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Iodine Catalysis in Aqueous Medium: An Improved Reaction System for Knoevenagel and Nitroaldol Condensation

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Abstract A convenient method for Knoevenagel and Nitroaldol condensation has been developed by using the inexpensive and environmentally friendly reagent I_2/K_2CO_3 at room temperature in aqueous medium. The reaction condition is mild and simple with good to high product yields for both Knoevenagel as well as Nitroaldol condensation.

Keywords Molecular iodine · Knoevenagel condensation · Nitroaldol condensation · Arylidene compounds · β-Nitroalkanol

1 Introduction

The Knoevenagel and Nitroaldol condensation are among the most useful and widely employed methods for carbon–carbon formation in organic chemistry.The arylidene compounds have numerous applications in the synthesis of fine chemical [1], hetero Diels-Alder reactions [2] and in the synthesis of carbocyclic as well as heterocyclic [3] compounds of biological significance. In addition, the 2-nitroalkanols are particularly versatile intermediates for the synthesis of nitroalkenes, 2-aminoalcohols, 2-nitroketones, (S)-propanolol [4], or (S)-(K)-pindolol [5], antibiotics [6].The reactions are usually catalysed by bases [7] in organic solvents. Lewis acids [8], surfactants [9], layered silicate [10] and ionic liquids [11] have also been employed to catalyse the reactions.

With the increasing public concern over environmental degradation, the use of environmentally benign solvents like water and solvent-free reactions represent very powerful green chemical technology procedures from both the economical and synthetic point of view. They have many advantages, such as reduced pollution, lower cost, enhanced the rate of many organic reactions, and simplicity in processing which are beneficial to the industry as well as to the environment. Recently, water as the green solvent has been proven to be an efficient medium for Knoevenagel [12] and Nitroaldol [13] condensation.

Nowdays, the usage of molecular iodine has drawn considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhance its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations [14]. Previously, we have reported a facile method for the synthesis arylidene derivatives from aromatic aldehydes and malononitrile or ethyl cyanoacetate using I_2 and K_2CO_3 as the catalysts in EtOH at room temperature in a short time [15]. To our surprise, the I_2 and K_2CO_3 can catalyze effectively Knoevenagel condensation in the aqueous medium when catalytic amount of KI was added to the solution. In addition, the system of $I_2/KI/K_2CO_3/H_2O$ can also catalyze effectively Nitroaldol condensation at room temperature when more amount of I_2 and K_2CO_3 was employed.

2 Experimental

Reagents are obtained from commercial resource. Products are all known compounds and were identified by comparing

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of their physical and spectra data with those reported in the literature.

2.1 Typical Procedure Condensation of *p*-Chlorobenzaldehyde with Malononitrile in EtOH

To a solution of *p*-chlorobenzaldehyde (10 mmol) and malononitrile (12 mmol) in EtOH (1 mL) were added I_2 (0.3 mmol) and K_2CO_3 (0.3 mmol). The mixture was stirred at room temperature. After 3 min, the solid produced was treated with $Na_2S_2O_3$ solution (5%) and EtOH (5%). The solid product (1.807 g, 95%) was identified by ^{1}H NMR and by comparison with an authentic sample needed no further purification. m.p. 160–161 °C (Lit [16a].m.p. 160–161 °C); IR (KBr, υ/cm^{-1}): 3032, 2225, 1654, 1554, 1308, 780. ^{1}H NMR (300 MHz, $CDCl_3$, δ) : 7.49 (d, J = 8.4 Hz, 2H, ArH), 7.71 (s, 1H, CH=), 7.83 (d, J = 8.7 Hz, 2H, ArH). Similarly, the others compounds (Tables 1 and 2) were synthesized and were confirmed by comparison of ^{1}H NMR with those described in the literatures and authentic samples.

2.2 Typical Procedure Condensation of *p*-Chlorobenzaldehyde with Malononitrile in Aqueous Media

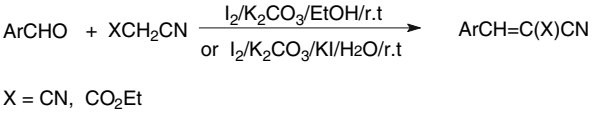
A solution of *p*-chlorobenzaldehyde (10 mmol) and malononitrile (12 mmol) was stirred at room temperature for 3 min, then an aqueous solution (2 mL) of KI (0.3 mmol), K_2CO_3 (0.3 mmol) and I_2 (0.3 mmol) was added and the mixture stirred at room temperature. After 3 min, the solid produced was treated with $Na_2S_2O_3$ solution (5%) and EtOH (5%). The solid product (1.810 g, 95%) was identified by ^{1}H NMR and by comparison with an authentic sample needed no further purification.

