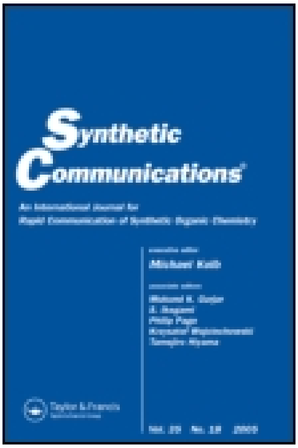

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1-n-Butyl-3-Methylimmidazolium Tetrafluoroborate-Promoted Green Synthesis of 5-Arylidene Barbituric Acids and Thiobarbituric Acid Derivatives

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1-*n*-Butyl-3-Methylimmidazolium Tetrafluoroborate–Promoted Green Synthesis of 5-Arylidene Barbituric Acids and Thiobarbituric Acid Derivatives

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Abstract: The room temperature ionic liquid 1-*n*-butyl-3-methylimmidazolium tetrafluoroborate ([bmim]BF_4) was used to promote the synthesis of 5-arylidene barbituric acids and thiobarbituric acid derivatives under the solid-state conditions of grinding or microwave irradiation without organic solvent. The yields were 77.9–96.2%. It is shown that the proposed method is fast, efficient, and environmentally benign.

Keywords: 5-Arylidene barbituric acid, 5-arylidene thiobarbituric acid, ionic liquid, synthesis

The derivatives of 5-arylidene barbituric acids are an important class of hypnotic and sedative compounds; the arylidene thiobarbituric acid derivatives are valuable intermediates in synthesis of arylthiobarbituric derivatives, heterocyclic compounds, and as medicinal antioxidants, organic thermal stabilizers, and charge-generating agents. It is well known that 5-arylidene barbituric acids and thiobarbituric acids derivatives could be prepared by the Knoevenagel condensation reaction of carbonyl compounds with barbituric acid or 2-thiobarbituric acid in homogeneous systems[1,2] or

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under solvent-free conditions.[3,4] However, these methods have not been entirely satisfactory and are associated with shortcomings such as longer reaction time, lower yields, and production of waste organic solvent.

There has been a growing interest in using ionic liquids as green media in organic synthesis and these are foreseen as an active area of research in the future because of their negligible vapor pressure, tunable polarity, high thermal stability, good solvating ability, and ease of recyclability.[5–7] Microwave-assisted synthesis also received considerable attention in recent years because of its rate enhancement when compared with conventional heating.[8,9]

In continuation our endeavor in green chemistry,[10,11] herein we report a simple and efficient procedure for the preparation of 5-alkylene barbituric acids derivatives under the solid-state conditions of grinding or microwave irradiation in room temperature ionic liquid 1-*n*-butyl-3-methylimmidazolium tetrafluoroborate ([bmim]BF_4) (Scheme 1).

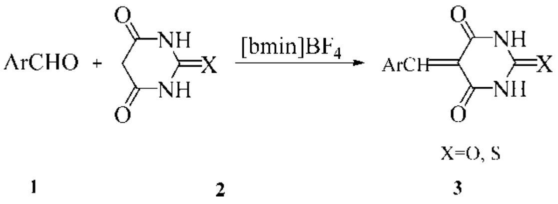
EXPERIMENTAL

Melting points were recorded on an electrothermal apparatus and are uncorrected. ^1H NMR (400 MHz) and ^{12}C NMR (100 MHz) spectra were determined with a JEOL-JNM-GSX 400 spectrometer (DMSO-d_6) using TMS as internal standard. IR spectra (cm^{-1}) were measured with a Jasco FT/IR-800 spectrometer. UV spectra were measured with UV-1100 photemeter. [bmim]BF_4 were synthesized according to the literature.[12]

General Procedure

Synthesis Under Grinding Conditions

The mixture of 2.2 mmol of aromatic aldehydes **1**, 2 mmol of barbituric acid or 2-thiobarbituric acid **2** and, 0.2 mL of [bmim]BF_4 were ground with an agate mortar and pestle for 5 min and kept standing at room temperperture for 2 h. The products were washed with 5 mL of water, 2 mL of diethyl ether, and



Scheme 1.

5 mL of boiling water respectively. The products **3a–3p** were given as shown in Table 1.

Synthesis Under Microwave-Irradiation Conditions

The mixture of 2.2 mmol of aromatic aldehydes **1**, 2 mmol of barbituric acid or 2-thiobarbituric acid **2**, and 0.2 mL of [bmim]BF_4 was mixed thoroughly in a 10-mL beaker. The mixture was subjected to microwave irradiation for 20 s (160 W); then, the products were washed with 5 mL of water, 2 mL of diethyl ether, and 5 mL of boiling water respectively. The products **3a–3p** were given as shown in Table 1.

