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An Eco-friendly Method for Synthesis of Symmetrical and Unsymmetrical Benzoin Derivatives

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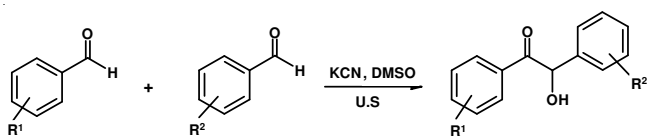
A rapid, highly efficient and mild green synthesis of symmetrical and unsymmetrical benzoin derivatives was achieved from the reaction of benzaldehyde derivatives with potassium cyanide in dimethyl sulfoxide under argon gas and ultrasound. This simple method affords benzoin derivatives at room temperature in short reaction times with high yield and purity.

Key Words: Benzoin condensation, Dimethylsulfoxide, Potassium cyanide, Ultrasound.

INTRODUCTION

α-Hydroxyketones are important building blocks for the synthesis of several drugs and natural products[1-12]. For this reason, many chemical methods for their synthesis are described in literature[13-21]. The cyanide ion-catalyzed condensation of aromatic aldehydes to the corresponding benzoins has great synthetic utility. According to a well documented classical benzoin condensation mechanism, cyanide ion catalyzed generation of acyl anion is the key step in this transformation[22,23]. Many improvements have been made for the symmetrical benzoin condensation utilizing thiazolium and triazolium salts[24-35] but synthesis of unsymmetrical benzoins, under traditional conditions, have problems associated with the formation of four possible benzoins, two of them being isomeric[36-39]. Furthermore, some of the reported methods suffer from drawbacks such as longer reaction time, lower yields, expensive catalysts, harsh conditions or complexity of work-up. So the development of a milder, simpler, greener and more efficient procedure for the synthesis of symmetrical and unsymmetrical benzoins is highly desirable. Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis in the last two decades, compared with traditional methods, the procedure is more convenient. A large number of organic reactions can be carried out in higher yield, shorter reaction time or milder conditions under ultrasonic irradiation[40]. Herein, we wish to report a general, efficient and eco-friendly method for the synthesis of symmetrical and unsymmetrical benzoin derivatives using potassium cyanide in dimethyl sulfoxide under argon gas and ultrasound (**Scheme-I**).



Scheme-I: Synthesis of benzoins in DMSO under argon gas and ultrasound

EXPERIMENTAL

In a typical procedure chemicals were purchased from Merck chemical company. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded by Bruker DRX-500 Avance spectrometer. Tetramethyl silane (TMS) was used as an internal reference. A Magna-550 Nicolet recorded IR spectra. Vibrational transition frequencies were reported as wave numbers (cm^{-1}). A mass spectrum was recorded by QP-1100EX Shimadzu spectrometer. Sonication was performed in a UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The operating frequency was 24 kHz and the output power was 0-400 Watt through manual adjustment. UV spectra were recorded on a Hitachi 200-20 spectrometer using spectrophotometric grade ethanol (Baker). Melting points were obtained with an electrothermal micro melting point apparatus and are uncorrected.

General procedure for synthesis of 2a-f: To synthesize the symmetrical benzoins, a solution of 2 mmol of benzaldehyde derivatives in 10 mL of DMSO is mixed with 1 g of KCN (96-98 %). This reaction was completed under argon gas and ultrasound for a few minutes. The instantaneous crystallization of the product observed with benzoin is unusual. Purification

generally can be accomplished by recrystallization from ethanol and evaporation of the solvent.

General procedure for synthesis of 2e-j: To synthesize the unsymmetrical benzoins, 2 mmol of donor benzaldehyde, 10 mmol of acceptor benzaldehyde, 10 mL of DMSO and 1.08 g of potassium cyanide were used. This reaction was completed under argon gas and ultrasound for a few minutes. The instantaneous crystallization of the product observed with benzoin is unusual. Purification generally can be accomplished by recrystallization from ethanol and evaporation of the solvent.

The structure of these compounds has been investigated using different methods of spectroscopy and spectrometry: UV, ^{1}H NMR, ^{13}C NMR, IR and MS.

Compound (a), benzoin: UV (CH_3OH) λ_{max}: 230 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.56 (1H, s, OH), 5.71 (1H, s, CH), 7.23-7.68 (10H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 68.41 (CH), 125.27 (2CH), 128.12 (CH), 129.67 (2CH), 131.05 (2CH), 131.27 (2CH), 133.42 (C), 138.61 (C), 197.10 (CO); IR (KBr, ν_{max}, cm^{-1}): 3250-3500 (OH, m), 1670 (CO, s), 1450, 1600 (C=C, m), 690, 750 (=C-H, s).

