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# Microwave-assisted reaction in synthesis of tetra- and hexa-cyclic spiro systems

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The reaction of 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid and barbituric acid yielded 2,2'-(2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis[3-(4-chloro-3-methyl)benzoylpropionic acid], which was reacted with hydroxylamine hydrochloride and hydrazine hydrate to give the corresponding spiro compounds. The spiro compound, containing a pyridazine moiety, was reacted with $PCl_5/POCl_3$ to give the dichloro derivative, which was reacted with sodium azide, monosaccharide hydrazones and acidhydrazides to give the tetrazolo and the triazolo derivatives respectively. All the reactions were carried out under conventional and microwave reaction conditions.

**Key words**: spiro compounds, microwave, monosaccharide hydrazones.

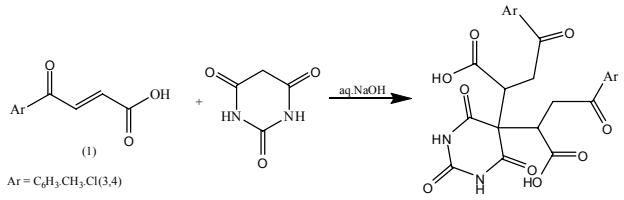
## INTRODUCTION:

Microwave irradiation has gained popularity as a powerful tool for rapid and efficient synthesis of a variety of organic compounds, because of the selective absorption of microwave energy by polar molecules [1–4]. In this work the author sought to investigate the behaviour of 3-(4-chloro-3-methyl) benzoylprop-2-enoic acid in regard to barbituric acid by using the microwave radiation, with the aim to synthesize tetra- and hexa-cyclic spiro systems with anticipated pharmaceutical action.

## RESULTS AND DISCUSSION

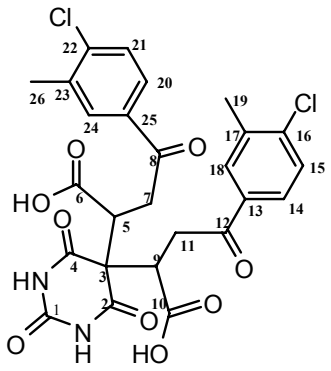
It is well known that barbituric acid is added readily to β-aroylacrylic acid as carbon nucleophile generated from the active methylene group under the influence of basic catalysts [5]. Thus, when 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid **1** was reacted with barbituric acid under conventional and microwave irradiation it gave the same product **2**. 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid **1** can be attacked by nucleophiles either at the unsaturated carbon in β position to the aroyl carbonyl group or caboxyl group. As the aroyl carbonyl group is better activated than the carboxyl group, so the attack occurs predominantly at the carbon in β position to the aroyl carbonyl group.

The formation of **2** was supposed to occur through the nucleophilic attack of the anion formed from the barbituric acid on the unsaturated carbon in β position to the aroyl carbonyl, followed by further addition to the unsaturated carbon atom in β position of a second molecule of the 3-(4-chloro-3-methyl) benzoylprop-2-enoic acid **1**.




Scheme(1)

**Table 1**. $^{13}$C-NMR data for compound No **2** [8].

| Structure | $^{13}$C-NMR |
|---|---|
|  | 150.7 ($C_1$), 170.4 ($C_2$), 48.9 ($C_3$), 170.4 (C4), 39.0 (C5), 173.8 ($C_6$), 38.3 (C7), 196.9 ($C_8$), 39.0 ($C_9$), 173.8 ($C_{10}$), 38.3 ($C_{11}$), 196.9 ($C_{12}$), 133.8 ($C_{13}$), 127.1 ($C_{14}$), 128.0 ($C_{15}$), 138.4 ($C_{16}$), 135.2 (C17), 130.5 ($C_{18}$), 19.5 ($C_{19}$), 127.1 ($C_{20}$), 128.0 ($C_{21}$), 138.4 ($C_{22}$), 135.2 ($C_{23}$), 130.5 ($C_{24}$), 133.8 ($C_{25}$), 19.5 ($C_{26}$) |

Excitation with microwave radiation results in the molecules orientating their dipoles within the external field. The strong agitation, provided by the reorientation of molecules, in phase with the electrical field excitation, causes an intensive internal heating. By comparing the reaction rates of the case, where the reaction is carried out under irradiation and the case of conventional heating, it was found that a reaction that takes several hours under conventional conditions can be completed in the course of minutes under irradiation.