From Table 1, we can see that a wide range of aromatic aldehydes, which contain either electron-donating groups or electron-withdrawn groups, can undergo the condensation reaction with reasonably high yields. In contrast, the yields of the products were very low if ionic liquid was not added to the mixture of reactants, such as the yield of **3h** (25% and 21% under grinding and microwave irradiation condition respectively without ionic liquid).

In conclusion, we have developed a simple and efficient method for the preparation of 5-alkylene barbituric acids derivatives with high yield, time savings, and minimal environment impact.

Table 1. Condensation reaction of aromatic aldehydes and barbituric acid or 2-thiobarbituric acid

Entry	Ar	X	mp (°C)	mp (°C)[Lit]	Yield (%)[a]	Yield (%)[b]
3a	4-$(CH_3)_2NC_6H_4$	O	272–273	274–276[4]	96.2	98.7
3b	3-$O_2NC_6H_4$	O	242–243	245–245.5[4]	78.7	89.4
3c	4-ClC_6H_4	O	292–293	298.5–300.5[4]	77.9	81.8
3d	2-$CH_3OC_6H_4$	O	267–268	267.5–268[4]	91.9	92.3
3e	4-HOC_6H_4	O	>300	>300[4]	95.2	98.2
3f	4-$CH_3OC_6H_4$	O	287–289	287–289[4]	93.1	95.4
3g	$C_6H_5CH{=}CH$	O	251–253	2504	79.8	87.3
3h	4-$(CH_3)_2NC_6H_4$	S	258–259	257–258.3[13]	87.8	95.3
3i	3-$O_2NC_6H_4$	S	261–263	261.5–264.5[13]	91.5	89.7
3j	2-$O_2NC_6H_4$	S	247–248	246–247[13]	92.5	94.6
3k	3,4-$(OCH_2O)C_6H_3$	S	>300	>300[13]	94.2	90.1
3l	2-$CH_3OC_6H_4$	S	284–285	288.5–289.5[13]	91.5	90.6
3m	4-ClC_6H_4	S	>300	>300[13]	92.8	85.7
3n	2- ClC_6H_4	S	234–236	234–235.5[13]	91.8	89.4
3o	4-$CH_3OC_6H_4$	S	>300	>300[13]	92.4	94.4
3p	$C_6H_5CH{=}CH$	S	264–266	264.5–265.5[13]	95.9	96.1

[a] Yields of grinding reaction.

[b] Yields of microwave irradiation reaction.

3a: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.12 (s, 6H), 6.80 (d, $J = 9.2$ Hz, 2H), 8.15 (s, 1H), 8.42 (d, $J = 9.5$ Hz, 2H), 10.90 (s, 1H), 11.03 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 39.65, 109.53, 111.18, 119.97, 139.03, 150.29, 154.16, 155.47, 162.69, 164.68; IR (KBr): 3549, 3200, 1730, 1680, 1655, 1608, 1377 cm^{-1}.

3b: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.64–8.32 (m, 4H), 8.90 (s, 1H), 11.36 (s, 1H), 11.51 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 121.79, 125.77, 126.50, 129.78, 134.81, 131.85, 147.52, 150.67, 151.78, 161.90, 163.24.

3c: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.54 (d, $J = 8.6$ Hz, 2H), 8.08 (d, $J = 8.6$ Hz, 2H), 8.25 (s, 1H), 11.27 (s, 1H), 11.41 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 119.67, 128.07, 131.57, 134.65, 136.70, 150.13, 152.95, 161.55, 163.17; IR (KBr): 3213, 3094, 1755, 1701, 1669, 1550 cm^{-1}.

3d: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 3H), 6.98 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 7.50–7.54 (m, 1H), 8.01 (dd, $J = 1.2$ Hz, 7.5 Hz, 1H), 8.50 (s, 1H), 11.16 (s, 1H), 11.34 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 55.89, 110.97, 118.57, 119.46, 121.50, 132.44, 134.09, 149.88, 150.22, 158.99, 161.42, 163.39; IR (KBr): 3200, 3085,1715, 1695, 1650, 1580 cm^{-1}.

3e: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.88 (d, $J = 118.1$ Hz, 2H), 8.21 (s, 1H), 8.33 (d, $J = 8.1$ Hz, 2H), 10.82 (s, 1H), 11.12 (s, 1H), 11.25 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 114.22, 115.52, 123.82, 138.30, 150.22, 155.55, 162.29, 163.03, 164.11; IR (KBr): 3274, 3090, 1718, 1697, 1670, 1614, 1535, 1219, 1186 cm^{-1}.

3f: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.86 (s, 3H), 7.15 (d, $J = 8.3$ Hz, 2H), 8.43 (d, $J = 8.3$ Hz, 2H), 8.24 (s, 1H), 11.04 (s, 1H), 11.17 (s, 1H); IR (KBr): 3200, 3085, 1715, 1695, 1650, 1580, 1418 cm^{-1}.

