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Full Papers

A Novel Eco-Friendly Process for the Synthesis of 2-Chlorobenzylidenemalononitrile and ITS Analogues Using Water As a Solvent

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Abstract:

A simple and novel eco-friendly process for the synthesis of 2-chlorobenzylidene malononitrile (CS) and their analogues in water using 1-methyl imidazole (catalyst) has been developed. The reaction conditions for the preparation of CS are optimized for large scale applications.

Introduction

Benzylidene malanonitriles have received much attention as cytotoxic agents against tumours, and some of the derivatives have also been used as rodent control agents.[1,2] 2-Chlorobenzylidene malononitrile (CS) is one of the most potent lachrymator skin irritants and is a well-known riot control agent[3] used by law enforcing agencies during civil disturbances. Various methods[4] have been reported for the synthesis and process development of 2-chlorobenzylidene malononitrile/analogues and were prepared by Knoevenagel condensation of the corresponding substituted benzaldehydes with malononitrile in the presence of different bases as catalyst in organic solvents, such as cyclohexane, methanol, or ethanol. In recent years, environmentally benign synthetic methods have received considerable attention due to world-wide concerns over chemical wastes and future resources. Thus, green chemistry approaches have been developed for various existing processes.[5]

The Knoevenagel condensation has been an important tool for constructing the α,β-unsaturated structure unit from a carbonyl and an active methylene compound.[6] In recent years, this reaction was exploited with various inorganic environmental friendly solid bases[7] such as $AlPO_4-Al_2O_3$, alkylamine-functionalized silica gel, ZnO or MgO, xonolite, KF/Al_2O_3, zeolite CsX, etc. as alternative catalysts to organic bases. Microwave, infrared radiation, and ultrasound-promoted Knoevenagel condensations were also reported.[8,9] In addition, condensations by ball-milling/grinding under solvent-free conditions were also studied.[10] In the case of solvent-free, microwave, or IR heating reactions, the yield and the purity were less[7,11] and these methods were pertinent to preparative scale[8] only. Morrison et al. reported Knoevenagel reactions in ionic liquid solvents as an environmentally benign approach.[12] Condensation of benzaldehyde and malononitrile in ionic solvents occurred in 22 h, the yield was 77%, and recycling of ionic liquid resulted in 39% yield only.[12] Thus the drawbacks of the known methods for the production of benzylidenemalononitriles include more reaction time, low yield, less purity, use of hazardous inflammable organic solvents, and more cost.

Herein we report a simple, clean, efficient, environment and eco-friendly process for the synthesis 2-chlorobenzylidenemalononitrile (CS) in water, and the conditions were optimized for upscaling to the manufacturing process. The water used was recycled for further runs to reduce the effluent load. In addition, few analogues of CS were also synthesized in water by following the same process.

Results and Discussion

1. Preparation of CS in Water Using Different Catalysts. Knoevenagel condensation is a base-catalyzed reaction. To investigate the effect of base on the reactivity, condensation reactions of 2-chlorobenzaldehyde with malononitrile were carried out at preparative scale with different catalysts in water at 35 °C. The effect of catalyst on reaction time

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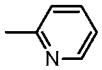
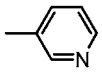
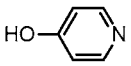
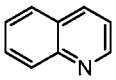
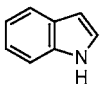
Table 1. **Synthesis of 2-chlorobenzylidenemalononitrile in water using various catalysts**

S.No.	Catalyst used	Reaction Time/min
1		7
2		12
3		7
4		5
5		19
6		7
7		7
8		9
9		4
10		6
11		37
12	$(C_2H_5)_2$ NH	9
13	$(C_2H_5)_3$ N	5
14	$(i\text{-}C_3H_7)_2$ NH	8