2.3 Typical Procedure Condensation of *p*-Nitrobenzaldehyde with Nitromethane in Aqueous Media

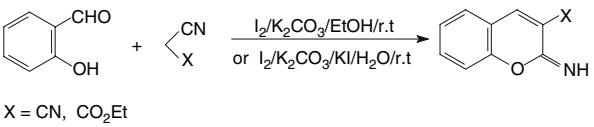
A solution of *p*-nitrobenzaldehyde (1 mmol) and nitromethane (5 mmol) was stirred at room temperature for 3 min, then an aqueous solution (2 mL) of KI (0.3 mmol), K_2CO_3 (0.3 mmol) and I_2 (0.3 mmol) was added and the mixture stirred for 2 h at room temperature. The mixture was treated with aqueous $Na_2S_2O_3$ (10%, 5 mL). Then the solution was extracted with Et_2O (3 × 10 mL). The organic layer was dried and concentrated, and the crude product was purified by column chromatography on silica gel (EtOAc:petroleum ether = 2:9) to afford 190 mg (90%) of pure product 2-Nitro-1-(4-nitrophenyl)ethanol. m.p. 82–84 °C (Lit [16b].m.p. 83–85 °C); IR (KBr, υ/cm^{-1}): 3498, 1541, 1516, 1413, 1370, 1342, 1080, 851. ^{1}H NMR ($CDCl_3$, δ) : 3.01–3.63 (br, 1H), 4.47–4.65 (m, 2H), 5.45–5.77 (m, 1H), 7.63–7.65 (m, 2H,), 8.21–8.23 (m, 2H).

3 Results and Discussion

According to our previously reported reaction conditions about Knoevenagel condensation, long reaction times were needed and low yields were obtained without K_2CO_3 or molecular iodine, such as the condensation of *p*-chlorobenzaldehyde with malononitrile, it could only give 50% yield without K_2CO_3 and give 30% yield without molecular iodine [15]. So we investigated Knoevenagel condensation of various aromatic aldehydes with malononitrile or ethyl cyanoacetate in the system of I_2/KI/K_2CO_3/H_2O and the system of I_2/K_2CO_3/EtOH (Scheme 1). The results were summarized in Table 1. Table 1 showed the aromatic aldehydes, having different substituents such as chloro, nitro, methoxy, methyl, etc. were converted to the corresponding arylidene derivatives with high yields in EtOH or H_2O. The aromatic aldehydes with electron-withdrawing groups such as chloro, nitro. proceeded at faster rates than those with electron-donating groups such as methoxy, methyl, etc. The reactions with malononitrile were also faster than with ethyl cyanoacetate. A longer reaction time would be necessary and lower yield was obtained under solvent-free condition than in the solvent EtOH or H_2O (entry 2). However, the higher yields were obtained in H_2O than in EtOH. It was interesting that the reaction time of *p*-hydroxybenzaldehyde with malononitrile or ethyl cyanoacetate were shorter in H_2O than in EtOH (entries 6 and 14), which was different with the others. So we also examined the reaction of *o*-hydroxybenzaldehyde with malononitrile or ethyl cyanoacetate (Scheme 2), which underwent cyclization as a result of nucelophilic attack by hydroxy group on the cyano group. Thus 2-imino-2*H*-1-benzopyran-3-carbonitrile and 2-imino-2*H*-1-benzopyran-3-carboxylate were formed in excellent yields (Table 2). Similarly, the reactions were also faster in H_2O than in EtOH.



Scheme 1



Scheme 2

Table 1 I_2/K_2CO_3 catalyzed Knoevenagel condensation at room temperature[a]

Entry	Ar	X	Solvent	Reaction time (min)	Yield (%)[b]
1	Ph	CN	EtOH	12	80
			H_2O	12	86
2	4-ClPh	CN	EtOH	3	95
			H_2O	3	95
			–	40	70[c]
3	4-NO_2Ph	CN	EtOH	2	93
			H_2O	2	98
4	3-NO_2Ph	CN	EtOH	6	90
			H_2O	6	97
5	4-MePh	CN	EtOH	10	86
			H_2O	14	91
6	4-HOPh	CN	EtOH	16	86
			H_2O	2	90
7	4-MeOPh	CN	EtOH	14	80
			H_2O	18	85
8	4-(Me_2)NPh	CN	EtOH	24	75
			H_2O	30	83
9	Ph	COOEt	EtOH	60	80
			H_2O	80	85
10	4-ClPh	COOEt	EtOH	50	85
			H_2O	60	90
11	4-NO_2Ph	COOEt	EtOH	25	87
			H_2O	35	91
12	3-NO_2Ph	COOEt	EtOH	30	94
			H_2O	40	96
13	4-MePh	COOEt	EtOH	70	85
			H_2O	90	87
14[d]	4-HOPh	COOEt	EtOH	70	81
			H_2O	10	89
15[d]	4-MeOPh	COOEt	EtOH	70	89
			H_2O	90	92
16[d]	4-(Me_2)NPh	COOEt	EtOH	70	75
			H_2O	90	81

[a] Mmol ration of aldehyde/malononitrile or ethyl cyanoacetate/I_2/K_2CO_3 is 10.0/12.0/0.3/0.3. The KI(0.3 mmol) was added when the reaction was accomplished in H_2O

[b] Isolated yields

[c] The reaction was accomplished under solvent-free condition

[d] Mmol ration of aldehyde/ethyl cyanoacetate/I_2/K_2CO_3 is 10.0/12.0/0.6/0.6. The KI(0.6 mmol) was added when the reaction was accomplished in H_2O

