benzaldehyde (4.7 mmole), Malonic acid (4.7 mmole), Amine (6.7 mmole), Piperidine (0.8 mmole) Toluene (5 ml), reflux; [a]isolated yield; [b]Ultrasound assisted; [c]Microwave assisted.

It was found that of the tested amines in combination with catalytic amount of piperidine only the use of TEA afforded a yield of cinnamic acid comparable to those obtained with the conventional processes using pyridine. The results obtained indicated a significant trend. Malonic acid is not soluble in toluene and did not show any reaction by itself and also with TBA and TOA. Of the tested aliphatic *N*-base TEA alone was found to favor the reaction indicating that it not only helped solubilize the acid but also helped shifting reaction equilibrium through formation of a toluene soluble complex (Scheme 2). Absence of any reaction in TBA and TOA indicated that increasing carbon chain length on tertiary amine hindered soluble complex for further condensation thereby not being able to catalyze the reaction. Computational analysis on Discovery Studio 3.5 software was used to explore the energy minimized conformations of respective amine and malonic acid ion pair complexes under CHARMm force field. The analysis clearly brought out the relative hindrance of $-CH_2$ proton of malonic acid for the formation of carbanion for further condensation with aromatic aldehyde (Fig.2). The energy minimized structure of $-CH_2$ proton of malonic acid was found to be sterically hindered by C_2,C_3, and C_4 protons of TBA and C_7 and C_8 protons of TOA. Whereas in case of TEA such hindrance was absent due to shorter carbon chain.

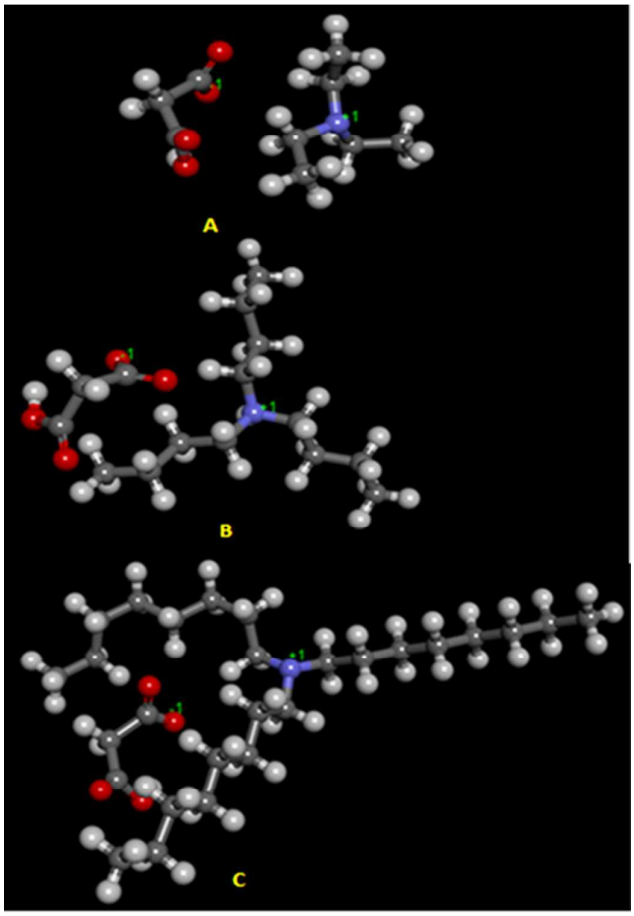
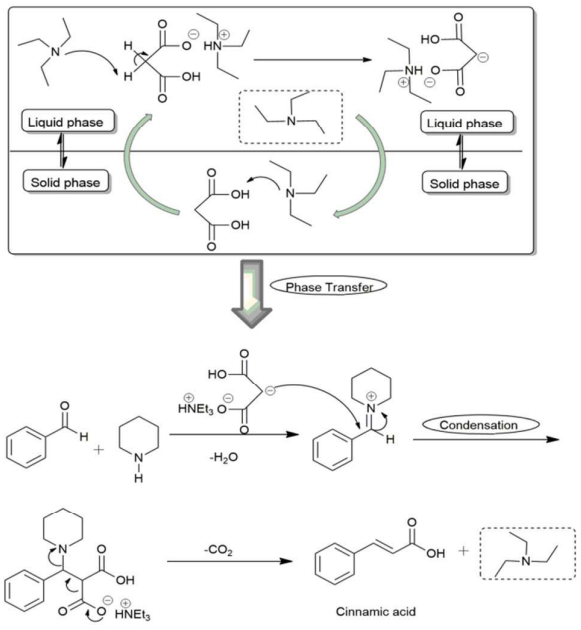


Fig 2.Energy minimized conformations of malonic acid complex with A) TEA B) TBA C) TOA showing the steric hindrance of malonic acid.



