CO_2 absorbing cost-effective ionic liquid for synthesis of commercially important alpha cyanoacrylic acids: A safe process for activation of cyanoacetic acid†‡

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Cost-effective and carbon dioxide absorbing ionic liquid, tri-(2-hydroxyethyl) ammonium acetate, was shown to perform multiple roles in Knoevenagel condensation. It acted as an environmentally benign solvent, as an activating catalyst for the less reactive cyanoacetic acid and also as a risk reduction medium for the unevenly generated large amount of CO_2 gas for large scale reactions. The reaction was scaled up for multi-gram synthesis of commercially important alpha cyanoacrylic acids.

1. Introduction

Although the Knoevenagel reaction is simple when used on laboratory scale batches, it has some critical drawbacks when carried out on a large scale in industry. The vigorous and uneven generation of carbon dioxide gas, due to unreacted cyanoacetic acid or malonic acid and also during the subsequent decarboxylation of the product, is a critical problem. The presence of volatile organic solvents and bases such as pyridine and piperdine make the system even more unsafe. The sudden excess of gas along with volatile organic solvents at higher temperature and pressure can lead to bursting of equipment due to excess pressure.[1] Although some development has been reported in this regard previously,[1] the green chemistry aspect has not been covered extensively. Hence, it is desirable to develop an alternative technology to avoid potential hazards of sudden gas evolution associated with Knoevenagel condensation.

Another difficulty with this reaction is that the Knoevenagel condensation, although simple when carried out with malononitrile and cyanoacetate esters, does not proceed smoothly under standard conditions of mild acid or base when the less reactive cyanoacetic acid is used as the nucleophile and ketones are the electrophiles.[2] No significant development has been reported in recent years for the Knoevenagel condensation of cyanoacetic acid. Many of the earlier reports indicate that cyanoacetic acid condensation with aldehyde leads to decarboxylated products.[3–5] To the best of our knowledge only few generalized methods are reported wherein diverse carbonyl compounds are used for condensation, and the subsequent decarboxylation does not occur.[6–9] Use of environmentally unfriendly reagents and solvents like piperdine, pyridine, benzene, potassium cyanide, sodium cyanide, chloroacetic acid and acetic acid makes all these methods less acceptable.[3,4,6–10] Hence, a versatile, rapid, safe and environmentally friendly method for cyanoacetic acid condensation with carbonyl compounds which could lead to many important intermediates is relevant to explore.

Application of ionic liquids (ILs) has now become a topic of wide interest in many disciplines of science and technology. Ionic liquids are now being utilized effectively in industries and many such processes are currently in operation on industrial scales.[11,12] However, use of ILs in industries is still limited mostly due to the expensive cations and anions used in their synthesis. It is therefore relevant to explore and utilize cheaper ionic liquids to make them economically viable. In this context, recently many cost-effective alkanolamine based ILs have been identified.[13] We have recently reported the application and catalytic potential of alkanolamine based ionic liquids for environmentally friendly organic synthetic methodology.[14] These alkanolamines and their salts are extensively being studied for their synthetic as well as engineering applications in industries including absorption of large amounts of CO_2 evolved in industries by combustion of coals. The gas absorption potential of these alkanolamines and their salts is very well established and its proposed mechanism has been studied in detail.[13,15] Encouraged by these facts the possibility of these ionic liquids as risk reduction medium in large scale gas evolving reactions was studied in detail.

2. Results and discussion

Reactions of structurally diverse aldehydes and ketones with various active methylene compounds were carried out in tri-(2-hydroxyethyl) ammonium acetate. Reactions of aldehydes with cyanoacetic acid were carried out at 80 °C (Scheme 1). It was observed that aromatic aldehydes reacted smoothly with cyanoacetic acid leading to good yields of the alpha cyano acrylic acids in all cases (Table 1, entries 1–10). Yields of the products improved when excess (1.5 molar equivalent) of cyanoacetic acid was used instead of using equimolar quantities.

