

ของเหลวไอออนิก 1-บิวทิล-3-เมทิลอิมิดาโซเลียมโบรไมด์ ([Bmim][Br])
ทำหน้าที่เป็นทั้งตัวทำละลายและตัวเร่งปฏิกิริยาสำหรับปฏิกิริยาสีเขียว
ของการควบแน่นเบนโซอินแบบตรงกันข้าม
**Ionic Liquid 1-Butyl-3-methylimidazolium Bromide ([Bmim][Br])
Acted as Both Solvent and Catalyst for a Green Reaction of Cross
Benzoin Condensation**

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บทคัดย่อ

ปฏิกิริยาการควบแน่นเบนโซอินโดยใช้ของเหลวไอออนิก คือ 1-บิวทิล-3-เมทิลอิมิดาโซเลียมโบรไมด์ ([Bmim][Br]) เป็นตัวเร่งปฏิกิริยาและเป็นตัวกลางในสภาวะเบสมีโซเดียมไฮดรอกไซด์ ให้ผลิตภัณฑ์ที่คาดหวัง คือ ครอส-เบนโซอิน **4a-i** ในร้อยละของสารผลิตภัณฑ์ปานกลาง (60-70%) รวมถึงเกิดผลิตภัณฑ์ในรูปแบบโฮโม-เบนโซอิน **5a-d** และ **6a** เป็นผลผลิตข้างเคียงในร้อยละของสารผลิตภัณฑ์ต่ำ (9-18%)

คำสำคัญ: ควบแน่นเบนโซอินแบบตรงกันข้าม 1-บิวทิล-3-เมทิลอิมิดาโซเลียมโบรไมด์ ของเหลวไอออนิก เบนโซอิน

Abstract

Cross benzoin condensation using room temperature ionic liquids, namely 1-butyl-3-methylimidazolium bromide ([Bmim][Br]), acted as catalyzed and a solvent under NaOH base condition to afford desired cross-benzoin products **4a-i** in satisfactory yields (60-70%). Homo-benzoin condensation **5a-d** and **6a** also were occurred as side reactions in 9-18% yields.

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Introduction

Reactions catalyzed by *N*-heterocyclic carbenes (NHCs) were known long before the first isolation and characterization of a stabilized carbene [1]. Thiamine, or vitamin B1, shown as its chloride salt, has been known as a catalyst for the benzoin reaction for over 50 years and was the first known NHC organocatalyst. The mode of action for thiamine in the benzoin reaction was elucidated by Breslow in 1958 that the thiazol-2-ylidene, presented after deprotonation of the precursor thiazolium salt, was the active catalyst [1]. The postulated catalytic cycle analogous to the previously known cyanide-catalyzed synthesis of benzoin is shown in Figure 1 [2].

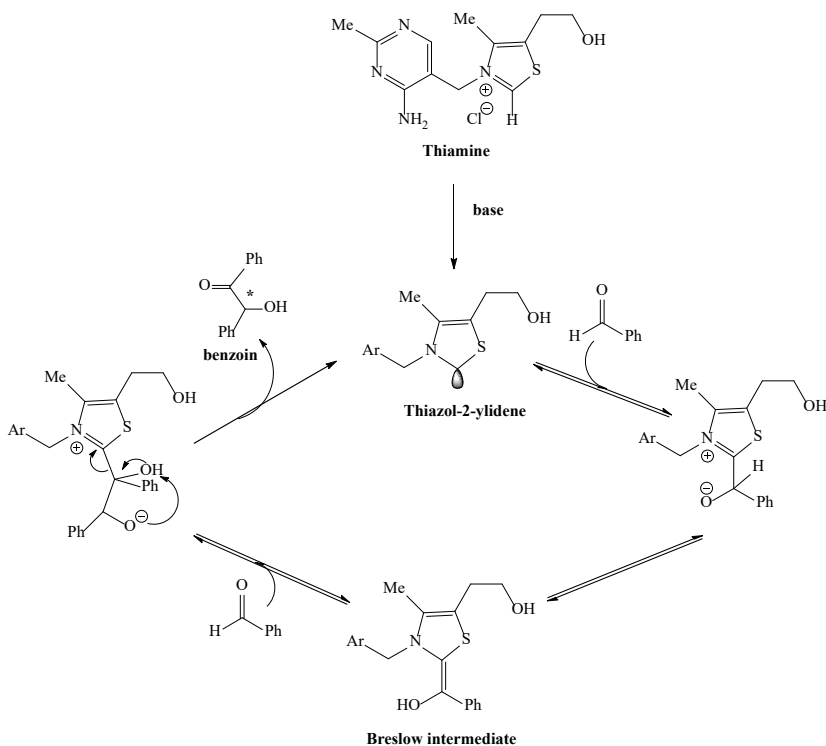


Figure 1. Catalytic cycle of the benzoin condensation proposed by R. Breslow

Cross benzoin condensation is one of the oldest C-C bond forming reactions between aldehydes and aldehydes in organic chemistry and has been developed for classical organic synthesis using cyanide ion including thiazolium and imidazolium catalyst as show in Figure 2.