Scheme 2 Possible mechanism for pyridine free Knoevenagel condensation via phase transfer catalysis by using TEA.

The possible mechanism involving the dual role of TEA as a phase transfer catalyst as well as a base is depicted in Scheme 2. It can be speculated that formation of cinnamic acid occurred in three steps: a) Phase transfer with carbanion formation; b) Condensation; and c) Elimination. Formation of malonic acid and TEA complex was confirmed by ATR-FTIR spectroscopy (Fig. 3). The ATR-FTIR spectra overlay of malonic acid, the intermediate (malonic acid-TEA complex) and TEA clearly indicates the diminishing of broad characteristic peak (-COOH) around 3000 cm^{-1} in FTIR spectrum of the intermediate. The condensation step with decarboxylation was monitored by on FTIR analysis of intermediate and reaction mass after completion of reaction (Fig.4).The FTIR overlay of intermediate and reaction mixture indicates the presence of characteristic peak for α, β-unsaturated carboxylic acid at 3500cm^{-1}.

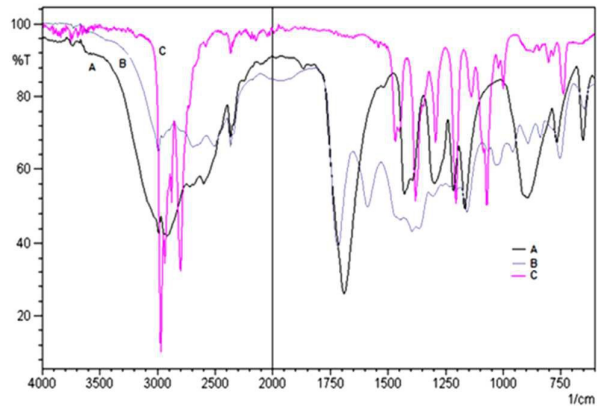


Fig.3ATR -FTIR of overlay of malonic acid, malonic acid TEA complex and TEA, A: Malonic acid, B: Malonic acid–TEA complex, C: TEA.

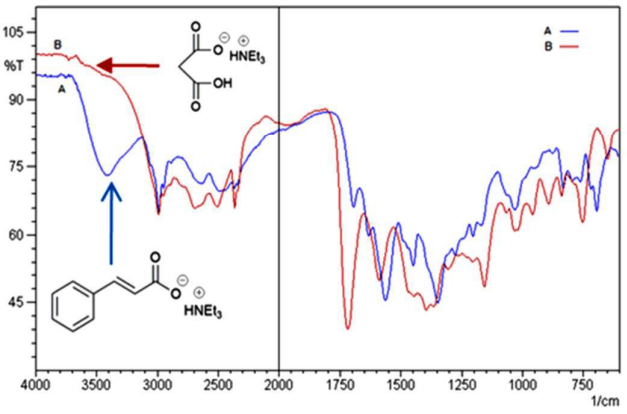


Fig.4 ATR-FTIR overlay of malonic acid-TEA complex and malonic acid (A: reaction mass, B malonic acid-TEA complex)

Influence of molar ratio of TEA and Piperidine

Optimization around stoichiometric molar ratios of involved reactants plays a crucial role for developing economical as well as environmentally safer process[30],[31]. However, optimal concentration of a catalyst often defies stoichiometry [32]. In the present protocol, piperidine played the role of a base

catalyst while TEA played the dual role of a catalyst as well as a base promoter. In order to optimize the molar ratio of TEA and piperidine, the model reaction between benzaldehyde and malonic acid was conducted in presence of different molar ratios. The results are shown (Table 2).