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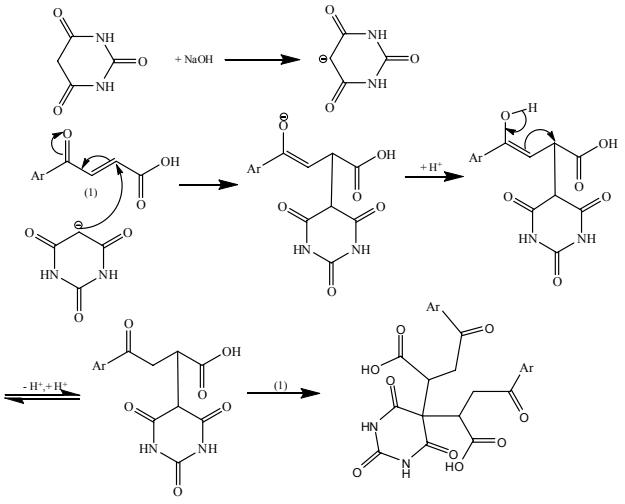
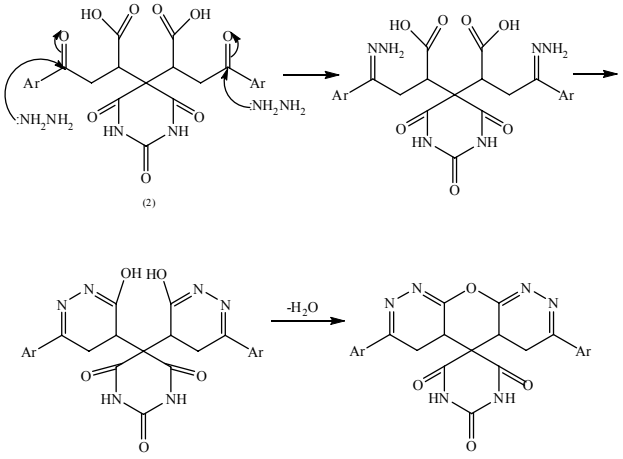


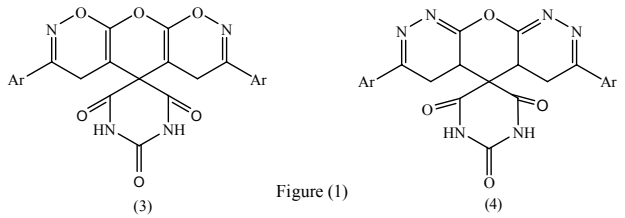
(2)

Scheme(2)



Scheme(3)

The benzoylpropionic acid **2** was reacted under conventional and microwave irradiation conditions with hydroxylamine hydrochloride in pyridine to afford the spiro compound with oxazine moiety **3**, while its reaction with hydrazine hydrate afforded the spiro compound with pyridazine moiety **4**.



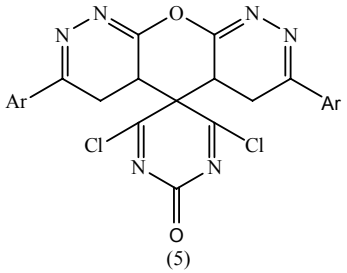
(3) (4)

Figure (1)

The formation of compound **4** under microwave irradiation was carried out under solvent-free conditions; the procedure gives the product in excellent yield (98%) within 3 minutes avoiding problems associated with solvent use such as cost, handling and safety precautions, because of fire hazard due to occurrence of sparks in microwave ovens. But the reaction is less effective and it takes 6 hours to be completed, when carried out in ethanol under reflux and the corresponding derivative was obtained in 50% yield.