3g: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.43–7.67 (m, 5H), 7.68 (d, 1H), 8.00 (d, 1H), 8.43 (m, 1H), 11.22 (s, 1H), 11.27 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 116.02, 124.59, 128.90, 129.56, 131.48, 135.62, 150.73, 152.96, 154.07, 163.39, 163.53.

3h: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.15 (s, 6H), 6.81 (d, $J = 9.4$ Hz, 2H), 8.14 (s, 1H), 8.45 (d, $J = 9.4$ Hz, 2H), 12.02 (s, 1H), 12.12 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 94.21, 109.68, 111.93, 120.83, 140.18, 155.22, 156.61, 160.89, 163.47, 177.93; IR: 3065, 1649, 1527, 1485, 1458, 1359 cm^{-1}.

3i: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.78 (s, 1H), 7.89 (t, $J = 8.0$ Hz), 7.97 (d, $J = 7.4$ Hz, 1H), 9.32 (d, $J = 7.4$ Hz, 1H), 10.13 (s, 1H), 11.71 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 173.0, 162.9, 178.2, 147.6, 145.7, 137.1, 135.0, 133.6, 130.8, 128.5, 123.9; IR (KBr): 3447, 3069, 1711, 1660, 1610, 1585, 1523, 1386, 1352 cm^{-1}.

3j: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.62 (d, $J = 7.7$ Hz, 1H), 7.69 (t, $J = 8.4$ Hz, 1H), 7.79 (t, $J = 7.5$ Hz, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 8.63 (s, 1H), 12.33 (s, 1H), 12.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 120.48, 123.96, 130.27, 130.36, 131.44, 133.65, 146.16, 153.18, 159.05, 160.50, 178.92; IR (KBr): 3269, 3163, 3030, 1724, 1697, 1630, 1543, 1520, 1442, 1354 cm^{-1}.

3k: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.20 (s, 2H), 7.10 (d, $J = 8.2$ Hz, 1H), 7.80 (dd, $J = 1.7$ Hz, $J = 8.2$ Hz, 1H), 8.23 (s, 1H), 8.30 (d, $J = 1.7$ Hz, 1H), 12.31 (s, 1H), 12.41 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 78.84, 102.22, 106.19, 108.49, 115.85, 128.47, 131.39, 148.25, 152.67, 159.88, 162.02, 178.14; IR (KBr): 3231, 3165, 1691, 1670, 1523, 1452, 1386 cm^{-1}.

3l: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.88 (s, 3H), 6.98 (t, $J = 7.6$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 7.53–7.56 (m, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 8.53 (s, 1H), 12.27 (s, 1H), 12.41 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 55.90, 111.01, 118.42, 119.47, 121.34, 132.58, 134.76, 150.56, 159.24, 161.63, 178.53; IR (KBr): 3125, 3072, 1705, 1655, 1595, 1537, 1437, 1390 cm^{-1}.

3m: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.55 (d, $J = 8.6$ Hz, 2H), 8.13 (d, $J = 8.6$ Hz, 2H), 8.26 (s, 1H), 12.36 (s, 1H), 12.48 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 119.62, 128.08, 131.45, 134.87, 137.10, 159.35, 161.40, 162.85, 178.50; IR (KBr): 3055, 1701, 1657, 1568, 1537, 1421, 1388 cm^{-1}.

3n: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.37 (t, $J = 7.2$ Hz, 1H), 7.49 (t, $J = 8.4$ Hz, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz, 1H), 8.31 (s, 1H), 12.35 (s, 1H), 12.53 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 121.63, 126.25, 127.82, 128.86, 131.96, 132.24, 133.381, 150.191, 158.75, 160.81, 178.77; IR (KBr): 3086, 1720, 1680, 1595, 1562, 1454, 1379 cm^{-1}.

3o: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.89 (s, 3H), 7.08 (d, $J = 9.1$ Hz, 2H), 8.27 (s, 1H), 8.42 (d, $J = 9.1$ Hz, 2H), 12.28 (s, 1H), 12.37 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 55.71, 114.02, 115.52, 125.21, 129.56, 131.73, 134.51, 159.87, 163.90, 178.19; IR (KBr): 3069, 1695, 1651, 1601, 1562, 1522, 1431, 1269 cm^{-1}.

3p: ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.50 (t, $J = 3.0$ Hz, 3H), 7.69–7.71 (m, 2H), 7.79 (d, $J = 15.4$ Hz, 1H), 8.06 (d, $J = 11.8$ Hz, 1H), 8.45 (dd, $J = 15.4$ Hz, $J = 11.8$ Hz, 1H), 12.33 (s, 1H), 12.37 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 115.81, 124.47, 128.72, 129.25, 131.44, 135.17, 153.68, 154.59, 160.76, 161.27, 178.46; IR (KBr) ν: 3074, 1653, 1599, 1556, 1522, 1450, 1379 cm^{-1}.

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