In order to optimize the molar ratios, the molar ratio of TEA to benzaldehyde was varied from 0.5 to 1.5 with constant molar ratio of piperidine (0.18), and the molar ratio of piperidine to benzaldehyde was varied from 0 to 0.36 with constant molar ratio of TEA (1.3). In absence of piperidine there is no formation of cinnamic acid. Thus it was notated that the addition of catalytic amount of piperidine significantly improves the yield. The addition of piperidine promotes the condensation step during formation of cinnamic acid (Scheme 2). In case of TEA concentration it was found that increasing TEA concentration initially increased the yield of cinnamic acid but then decreased remarkably after an optimum. The same case was seen to happen with concentration piperidine as well since the optimal ratio of TEA and piperidine significantly improves the cinnamic acid yield. The decrease in yield of cinnamic acid at higher concentrations of both TEA and piperidine may be attributed to highly basic conditions that favor double decarboxylation of cinnamic acid. This is in line with the reported observations with respect to piperidine concentrations used in pyridine [12].

Table 2. Influence of molar ratio of TEA and Piperidine.

Sr.No	Catalyst used	Molar ratio	Yield[a] (%)
1	TEA	0.5	21.28
		1	34.04
		1.3	90.32
		1.5	53.19
2	Piperidine	0	0
		0.09	21.28
		0.18	90.32
		0.36	55.32

[a] Isolated yield. Reaction condition: Benzaldehyde (4.7 mmole), Malonic acid (5.2 mmole), Toluene (5 mL) reflux for 2h.

Influence of solvent

Use of a base miscible benign solvent in place of neat pyridine or TEA was considered useful for reducing volatility of the reaction mixture and rendering the system safer to handle[33],[34]. In order to investigate the role of solvent, non-polar solvent toluene; moderately polar solvent tetrahydrofuran (THF); polar solvent methanol; and polar aprotic solvent acetonitrile (ACN) were selected. The influence of solvent choice on the yield of cinnamic acid is seen in Fig. 5.

It was found that of the tested solvents, the best yield of cinnamic acid was obtained in toluene. THF, ACN and methanol did not give significant reaction possibly due to the higher stability of carbanion of malonic acid in these solvents through hydrogen bonding thus resulting in suppression of the next condensation step (Scheme 2) and preventing nucleophilic attack by malonic acid on carbonyl carbon of aldehyde. Such a stability of malonic acid carbanion was not probably possible in toluene. Further, toluene also provides a medium since TEA and its quaternary ammonium salt with malonic acid are both soluble in toluene and thus nucleophilic addition on the partly soluble aldehyde can be expected to take place effectively with elimination of water that could be distilled off as azeotrop with toluene. Since totally solvent free reactions offer advantages and are preferred as green and techno-economically processes [35],[36] the Knoevenagel condensation under investigation was also studied under solvent free reaction condition with TEA acting as reaction medium. It was found that solvent free reaction conditions also gave good yield of cinnamic acid comparable with yield obtained in toluene (90%).

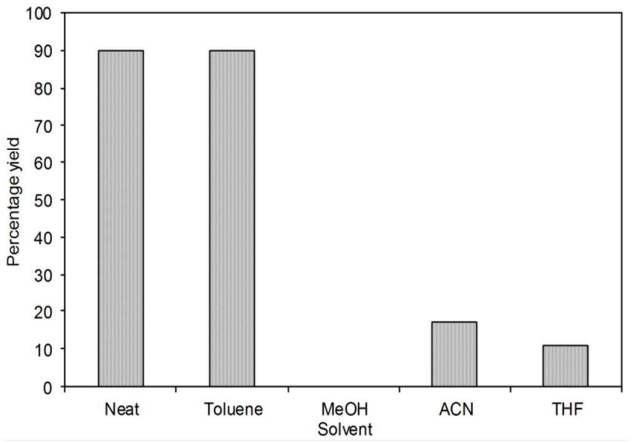


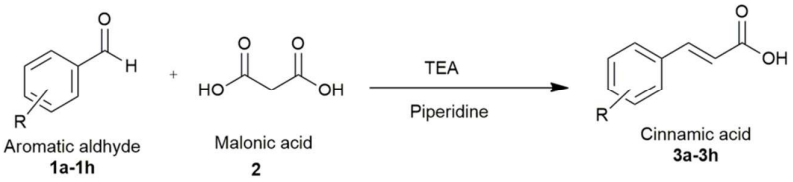
Fig 5. Influence of solvent on percentage yield of cinnamic acid in presence of pyridine free condition.