Compound (b), 4,4'-dimethylbenzoin: UV (CH_3OH) λ_{max}: 238 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.23 (3H, s, CH_3), 2.35 (3H, s, CH_3), 4.62 (1H, s, OH), 5.90 (1H, s, CH), 7.23 (4H, d, CH), 7.64 (4H, d, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.47 (CH_3), 20.29 (CH_3), 69.17 (CH), 126.17 (2CH), 127.42 (2CH), 127.55 (2CH), 128.02 (2CH), 134.19 (C), 135.24 (C), 137.67 (C), 139.08 (C), 196.31 (CO); IR (KBr, ν_{max}, cm^{-1}): 3200-3450 (OH, m), 1675 (CO, s), 1450, 1600 (C=C, m), 830 (=C-H, s).

Compound (c), 3,3'-dimethylbenzoin: UV (CH_3OH) λ_{max}: 239 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.27 (3H, s, CH_3), 2.31 (3H, s, CH_3), 4.56 (1H, s, OH), 5.88 (1H, s, CH), 6.90-7.63 (8H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.39 (CH_3), 20.17 (CH_3), 69.21 (CH), 124.41 (CH), 126.91 (CH), 127.22 (CH), 128.03 (CH), 128.87 (CH), 129.15 (CH), 130.56 (CH), 131.37 (CH), 135.71 (C), 138.03 (C), 140.49 (C), 142.13 (C), 196.24 (CO); IR (KBr, ν_{max}, cm^{-1}): 3220-3550 (OH, m), 1685 (CO, s), 1480, 1620 (C=C, m), 690, 780 (=C-H, s).

Compound (d), 3,3'-dichlorobenzoin: UV (CH_3OH) λ_{max}: 234 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.32 (1H, s, OH), 5.94 (1H, s, CH), 7.26-8.12 (8H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 71.18 (CH), 125.03 (CH), 126.21 (CH), 126.97 (CH), 128.46 (CH), 129.59 (CH), 130.92 (CH), 131.38 (CH), 132.73 (CH), 134.41 (C), 135.10 (C), 135.68 (C), 136.73 (C), 195.47 (CO); IR (KBr, ν_{max}, cm^{-1}): 3200-3500 (OH, m), 1650 (CO, s), 1440, 1620 (C=C, m), 700, 780 (=C-H, s).

Compound (e), 3,3'-dinitrobenzoin: UV (CH_3OH) λ_{max}: 248 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.45 (1H, s, OH), 5.73 (1H, s, CH), 7.26-8.12 (8H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 72.45 (CH), 124.39 (CH), 124.88 (CH), 125.70 (CH), 126.57 (CH), 132.09 (CH), 132.96 (CH), 133.41 (C), 134.10 (C), 134.68 (CH), 135.18 (CH), 151.69 (C), 152.12 (C), 193.33 (CO); IR (KBr, ν_{max}, cm^{-1}): 3150-3550 (OH, m), 1650 (CO, s), 1460, 1580 (C=C, m), 1330, 1540 (NO2, s), 700, 775 (=C-H, s); m/z: 302 (M^+), 152, 150, 77.

Compound (f), 2,2'-dinitrobenzoin: UV (CH_3OH) λ_{max}: 240 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.66 (1H, s, OH), 4.87 (1H, s, CH), 7.45-8.19 (8H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 71.79 (CH), 124.78 (CH), 125.06 (CH), 126.46 (CH), 128.98 (CH), 129.61 (CH), 130.17 (CH), 131.66 (CH), 133.82 (CH), 135.74 (C), 138.37 (C), 145.03 (C), 146.51 (C), 187.63 (CO); IR (KBr, ν_{max}, cm^{-1}): 3200-3500 (OH, m), 1630 (CO, s), 1430, 1575 (C=C, m), 1350, 1550 (NO2, s), 750 (=C-H, s).

Compound (g), 4-methylbenzoin: UV (CH_3OH) λ_{max}: 232 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (3H, s, CH_3), 4.56 (1H, s, OH), 5.94 (1H, s, CH), 7.19-7.84 (9H, m, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.66 (CH_3), 67.02 (CH), 127.73 (2CH), 128.44 (CH), 129.04 (2CH), 129.26 (2CH), 129.36 (2CH), 130.95 (C), 139.32(C), 144.94 (C), 198.47 (CO); IR (KBr, ν_{max}, cm^{-1}): 3150-3500 (OH, m), 1675 (CO, s), 1430, 1575 (C=C, m), 780, 830 (=C-H, s); m/z: 226 (M^+), 119, 107, 77.