Table 2 The condensation of *o*-hydroxybenzaldehyde with malononitrile or ethyl cyanoacetate

Entry	X	Solvent	Reaction time (min)	Yield (%)[a]
1[b]	CN	EtOH	10	84
		H_2O	3	91
2[c]	COOEt	EtOH	70	81
		H_2O	20	87

[a] Isolated yields

[b] Mmol ration of *o*-hydroxybenzaldehyde/malononitrile /I_2/K_2CO_3 is 10.0/12.0/0.3/0.3. The KI(0.3 mmol) was added when the reaction was accomplished in H_2O

[c] Mmol ration of *o*-hydroxybenzaldehyde/ethyl cyanoacetate/I_2/K_2CO_3 is 10.0/12.0/0.6/0.6. The KI(0.6 mmol) was added when the reaction was accomplished in H_2O

We next examined the Nitroaldol condensation in the aqueous medium (Scheme 3). Initially, the Nitroaldol reaction of nitromethane with 4-nitrobenzaldehyde was explored in several solutions in order to show the advantages of the aqueous medium (Table 3). Table 3 summarized the results of the initial studies. In each instance, the reaction was carried out at ambient temperature with the given reaction time. The reaction solution has a great influence on the reaction. The reaction didn't take place when ether or PhMe was used as a solution (entries 1 and 2). Increasing the polarity of solution could remarkably enhance both reaction yield and rate, like in DMF, the reaction could be completed within 2 h with high yield (entry 7). And when the reaction solvent was changed from EtOH to EtOH–H_2O(1:1), the reaction yield was slightly

Table 3 Effect of the different solvent on the reaction of nitromethane with *p*-nitrobenzaldehyde[a]

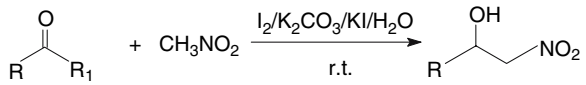
Entry	Solvent	Reaction time (h)	Yield (%)[b]
1	EtOEt	7	0
2	PhMe	7	0
3	THF	7	47
4	EtOH	7	63
5	EtOH–H_2O(1:1)	7	90
6	CH_3OH	5	94
7	DMF	2	95
8	H_2O	2	99[c]

[a] Mmol ratio of I_2/K_2CO_3/nitromethane/*p*-nitrobenzaldehyde is 0.3/0.3/1.0/5.0

[b] Isolated yields based on the *p*-nitrobenzaldehyde by HPLC

[c] The KI(0.3 mmol) was added

increased (entries 4 and 5). So we carried out the reaction in the aqueous medium (entry 8), the result showed that water was more satisfied to obtain excellent yield in short time than other solutions.



R = Aryl or alkyl; R_1 = H or CH_3

Scheme 3

Then, we investigated Nitroaldol condensation of various carbonyl compounds with nitromethane in aqueous medium (Table 4). It was found that both aromatic and aliphatic aldehydes reacted efficiently with nitromethane promoted by I_2 and K_2CO_3. Table 4 showed the aromatic aldehydes, having different substituents such as chloro, nitro, methoxy, methyl, etc. were converted to the corresponding 2-Nitroalkanol derivatives in high yields. However, the aromatic aldehydes which have electron-withdrawing groups such as chloro, nitro. proceeded at faster rates than those with electron-donating groups such as methoxy, methyl, etc. And low yields were obtained without molecular iodine with longer reaction times (entries 1 and 8). We also found that the *para*-substitution groups of aromatic aldehydes favored the Henry reaction in comparison with the *ortho*-substitution because of the steric hindrance of *ortho*-substitution (entries 2, 3, 5, 6, 8 and 9). However, the reaction failed to proceed with ketones under the same reaction conditions (entries 13 and 14).

In conclusion, the present synthetic method is a simple, inexpensive, effective and green synthesis of arylidene compounds and β-Nitroalkanols with iodine, potassium iodide, potassium carbonate in water at room temperature. The advantages of the present reaction are the elimination of the metals, organic solvents and toxic reagents, operational simplicity and high yields of products.

Table 4 I_2/K_2CO_3 catalyzed Nitroaldol condensation at room temperature[a]

Entry	R	R_1	Reaction time (h)	Yield (%)[b]
1	Ph	H	3	90
			12	26[c]
2	4-NO_2Ph	H	2	99
3	2-NO_2Ph	H	2	94
4	3-Pyridine	H	2	99
5	4-ClPh	H	2	96
6	2-ClPh	H	2	88
7	4-MeOPh	H	5	96
8	4-MePh	H	5	95
			12	20[c]
9	2-MePh	H	5	86
10	CH_3CH_2	H	5	83
11	$CH_3CH_2CH_2$	H	5	89
12	Furan	H	5	96
13	Ph	CH_3	12	0
14	CH_3CH_2	CH_3	12	0

[a] Mmol ration of aldehyde/nitromethane/I_2/KI/K_2CO_3 is 1.0/5.0/0.3/0.3/0.3; H_2O: 2 mL

[b] Yields based on the aldehydes by HPLC

[c] The reaction was accomplished without iodine

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