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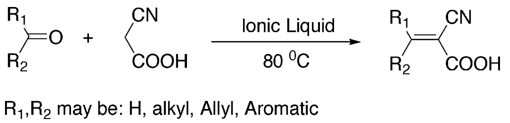
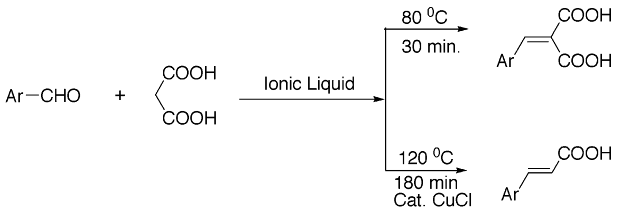
Table 1 Knoevenagel condensation of carbonyl compounds in alkanolamine ionic liquid

Sr. no.	Aldehyde/ketone	Active methylene compound[a]	Temp. (°C)	Time (min.)	Isolated[b] yield %	m.p. (m.p.[4,6,7,10]) °C
1	benzaldehyde	CAA	80	45	84	179 (178)
2	3-NO_2 benzaldehyde	CAA	80	45	81	167 (167)
3	4-OH benzaldehyde	CAA	80	45	78	224 (223)
4	furfuraldehyde	CAA	80	45	82	215 (218)
5	2-Cl benzaldehyde	CAA	80	60	72	208 (209)
6	piperonal	CAA	80	60	78	230 (231)
7	4-OCH_3 benzaldehyde	CAA	80	60	79	228 (227)
8	4-OH,3-OCH_3benzaldehyde	CAA	80	60	87	199 (199)
9	3-NO_2,4-OH,5-OCH_3 benzaldehyde	CAA	80	60	82	214
10	salicylaldehyde	CAA	80	45	87	228 (228)
11	cinnamaldehyde	CAA	80	45	83	206 (209)
12	acetophenone	CAA	80	240	NR[c]	—
13	acetone	CAA	reflux	240	55[c]	131 (132)
14	benzophenone	CAA	80	240	NR[c]	—
15	benzaldehyde	MA	80	30	67[d]	191(192)
16	furfuraldehyde	MA	80	30	62[d]	195 (195)
17	benzaldehyde	MA	120	180	70[e]	133 (133)
18	3,4-dimethoxy benzaldehyde	MA	120	180	60[e]	181 (181)
19	benzaldehyde	ECA	80	45	82	49 (50)
20	4-OCH_3 benzaldehyde	ECA	80	45	78	80 (80)
21	4-OH benzaldehyde	CAM	80	60	68	245 (246)
22	4-Cl benzaldehyde	CAM	80	60	72	209 (210)
23	4-OCH_3 Benzaldehyde	MN	RT	5	87	115 (115)
24	cinnamaldehyde	MN	RT	10	77	127 (128)
25	cyclohexanone	MN	RT	240	78[d]	Liq.
26	acetone	MN	RT	240	80	Liq.
27	acetophenone	MN	RT	300	72[d]	92 (92)
28	benzophenone	MN	RT	300	62	138 (138)

[a] 1.5 equivalent of cyanoacetic acid was used. [b] Evaluated by weight of isolated alkenes after purification (all products are known compounds and exhibit satisfactory spectroscopic data of ^{1}HNMR and IR). [c] Catalytic sodium methoxide was used. [d] Formation of impurities was observed. [e] 1 mol% CuCl was added, exclusive monocarboxylic acid obtained, NR: no reaction, CA: cyanoacetic acid, MA: malonic acid, ECA: ethyl cyanoacetate, MN: malononitrile, CAM: cyanoacetamide.



Scheme 1 Knoevenagel condensation of carbonyl compounds with cyanoacetic acid.



Scheme 2 Selective Knoevenagel condensation of aromatic aldehyde with malonic acid in ionic liquid.