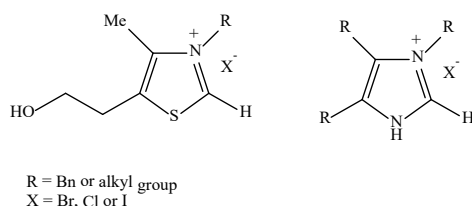
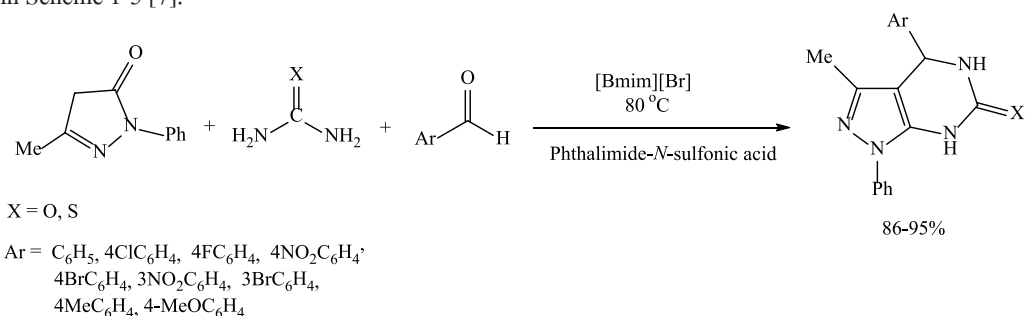
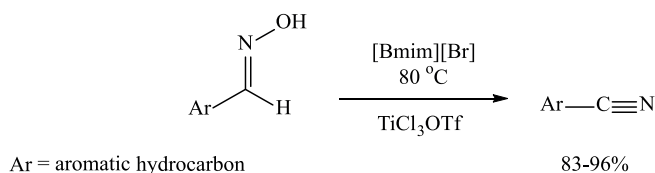


Figure 2. Structure of catalyzed thiazolium and imidazolium salts for the cross benzoin condensation

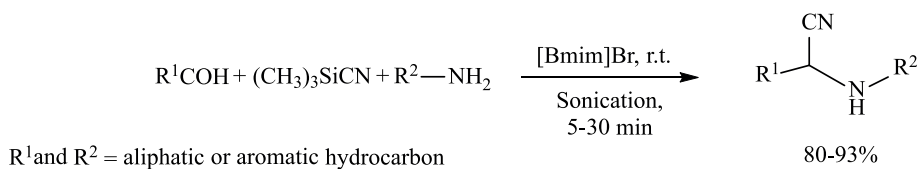
Recently, room temperature ionic liquids [RTILs], namely 1-butyl-3-methylimidazolium bromide [Bmim][Br] has attracted growing attention because of their unique features such as nonvolatility, thermal stability and variability with respect to the choice of organic cations, anions and side-chain attached to the organic cation. As neoteric solvents instead of conventional organic solvents. [Bmim][Br] has been used in many organic reactions to synthesis various important compounds such as 3-methyl-1,4-diphenyl-1,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidine-6-ones/thiones [3], aryl nitrile [4], α -aminonitriles [5], of 2-methyl-4-phenylpyrano[3, 2-c] chromen-5(4*H*)-one and warfarin [6] and Stetter reaction as illustrated in Scheme 1-5 [7].



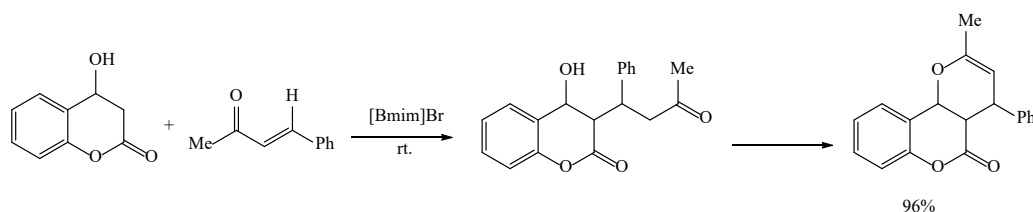
Scheme 1 Synthesis of 3-methyl-1,4-diphenyl-1,4,5,7-tetrahydro-pyrazolo[3,4-d]pyrimidine-6-ones/thiones