required for the formation of 2-chlorobenzylidenemalononitrile is given in Table 1. It was observed that there was a direct relationship between the electron-donating potential of nitrogen atom of the base in water and the reaction time. It is evident that, in the case of methyl pyridines, the inductive effect of methyl group decreased the reaction time. In 4-hydroxypyridine, the availability of the lone pair of electrons of a nitrogen atom is reduced due to resonance; therefore the reaction time enhanced drastically. The reactivity of quinoline was similar to that of methyl pyridines, but indole showed poor activity due to increased delocalization of the lone pair and its exceedingly low basicity (pK_a −2). In the case of aliphatic bases, the reactivity or the basic strength of these bases in water is determined not only by electron availability on the nitrogen atom but also by the extent to which the cation, formed by uptake of a proton, can undergo hydration and so become stabilised. The more hydrogen atoms attached to nitrogen in the cation, the greater the possibilities of powerful hydration via bonding between these and water. Therefore the reaction time was high for aliphatic bases even though pK_a values (11−14) of these bases in water are very high; i.e., the catalyst activity of these bases is less.[13] It was observed that the reaction time using diethylamine was 2-fold greater than that using triethylamine as catalyst. Among three imidazoles used, i.e., imidazole, 1-methyl imidazole, and 2-methyl imidazole, 1-methyl imidazole showed maximum activity due to a $+I$ effect of CH_3 directly attached to nitrogen atom. The exceptionally less reaction time with high yield of CS (quantitative) was obtained using 1-methyl imidazole as catalyst.

Overall, among the various catalysts investigated for the preparation of CS, 1-methyl imidazole proved to be efficient in terms of reaction time, product yield, and purity. Therefore this catalyst was selected for further studies.

2. Effect of Catalyst (1-Methyl Imidazole) Concentration in the Preparation of CS in Water. To find out the optimum quantity of catalyst required for the synthesis of CS, experiments were carried out with different quantities of 1-methyl imidazole (0.0025 M to 0.1 M of catalyst per 1 mol of 2-chlorobenzaldehyde/malononitrile, Figure 1). The reaction occurred at all concentrations of the catalyst used. It was observed that the reaction time was inversely proportional to the amount of catalyst. However, when the reactions were carried out with higher concentrations of 1-methyl imidazole, the reactions took place rapidly and solid CS formed in lumps containing aldehyde/malononitrile trapped in it. This in turn affected the purity and yield of CS isolated by filtration. The product was slightly coloured with increasing concentrations of the catalyst. Keeping into consideration the reaction time and purity/yield of CS, we chose as the optimum concentration of catalyst 0.01 M for 1 mol of either of the reactants.

3. Effect of Quantity of Water in the Preparation of CS. The next critical part was determining the minimum volume of water with which the reaction could be run. To find the optimum requirement of water required for the reaction, experiments were carried out with different mole ratios of water. The product formation occurred rapidly in all these reactions; when the quantity of water used was less, product was obtained in lumps containing unreacted aldehyde/malononitrile in its cavity. This resulted in the reduction in both yield and purity of the isolated product. When an adequate quantity of water was used, the reactants as well as product were homogeneously dispersed in the reaction medium, leading to pure fine particles of CS in high yield. It was observed that, at optimised conditions, the molar ratio of malononitrile/water required was found to be 1:30. The excess of water was uneconomical considering the increase in reaction time and reaction vessel and wastage of water.

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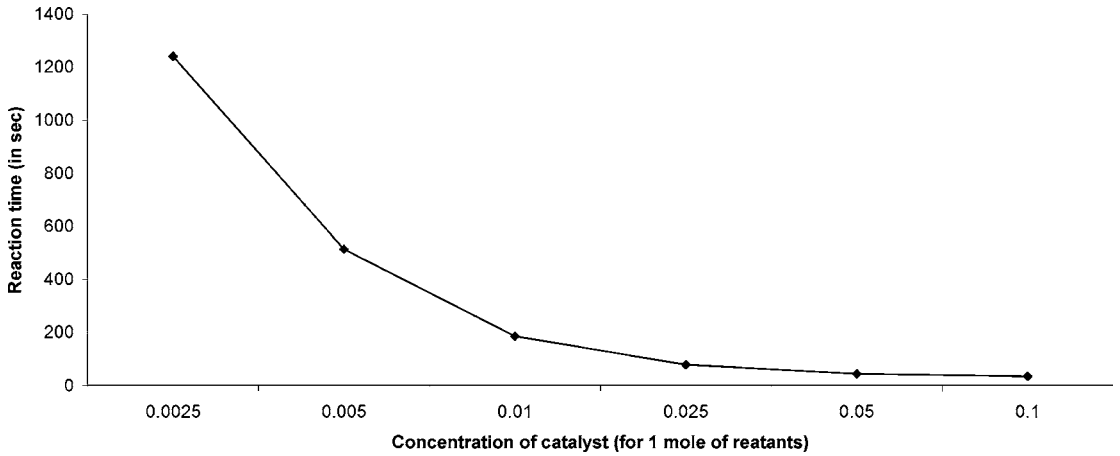