Compound (h), 4-methoxybenzoin: UV (CH_3OH) λ_{max}: 238 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (3H, s, OCH_3), 4.68 (1H, s, OH), 5.97 (1H, s, CH), 6.85 (2H, d, CH), 7.26-7.31 (3H, m, CH), 7.33 (2H, d, CH), 7.91 (2H, d, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.43 (CH3), 75.77 (CH), 113.92 (2CH), 126.26 (C), 127.69 (2CH), 128.41 (CH), 129.04 (2CH), 131.54 (2CH), 139.61 (C), 164.04 (C), 197.18 (CO); IR (KBr, ν_{max}, cm^{-1}): 3230-3520 (OH, m), 1685 (CO, s), 1420, 1580 (C=C, m), 1120, 1300 (C-O, s), 770, 830 (=C-H, s); m/z: 242 (M^+), 135, 107, 77.

Compound (i), 3'-bromo-4-methoxybenzoin: UV (CH_3OH) λ_{max}: 232 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.76 (3H, s, OCH_3), 4.55 (1H, s, OH), 5.78 (1H, s, CH), 6.58-7.32 (6H, m, CH), 7.78 (2H, d, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 54.79 (CH_3), 77.68 (CH), 115.34 (2CH), 122.50 (C), 126.49 (CH), 128.02 (CH), 129.43 (CH), 130.17 (CH), 132.96 (2CH), 133.27 (C), 138.13 (C), 164.69 (C), 196.01 (CO); IR (KBr, ν_{max}, cm^{-1}): 3160-3470 (OH, m), 1700 (CO, s), 1470, 1630 (C=C, m), 1100, 1280 (C-O, s), 780, 840 (=C-H, s); m/z: 322 (M^++2), 320 (M^+), 185, 135, 77.

Compound (j), 4-dimethylaminobenzoin: UV (CH_3OH) λ_{max}: 236 nm; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.97 (6H, s, CH_3), 4.59 (1H, s, OH), 5.76 (1H, s, CH), 6.36 (2H, d, CH), 7.15 (5H, m, CH), 7.91 (2H, d, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 41.18 (CH_3), 76.90 (CH), 112.54 (2CH), 124.83 (2CH), 127.49 (2CH), 128.32 (C), 131.93 (2CH), 138.66 (C), 157.52 (C), 195.70 (CO); IR (KBr, ν_{max}, cm^{-1}): 3200-3490 (OH, m), 1640 (CO, s), 1430, 1590 (C=C, m), 780, 830 (=C-H, s); m/z: 255 (M^+), 148, 107, 77.

RESULTS AND DISCUSSION

The benzoin condensation consists in the treatment of an aromatic aldehyde with potassium cyanide or sodium cyanide, usually in aqueous ethanolic solution. By the use of one mole of each of two different aromatic aldehydes, it is possible to prepare many unsymmetrical benzoins. The reaction is not applicable to all aromatic aldehydes. The condensation is affected greatly by the nature of the substituents in the aromatic nucleus. Many substituted benzaldehydes either do not react or yield products other than benzoins. In order that an aldehyde may form a symmetrical benzoin it must possess not only a relatively unsaturated carbonyl group but also a mobile hydrogen atom. Two aldehydes, neither of which forms a symmetrical benzoin, may form an unsymmetrical benzoin if one aldehyde is an acceptor and the other a donor of a hydrogen

atom. Benzaldehyde, which is both an acceptor and a donor, readily forms a benzoin. For instance, 4-dimethylaminobenzaldehyde does not form a symmetrical benzoin. However, it condenses with benzaldehyde, acting as a donor, to yield an unsymmetrical benzoin (**2j**). Benzaldehyde by contrast usually acts as an acceptor when it reacts with other aldehyde to form unsymmetrical benzoins. Two different aldehydes might be expected to yield a mixture of two symmetrical benzoins and unsymmetrical benzoins, but only a single unsymmetrical benzoin usually is isolable. The second unsymmetrical benzoin may be formed when the reactivity of the two aldehydes is similar[41,42]. In this work, symmetrical and unsymmetrical benzoins are obtained in high yield from the reaction of benzaldehyde derivatives in the presence of potassium cyanide and DMSO under argon gas and ultrasound. In an initial study, for examination of the solvent effect in this condensation, benzaldehyde derivatives was first reacted with KCN in the presence of ethanol (95 %) under ultrasound. The results are shown in Table-1. These first results indicate the shorter times of reaction to the conventional heating method. Also the yields of reaction are relatively increased in this way.