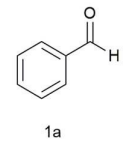
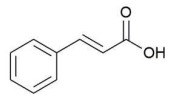
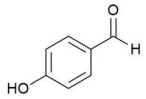
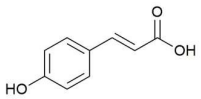
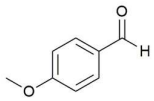
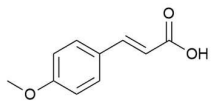
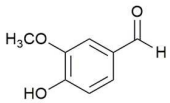
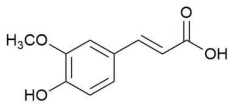
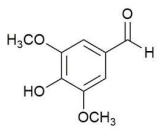
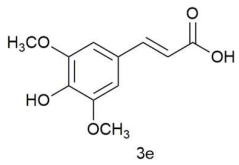
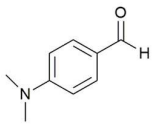
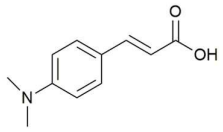
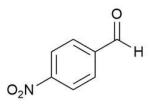
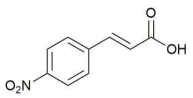
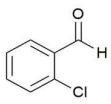
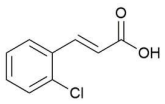
Use of different Substrates

In order to explore the scope of the present approach of using TEA in place of pyridine, various derivatives of aromatic aldehydes wi.th different electron donating and withdrawing substituents were screened under at the benzaldehyde optimized reaction conditions. The results on the influence of various substituents on the yield and purity of respective cinnamic acid are summarized in Table 3. It was found that of the tested aromatic aldehydes, aldehydes having electron donating as well as withdrawing substituent provided good to excellent isolated yields of the respective cinnamic acids.

The structural confirmations of all the synthesized derivatives of cinnamic acid were performed by using ATR FT-IR (Attenuated total reflection Fourier transform spectroscopy), high resolution LC-MS, and ^{1}H-NMR analysis. It was found that the all the compounds matched well to their respective characteristic spectral data. In order to confirm the purity of synthesized cinnamic acids, all the isolated but unpurified products were analyzed for their HPLC purity and all showed excellent HPLC peak purities (Table. 3). Thus, the present methodology was seen to provide cinnamic acids in high yields and purities without formation of side products.

Table 3. Substrate study for pyridine free Knoevenagel reaction for synthesis of cinnamic acids[a]



Sr.no	Substrate	Product	Yield[b] (%)	HPLC Purity[c](%)
1	 1a	 3a	90	96
2	 1b	 3b	88	99
3	 1c	 3c	89	100
4	 1d	 3d	87	99
5	 1e	 3e	77	100
6	 1f	 3f	80	100
7	 1g	 3g	84	100
8	 1h	 3h	89	98

[a]Reaction conditions: aldehyde (1eq), malonic acid (1eq), TEA (1.3eq), piperidine (0.18eq), reaction time 2h, reflux temperature.[b]Isolated yield, [c]HPLC area% purity.

Conclusions

A new strategy for synthesis of cinnamic acids was successfully investigated using a pyridine free Knoevenagel condensation in the presence of triethlyamine, as neat solvent or in combine action with toluene with catalytic amounts of piperidine. To the best of our knowledge this is the first report on exploring triethlyamine as a base in place of pyridine for condensation of aromatic aldehyde and malonic acid. The *in situ* FTIR analysis was performed to investigate the reaction mechanism. It was found that the triethlyamine also plays a dual role of a base as well as a solubilizing agent for promoting the reaction both in toluene and TEA itself. The investigated methodology provides acceptable yields of the different cinnamic acids synthesized while being carried out in toluene as well as under solvent free conditions with low formation of by-products.

Experimental

All the chemicals and reagents were used are of synthetic grade chemicals and obtained from commercial suppliers and used without further purification. The solvents used for the reactions are of commercial grade pure solvents. Solvents used for HPLC analysis is of HPLC grade solvents. The entire samples before the HPLC analysis were diluted at appropriate concentrations and filtered through 0.2 micron PTFE filter paper before HPLC analysis. The structural characterization of synthesized compounds was obtained after the recrystallization.