Figure 1. **Effect of catalyst amount on reaction time for the preparation of CS in water medium.**

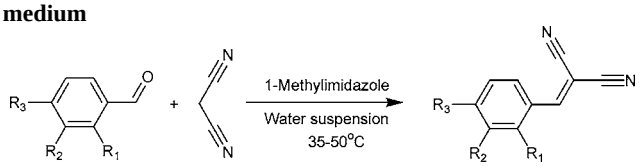
4. Optimized Conditions for the Preparation of CS in Water. From the above experiments, it is concluded that the molar ratio 1:1:0.01:30 of 2-chlorobenzaldehyde/malononitrile/1-methylimidazole (catalyst)/water was required to obtain CS in high yield and high purity.

5. Upscaling of Preparation of CS in Water. Synthesis of 2-chlorobenzylidenemalononitrile in water was performed at a preparative scale of 0.01 mol of CS to a bench scale of 10 mol of CS (1.88 kg) using 1-methyl imidazole as catalyst under the above optimized reaction conditions for large scale applications. It was observed that the purity and yield of CS remained same in all the batches. An preparative scale, the temperature of the reaction was kept at 35 °C to maintain homogeneous malononitrile suspension in water (since melting point of malononitrile is 32−34 °C). The reaction was exothermic, and it was maintained below 50 °C in the bench scale experiments by either external cooling of the reaction vessel with ambient temperature water or controlled addition of 2-chlorobenzaldehyde. If the temperature was not maintained below 50 °C, reaction was so rapid that CS was obtained in lumps instead of fine particles.

6. Recycling of Mother Liquor. The filtrate water from the above experiments was reused continuously in the repeated runs by the same procedure for the preparation of CS. It was found that there was no change either in yield or in purity of the product. However, it may be mentioned that recycled water after 10 repeated runs leads to slight colouring of the product. By conventional methods[4] for the production of CS, volatile organic solvents such as cyclohexane, methanol, and ethanol were used. Since CS is soluble in these solvents, they were removed by distillation to isolate CS. The product thus obtained was recrystallized from organic solvent; therefore the actual yield of the product was less than the required yield. Moreover, high inflammability and high volatility of these solvents pose fire and environmental hazards. The effluent containing used solvent was either disposed as such or destroyed by incineration.

The other solvent-free reaction for the production of CS involved three steps: (i) the mixture of the reactants viz 2-chlorobenzaldehyde, malononitrile, and piperidine as base catalysts was allowed to react at 35−60 °C; (ii) reaction mixture was heated at 60−105 °C under a partial vacuum gave 80% yield; and (iii) the vacuum was decreased further to 10 mmHg while heating was rapidly increased to at least 120 °C. In this reaction, yields depended on mixing of the reactants, and the overall yield was <80% only after the water produced in the reaction and base catalyst used were removed by heating under a vacuum at 120 °C. This lead to loss of CS by vaporisation; heating of CS to 120 °C lead to colouration to the product. The process is also not cost-effective.

Table 2. **Synthesis of benzylidenemalononitriles in water medium**



Yield 97-99 %

no.	R_1	R_2	R_3	reaction time/min	mp[a] (°C)
1	H	H	H	19.6	83
2	OH	H	H	1.66	166
3	H	OH	H	0.75	153
4	H	H	OH	1.75	187
5	Cl	H	H	3.1	94
6	Br	H	H	50	90
7	F	H	H	3.16	119
8	H	H	Cl	2.0	163
9	H	H	Br	2.0	91
10	OCH_3	H	H	22	84
11	H	OCH_3	H	2	104
12	H	H	OCH_3	3.16	114
13	H	OCH_3	OH	11	134
14	NO_2	H	H	2.5	138
15	H	NO_2	H	5.5	98
16	H	H	NO_2	2.0	160
17	Cl	H	Cl	1.5	150
18	H	H	$N(CH_3)_2$	7.0	178
19	H	H	COOH	1.0	188

[a] Mp's are uncorrected and are in agreement with the reported values.