The formation of the spiro compounds **3** and **4** possibly takes place *via* formation of bis-monohydrazone derivative followed by cyclization. A proposed mechanism for the formation of compound **4** is shown in Scheme 3.

The spiro compound with pyridazine moiety **4** was treated with $PCl_5/POCl_3$ under conventional and microwave irradiation conditions to give the dichloro derivative **5**. The reaction can be performed within minute's time interval and in excellent yield, when carried out in microwave irradiation conditions (Table 2).



(5)

Figure (2)

Treatment of the dichloro compound **5** with

(10.69), 153 (48.47), 128 (14.58), 105 (100), 77 (45.97) and 55 (46.39); Anal. calcd. for $C_{26}H_{22}Cl_2N_2O_9$: C, 54.11; H, 3.81; Cl, 12.28; N, 4.85; Found: C, 54.32; H, 3.72; Cl, 12.36; N, 4.79.

*Synthesis of spiro compound with oxazine moiety* **3**. *(A) By conventional heating*. A mixture of the acid **2** (0.01mol) and hydroxylamine hydrochloride (0.01mol) in pyridine was refluxed for 3 h. The reaction mixture was poured onto ice/HCl, filtered, washed with water and recrystallized from ethanol.

*(B) By microwave radiation*. A mixture of the acid **2** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in the smallest amount of pyridine was irradiated with microwaves at $P$ = 540 W for 4 min (Table 2). The reaction mixture was poured onto ice/HCl, filtered, washed with water and recrystallized from ethanol.

The product was brown crystals, m.p. 240–242°C; IR $cm^{-1}$: 1624 (C=C), 1655 (C=N), 1684 (C=O), and 3426 (NH). $^1$H NMR (DMSO) δ: 2.4 (s, 6H, $2CH_3$), 4.1 (s, 4H, $2CH_2$), 6.7–7.9 (m, 6ArH) and 11.1 (s, 2H, 2NH). MS m/z: 510 (54.29), 386 (45.71), 385 (45.71), 343 (34.29), 309 (37.14), 172 (68.57), 80 (82.86), and 58 (100). Anal. calcd. for $C_{26}H_{18}Cl_2N_4O_6$: C, 56.45; H, 3.25; Cl, 12.81; N, 10.12; Found: C, 55.95; H, 3.19; Cl, 12.67; N, 10.15.

*Synthesis of spiro compound with pyridazine moiety* **4**. *(A) By conventional heating*. A mixture of the acid **2** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was refluxed for 6 h. The solid phase that separated out after concentrating and cooling down was filtered off and recrystallized from methanol to give **4**.

*(B) By microwave radiation*. A mixture of the acid **2** (0.01 mol) and hydrazine hydrate (0.01 mole) was irradiated under microwaves at $P$ = 540 W for 3 min (Table 2). The solid phase that separated out, was filtered off and recrystallized from methanol to give **4**.

The product was yellow crystals m.p. 220–222°C, IR $cm^{-1}$: 1592 (C=N), 1682 (C=O) and 3330 (NH). $^1$H NMR (DMSO) δ: 1.10–1.80 (m, 4H, $2CH_2$), 2.19–2.39 (m, 2H, 2CH), 2.48, 2.49 (2s, 6H, $2CH_3$), 6.9–8.0 (m, 6H, ArH), and 11.18 (s, 2H, 2NH). MS m/z: 407 (1.4), 398 (10.3), 220 (57.2), 219 (63.8), 162 (31.2), 127 (100), 128 (82.3) and 52 (20.5). Anal. calcd. for $C_{26}H_{20}Cl_2N_6O_4$: C, 56.65; H, 3.26; Cl, 12.86; N, 15.24; Found: C, 56.70; H, 3.73; Cl, 12.83; N, 15.30.

