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PREPARATION OF BENZYLIDENE BARBITURIC ACIDS PROMOTED BY INFRARED IRRADIATION IN ABSENCE OF SOLVENT

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Abstract: *Several benzaldehydes were condensed with barbituric acid under infrared irradiation, in absence of solvent, affording the corresponding 5-benzylidene barbituric acids.*

Some barbituric acid derivatives have been widely used as sedative, hypnotic, anticonvulsant, antispasmodic, as well as local anaesthetic agents.[1,2] Benzylidene barbituric acids are useful as potential organic oxidizers,[3] for the preparation of oxadeazaflavines,[4] and for the unsymmetrical synthesis of disulfides.[5] Some of them have been recently studied as non linear optical materials.[6]

It is also worth mentioning that for the purification of the thermolabile organometallic compounds[7] an infrared lamp has been employed giving efficient heat transfer to speed up sublimation. As a part of our research work, recently we have employed a commercial bentonitic clay, Tonsil Actisil FF (TAFF), and infrared irradiation in order to carry out several reactions.[8] Thus, this work deals with the potential of infrared irradiation to promote the formation of several 5-benzylidene barbituric acids, in the absence of solvent. These molecules were obtained by means of a Knoevenagel condensation between barbituric acid (**2**) and various benzaldehydes **1a-1k (Scheme 1)**.

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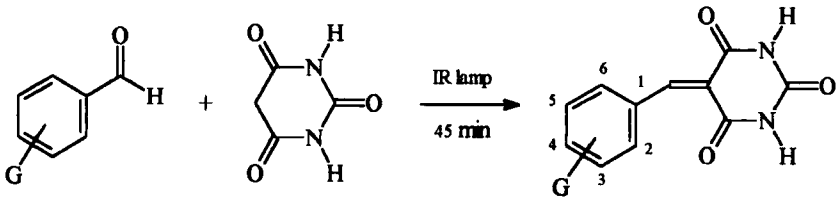

1a-k **2** **3a-k**

Scheme 1

Table 1. Knoevenagel Reaction Between Various Aldehydes and Barbituric Acid Promoted by Infrared Irradiation in the Absence of Solvent.

BENZALDEHYDE	G	PRODUCT	YIELD[a] (%)[b]
1a	H	**3a**	74 (80)[9]
1b	2-methoxy	**3b**	66 (90)[15]
1c	2-chloro	**3c**	67*
1d	4-N,N'-dimethylamino	**3d**	81 (88)[9]
1e	4-methyl	**3e**	82 (88)[15]
1f	4-methoxy	**3f**	45*
1g	4-fluoro	**3g**	48*
1h	4-chloro	**3h**	62 (61)[9]
1i	4-bromo	**3i**	43*
1j	3,4-methylenedioxy	**3j**	65 (54)[10]
1k	2,3,4-trimethoxy	**3k**	74*

[a] After purification by column chromatography and/or recrystallization, [b]numbers in parentheses refer to know yields by other methods. * this compounds has been reported in differents studies[16,17].

DISCUSSION

Table 1 summarizes the experiments performed by this method to prepare benzylidenebarbituric acids **3a-3k**. These compounds were obtained in good yields and adequate reaction times.

This novel technique offers clean and easy method for the preparation of these molecules. Most of the reactions described in Table 1 showed no further progress after 45 min, as evidenced by *tlc*. In addition, we observed that at longer reaction times, oxidation

of the aldehydes to the corresponding acids took place. This method provided additional advantages such as easy of work-up and the use of no solvent. We believe that our results showed that infrared irradiation can be used as a valuable means for activating organic compounds. To our knowledge, this is the first time that this energy source has been used for the promotion of Knoevenagel condensation, in contrast to traditional methods, which require acid or basic catalysis.[9-13]

EXPERIMENTAL SECTION: All benzaldehydes are commercially available (Aldrich Chemical Co.) and were employed without further purification. The barbituric acid were prepared as described in the literature.[14] The reactions were monitored by *tlc* (AcOEt/hexane, 8:2) performed on percoated (0.25 mm) Merk silica-gel 60-F_{254} aluminum sheets, the products visualization was done using a 254 nm UV lamp. Melting points are uncorrected and were determined on a Fisher-Johns apparatus. IR spectra (KBr) were recorded on a Perkin Elmer 283 B spectrophotometer. The EIM spectra were performed on a JEOL JMS-SX 102 instrument. NMR spectra were acquired on a Varian Gemini-300 (300 MHz, ^{1}H; 75 MHz ^{13}C) spectrometer, TMS was used as internal standard and DMSO-d_6 as the solvent.