The time required for completion of reaction was shorter in the case of aromatic aldehydes (45–60 minutes) (entries 1–10) compared to aliphatic ketones and allylic aldehyde (60–240 minutes) (entries 11–13). When reaction of acetone with cyanoacetic acid was carried out under similar conditions, the yield obtained initially was not satisfactory. Addition of sodium methoxide (20 mol%) enhanced the reaction rate considerably in this case and significant improvement in the yield was observed (entry 13). Under similar conditions, reaction of cyclohexanone leads to the formation of impurities. No product formation was observed when benzophenone and acetophenone were reacted with cyanoacetic acid even though the reactions were continued for longer periods and at higher temperatures with sodium methoxide as catalyst (entries 12, 14).

In the case of other active methylene compounds, for example malonic acid, reaction with aromatic aldehydes gave either malonic acid derivatives or cinnamic acid derivatives (Scheme 2) depending on the reaction parameters. Careful control of reaction time and temperature led to good yields of malonic acid derivatives (entries 15–16). Increase in reaction temperature and time offered the cinamic acid derivatives as major products, however addition of catalytic cuprous chloride (1 mol%) significantly increased the reaction rate to form exclusively monocarboxylic acid product (entries 17–18). Ethyl cyanoacetate reacted with aromatic aldehydes to give the respective products without any decarboxylation in good yields under similar conditions (entries 19–20). Similarly, cyanoacetamide reacted with aromatic aldehydes to give the respective products in reasonable yields (entries 21–22). Reactions of aldehydes and ketones were also carried out with malononitrile. Very fast reactions (5–30 min) of aromatic aldehydes with malononitrile in the presence of IL were observed at room temperature. The yields were excellent for both the aldehydes reacted (entries 23–24). Ketones (entries 25–28) reacted with malononitrile but the time required for optimum conversion was longer (240–300 min) as compared to aldehydes. In reactions of ketones bearing alpha hydrogen atoms, impurities, which were identified as self condensation products of ketones were observed, in addition to the desired products (entries 25, 27). This was confirmed by carrying out the self condensation of ketones such as acetophenonone and cyclohexanone under similar conditions with ionic liquid without the addition of nucleophile such as malononitrile. The formed impurity was identified by chromatographic comparison with the authentic sample.

Experiments for testing the recyclability of ionic liquid were performed using 4-methoxybenzaldehyde and cyanoacetic acid as reactants. The recovered ionic liquid was used successively three times showing no significant loss in its catalytic activity. No structural changes were observed in ionic liquid after recycling.

Studies on carbon dioxide absorption were performed on two 50 g batches using tri-(2-hydroxyethyl) ammonium acetate in a high pressure autoclave under conditions similar to those employed for Knoevenagel condensation. The study was performed at two different temperatures 50 °C and 80 °C and initial CO_2 pressure of 2.757 kPa (400 psi) and 3.447 kPa (500 psi) respectively. The drop in pressure due to ionic liquid absorption was recorded at regular intervals of 10 minutes. A considerable drop in pressure was observed in the reaction vessel at both the temperatures (Fig. 1).

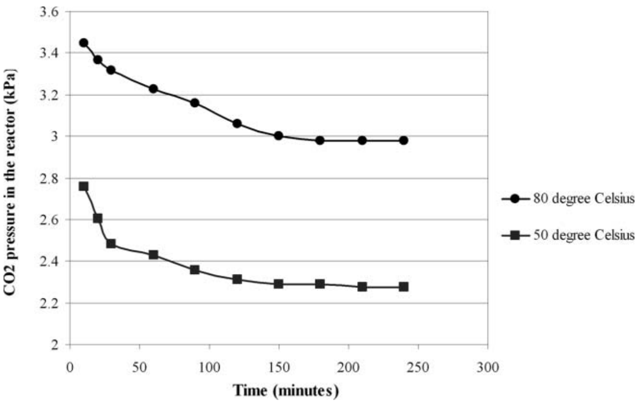


Fig. 1 CO_2 pressure drop due to absorption in ionic liquid at constant temperature.