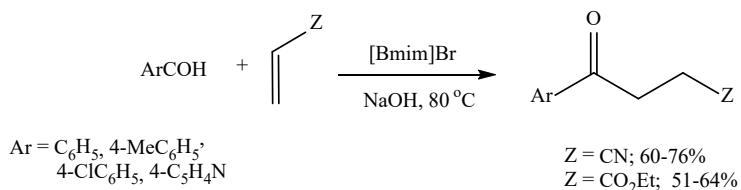
Scheme 2 Synthesis of aryl nitriles



Scheme 3 Synthesis of α -aminonitriles



Scheme 4 Synthesis of warfarin



Scheme 5 Stetter reaction [Bmim]Br as solvent and precatalyst

In our group, much attention has been paid for the synthesis and applications of 1-butyl-3-methylimidazolium bromide [Bmim]Br in organic synthesis. In our previous reports, Benzoin condensation [8] and Stetter reaction catalysed by *N,N*-dimethylbenzimidazolium iodide and NaOH were successfully performed in neutral ionic liquid [bmim][PF₆] [9] including Stetter reaction catalysed by *N,N*-dimethylbenzimidazolium iodide in [Bmim][OH] [10] and Stetter reaction catalysed and reaction medium by 1-Butyl-3-methylimidazolium bromide [7]. As part of our continuing interest in carrying out reaction in [Bmim]Br as green solvent and catalyst, our new approach reported herein involved the use of [Bmim]Br as reaction medium for Cross benzoin condensation.

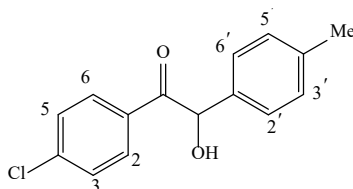
Materials and Methodology

Materials were used as received from commercial sources. Melting points were determined with a Sanyo Gallenkamp apparatus and compared with those of known samples. IR spectra were recorded on a Shimadzu spectrometer. The ¹H and ¹³C NMR spectra were recorded in CDCl₃ and obtained using a VARIAN MERCURY plus (400 MHz FT-NMR).

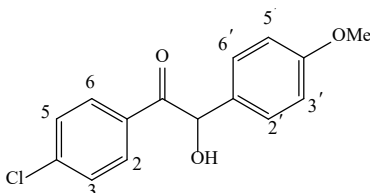
General Procedure for the Cross Benzoin Condensation

A mixture of [Bmim][Br] (**3**) (1.0 mmol) and NaOH (0.2 mmol) were added different of aromatic aldehydes in ratio 1:1 (1.0 mmol) at room temperature. The temperature was raised to 80 °C and the resulting mixture was stirred for 2.5–5.0 h. After completion of the reaction, as indicated by TLC (100% dichloromethane), the reaction mixture was extracted with EtOAc (3 × 80 mL). The combined organic extract was dried (anh. Na₂SO₄) and the solvent was removed under reduced pressure. The residue was purified using preparative thin layer chromatography on silica gel with dichloromethane as eluant. The purified cross-benzoin condensation products **4a-i**, homo-benzoin condensation products **5a-d** and **6a** with

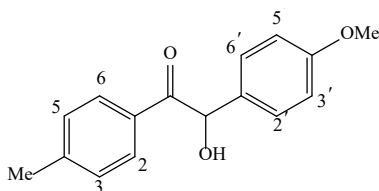
their physical data were listed below.



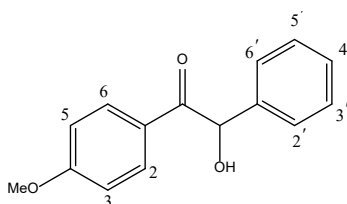
4-Chloro-4'-methylbenzoin (**4a**) was obtained as a yellow liquid; IR ν_{\max} : 3440, 3024, 2985, 2943, 1668, 1609, 1584, 1451, 1238, 1165 and 1098 cm^{-1} ; $^1\text{H NMR}$ δ 7.85 (2H, d, $J = 8.0$ Hz, 2-*H* and 6-*H*), 7.28-7.34 (4H, m, 3-*H*, 5-*H*, 2'-*H* and 6'-*H*), 6.84 (2H, d, $J = 8.0$ Hz, 3'-*H* and 5'-*H*), 5.76 (1H, s, *CH*) and 2.43 (3H, s, CH_3); $^{13}\text{C NMR}$ δ 21.4, 75.9, 114.1, 126.2, 129.1, 129.5, 132.5, 135.3, 138.4, 164.6 and 196.4.



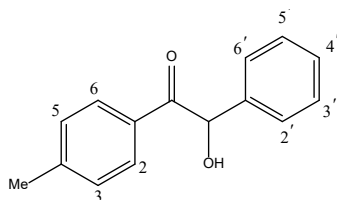
4-Chloro-4'-methoxybenzoin (**4b**) was obtained as a yellow liquid; IR ν_{\max} : 3432, 3030, 2980, 2923, 1663, 1602, 1574, 1423, 1258, 1173 and 1082 cm^{-1} ; $^1\text{H NMR}$ δ 7.88 (2H, d, $J = 8.8$ Hz, 2-*H* and 6-*H*), 7.25-7.30 (4H, m, 3-*H*, 5-*H*, 2'-*H* and 6'-*H*), 6.87 (2H, d, $J = 8.8$ Hz, 3'-*H* and 5'-*H*), 5.86 (1H, s, *CH*) and 3.83 (3H, s, OCH_3); $^{13}\text{C NMR}$ δ 55.5, 74.9, 114.0, 126.0, 129.0, 129.3, 131.5, 134.4, 138.1, 164.2 and 196.8.