General procedure for the preparation of 3a-3k. A mixture of **2** (1 mmol) and benzaldehyde **1** (1 mmol) were mixed, and placed in a round-bottomed flask (50 mL) equipped with a condenser, then irradiated by means of an infrared lamp and monitored by *tlc* for 45 min. After cooling, the product was extracted with Me_2CO (15 mL) and the solvent was evaporated under vacuum. The obtained solid was washed with hexane (3 x 10 mL) and with water (3 x 10 mL), and it was recristallyzed from EtOAc/hexane, affording **3a-3k.**

5-Benzylidenebarbituric acid (3a). Pink solid; mp 271-272 °C (lit.[9] 273 °C); IR (KBr) 3100-3060, 1730, 1670, 1540, 1430 cm^{-1}; ^{1}H NMR: δ 11.40 (s, 1H, NH), 11.22 (s, 1H, NH), 8.35 (s, 1H, HC=C), 8.13 (d, 2H, $J_{2-3} = J_{6-5} = 7.1$ Hz, $H_{2,6}$), 7.44 (m, 3H, $H_{3,4,5}$); ^{13}C NMR: δ 163.4 ($C{=}O_{trans}$), 162.0 ($C{=}O_{cis}$), 155.2 (HC=C), 150.6 (HNCONH), 133.6 ($C_{2,6}$), 133.1 (C_4), 132.5 (C_1), 128.5 ($C_{3,5}$), 119.3 (HC=C); MS (70 eV) 216 ($M^{+\cdot}$, 63), 215 (100), 172 (63), 145 (7), 129 (17), 102 (26).

5-(2-Methoxy)benzylidenebarbituric acid (3b). Yellow solid; mp 275-276.5 °C, (lit.[15] 264-266 °C); IR (KBr) 3090-3080, 1715, 1660, 1590, 1550 cm^{-1}; ^1H NMR: δ 11.42 (s, 1H, NH), 11.24 (s, 1H, NH), 8.56 (s, 1H, HC=C), 8.01 (dd, 1H, J_{6-5} = 7.6 Hz, J_{6-4} = 1.2 Hz, H_6), 7.50 (ddd, 1H, $J_{4-3} = J_{4-5}$ = 7.8 Hz, J_{4-6} = 1.2 Hz, H_4), 7.11 (dd, 1H, J_{3-4} = 7.8 Hz, J_{3-5} = 1.3 Hz, H_3), 6.98 (ddd, 1H, $J_{5-6} = J_{5-4}$ = 7.6 Hz, J_{5-3} = 1.3 Hz, H_5); ^{13}C NMR: δ 164.2 ($C{=}O_{trans}$), 162.0 ($C{=}O_{cis}$), 159.6 (C_2), 151.0 (HNCONH), 150.5 (HC=C), 134.8 (C_6), 133.0 ($C_{5/4}$), 122.4 (C_1), 120.1 (C_6), 119.0 (HC=C), 111.5 ($C_{4/5}$), 36.5 (OMe); MS (70 eV) 246 ($M^{+\cdot}$,15), 229 (40), 215 (100), 186 (55), 172 (45), 171 (8), 129 (10).

5-(2-Chloro)benzylidenebarbituric acid (3c). Yellow solid; mp 252-253 °C; IR (KBr) 3080-3060, 1735, 1700, 1660, 1550 cm^{-1}; ^1H NMR: δ 11.53 (s, 1H, NH), 11.26 (s, 1H, NH), 8.30 (s, 1H, HC=C), 7.75 (dd, 1H, J_{6-5}= 7.8 Hz, J_{6-4}= 1.2 Hz, H_6), 7.70 (dd, 1H, J_{3-4} = 7.6 Hz, J_{3-5} = 1.5 Hz, H_3), 7.47 (ddd, 1H, J_{5-6}= J_{5-4}= 7.8 Hz, J_{5-3}= 1.5 Hz, H_5), 7.37 (ddd, 1H, J_{4-5}= J_{4-3}= 7.6 Hz, J_{4-6}= 1.2 Hz, H_4); ^{13}C NMR: δ 162.9 ($C{=}O_{trans}$), 161.2 ($C{=}O_{cis}$), 150.5 (HNCONH), 150.2 (HC=C), 133.5 (C_2), 132.6 (C_1), 132.3 (C_6), 132.2 (C_3), 129.2 (C_5), 126.7 (C_4), 122.1 (HC=C); MS (70 eV) 250 ($M^{+\cdot}$, 5), 215 (100), 172 (96), 166 (11), 144 (7), 128 (18), 101 (15).

