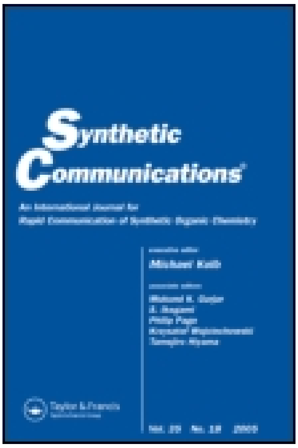

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SODIUM BENZOATE AS A GREEN, EFFICIENT, AND RECYCLABLE CATALYST FOR KNOEVENAGEL CONDENSATION

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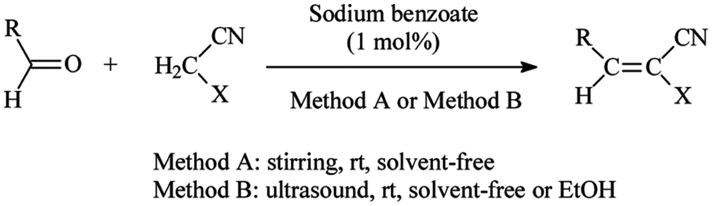
GRAPHICAL ABSTRACT



Abstract *Sodium benzoate was utilized as a novel efficient and green catalyst for the Knoevenagel condensation of aldehydes with active methylene compounds such as ethyl cyanoacetate and malononitrile to afford substituted olefins through the conventional stirring or under ultrasounic irradiation. Improvements were observed by carrying out the reactions under ultrasound irradiation. The reaction proceeded smoothly under mild conditions at room temperature, and the products were obtained in excellent yields within short times: The catalyst remains active and exhibits no substantial loss of activity for up to four reaction cycles.*

Keywords Catalysis; Knoevenagel; sodium benzoate; ultrasound irradiation

INTRODUCTION

Sodium benzoate is a common, safe food preservative and antimicrobial agent. Sodium benzoate works well in acidic media to inhibit yeasts, molds, and bacterial growth; is classified in the United States as Generally Recognized as Safe (GRAS), and is used in food up to the maximum permitted level of 0.1%.[1] From Microtox studies, the toxicity, in terms of the concentration that eliminated 50% of bacterial population or EC_{50}, of sodium benzoate was determined to be ~ 560 mg/L,[2] which was three to five orders of magnitude less than that of tributyltin (TBT) (~0.01–0.02 mg/L). Recognizing the commercial availability and low cost of sodium

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benzoate, it is used in a variety of products, such as cosmetics and pharmaceuticals, but more commonly in foods such as soda and fruit juice to preserve freshness.[3] However, its catalytic ability has been neglected for a long time. Sodium benzoate has been reported as a catalyst in only one organic reaction to our knowledge.[4] Therefore, the study of sodium benzoate as an environmentally benign catalyst is in demand.

The Knoevenagel condensation is one of the most important reactions in organic synthesis for carbon–carbon bond formation. It is usually performed in organic solvents in the presence of common bases.[5] In recent years, various catalysts have been employed to catalyze this reaction, each affording variable yields of Knoevenagel condensation compounds in solution or under solvent-free conditions. Using the methods indicated previously, there are still some limitations which exist, such as the long reaction time; the highly corrosive, expensive, and large amounts of catalysts needed; and the strict reactive condition (N_2 atmosphere or high temperature).[6,7] Hence, the introduction of efficient and new methods based on green methodology is still of interest.

Ultrasound has increasingly been used in organic synthesis in the past three decades. Compared with traditional methods, this method is more convenient and easily controlled. A large number of organic reactions can be carried out in greater yield, shorter reaction time, or milder conditions under ultrasonic irradiation.[8] We report here an efficient condensation between active methylene compounds and various aromatic aldehydes catalyzed by sodium benzoate through conventional stirring (method A) or under ultrasounic irradiation (method B).