General process for preparation of cinnamic acid

In a four necked round bottom flask with reflux condenser, thermometer, and addition funnel, toluene (5mL), malonic acid (4.7mmole), and triethlyamine (6.1mmole) were mixed for 3-4min. Aromatic aldehyde (4.7mmole) and piperidine (0.8 mmole) were added slowly with vigorous stirring. Then the reaction mixture was heated for 2-3h at reflux temperature. The reaction was continuously monitored after every half hour by TLC. After the complete consumption of aryl aldehyde, the resulting reaction mixture was taken for vacuum distillation to remove triethlyamine and solvent. The resulting viscous liquid was cooled at room temperature. Then 5mL of 5 % bicarbonate was added slowly through addition funnel and stirred for 10min. The resulting reaction solution was washed by 10ml of ethyl acetate and aqueous layer was collected. The resulting aqueous layer was cooled at 0ºC and then acidic pH of aqueous layer was adjusted by means of con HCl. The resulting solid was filtered, suck dried on suction pump and then dried at 60ºC in vacuum oven.

HPLC analysis

The HPLC analysis of all synthesized product were performed on Agilent 1200 HPLC system coupled with UV detector. The Agilent C18 column was used as stationary phase. The methanol water (30: 70) mobile phase was used for elution at 40ºC column temperature. All the samples were dissolved in mobile phase at appropriate dilution before HPLC analysis.

Product characterization

An NMR spectrum of the obtained product in DMSO-d_6 was obtained on a Bruker Advance 400 spectrometer (1H: 400 MHz, at 300 K). The spectrum was referenced against the NMR obtained internal standard and chemical shift are reported in ppm. The functional group characterization was done on a Shimadzu IR Prestige-21 instrument equipped with ATR-FTIR. The mass of obtained products was confirmed by high resolution mass spectrometer having Agilent Tripal-Quard LC MS 6520 coupled with Agilent 1200 HPLC. The FTIR, HR-LCMS and ^{1}HNMR characterization of all synthesized cinnamic acids (Table.3) was as,

Compound 3a: Cinnamic acid
FTIR (cm^{-1}): 2968, 2829, 1668 and 1624. HR LC-MS (cm^{-1}): 147.5000, 103.7000. ^{1}H-NMR: 7.97 (d, 2H), 7.68 (m, 2H), 7.50 (d, 2H), 6.63 (d, 1H).
Compound 3b: 4-Hydroxy cinnamic acid
FTIR (cm^{-1}): 3352, 2823, 1664 and 1625. HR LC-MS (cm^{-1}): 163.500, 110.800. ^{1}H-NMR: 9.80 (s, 1H), 7.76 (m, 1H), 7.48 (d, 2H), 6.99 (d, 2H), 6.39 (d, 1H).
Compound 3c: 4-Methoxy cinnamic acid
FTIR (cm^{-1}): 2935, 2841, 1672, 1624 and 1311. HR LC-MS (*m/z*): 177.5000, 133.7000, 118.7000. ^{1}H-NMR: 7.60 (d, 2H), 7.50 (d, 1H), 6.93 (d, 2H), 6.34 (d, 1H), 3.73 (s, 3H), 12.18 (s, 1H).
Compound 3d: 4-Hydroxy, 3-methoxy cinnamic acid
FTIR (cm^{-1}): 3427, 2968, 2837, 1685, 1614 and 1377. HR LC-MS (*m/z*):190.7000, 146.7000. ^{1}H-NMR: 7.70 (d, 1H), 7.48 (s, 1H), 7.45 (d, 1H), 7.16 (d, 1H), 6.44 (d, 1H), 3.93 (s, 3H).
Compound 3e: 4-Hydroxy, 3, 5-dimethoxy cinnamic acid
FTIR (cm^{-1}): 3429, 2968, 2841, 1687, 1618 and 1377. HR LC-MS (*m/z*): 223.6000. ^{1}H-NMR: 7.87 (d, 1H), 7.58 (s, 2H), 6.26 (d, 1H), 3.96 (s, 6H).
Compound 3f: 4-*N, N*-dimethyl amino cinnamic acid
FTIR (cm^{-1}): 2897, 2816, 1664, 1587, 1365 and 1186. HR LC-MS (*m/z*): 193.5000, 178.5000, 149.7000, 134.7000.H-NMR: 7.87 (d, 2H), 6.79 (d, 2H), 7.72 (d, 1H), 6.32 (d, 1H), 3.2 (s, 6H).
Compound 3g: 4-Nitro cinnamic acid
FTIR (cm^{-1}): 2939, 2835, 1631, 1616, 1516, 1423 and 1219. HR LC-MS (*m/z*): 192.6000, 148.7000. ^{1}H-NMR: 8.20 (d, 2H), 7.95 (d, 2H), 7.66 (d, 1H), 6.72 (d, 1H).
Compound 3h: 2-chloro cinnamic acid
FTIR (cm^{-1}): 2964, 2829, 1676, 1616, 1544, 1417 and 1276. HR LC-MS (*m/z*): 182.3000, 180.3000. ^{1}H-NMR: 7.51 (d, 1H), 6.58 (d, 1H), 7.44 (m, 2H), 7.89 (m, 2H).