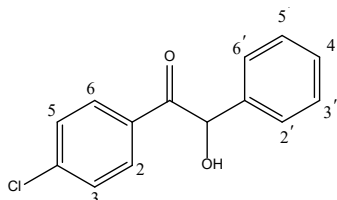
4-Methyl-4'-methoxybenzoin (**4c**) was obtained as a yellow liquid; IR ν_{\max} : 3424, 3053, 2959, 2929, 1678, 1612, 1594, 1450, 1222, 1140 and 1053 cm^{-1} ; $^1\text{H NMR}$ δ 7.80 (2H, d, $J = 7.8$ Hz, 3-*H* and 5-*H*), 7.35 (2H, d, $J = 8.0$ Hz, 2'-*H* and 6'-*H*), 7.29 (2H, d, $J = 8.0$ Hz, 3'-*H* and 5'-*H*), 6.78 (2H, d, $J = 7.8$ Hz, $J = 8.4$ Hz, 2-*H* and 6-*H*), 5.79 (1H, s, *CH*), 3.83 (3H, s, OCH_3) and 2.4 (3H, s, CH_3); $^{13}\text{C NMR}$ δ 21.1, 55.2, 74.3, 114.3, 125.2, 129.1, 129.2, 133.1, 134.9, 138.1, 164.7 and 196.5.



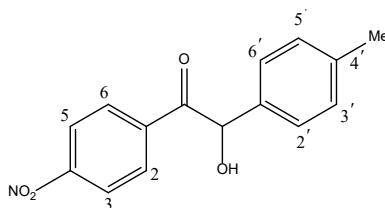
4-Methoxybenzoin (**4d**) was obtained as a yellow liquid; IR ν_{\max} : 3428, 3013, 2991, 2839, 1673, 1597, 1411, 1233, 1173 and 1065 cm^{-1} ; $^1\text{H NMR}$ δ 7.89 (2H, d, $J = 8.4$ Hz, 2-*H* and 6-*H*), 7.28-7.33 (4H, m, 2'-*H*, 3'-*H*, 4'-*H*, 5'-*H*, and 6'-*H*), 7.08 (2H, d, $J = 8.4$ Hz, 3-*H* and 5-*H*), 6.24 (1H, s, *CH*) and 3.81 (3H, s, OCH_3); $^{13}\text{C NMR}$ δ 55.8, 85.2, 114.2, 127.6, 129.0, 129.2, 129.6, 129.8, 136.6, 158.1 and 192.8.



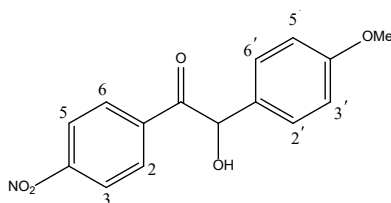
4-Methylbenzoin (**4e**) was obtained as a yellow liquid; IR ν_{\max} : 3398, 3043, 2976, 2844, 1667, 1577, 1431, 1230, 1143 and 1085 cm^{-1} ; $^1\text{H NMR}$ δ 7.49 (2H, d, $J = 8.8$ Hz, 3-*H* and 5-*H*), 7.25-7.31 (4H, m, 2'-*H*, 3'-*H*, 4'-*H*, 5'-*H*, and 6'-*H*), 6.98 (2H, d, $J = 8.8$ Hz, 3-*H* and 5-*H*), 6.34 (1H, s, *CH*) and 2.24 (3H, s, CH_3); $^{13}\text{C NMR}$ δ 21.3, 87.6, 127.6, 128.7, 128.8, 129.2, 129.6, 133.6, 136.7, 146.5 and 194.2.



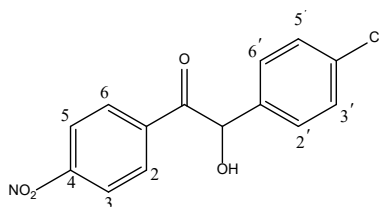
4-Chlorobenzoin (**4f**) was obtained as a yellow liquid; IR ν_{\max} : 3335, 3039, 2969, 2875, 1661, 1587, 1447, 1260, 1163 and 1029 cm^{-1} ; $^1\text{H NMR}$ δ 8.04 (2H, d, $J = 8.4$ Hz, 2-*H* and 6-*H*), 7.68 (2H, d, $J = 8.8$ Hz, 3-*H* and 5-*H*), 7.24-7.33 (4H, m, 2'-*H*, 3'-*H*, 4'-*H*, 5'-*H*, and 6'-*H*) and 6.37 (1H, s, *CH*); $^{13}\text{C NMR}$ δ 87.4, 127.6, 128.6, 129.1, 129.5, 130.1, 134.7, 136.7, 138.9 and 194.4.