The reaction mechanism for gas absorption by alkanolamine ionic liquids has been recently studied by Yuan and coworkers.[13] Using a similar approach, FTIR spectra of tri-(2-hydroxyethyl) ammonium acetate before and after the gas absorption were compared for identification of changes due to carbon dioxide absorption (Fig. 2). The appearance of a prominent new band at 1652 cm^{-1} was observed after the CO_2 absorption in the ionic liquid. This suggests the formation of an unstable carbamic acid intermediate in the zwitter-ionic form (Scheme 3). Persistent evolution of CO_2 gas from the ionic liquid was observed for several hours when the ionic liquid was kept at room temperature and atmospheric pressure after absorption. This indicated that tri-(2-hydroxyethyl) ammonium acetate absorbs carbon dioxide and slowly releases it under different experimental conditions.

The proposed mechanism for ionic liquid mediated Knoevenagel condensation could be explained by the formation of hydrogen bonding of ionic liquid with the reactants (Scheme 4). This facilitates the nucleophilic attack on carbonyl compounds, and subsequent dehydration leads to the product. Simultaneous removal of water during the reaction is not required presumably because the generated water molecules are involved in strong hydrogen bonding with the ionic liquid. Various intermediates of commercial importance were synthesized using the methodology (Table 2).

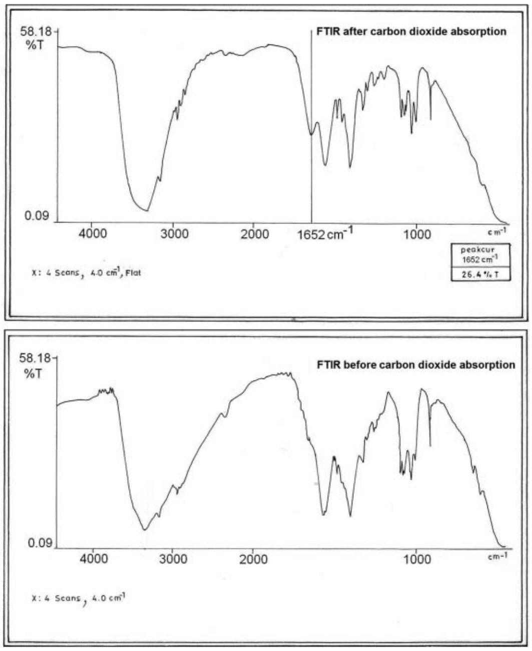
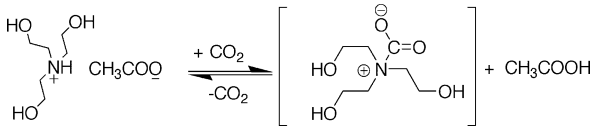


Fig. 2 FTIR spectra of the ionic liquid after and before CO_2 absorption.



Scheme 3 Proposed mechanism for CO_2 absorption by ionic liquid.

3. Experimental

3.1 General

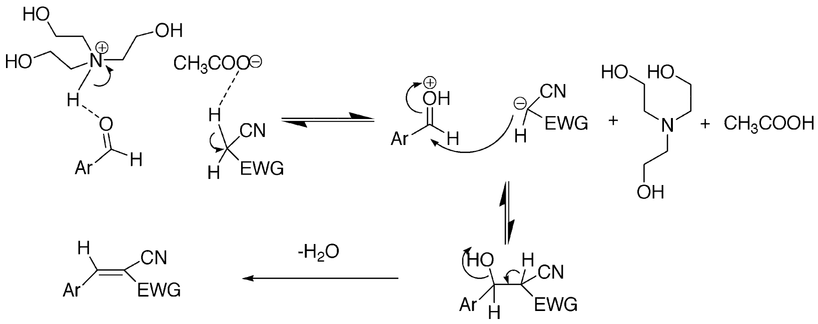
The ionic liquid was prepared by a previously reported method[13] without any modifications (Scheme 5), and characterized by FTIR, ^1H NMR and ^{13}C NMR spectroscopy. The reagents and solvents were commercially available. The products were purified using column chromatography wherever needed. All synthesized compounds are known, and identified by spectroscopic data, melting points and by comparison with available standards. FTIR spectra were obtained on a Perkin-Elmer infrared spectrometer with KBr discs and ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-D_6 on a JEOL 300 MHz spectrometer with TMS as internal standard.