*Synthesis of the dichloro derivative* **5.** *(A) By conventional heating*. A mixture of the spiro compound with pyridazine moiety **4** (0.01 mol) and $PCl_5$ (0.5 g) in $POCl_3$ (10 ml) was heated on a water bath for 3 h. The reaction mixture was poured gradually onto crushed ice and the solid phase that separated out was filtered off and recrystallized from methanol.

*(B) By microwave radiation*. A mixture of the spiro compound with pyridazine moiety **4** (0.01 mol) and $PCl_5$ (0.5 g) in $POCl_3$ (10 ml) was irradiated under microwaves at $P$ = 540 W for 5 min (Table 2). The reaction mixture was poured gradually onto crushed ice and the solid phase that separated out was filtered off and recrystallized from methanol.

The product was pale brown crystals, m.p. 230–232°C, IR $cm^{-1}$: 1602 (C=N) and 1687(C=O), $^1$H NMR (DMSO) δ: 2.10–2.13 (m, 4H, $2CH_2$), 2.40–2.45 (m, 2H, 2CH), 2.45 (s, 6H, $2CH_3$) and 7.2–8.1 (m, 6H, ArH). MS m/z: 564 (43.33), 432 (36.67), 358 (43.33), 324 (33.33), 233 (53.33), 234 (63.33), 78 (36.67), 70 (53.33), 72 (100), and 68 (40.00). Anal. calcd. for $C_{26}H_{18}Cl_4N_6O_2$: C, 53.10; H, 3.06; Cl, 24.11; N, 14.28; Found: C, 53.35; H, 3.03; Cl, 24.23; N, 14.24 .

*Synthesis of the spirotetrazolo derivative* **6**. A mixture of the dichloro derivative **5** (0.003 mol) and sodium azide (0.5 g/5 ml water) in DMF (30 ml) was refluxed for 3 h, cooled down and 100 ml of water was added. The solid phase that separated out was filtered off and recrystallized from ethanol.

The product was brown crystals, m.p. > 300°C, IR $cm^{-1}$: 1583 (C=C), 1597 (C=N), and 1685 (C=O). $^1$H NMR (DMSO) δ: 2.38–2.39 (m, 4H, $2CH_2$), 2.74, 2.88 (dd, 2H, 2CH), 2.49 (s, 6H, $2CH_3$), and 7.5–7.9 (m, 6H, ArH); MS m/z: 438 (13.9), 110 (32.0), 98 (24.3), 96 (54.0), 94 (25.9), 70 (56.0), 57 (91.3), 56 (100), and 54 (64.7). Anal. calcd. for $C_{26}H_{18}Cl_2N_{12}O_2$: C, 51.94; H, 2.99; Cl, 11.79; N, 27.94; Found: C, 51.64; H, 2.97; Cl, 11.84; N, 27.64.

*Synthesis of the triazolo derivatives* **7**. *(A) By conventional heating.* A solution of the dichloro derivative **5** (0.01 mol) and monosaccharide hydrazones namely glucose hydrazone, and mannose hydrazone (0.15 mol) in *n*-butanol (40 ml) was refluxed for 6 h. The solid phase that separated after concentrating and cooling down was filtered out and recrystallized from acetic acid.

*(B) By microwave radiation.* The dichloro derivative **5** (0.01 mol) and monosaccharide hydrazones namely glucose hydrazone, and mannose hydrazone (0.15 mol) in the smallest amount of *n*-butanol were irradiated with microwaves at $P$ = 630 W for 8 min (Table 2). The solid phase that separated was recrystallized from acetic acid.

The product was brown crystals, m.p. 260°C (dec.); IR $cm^{-1}$: 1545 (C=C), 1588 (C=N), 1683 (C=O), and 3061 (OH). $^1$H NMR (DMSO) δ: 1.30–1.50 (m, 4H, $2CH_2$), 2.34–2.36 (m, 2H, 2CH), 2.40

(s, 6H, 2$CH_3$), 3.75 (d, 2H, 2-CHOH–C<u>H</u>–N), 3.78–3.82 (m, 10H, carbohydrate moiety), 4.08 (br.s, 8H, 8OH), and 6.89–7.86 (m, 8H, 6ArH+2N=CH). MS m/z: 841 (36.36), 843 (48.48), 766 (33.33), 658 (36.36), 522 (33.33), 342 (42.42), 313 (51.52), and 170 (100). Anal. calcd. for $C_{38}H_{40}Cl_2N_{10}O_{10}$: C, 52.62; H, 4.61; Cl, 8.17; N, 16.14; Found: C, 52.35; H, 4.59; Cl, 8.20; N, 16.32 .