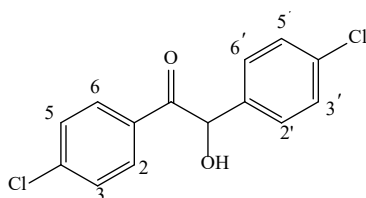
4-Nitro-4'-methylbenzoin (**4g**) was obtained as a yellow liquid; IR ν_{\max} : 3415, 3070, 2957, 2842, 1663, 1577, 1461, 1257, 1163 and 1041 cm^{-1} ; $^1\text{H NMR}$ δ 8.54 (2H, d, $J = 8.4$ Hz, 3-*H* and 5-*H*), 8.32 (2H, d, $J = 8.8$ Hz, 2-*H* and 6-*H*), 7.25 (2H, d, $J = 8.8$ Hz, 2'-*H*, and 6'-*H*), 7.11 (2H, d, $J = 8.4$ Hz, 3'-*H*, and 5'-*H*), 6.39 (1H, s, *CH*) and 2.19 (3H, s, CH_3); $^{13}\text{C NMR}$ δ 21.3, 87.6, 123.8, 126.5, 129.4, 129.6, 133.4, 137.5, 140.9, 151.9 and 194.7.



4-Nitro-4'-methoxybenzoin (**4h**) was obtained as a yellow liquid; IR ν_{\max} : 3401, 3013, 2942, 2848, 1665, 1577, 1452, 1261, 1173 and 1030 cm^{-1} ; $^1\text{H NMR}$ δ 8.57 (2H, d, $J = 8.8$ Hz, 3-*H* and 5-*H*), 8.36 (2H, d, $J = 8.8$ Hz, 2-*H* and 6-*H*), 7.29 (2H, d, $J = 8.8$ Hz, 2'-*H*, and 6'-*H*), 7.08 (2H, d, $J = 8.4$ Hz, 3'-*H*, and 5'-*H*), 6.38 (1H, s, *CH*) and 3.89 (3H, s, OCH_3); $^{13}\text{C NMR}$ δ 55.8, 87.9, 114.6, 123.7, 129.0, 129.8, 132.0, 141.7, 153.1, 159.2 and 195.1.

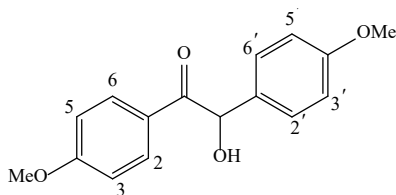


4-Nitro-4'-chlorobenzoin (**4i**) was obtained as a yellow liquid; IR ν_{\max} : 3379, 3045, 2980, 2848, 1668, 1568, 1435, 1273, 1144 and 1052 cm^{-1} ; $^1\text{H NMR}$ δ 8.52 (2H, d, $J = 8.8$ Hz, 3-*H* and 5-*H*), 8.34 (2H, d, $J = 8.8$ Hz, 2-*H* and 6-*H*), 7.31 (2H, d, $J = 8.8$ Hz, 2'-*H*, and 6'-*H*), 7.12 (2H, d, $J = 8.4$ Hz, 3'-*H*, and 5'-*H*) and 6.36 (1H, s, *CH*); $^{13}\text{C NMR}$ δ 87.6, 124.2, 129.1, 129.7, 129.9, 133.4, 134.0, 142.7, 152.9 and 194.9

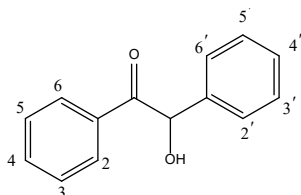


4,4'-Dichlorobenzoin (**5a**) was obtained as a white crystals; mp 87–88 °C (lit. 88 °C) [11]; IR (KBr) ν_{\max} : 3425, 3091, 3072, 1689, 1674, 1590, 1488, 1401, 1252, 1093, 979 and 812 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.75 (2H, d, $J = 8.4$ Hz, 2-*H* and 6-*H*), 7.32 (2H, d, $J = 8.4$ Hz, 3-*H* and 5-*H*), 7.24

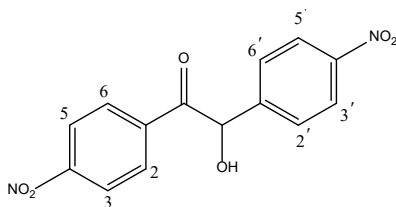
(2H, d, $J=8.4$ Hz, 3'-*H* and 5'-*H*), 7.18 (2H, d, $J=8.4$ Hz, 2'-*H* and 6'-*H*) and 5.81 (1H, s, *CH*); ^{13}C NMR (CDCl_3) δ 75.5, 129.0, 129.2, 129.4, 130.4, 131.5, 134.8, 137.1, 140.7 and 197.4.