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Notes and references

1 L. F. Tietze, U. Beifuss, *The Knoevenagel reaction In Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991.

2 H. M. Cho, M. Ueda, M. Tamaoka, K. Hamaguchi, Y. Aisaka, T. Kiso, R. Inoue, T. Ogino, T. Tatsuoka, T. Ishihara, I. Noguchi, S. Morita, *J. Med. Chem.* 1991,**34**, 1503-1505.
3 J. Nokami, K. Kataoka, K. Shiraishi, M.O safune, I. Hussain, and S. Sumida, *J. Org. Chem.* 2001, **66**, 1228-1232.
4 G. Kwak, M. Fujiki, *Macromolecules.* 2004, **37**, 2021-2025.
5 H. V.Chavan, B. P. Bandgar, *ACS Sustain. Chem. Eng.*2013, **1**, 929-936.
6 P. De, G.Y. Koumba, P. Constant, F. Bedos-Belval, H. Duran, N. Saffon, M. Daffe, M. Baltas, *J. Med. Chem.* 2011,**54**, 1449-1461.
7 P. Sharma, *J. Chem. Pharm. Res.*2011, **3**, 403-423.
8 T. Jackson, J.H Clark, D.J. Macquarrie, and J.H. Brophy, *Green Chem*. 2004,**6**, 193-195
9 R.K Hangarge, D.V. Jarikote, and M.S. Shingare, *Green Chem,* 2002, **4**, 266-268.
10 E. Knoevenagel, *Chem. Ber*. 1894, **27**, 2345.
11 O. Tanaka, O, H. Hiramatsu and K. Fujiwara, *Bull. Chem. Soc. Jpn.61*, **7**, 1988, 2473-2479.
12 V. Aldabalde, *Open J. Phys. Chem.*2011, **01**, 85–93.
13 J. Mcnulty, I.J.A Steere, S. Wolf, 1998,**39**, 8013-8016.
14 B. Gutmann, D. Obermayer, B. Reichart, B. Prekodravac, M. Irfan, J.M. Kremsner, O.C. Kappe, *Chemistry.*2010,**16**, 12182–12194.
15 D. Obermayer, M. Damm, O.C Kappe, *Chemistry.*2013,**19**, 15827-15830.
16 U.S. EPA. Health and Environmental Effects Profile for Pyridine. U.S. Environmental Protection Agency 1986, Washington, D.C., EPA/600/X-86/168 (NTIS PB89123384).
17 G. Aylward, *SI Chemical Data 6th Ed*;ISBN 978-0-470-81638-7, John Wiley and Sons, 2008.
18 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, A. Perry and M. Stefaniak, *Green Chem*. 2008, **10**, 31–36.
19 H. M. SawpathKumar. V Subbareddy. Anjaneyulu, J. S. Yadav, *Synth. Commun.*1998, **28**, 3811–3815.
20 D. Kumar, J. Sandhu, *Synth. Commun.*2010, **40**, 1915–1919.
21 H. Valizadeh, M. Mamaghani, A. Badrian, *Synth. Commun.*2005, **35**, 785–790.
22 M. Gupta, B. P Wakhloo, *ARKIVOC*, 2007, **i**, 94–98.
23 P.I. Dalko, L. Moisan, *Angew. Chem. Int. Ed. Engl.*2004, **43,** 5138–5175.
24 G. R. Krishnan, K. Sreekumar, *European J. Org. Chem.*2008, **28**, 4763–4768.
25 L. Zhu, N. Lei, Z. Miao, C. Sheng, C. Zhuang, J. Yao, W. Zhang, *Chinese J. Chem.*2012, **30**, 139-143.
26 A.K Mitra, N. Karchaudhuri, *Synth. Commun.* 1999, **29**, 573-581.
27 C.J. Simpson, M.J Fitzhenry, and N.P.J. Stamford,*Tet. Lett*. 2005, **46**, 6893- 6896.
28 M. Kidwai, N.K. Mishra, *Green Chemistry - Environmentally Benign Approaches*; ISBN 978-953-51-0334-9, InTech 2012.
29 Y. Ogiwara, K. Takahashi, T. Kitazawa, N. Sakai, *J. Org. Chem.*2015, **80**, 3101–3110.
30 Y. Ikushima, M. Arai, *Stoichiometric Organic Reactions, in Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH Verlag GmbH, Weinheim, Germany. 1999.
31 K.V. Narayanan, Lakshmikutty, B. *Sticheomitry and Process Calculations*; PHI Learning Pvt. Ltd., 2006.
32 C.H. Bartholomew, R. J. Farrauto, *Fundamentals of Industrial Catalytic Processes*; John Wiley & Sons, 2011.
33 R.A. Sheldon, *Green Chem.*2005,**7**,267-278.
34 P. Anastas, J.C. Warner, *Green Chemistry: Theory and practice*; Oxford University Press, Oxford, 1998.
35 C. Villa, E. Mariani, A. Loupy, C. Grippo, G.C Grossi, A. Bargagna, *Green Chem*. 2003, **5**, 623-626.
36 M.A.P. Martins, C. P. Frizzo, D.N. Moreira, L. Buriol, and P. Machado, *Chem. Rev*. 2009, **109**, 3885-4531.
37 Y. Qian, H.-J. Zhang, H. Zhang, C. Xu, J. Zhao and H.-L. Zhu, *Bioorg. Med. Chem.* 2010, **18**, 4991–4996.