TABLE-1
SYNTHESIS OF BENZOIN DERIVATIVES IN ETHANOL (95 %) UNDER ULTRASOUND

Entry	R^1	R^2	Time (min)	Yield (%)
a	H	H	5	92
b	4-CH_3	4-CH_3	35	65
c	3-CH_3	3-CH_3	45	58
d	4-Cl	4-Cl	10	72
e	3-NO_2	3-NO_2	7	78
f	2-NO_2	2-NO_2	15	43
g	4-CH_3	H	40	55
h	4-OCH_3	H	45	52
i	4-OCH_3	3-Br	30	78
j	4-$N(CH_3)_2$	H	20	67

In order to optimize the reaction conditions, we used DMSO and argon gas. DMSO was used as a solvent instead of ethanol (Table-2). The yields of reaction increased in the presence of DMSO which reflects to ability of DMSO to solvate the metal cation and not the cyanide anion thus increasing it activity for better nucleophilic attack. On the other side, some aldehydes such as benzaldehyde is easily oxidized to benzoic acid under O_2 which can impede the desired reaction, so freshly distilled benzaldehyde is used. We also used argon gas to create an inert atmosphere in reaction surrounding. In the presence of argon gas, the beautiful crystals of benzoic derivatives were formed, too.

TABLE-2
SYNTHESIS OF BENZOIN DERIVATIVES IN DMSO UNDER ARGON GAS AND ULTRASOUND

Entry	R^1	R^2	Time (min)	$m.p._{rep}/m.p._{lit}$ (ºC)	Yield (%)
a	H	H	3	133-135/134[43]	98
b	4-CH_3	4-CH_3	15	88-90/86-88[44]	87
c	3-CH_3	3-CH_3	20	Liquid[43]	91
d	4-Cl	4-Cl	6	86-88/88[43]	94
e	3-NO_2	3-NO_2	3	178-180/----	96
f	2-NO_2	2-NO_2	7	153-155/168-169[43]	67
g	4-CH_3	H	15	108-110/107-108[45]	82
h	4-OCH_3	H	20	106-108/106-106.5[45]	74
i	4-OCH_3	3-Br	15	87-89/88[37]	93
j	4-$N(CH_3)_2$	H	8	161-163/163.5-164.5[45]	97

Conclusion

This work demonstrates an expedient and highly efficient methodology for the synthesis of symmetrical and unsymmetrical benzoin derivatives using potassium cyanide in dimethyl sulfoxide under argon gas and ultrasound. In addition of efficiency and simplicity, this protocol provides a very fast, "green" and low cost procedure for the synthesis of benzoin derivatives. In total, a general method is used to constitute both electron-withdrawing and electron-donating constitutens.