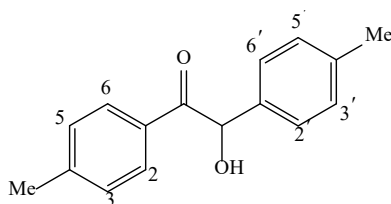
4,4'-Dimethoxybenzoin (**5b**) was obtained as white crystals; mp 104-106 °C (lit. 105-108 °C) [12]; IR (KBr) ν_{max} : 3464, 3075, 2919, 2842, 1666, 1598, 1465, 1314, 1267, 1170, 1022 and 828 cm^{-1} ; ^1H NMR δ 7.89 (2H, d, $J=8.8$ Hz, 2-*H* and 6-*H*), 7.24 (2H, d, $J=8.8$ Hz, 3-*H* and 5-*H*), 6.85 (2H, d, $J=6.0$ Hz, 2'-*H* and 6'-*H*), 6.83 (2H, d, $J=6.0$ Hz, 3'-*H* and 5'-*H*), 5.85 (1H, s, *CH*), 3.81 (3H, s, OCH_3) and 3.74 (3H, s, OCH_3); ^{13}C NMR δ 55.2, 55.5, 75.2, 113.9, 114.5, 126.3, 129.0, 131.6, 131.8, 159.6, 164.0 and 197.3.



Benzoin (**5c**) was obtained as white crystals; mp 134-136 °C (lit. 134-136 °C) [13]; IR (KBr) ν_{max} : 3418, 2935, 1678, 1597, 1450, 1341, 1207 and 757 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.92 (2H, d, $J=8.0$ Hz, 2-*H* and 6-*H*), 7.53 (1H, t, $J=7.6$ Hz, 4-*H*), 7.39 (2H, t, $J=7.6$ Hz, 3-*H* and 5-*H*), 7.25-7.32 (5H, m, 2'-*H*, 3'-*H*, 4'-*H*, 5'-*H*, and 6'-*H*), 5.96 (1H, s, *CH*), 4.52 (1H, br s, *OH*); ^{13}C NMR (CDCl_3) δ : 76.1, 127.7, 128.6, 128.7, 129.2, 133.6, 133.9, 139.1, 198.8.



4,4'-Dinitrobenzoin (**5d**) was obtained as a yellow liquid; IR ν_{max} : 3444, 3055, 2987, 2856, 1667, 1571, 1433, 1263, 1155 and 1019 cm^{-1} ; ^1H NMR δ 8.54 (2H, d, $J=8.8$ Hz, 3-*H* and 5-*H*), 8.35 (2H, d, $J=8.8$ Hz, 2-*H* and 6-*H*), 8.29 (2H, d, $J=8.8$ Hz, 3'-*H*, and 5'-*H*), 7.48 (2H, d, $J=8.4$ Hz, 2'-*H*, and 6'-*H*) and 6.34 (1H, s, *CH*); ^{13}C NMR δ 87.4, 122.9, 124.1, 129.2, 131.1, 141.9, 142.0, 147.1, 152.4 and 194.8

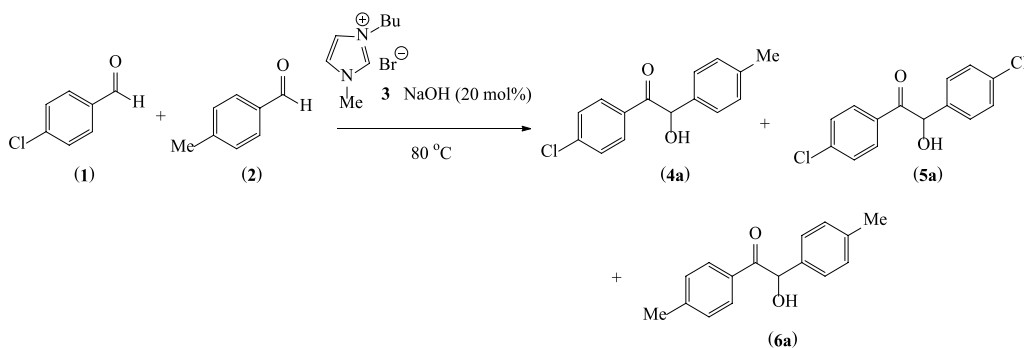


4,4'-Dimethylbenzoin (**6a**) was obtained as a white crystals; mp 73–75 °C (lit. 75–76 °C) [12]; IR (KBr) ν_{\max} : 3458, 3030, 2921, 2865, 1673, 1607, 1512, 1409, 1387, 1277, 1178, 1077 and 722 cm^{-1} ; ^1H NMR δ 7.81 (2H, d, $J = 8.4$ Hz, 2-*H* and 6-*H*), 7.21 (2H, d, $J = 8.4$ Hz, 3-*H* and 5-*H*), 7.18 (2H, d, $J = 8.0$ Hz, 2'-*H* and 6'-*H*), 7.11 (2H, d, $J = 8.0$ Hz, 3'-*H* and 5'-*H*), 5.89 (1H, s, *CH*), 2.35 (3H, s, CH_3) and 2.28 (3H, s, CH_3); ^{13}C NMR (CDCl_3) δ 21.1, 21.7, 75.8, 127.6, 129.3, 129.4, 129.8, 131.0, 136.4, 138.3, 144.9 and 198.6.