RESULTS AND DISCUSSION

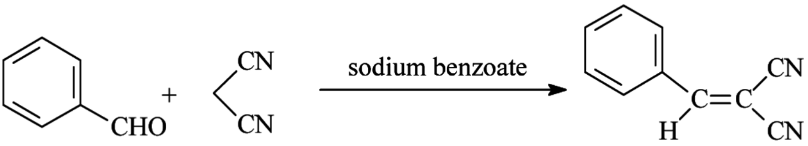
At the begining, to evaluate the effect of the amount of catalyst on Knoevenagel condensation, we investigated its efficiency in a model reaction between benzaldehyde and malononitrile through method A. The yield was 96.7%, when sodium benzoate was 1 mol% (Table 1, entry 3, and Scheme 1). There was no obvious increase in the yield when more catalyst was added. The decrease in reactivity with the decrease in the amount of sodium benzoate also shows that the Knoevenagel condensation is a base-catalyzed reaction in the procedure described in this study.

To investigate the influence of the solvents, the model reaction was carried out through method A in various solvents and also under solvent-free conditions. As shown in Table 2, in comparison to conventional methods in solvent the yield of

Table 1. Effect of catalyst amount on Knoevenagel condensation of benzaldehyde with malononitrile through method A

Entry	Amount (mol %)	Time (min)	Yield (%)[a]
1	0.25	27	94.3
2	0.5	22	96.7
3	1	15	96.7
4	2	15	95.5
5	5	13	96.5

[a] Isolated yield.



Scheme 1. Knoevenagel condensation of benzaldehyde with malononitrile with different amounts of sodium benzoate.

the reaction under solvent-free condition was greater and the reaction time was shorter (Scheme 2). The reaction also proceeded well in ethanol, whereas in the other solvents the reaction proceeded slowly. Consequently, the remainder of reactions through both method A and method B were carried out under solvent-free conditions.

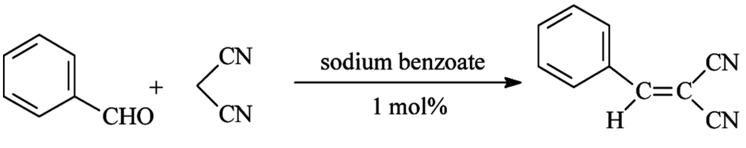
We also observed the effect of frequency of ultrasounic irradiation on the Knoevenagel condensation of furfural with ethyl cyanoacetate. The reaction rate was compared at 45, 80, and 100 kHz having the same output power of 300 W. Compared to the reaction without ultrasounic irradiation (Table 2, entry 6), in the presence of ultrasound the yield was 98.7% only after 10 min for 45 kHz (Table 2, entry 7). Experiments performed with variable frequency (80 and 100 kHz) showed the same trend. These facts mean that ultrasound could enhance this reaction, catalyzed by sodium benzoate, and there was an optimum frequency of 45 kHz for effective Knoevenagel condensation. As a result, further experiments were carried out with 45-kHz ultrasounic irradiation.

After optimizing the reaction conditions, aromatic aldehydes were treated with various active methylene compounds such as ethyl cyanoacetate and malononitrile in

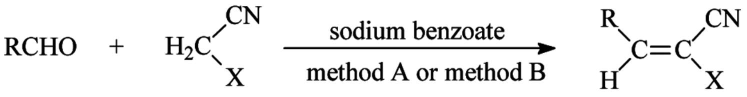
Table 2. Effect of reaction conditions on Knoevenagel condensation catalyzed by sodium benzoate

Entry	Solvent[a]	Ultrasound (kHz)	Time (min)	Yield (%)[b]
1	C_2H_5OH	–	15	96.4
2	CH_3CN	–	50	85.1
3	THF	–	240	96.3
4	1, 4-Dioxane	–	100	76.9
5	Acetone	–	600	0
6	Solvent-free	–	15	96.7
7	Solvent-free	45	10	98.7
8	Solvent-free	80	12	98.3
9	Solvent-free	100	13	96.3

[a] The reaction was carried out in 2 mL of solvent.
[b] Isolated yield.



Scheme 2. Knoevenagel condensation of benzaldehyde with malononitrile under different reaction conditions.



1 **2** **3**

Scheme 3. Knoevenagel condensations of aldehydes with active methylene compounds catalyzed by sodium benzoate.

the presence of sodium benzoate under ultrasounic irradiation or through conventional stirring (Scheme 3). All of the comparative results are shown in Table 3.

The reactions were first carried out through the conventional stirring under solvent-free conditions at room temperature. As shown in Table 3, the corresponding products were obtained in good to excellent yields in several minutes except for the condensation of ethyl cyanoacetate.