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REFERENCES

1. A.G. Chaudhary, D.G.I. Kingston, *Tetrahedron Lett.*, **34**, 4921 (1993).
2. R. Uchida, K. Shiomi, T. Sunazuka, J. Inokoshi, A. Nishizawa, T. Hirose, H. Tanaka, Y. Iwai and S. Omura, *J. Antibiot.*, **49**, 886 (1996).
3. W.R. Roush, K. Briner, B.S. Kesler, M. Murphy and D.J. Gustin, *J. Org. Chem.*, **61**, 6098 (1996).
4. J. Du Bois, C.S. Tomooka, J. Hong and E.M. Carreira, *Acc. Chem. Res.*, **30**, 364 (1997).
5. A.S. Demir, H. Hamamci, C. Tanyeli, I. Akhmedov and F. Doganel, *Tetrahedron: Asymm.*, **9**, 1673 (1998).
6. M. Kawase, H. Sakagami, K. Kusama, N. Motohashi and S. Saito, *Bioorg. Med. Chem. Lett.*, **9**, 3113 (1999).
7. F. Babudri, V. Fiandanese, G. Marchese and A. Punzi, *Tetrahedron*, **55**, 2431 (1999).
8. V.M. Girijavallabhan, A.K. Ganguly, P.A. Pinto and O.Z. Sarre, *Bioorg. Med. Chem. Lett.*, **1**, 349 (1999).
9. W. Adam, M. Lazarus, C.R. Saha-Moller and P. Schreier, *Acc. Chem. Res.*, **32**, 837 (1999).
10. Q.K. Fang, Z. Han, P. Grover, D. Kessler, C.H. Senanayake and S.A. Wald, *Tetrahedron: Asymm.*, **11**, 3659 (2000).
11. O.B. Wallace, D.W. Smith, M.S. Deshpande, C. Polson and K.M. Felsenstein, *Bioorg. Med. Chem. Lett.*, **13**, 1203 (2003).
12. T. Tanaka, M. Kawase and S. Tani, *Bioorg. Med. Chem.*, **12**, 501 (2004).
13. W. Adam, M. Muller and F. Prechtl, *J. Org. Chem.*, **59**, 2358 (1994).
14. W. Adam, R.T. Fell, V.R. Stegmann and C.R. Saha-Moller, *J. Am. Chem. Soc.*, **120**, 708 (1998).
15. W. Adam, C.R. Saha-Moller, C.-G. Zhao, *Tetrahedron: Asymm.*, **9**, 4117 (1998).
16. W. Adam, R.T. Fell, C.R. Saha-Moller, C.-G. Zhao, *Tetrahedron: Asymm.*, **9**, 397 (1998).
17. F.A. Davies and B.-C. Chen, *Chem. Rev.*, **92**, 919 (1992).
18. T. Hashiyama, K. Morikawa and K.B. Sharpless, *J. Org. Chem.*, **57**, 5067 (1992).
19. T. Wirth and U.H. Hirt, *Tetrahedron: Asymm.*, **8**, 23 (1997).
20. T. Koike, K. Murata and T. Ikariya, *Org. Lett.*, **2**, 3833 (2000).
21. Y. Zhu, L. Shu, Y. Tu and Y. Shi, *J. Org. Chem.*, **66**, 1818 (2001).
22. A.J. Lapworth, *J. Chem. Soc.*, **83**, 995 (1903).
23. J.P. Kuebrich, R.L. Schowen, M.-S. Wang and M.E. Lupes, *J. Am. Chem. Soc.*, **93**, 1214 (1971).
24. M.J. White and F.J. Leeper, *J. Org. Chem.*, **66**, 5124 (2001).
25. J.H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer and G. Raabe, *Helv. Chim. Acta*, **79**, 61 (1996).
26. D. Enders, K. Breuer and J.H. Teles, *Helv. Chim. Acta*, **79**, 1217 (1996).
27. D. Enders and U. Kallfass, *Angew. Chem. Int. Ed.*, **41**, 1743 (2002).
28. T. Ukai, R. Tanaka and S. Dokawa, *J. Pharm. Soc. Jpn.*, **63**, 296 (1943).
29. R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958).
30. H. Stetter, Y. Ramsch and H. Kuhlmann, *Synthesis*, 733 (1976).
31. J. Castells, F. Lopez-Calahorra and L. Domingo, *J. Org. Chem.*, **53**, 4433 (1988).

32. T. Matsumoto, M. Ohishi and S. Inoue, *J. Org. Chem.*, **50**, 603 (1985).
33. J.C. Sheehan and T. Hara, *J. Org. Chem.*, **39**, 1196 (1974).
34. R.L. Knight and F.J. Leeper, *J. Chem. Soc., Perkin Trans. I*, 1891 (1998).
35. D. Enders and K. Breuer, in eds: E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Addition of Acyl Carbanion Equivalents to Carbonyl Groups and Enones In: Comprehensive Asymmetric Catalysis; Springer Verlag: Berlin, Vol. 3, pp. 1093-1102 (1999).
36. J.S. Buck and W.S. Ide, *J. Am. Chem. Soc.*, **52**, 220 (1930).
37. J.S. Buck and W.S. Ide, *J. Am. Chem. Soc.*, **52**, 4107 (1930).
38. G. Semerano, *Gazz. Chim. Ital.*, **71**, 447 (1941).
39. K.W. Merz and D. Plauth, *Chem. Ber.*, **90**, 1744 (1957).
40. J.-T. Li, S.-X. Wang, G.-F. Chen and T.-S. Li, *Curr. Org. Synth.*, **2**, 415 (2005).
41. M. Tiffeneau and J. Levy, *Bull. Soc. Chim. (France)*, **49**, 725 (1931).
42. J.S. Buck and W.S. Ide, *J. Am. Chem. Soc.*, **54**, 3302 (1932).
43. J.S. Buck and W.S. Ide, Organic Reactions, The Synthesis of Benzoins, John Wiley and Sons, Vol. 4, pp. 300-303 (1948).
44. Y. Liu, X. Xu and Y. Zhang, *Tetrahedron*, **60**, 4867 (2004).
45. J.F. Sobieski, Ph.D. Dissertation, The Institute of Paper Chemistry, Appleton, Wisconsin (1967).