Results and discussion

In this study, we conducted cross benzoin condensation employed 1 equivalent of aromatic aldehydes as substrate. According to previous work, which report by Shekouhy's group [5]. We began to briefly examine an effective amount of [Bmim][Br] (**3**) for the nucleophilic coupling of 4-chlorobenzaldehyde (**1**) with 4-methylbenzaldehyde (**2**) in the presence of 20 mol% of NaOH at 80 °C. Employment of 100 mol% of 1-butyl-3-methylimidazolium bromide (**3**) revealed the best result affording the cross-benzoin **4a** as a major product in satisfactory 68% yield; Homo-benzoin **5a** and **6a** were obtained in 14 and 11% yield as illustrated in Table 1, entry 3.

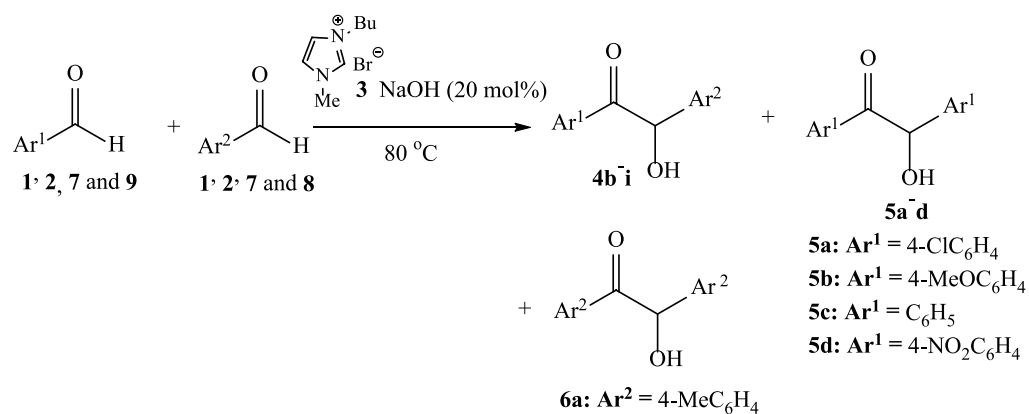
Table 1 Optimization condition for cross benzoin condensation between 4-chlorobenzaldehyde (**1**) and 4-methylbenzaldehyde (**2**) catalyzed by [Bmim][Br] (**3**) in the presence of NaOH at 80 °C



Entry	Molar Ratio of Aldehydes (1) and (2)	Mol% of [Bmim][Br] (3)	%Yield (4a)	%Yield (5a)	%Yield (6a)
1	1:1	20	45	11	7
2	1:1	50	56	13	9
3	1:1	100	68	14	11