3.2 Typical experimental procedure (Table 1, entries 1–14)

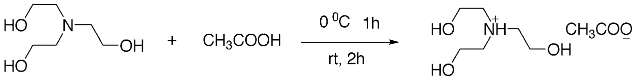
Cyanoacetic acid (0.94 g, 0.011 mol) and 4-methoxy benzaldehyde (1.0 g,0.0074 mol) were stirred with 2 g of ionic liquid in a round bottom flask and reaction mixture was heated to 80 °C. The reaction was monitored by TLC and after

Table 2 Commercial applications of selected alpha cyanoacrylic acids

Sr. no. (Table 1)	Compound	Commercial application
3	(E)-2-cyano-3-(4-hydroxyphenyl)acrylic acid	High value matrix substance in MALDI MS
8	(E)-2-cyano-3-(4-hydroxy-3-methoxyphenyl)acrylic acid	High value matrix substance in MALDI MS
9	(E)-2-cyano-3-(4-hydroxy-3-methoxy-5-nitrophenyl)acrylic acid	Possible entacapone intermediate
4	(E)-2-cyano-3-(furan-2-yl)acrylic acid	Intermediate for animals food-preservative
11	(2E,4E)-2-cyano-5-phenylpenta-2,4-dienoic acid	Intermediate for agrochemicals



Scheme 4 Proposed mechanism for IL catalyzed Knoevenagel condensation.



Scheme 5 Synthesis of ionic liquid tri-(2-hydroxyethyl) ammonium acetate.

completion, (E)-2-cyano-3-(4-methoxyphenyl)acrylic acid, was isolated (1.33 g,79%) by acidification with aqueous hydrochloric acid (pH~5) at 5 °C and subsequent filtration. Traces of aldehyde if any, were removed by washing the product with hexane.

3.3 Typical experimental procedure (Table 1, entries 23–28)

Malononitrile (0.4884 g, 0.0074 mol) and 4-methoxy benzaldehyde (1 g, 0.0074 mol) were stirred with 2 g of ionic liquid in a round bottom flask at room temperature. The reaction was monitored by TLC and after completion, 2-(4-methoxybenzylidene)malononitrile (1.177 g, 87%) was isolated by quenching the reaction mixture with water at 5 °C and subsequent filtration. Traces of aldehyde if any, were removed by washing the product with hexane.

3.4 Experimental procedure for a larger batch

To 200 g ionic liquid in a three neck round bottom flask with overhead stirrer, cyanoacetic acid (93.5 g, 1.1 mol) was added and the temperature was raised to 85 °C. To this, 4-methoxy benzaldehyde (100 g, 0.74 mol) was added portion wise over a period of 15 min. The reaction was monitored by TLC. After completion of the reaction (3 hours) (E)-2-cyano-3-(4-methoxyphenyl) acrylic acid was isolated (122 g, 82%) by quenching the reaction mixture in 2 liters of chilled water, acidification with aqueous hydrochloric acid (pH ~ 5–6) and subsequent filtration. Traces of aldehyde were removed by washing the product with hexane. The ionic liquid was recovered by evaporating the water under reduced pressure.

(A similar ratio of reactants and IL gave 80% yield from a 10 g batch of 4-methoxy benzaldehyde.)