7. Synthesis of CS Analogues in Water. The feasibility of extending above reaction for the preparation of various other benzylidenemalononitriles was attempted at laboratory scale. Thus the optimum conditions observed for the preparation of CS were used for the synthesis of various other benzylidenemalononitriles as shown in (Table 2). The CS

analogues were synthesised at laboratory scale by the mixing of an equimolar quantity of corresponding aldehyde and malononitrile suspension in water at 35 °C using 1-methyl imidazole as catalyst (1/100 mol of malononitrile). In general, the reactions were very fast (1−20 min) and gave nearly quantitative yield of the products. The solid products were separated simply by filtration and dried under a vacuum. The yield and purity were >97%. The physical and spectral data of the synthesized compounds were in agreement with the reported data.

Conclusions

In summary, a simple, efficient, economical, and eco-friendly process for the synthesis and upscaling of 2-chlorobenzylidenemalononitrile in water medium using 1-methyl imidazole as catalyst was developed. The main advantages of the present developed method are as follows: (i) no organic solvent is required; (ii) the condensation reaction is carried out very efficiently at 35 °C, at which homogeneous dispersion of malononitrile in water medium occurred; (iii) CS is insoluble in water, and thus the product is isolated by simple filtration and yields are also high (99%); (iv) water used in the reaction media is recycled which enhances the green perspective; and (v) since all the operations of the reaction such as addition of reactant, separation, and drying are carried out in ambient temperature, overall, this is an energy-saving process.

Experimental Section

General. All of the chemicals used in this study were purchased from Across Organics and were used without any further purification. The reactions were carried out in ordinary water without distilling it. The melting points are uncorrected. Infrared spectra were recorded as KBr pellet using a Perkin-Elmer FT-IR spectrophotometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 400 NMR, with tetramethylsilane (TMS) used as an internal standard. Chemical shifts (δ) were recorded in parts per million (ppm) from the internal standard (TMS = 0.00).

Gas chromatography−mass spectrometry (GC−MS) was performed using a Hewlett-Packard 6890 gas chromatograph equipped with a split/splitless injector and a capillary column (30 m × 0.32 mm i.d., 0.25 μm film thickness, BP-5 stationary phase, SGE) directly coupled to a Hewlett-Packard 5973 quadrupole mass spectral detector and integral data system. Ionization was done by electron impact at 70 eV and 230 °C. The carrier gas was helium.

Preparation of CS and Its Analogues (General Procedure): To a mixture of malononitrile (2.64 g, 0.04 mol) and 1-methyl imidazole (0.03 g, 0.0004 mol) in water (21.6 mL) at 35 °C, corresponding aldehyde (0.04 mol) was added with constant stirring. For example, in the case of 2-chlorobenzaldehyde, 5.62 g (0.04 mol) were used. The crystalline solid was obtained, separated by filtration and dried under a vacuum (∼25 mm) at room temperature. The yields were 97−99%, and purity (by GC) was >99%.

Scalable Process for 2-Chlorobezylidenemalononitile (CS): In a 10 L three neck-round-bottom flask equipped with thermometer, pressure equalising funnel, and magnetic stirrer, water (5400 mL) was taken. To this malononitrile (660.6 g, 10 mol) and then 1-methyl imidazole (10 mL, 0.1 mol) were added with constant stirring at 35 °C. To this 2-chlorobenzaldehyde (1405 g, 10 mol) was added slowly in 30 min with continuous stirring through the pressure equalising funnel. The reaction was exothermic, and the temperature of the reaction mixture was maintained below 50 °C during addition of 2-chlorobenzaldehyde by cooling of the reaction flask with water. (Alternatively, when the same quantity of 2-chlorobenzaldehyde was added in 90 min, the temperature was below 50 °C without any requirement of cooling of the reaction flask.) After the complete addition, the reaction mixture was stirred for 15 min. The white crystalline solid CS thus obtained was filtered and then dried under vacuum (25 mm Hg) at room temperature.

Mother liquor obtained after filtration of white solid was reused for further runs (10 times) for the preparation of CS by the same procedure. The yield and purity of the product in all the runs remained same.

Yield 99%; Purity 99%. mp 93−94 °C.

IR (KBr): 3051 (C−H aromatic), 2230 (C≡N), 1585, 1443, 1378 (C=C).

H^1 NMR ($CDCl_3$): δ 7.2−7.9 (m, 3H, ϕ), 8.2 (d, 1H, ϕ), 8.3 (s, 1H =CH−).

MS (*m*/*z*): 153 (M^+ − Cl, 100), 188 (M^+), 126, 75, 99, 63, 51, 137.

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