The condensation reactions also were carried out under ultrasounic irradiation at room temperature. As seen in Table 3, the reaction times were reduced and most of the yields were improved under ultrasound.

We found that the reaction proceeded much faster with acidic malononitrile than with ethyl cyanoacetate. The aldehydes, containing electron-donating or electron-withdrawing groups, all gave the desired products in excellent yields in short times (from 7 to 60 min through method A and from 5 to 40 min through method B) (Table 3, entries 1–7). Compared to the Knoevenagel reactions of malononitrile with aromatic aldehydes, the reactions of ethyl cyanoacetate with the same aromatic aldehydes needed longer time. However, both the conventional magnetic stirring and the ultrasounic irradiation afforded the desired arylmethylenemalonitriles and ethyl α-cyanocinnamates as the single products. The results indicate that only *E* isomers of the olefinic products were produced when ethyl cyanoacetate was used.

Table 3. Knoevenagel condensation catalyzed by sodium benzoate under ultrasound irradiation or through conventional stirring

				Time (min)		Yield (%)[c]		M.p. (°C)	
Entry	R	X	Compound	A[a]	B[b]	A[a]	B[b]	Found	Reported
1	C_6H_5	CN	**3a**	15	10	96.7	98.7	82–83	82–83[9]
2	2-Furyl	CN	**3b**	13	10	90.1	96.2	65–66	65–66[9]
3	2-ClC_6H_4	CN	**3c**	7	5	87.2	90.8	93–95	95–96[10]
4	2, 4-$Cl_2C_6H_3$	CN	**3d**	14	7	95.1	98.3[d]	154–155	154–155[11]
5	4-$CH_3OC_6H_4$	CN	**3e**	15	7	86.8	93.7	111–113	110–112[9]
6	4-OHC_6H_4	CN	**3f**	23	10	98.8	98.2[d]	185–186	183–184[12]
7	Vanillin	CN	**3g**	60	40	85.8	92.3[d]	133–135	135–136[10]
8	2-Furyl	COOEt	**3h**	350	210	95.0	95.9	86–87	86–87[9]
9	2, 4-$Cl_2C_6H_3$	COOEt	**3i**	180	108	98.2	99.0	83–84	83–84[10]
10	4-OHC_6H_4	COOEt	**3j**	360	192	84.8	90.4	164–167	162–164[9]

[a] A, without ultrasound irradiation.
[b] B, under ultrasound irradiation.
[c] Isolated yield.
[d] Under ultrasound irradiation in 2 mL C_2H_5OH.

Table 4. The reuse of sodium benzoate

Cycle	1	2	3	4
Yield (%)[a]	98.6	98.0	97.5	97.3

[a]Isolated yield.

Table 5. Knoevenagel condensation of benzaldehyde with malononitrile catalyzed by different catalysts

Entry	Catalyst and Conditions	Amount (mol%)	Time (min)	Yield (%)[a]	Ref.
1	$C_6H_5CO_2Na$/solvent-free	1	10	98.7	-[b]
2	MgF_2/EtOH	31	150	93	13
3	I_2/K_2CO_3/EtOH	30	12	80	14
4	[2-aemin][PF_6]/H_2O	0.8	20	92	15
5	HEAPs/H_2O	10	10	95	16
6	[C_4dabco][BF_4]/H_2O	15	<1	100	17

[a]Isolated yield.
[b]Under ultrasound irradiation.

Mention must be made here that 2 mL C_2H_5OH had to be added when solid aldehydes were treated with malononitrile under ultrasounic irradiation conditions (Table 3, entries 4,6, and 7). The volume of malononitrile was so small that the aldehydes, malononitrile, and catalyst were difficult to mix thoroughly under ultrasounic irradiation without stirring, and this may lead to prolonged reaction times.

The miscibility of sodium benzoate with water made the workup process quite easy, as the catalyst could be removed from the product simply by washing the product with 5% aqueous alcohol. The catalyst in the aqueous phase could be recovered by removing the water under vacuum and then washing the catalyst with acetone and drying it at rt. Catalyst reusability was assessed in the reaction of benzaldehyde with malononitrile under ultrasound irradiation. Table 4 shows the catalyst can be reused four times without significant decrease of the reactivity.