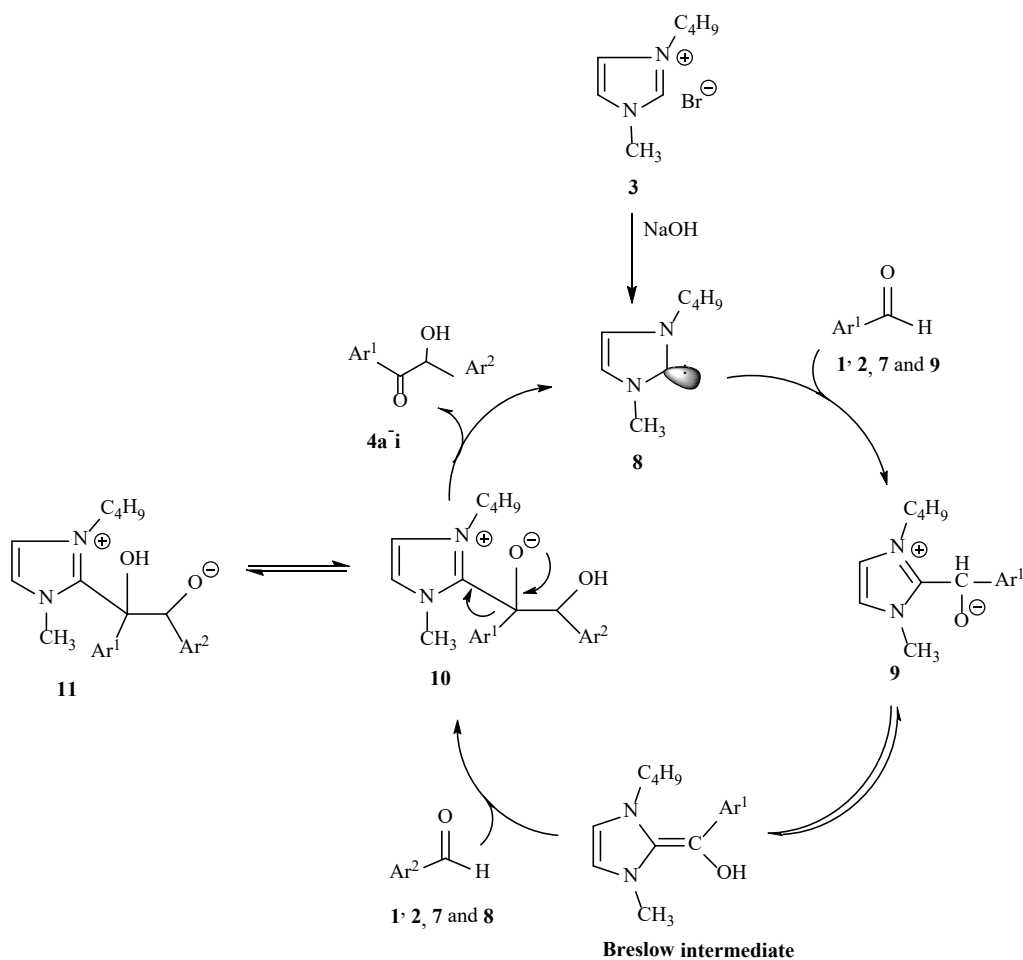
Cross benzoin condensation between aromatic aldehydes **1**, **2**, **8** and **9** with aromatic aldehydes **1**, **2**, **7** and **8** under optimized conditions performed by [Bmim][Br] (**3**) as both solvent and precatalyst in the presence of NaOH (20 mol%) to give satisfactorily yields of the cross-benzoin products **4b-i**. The isolated products of homo-aroin **5a-d** and **6a** were occurred as minor side products as illustrated in Table 2.

Table 2 Cross benzoin condensation between aromatic aldehydes **1a**, **2a** and aromatic aldehydes **7a**



Entry	Ar ¹	Ar ²	% Yield	
			Cross-benzoin	Homo-benzoin
1	4-ClC ₆ H ₄ (1)	4-MeOC ₆ H ₄ (7)	70 (4b)	15 (5a) 12 (5b)
2	4-MeC ₆ H ₄ (2)	4-MeOC ₆ H ₄ (7)	60 (4c)	14 (6a) 9 (5b)
3	4-MeOC ₆ H ₄ (7)	C ₆ H ₅ (8)	62 (4d)	11 (5b) 21 (5c)
4	4-MeC ₆ H ₄ (7)	C ₆ H ₅ (8)	64 (4e)	9 (6a) 17 (5c)
5	4-ClC ₆ H ₄ (1)	C ₆ H ₅ (8)	67 (4f)	18 (5a) 10 (5c)
6	4-NO ₂ C ₆ H ₄ (9)	4-MeC ₆ H ₄ (2)	61 (4g)	9 (5d) 14 (6a)
7	4-NO ₂ C ₆ H ₄ (9)	4-MeOC ₆ H ₄ (7)	60 (4h)	7 (5d) 13 (5b)
8	4-NO ₂ C ₆ H ₄ (9)	4-ClC ₆ H ₄ (1)	63 (4i)	11 (5d) 18 (5a)

Catalytic activity of 1-butyl-3-methylimidazolium bromide [Bmim][Br] (**3**) result from deprotonation of the 2-H proton of imidazolium cation to give *N*-heterocyclic carbene **8** (NHC). Aldehyde nucleophilic **1**, **2**, **7** and **9** attract (1 equivalent) produced the adduct **9**, which proton transfer leads to Breslow intermediate. Subsequent 1 equivalent of nucleophilic addition to generated the adduct **10** which can reverse to adduct **11**. Transformation of adduct **10** by eliminate catalyst to give cross benzoin products **4a-i** and regenerated the NHC catalyst **8** as shown in scheme 6.



Scheme 6 Catalytic cycle for [Bmim][Br] (3) catalyzed the cross benzoin condensation

Conclusion

Cross benzoin condensation using by different of aromatic aldehydes catalyzed by 100 mol% of 1-butyl-3-methylimidazolium bromide (3) was described. [Bmim][Br] acted as both solvent and catalyst for green synthesis of cross benzoin 4a-i in the presence of NaOH (20%) as a additive base. Although homo-benzoin products 5a-d and 6a occurred competitively. Finally, for the cross-benzoin condensation is a simple synthetic method for affording cross-benzoin products 4a-i, homo-benzoin products 5a-d and 6a, which are important intermediates in synthesis of various natural and medicinal compounds.

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