3.5 Spectroscopic data for ionic liquid and selected compounds

Tri-(2-hydroxyethyl) ammonium acetate. IR (KBr, ν_{max}/cm^{-1}): 3310, 3154, 2936, 1560, 1482, 1456, 1404, 1326, 1295, 1092, 1077, 1062, 1025, 1000, 911; δ_H (300 MHz; DMSO-d$_6$): 1.792 (s, 3H, CH_3COO), 2.4 (t, 6H, $J = 6$ Hz, CH_2N), 3.32 (t, 6H, $J = 6$ Hz CH_2O), 5.4, (br s, 3H, OH); δ_C (300 MHz; DMSO-d$_6$): 21.16, 57.15, 59.13, 172.

(Table 1. Entry 7). Yellow crystals, melting point 228 °C. IR (KBr, ν_{max}/cm^{-1}): 2824, 2550, 2230, 1697, 1602, 1587, 1492, 1430, 1290, 1213, 1094, 921, 833.

δ_H (300 MHz; DMSO-d$_6$): 3.85 (s, 3H, OCH_3), 7.11(d, 2H, $J = 9$ Hz, ArH), 8.03 (d, 2H, $J = 9$ Hz, ArH), 8.23 (s, 1H); δ_C (300 MHz; DMSO-d$_6$); 53, 104, 119, 121, 128, 137, 158, 167, 168.

(Table 1. Entry 13). White crystals, melting point 131 °C. IR (KBr, ν_{max}/cm^{-1}): 3410, 2886, 2219, 1699, 1602, 1411, 1367, 1290, 1255, 1089, 917, 780, 759, 599; δ_H (300 MHz; $CDCl_3$; Me_4Si): 2.36 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 10 (s br, 1H, COOH).

δ_C (300 MHz; $CDCl_3$; Me_4Si); 23.27, 27.95, 104.5, 115.22, 166.7, 177.2.

(Table 1. Entry 20). Yellow crystals, melting point 80 °C. IR (KBr, ν_{max}/cm^{-1}): 2990, 2916, 2215, 1710, 1584, 1561, 1513, 1431, 1262, 1211, 1184, 1127, 1089, 1017, 837; δ_H (300 MHz; $CDCl_3$; Me_4Si): 1.39 (t, $J = 7.1$ Hz, 3H, CH_3), 3.89 (s, 3H, OCH_3), 4.38 (q, $J = 7.1$ Hz, 2H, CH_2), 7.01 (d, $J = 9$ Hz, 2H, ArH), 8.02 (d, $J = 9$ Hz, 2H, ArH), 8.19 (s, 1H, CH); δ_C (300 MHz; $CDCl_3$; Me_4Si): 14.2, 55.6, 62, 99.36, 114.7, 116.2, 124.37, 133, 154.4, 163.13, 163.79.

(Table 1. Entry 23). Yellow crystals, melting point 115 °C. IR (KBr, ν_{max}/cm^{-1}): 2921, 2211, 1603, 1571, 1512, 1406, 1369, 1319, 1277, 1183, 1155, 1093, 1021, 833; δ_H (300 MHz; $CDCl_3$;

Me_4Si): 3.92 (s, 3H, CH_3O), 7.01 (t, $J = 9$ Hz, 2H, ArH), 7.66 (s, 1H, CH), 7.90 (d, $J = 9$ Hz, 2H, ArH); δ_C (300 MHz; $CDCl_3$; Me_4Si): 55, 114, 124, 133, 158, 164.

4. Conclusion

Interestingly, the cost-effective and less explored ionic liquid, tri-(2-hydroxyethyl) ammonium acetate performed multiple roles in this methodology such as acting as an environmentally benign solvent, an activating catalyst for the less reactive cyanoacetic acid and also as a risk reduction medium for unevenly generated CO_2 gas during the reaction. Another important aspect of this methodology is that alpha cyanoacrylic acids, useful intermediates in pharmaceuticals and fine chemicals could easily be synthesized. Scale up of the reaction parameters were successfully carried out for multi-gram batch size. The ionic liquid was recycled three times without any significant loss in the catalytic activity.

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