To show the merit of sodium benzoate in comparison with the other catalysts used for the same reaction, we have tabulated some of the results in Table 4. As is evident from the results, the required amount for the most catalysts used for this purpose is more than 1 mol% and also the required reaction time is longer. Mention must be made here that some catalysts are expensive, complex, or unavailable and solvents are necessary.

CONCLUSION

In conclusion, we have demonstrated a facile and efficient method for the Knoevenagel condensation of aromatic aldehydes with active methylene compounds under both ultrasounic irradiation and conventional stirring conditions in the presence of sodium benzoate. Improvements in rates and yields of the reactions were observed by carrying out the reactions under ultrasounic irradiation. The catalyst remained active and exhibited no substantial loss of activity for up to four reaction cycles. The attractive features of this procedure were the mild reaction conditions, good yields, cleaner reaction profiles, and operational simplicity, all of which make it a useful and attractive strategy for the preparation of substituted olefins.

EXPERIMENTAL

All reagents were purchased and used without further purification. Melting points were determined using an XT-4 micro-melting-point apparatus. Infrared (IR) spectra were recorded on a Nicolet Avatar 360 Fourier-transform instrument in KBr with absorption in cm^{-1}. ^{1}HNMR spectra were recorded on a Bruker ARX-300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Ultrasonication was performed in a KQ-300VDE ultrasounic cleaner with frequencies of 45, 80, and 100 kHz and an output power of 300 W.

General Procedure for Knoevenagel Condensation Through Method A

Aldehyde (10 mmol) and the active methylene compound (10 mmol) were mixed thoroughly, and then 0.1 mmol of sodium benzoate was added. The reaction mixture was stirred for the specified time at room temperature. After completion of the reaction, the reaction mixture was treated with cold 5% aqueous alcohol (30 mL). The product was filtered and dried, and, in general, no further purification method was required. All the products were previously reported and were characterized by comparing mp, IR, and ^{1}H NMR with litrature data.

General Procedure for Knoevenagel Condensation Through Method B

Aldehyde (10 mmol), active methylene compound (10 mmol), and 0.1 mmol of sodium benzoate were put in a flask. The flask was located at the maximum energy area in the ultrasonic cleaner and addition or removal of water was used to control the temperature of the water bath at room temperature. After completion of the reaction, the subsequent steps were the same as in method A.

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REFERENCES

1. Sagoo, S. K.; Board, R.; Roller, S. Chitosan potentiates the antimicrobial action of sodium benzoate on spoilage yeasts. *Lett. Appl. Microbiol.* **2002**, *34*, 168–172.
2. Haque, H.; Cutright, T. J.; Newby, B. M. Z. Effectiveness of sodium benzoate and benzoic acid as freshwater low toxicity antifoulants when dispersed in solution and entrapped in silicone coatings. *Biofouling* **2005**, *21*, 109–119.
3. (a) Jones, J. M. *Food Safety*; Eagan Press: St. Paul, MN, 1992; pp. 93–96 (b) Archer, A. W. Determination of benzoic and sorbic acids in orange juice by high-performance liquid

chromatography. Analyst **1980**, *105*, 407–409; (c) Gagliardi, L.; De Orsi, D.; Manna, L.; Tonelli, D. HPLC determination of clobetasol propionate in cosmetic products. *J. Liq. Chromatogr. Rel. Technol*. **1997**, *20*, 1797–1808; (d) Mandrou, B.; Bressolle, F. Thinlayer chromatography reflectometric determination of benzoic and sorbic acids in fruit beverages. *J. Assoc. Off. Anal. Chem*. **1980**, *63*, 675–678; (e) Mandrou, B.; Nolleau, V.; Gastaldi, E.; Fabre, H. Solid-phase extraction as a clean-up procedure for the liquid chromatographic determination of benzoic and sorbic acids in fruit-derived products. *J. Liq. Chromatogr. Rel. Technol*. **1998**, *21*, 829–842; (f) Foulke, J. E. Cooking up the new food label. *FDA Consumer* **1993**, *27*, 33–38.