5-(4-N,N'-Dimethylamino)benzylidenebarbituric acid (3d). Orange solid; mp 262-263 °C (lit.[9] 275 °C, dec); IR (KBr) 3095-3080, 1700, 1640, 1600, 1500 cm^{-1}; ^1H NMR: δ 11.05 (s, 1H, NH), 10.90 (s, 1H, NH), 8.45-6.82 (AA'BB' system, 4H, $H_{2,3,5,6}$), 8.18 (s, 1H, HC=C), 3.12 (s, 6H, 2Me); ^{13}C NMR: δ 165.0 ($C{=}O_{trans}$), 163.3 ($C{=}O_{cis}$), 155.8 (HC=C), 155.0 (C_4), 150.6 (HNCONH), 139.2 ($C_{2,6}$), 120.0 (C_1), 111.7 ($C_{3,5}$), 110.0 (HC=C), 40.0 (2Me); MS (70 eV) 259 ($M^{+\cdot}$, 100), 242 (5), 258 (66), 215 (22), 172 (10), 144 (12), 129 (8), 101 (5).

5-(4-Methyl)benzylidenebarbituric acid (3e). Yellow solid; mp 297-298 °C (lit.[15] 210-212 °C); IR (KBr) 3090-3080, 1727, 1680, 1654, 1570 cm^{-1}; ^1H NMR: δ 11.40 (s, 1H, NH), 11.24 (s, 1H, NH), 8.35 (s, 1H, HC=C), 8.10-7.37 (AA'BB' sytem, 4H, $H_{2,3,5,6}$), 3.40 (s, 3H, Me); ^{13}C NMR: δ 163.9 ($C{=}O_{trans}$), 162.0 ($C{=}O_{cis}$), 155.3 (HC=C), 150.5 (HNCONH), 143.7 (C_4), 134.2 ($C_{2,6}$), 130.3 (C_1), 129.3 ($C_{3,5}$), 118.3 (HC=C), 21.7 (Me). MS (70 eV) 230 ($M^{+\cdot}$, 38), 229 (39), 215 (100), 186 (57), 172 (38), 143 (13), 115 (30).

5-(4-Methoxy)benzylidenebarbituric acid (3f). Yellow solid; mp 276-277 °C, IR (KBr) 3090-3080, 1708, 1670, 1650, 1540, 1200 cm^{-1}; ^1H NMR: δ 11.30 (s, 1H, NH), 11.15 (s, 1H, NH), 8.29 (s, 1H, HC=C), 8.10-7.36 (AA'BB' system, 4H, $H_{2,3,5,6}$), 3.85 (s, 3H, MeO); ^{13}C NMR: δ 164.2 ($C{=}O_{trans}$), 163.8 ($C{=}O_{cis}$), 162.5 (C_4), 155.3 (HC=C), 137.3 ($C_{2,6}$), 150.5 (HNCONH), 125.5 (C_1), 115.9 (HC=C), 114.3 ($C_{3,5}$), 56.0 (MeO); MS (70 eV) 246 ($M^{+\cdot}$, 100), 245 (67), 215 (100), 202 (49), 172 (38), 159 (9), 145 (5), 117 (6).

5-(4-Fluoro)benzylidenebarbituric acid (3g). Pink Yellow solid; mp 309-310 °C; IR (KBr) 3090-3080, 1725, 1680, 1655, 1500 cm^{-1}; ^1H NMR: δ 11.45 (s, 1H, NH), 11.31 (s, 1H, NH), 8.26 (s, 1H, HC=C), 8.24 (dd, 2H, ^3J = 4.35 Hz, ^4J = 3.4 Hz, $H_{2,6}$), 7.36 (dd, 2H, ^3J = 4.3 Hz, $H_{3,5}$); ^{13}C NMR: δ 164.0 (C_4, $^1J_{C\text{-}F}$ = 251.5 Hz), 163.5 (CO_{trans}), 161.7 (CO_{cis}), 154.0 (HC=C), 150.2 (HNCONH), 136.8 ($C_{2,6}$, $^3J_{C\text{-}F}$ = 9.3 Hz), 129.2 (C_1, $^4J_{C\text{-}F}$ = 3.0 Hz), 119.0 (HC=C), 115.2 ($C_{3,5}$, $^2J_{C\text{-}F}$ = 21.5 Hz). MS (70 eV) 234 ($M^{+\cdot}$, 62), 233 (100), 215 (4), 191 (6), 190 (54), 163 (6), 147 (20), 120 (22), 97 (7).