*Synthesis of the spirotriazolopyridazine derivatives* **8**, **9**. *(A) By conventional heating.* A solution of the dichloro derivative **5** (0.01 mol) and the acylhydrazines (0.01 mol), namely benzoylhydrazine and salicyloylhydrazine in 30 ml butanol was heated under reflux for 48 h. The solid phase that separated after concentrating and cooling down was filtered out and recrystallized from ethanol.

*(B) By microwave radiation*. The dichloro derivative **5** (0.01 mol) and the acylhydrazines (0.01 mol), namely benzoylhydrazine and salicyloylhydrazine in the smallest amount of *n*-butanol were irradiated under microwaves at *P* = 720 W for 8, 10 min (Table 2). The solid phase that separated was recrystallized from ethanol.

*Spirotriazolopyridazine derivatives* **8**. The products were brown crystals, m.p. > 300°C, IR $cm^{-1}$ 1550 (C=C), 1600 (C=N), and 1660 (C=O). $^1$H NMR (DMSO) δ: 1.22 (m, 4H, 2$CH_2$), 2.3–2.40 (m, 2H, 2CH), 2.49 (s, 6H, 2$CH_3$), and 7.62–8.51 (m, 16H, ArH). MS m/z: 740 (32.35), 704 (32.35), 467 (32.35), 327 (55.88), 276 (32.35), 196 (32.35), 168 (100), and 96 (29.41). Anal. calcd. for $C_{40}H_{28}Cl_2N_{10}O_2$: C, 63.94; H, 3.72; Cl, 9.43; N, 18.63; Found: C, 63.65; H, 3.82; Cl, 9.31; N, 18.71.

*Spirotriazolopyridazine derivatives* **9**. The products were brown crystals, m.p. > 300°C, IR $cm^{-1}$ 1550 (C=C), 1601 (C=N), 1671 (C=O) and 3199 (OH). $^1$H NMR (DMSO) δ: 1.23 (m, 4H, 2$CH_2$), 2.43–2.46 (m, 2H, 2CH), 2.46 (s, 6H, 2$CH_3$), 7.1–8.6 (m, 14, ArH), and 11.02 (br.s, 2H, 2OH). MS m/z: 322 (35.58), 320 (100.0), 194 (40.14), 126 (43.89), 96 (51.84), 84 (66.47), 68 (68.11), and 56 (66.35). Anal. calcd. for $C_{40}H_{28}Cl_2N_{10}O_4$: C, 61.33; H, 3.57; Cl, 9.05; N, 17.87; Found: C, 61.17; H, 3.68; Cl, 9.11; N, 17.76.

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## СИНТЕЗ НА ТЕТРА- И ХЕКСАЦИКЛИЧНИ СПИРО СИСТЕМИ ПОД ДЕЙСТВИЕ НА МИКРОВЪЛНИ


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При реакцията на 3-(4-хлоро-3-метил)бензоилпроп-2-енова киселина и барбитурова киселина е получена 2,2'-(2,4,6-триоксохексапиримидин-5,5-диил)бис[3-(4-хлоро-3-метил)бензоилпропионова киселина, която реагира с хидроксиламин хидрохлорид и хидразин хидрат до съответните спиро съединения. При реакцията на спиро съединенията, съдържащи пиридазинова част, с $PCl_5$/$POCl_3$ се получава дихлорно производно, което реагирайки с натриев азид, монозахарид хидразони и ацилхидразиди образува съответни тетразоло- и триазоло-производни. Всички реакции са проведени при обикновени условия и при облъчване с микровълни.