4. Moorhoff, C. M.; Schneider, D. F. Sodium benzoate as a mild base catalyst for the tandem Michael–Aldol self-condensation of γδ-unsaturated β-ketoesters. *Monatsh. Chem.* **1998**, *129*, 409–417.
5. Reeves, R. L. *The Chemistry of the Carbonyl Group*; S. Patai (Ed.); Interscience: New York, 1967; 593.
6. (a) Choudary, B. M.; Kantam, M. L.; Kavita, B.; Reddy, C. V.; Figueras, F. Catalytic C–C bond formation promoted by Mg–Al–O–t-Bu hydrotalcite. *Tetrahedron* **2000**, *56*, 9357–9364; (b) Mitra, A. K.; De, A.; Karchaudhuri, N. Solvent-free microwave-enhanced Knoevenagel condensation of ethyl cyanoacetate with aldehydes. *Synth. Commun.* **1999**, *29*, 1532–2432; (c) Wang, S. X.; Li, J. T.; Yang, W. Z.; Li, T. S. Improved synthesis of chalcones under ultrasound irradiation. *Ultrason. Sonochem.* **2002**, *9*, 237–239.
7. (a) Rong, L. C.; Li, X. Y.; Wang, H. Y.; Shi, D. Q.; Tu, S. J.; Zhuang, Q. Y. Efficient green procedure for the Knoevenagel condensation under solvent-free conditions. *Synth. Commun.* **2006**, *36*, 2407–2412.
8. (a) Bremner, D. H. Recent advances in organic synthesis utilizing ultrasound. *Ultrason. Sonochem.* **1994**, *1*, S119–S124; (b) Boldyrev, V. V. Mechanochemistry and sonochemistry. *Ultrason. Sonochem.* **1995**, *2*, S143–S145 (c) Price, G. J. Recent developments in sonochemical polymerisation. *Ultrason. Sonochem.* **2003**, *10*, 277–283; (d) Toma, S.; Gaplovsky, A.; Luche, J. The effect of ultrasound on photochemical reactions. *Ultrason. Sonochem.* **2001**, *8*, 201–207.
9. Liu, Y.; Liang, J.; Liu, X.-H.; Fan, J.-C.; Shang, Z.-C. Polyethylene glycol (PEG) as a benign solvent for Knoevenagel condensation. *Chin. Chem. Lett.* **2008**, *19*, 1043–1046.
10. Ren, Z.-J.; Cao, W.-G.; Tong, W.-Q. The Knoevenagel condensation reaction of aromatic aldehydes with malononitrile by grinding in the absence of solvents and catalysts. *Synth. Commun.* **2002**, *32*, 3475–3479.
11. Wang, X.-S.; Zeng, Z.-S.; Li, Y.-L.; Shi, D.-Q.; Tu, S.-J. Simple procedure for the synthesis of arylmethylenemalononitrile without catalyst. *Synth. Commun.* **2005**, *35*, 1915–1920.
12. Zhang, J.-C.; Han, B.-X.; Zhu, A.-L.; Ma, X.-M. Knoevenagel condensation catalyzed by 1,1,3,3-tetramethylguanidium lactate. *Synth. Commun.* **2006**, *36*, 3305–3017.
13. Kumbhare, R. M.; Sridhar, M. Magnesium fluoride–catalyzed Knoevenagel reaction: An efficient synthesis of electrophilic alkenes. *Catal. Commun.* **2008**, *9*, 403–405.
14. Ren, Y.-M.; Cai, C. Iodine catalysis in aqueous medium: An improved reaction system for Knoevenagel and nitroaldol condensation. *Catal. Lett.* **2007**, *118*, 134–138.
15. Cai, Y.-Q.; Peng, Y.-Q.; Son, G.-H. Amino-functionalized ionic liquid as an efficient and recyclable catalyst for Knoevenagel reactions in water. *Catal. Lett.* **2006**, *109*, 61–64.
16. Fang, D.; Fei, Z.-H.; Liu, Z.-L. The Knoevenagel reaction in water catalyzed by zwitterionic liquids. *Monatsh. Chem.* **2008** *139*, 799–803.
17. Xu, D. Z.; Liu, Y. J.; Shi, S.; Wang, Y. M. A simple, efficient, and green procedure for Knoevenagel condensation catalyzed by [C_4DABCO][BF_4] ionic liquid in water. *Green Chem.* **2010**, *12*, 514–517