Graphical Abstract

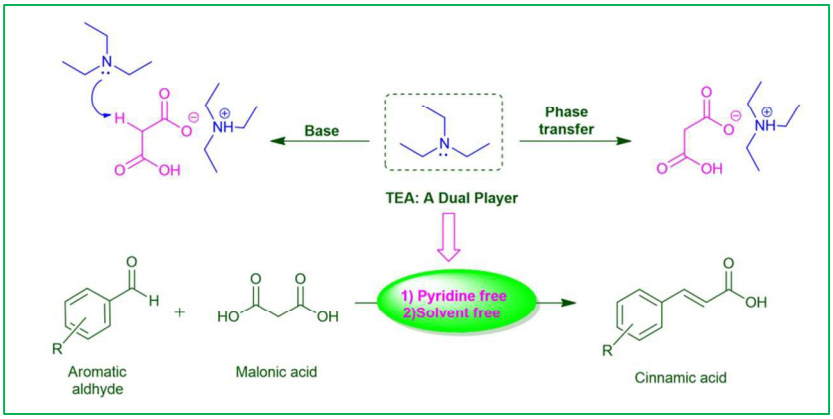
Triethylamine: A Potential *N*-Base Surrogate for Pyridine in Knoevenagel Condensation of Aromatic Aldehyde and Malonic Acid

Hitesh S. Pawar[a], Adhirath S. Wagh[a] and Arvind M. Lali*[a,b]

[a] *DBT-ICT Centre for Energy Biosciences, Institute of Chemical Technology, N.P.Marg Matunga (w), Matunga, Mumbai, India.Fax: 91 22 3361 1020; Tel: 91 22 3361 1111(Extn. 2301);E-mail: hiteshudct@gmail.com*

[a,b*] *Department of Chemical engineering, Institute of Chemical Technology, N.P.Marg Matunga (w), Matunga, Mumbai, India. Fax: 91 22 3361 1020; Tel: 91. E-mail: arvindmlali@gmail.com*

- **TOC entry**



- **TEXT entry**

Triethyl amine was successfully examined as potent *N*-base surrogate for Knoevenagel condensation to produce cinnamic acids without compromising product yield.