5-(4-Chloro)benzylidenebarbituric acid (3h). Brown solid; mp 280-281 °C (lit [9] 268 °C, dec); IR (KBr) 3100-3080, 1730, 1680, 1654, 1565 cm^{-1}; ^1H NMR: δ 11.45 (s, 1H, NH), 11.25 (s, 1H, NH), 8.25 (s, 1H, HC=C), 8.05-7.40 (AA'BB' system, 4H, $H_{2,3,5,6}$); ^{13}C NMR: δ 163.8 ($C{=}O_{trans}$), 162 ($C{=}O_{cis}$), 153.5 (HC=C), 150.5 (HNCONH), 137.2 (C_4), 135.0 ($C_{2,6}$), 132.0 (C_1), 128.5 ($C_{3,5}$), 120.0 (HC=C). MS (70 eV) 250 ($M^{+\cdot}$, 74), 249 (100), 215 (60), 206 (57), 172 (37), 163 (20), 129 (9), 101 (15).

5-(4-Bromo)benzylidenebarbituric acid (3i). Yellow solid; mp 292-293 °C*; IR (KBr) 3095-3080, 1739, 1670, 1654, 1560 cm^{-1}; ^1H NMR: δ 11.42 (s, 1H, NH), 11.25 (s, 1H, NH), 8.25 (s, 1H, HC=C), 8.00-7.78 (AA'BB' system, 4H, $H_{2,3,5,6}$); ^{13}C NMR: δ 163.1 ($C{=}O_{trans}$), 160.0 ($C{=}O_{cis}$), 150.0 (HNCONH), 153.0 (HC=C), 134.6 ($C_{2,6}$), 131.9 (C_1), 131.0 ($C_{3,5}$), 127.8 (C_4), 119.7 (HC=C). MS (70 eV) 295 ($M^{+\cdot}$, 83), 252 (41), 215 (100), 172 (54), 144 (5), 143 (6), 115 (8), 101 (30).

5-(3,4-Methylenedioxy)benzylidenebarbituric acid (3j). Yellow solid; mp 320 °C (lit.[10] 265 °C, dec); IR (KBr) 3100-3080, 1708, 1670, 1650, 1550 cm^{-1}; ^1H NMR: δ 11.38 (s, 1H, NH), 11.23 (s, 1H, NH), 8.30 (d, 1H, $J_{2\text{-}6}$ = 1.5 Hz, H_2), 8.23 (s, 1H, HC=C), 7.78 (dd, 1H,

$J_{6\text{-}5}$ = 8.2 Hz, $J_{6\text{-}2}$ = 1.5 Hz, H_5), 7.11 (d,1H, $J_{5\text{-}6}$ = 8.2 Hz, H_5), 6.22 (s, 2H, CH_2); ^{13}C NMR: δ 164.2 ($C{=}O_{trans}$), 163.5 ($C{=}O_{cis}$), 155.4 (HC=C), 152.0 (HNCONH), 150.0 (C_3), 148.0 (C_4), 134.0 (C_2), 126.8 (C_1), 116.7 (HC=C), 113.1 (C_6), 108.2 (C_5), 102.5 (CH_2); MS (70 eV) 260 (M^+, 100) 259 (63), 216 (43), 215 (5), 187 (8), 173 (21), 161 (9), 145 (17).

5-(2,3,4-Trimethoxy)benzylidenebarbituric acid (3k). Orange solid; mp 257.5-259 °C; IR (KBr) 3095-3080, 1708, 1690, 1658, 1595, 1308, 1270, 1120 cm^{-1}; ^1H NMR: δ 11.34 (s, 1H, NH), 11.11 (s, 1H, NH), 8.50 (s, 1H, HC=C), 8.39 (d, 1H, H_6), 6.92 (d, 1H, H_5), 3.93 (s, 3H, MeO-C_2), 3.95 (s, 3H, MeO-C_3), 3.75 (s, 3H, MeO-C_4); ^{13}C NMR: δ 164.1 ($C{=}O_{trans}$), 162.5 ($C{=}O_{cis}$), 158.6 (C_2), 155.9 (C_3), 150.6 (HNCONH), 149.8 (HC=C), 141.0 (C_4), 130.0 (C_6), 119.7 (C_1), 118.5 (HC=C) 107.8 (C_5), 62.3 (MeO-C_2), 61.0 (MeO-C_2), 56.9 (MeO-C_3); MS (70 eV) 246 (M^+,15), 215 (100), 229 (4), 202 (5), 185 (5), 172 (81), 171 (8), 129 (10), 101 (8).

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