

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

M. I. Marzouk*

Department of Chemistry, Faculty of Science, Ain Shams University, Abassia, Cairo, Egypt

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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 $\text{PCl}_5/\text{POCl}_3$ 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 carboxyl 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**.

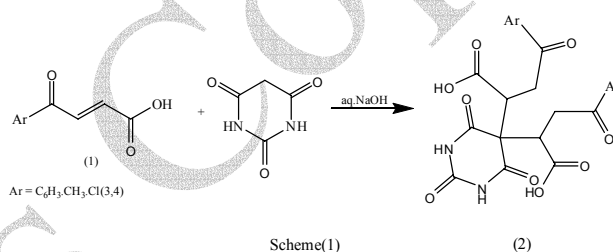
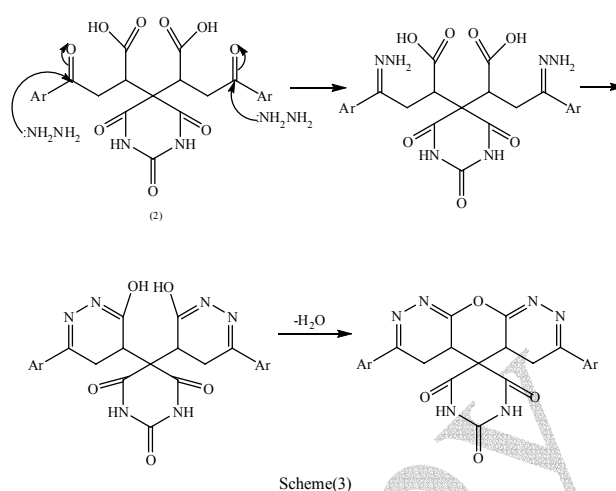
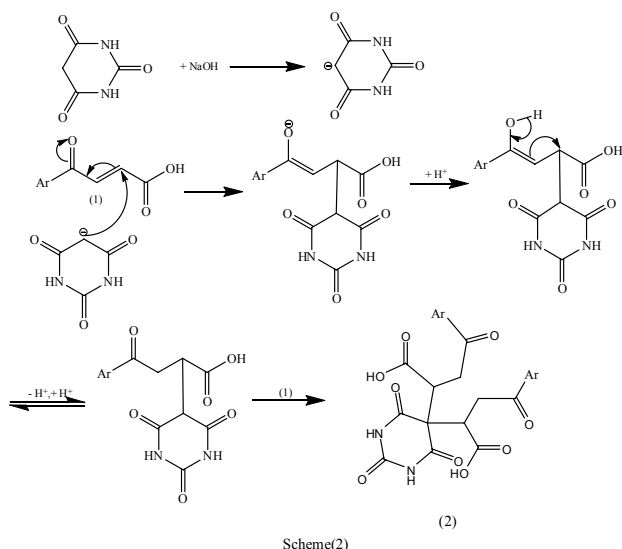


Table 1. ^{13}C -NMR data for compound No 2 [8].

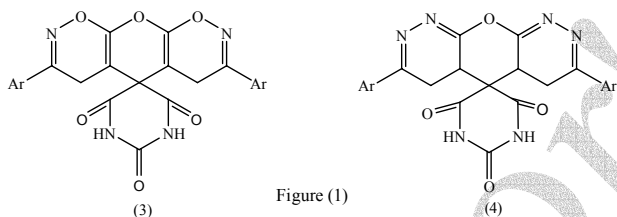
Structure	^{13}C -NMR
	150.7 (C ₁), 170.4 (C ₂), 48.9 (C ₃), 170.4 (C ₄), 39.0 (C ₅), 173.8 (C ₆), 38.3 (C ₇), 196.9 (C ₈), 39.0 (C ₉), 173.8 (C ₁₀), 38.3 (C ₁₁), 196.9 (C ₁₂), 133.8 (C ₁₃), 127.1 (C ₁₄), 128.0 (C ₁₅), 138.4 (C ₁₆), 135.2 (C ₁₇), 130.5 (C ₁₈), 19.5 (C ₁₉), 127.1 (C ₂₀), 128.0 (C ₂₁), 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.

* E-mail: douda56@yahoo.com



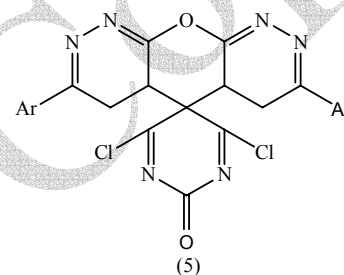
The benzoylpropionic acid **2** was reacted under conventional and microwave irradiation conditions with hydroxylamine hydrochloride in pyridine to afford the spiro compound with oxazine moiety **3**, while its reaction with hydrazine hydrate afforded the spiro compound with pyridazine moiety **4**.



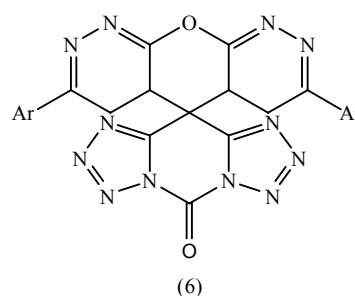
The formation of compound **4** under microwave irradiation was carried out under solvent-free conditions; the procedure gives the product in excellent yield (98%) within 3 minutes avoiding problems associated with solvent use such as cost, handling and safety precautions, because of fire hazard due 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-mono-hydrazone 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 $\text{PCl}_5/\text{POCl}_3$ 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).

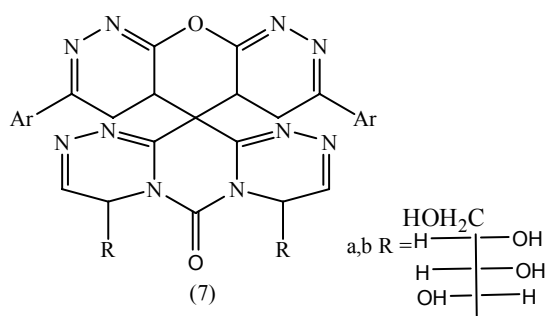


Treatment of the dichloro compound **5** with sodium azide in DMF afforded the tetrazolo derivative **6**. Each of the two carbons attached to the two chlorine atoms has electron deficiency and can easily be attacked by a strong nucleophile such as the azide ion (N_3^-), followed by ring closure to afford the desired product bis-tetrazole.



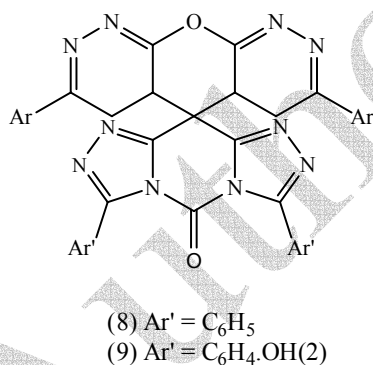
It was reported [6] that heterocyclic nucleosides show broad-spectrum antiviral activity. In this investigation, the author sought to study the behaviour of the dichloro derivative towards the hydrazones of glucose and mannose with the aim to obtain a nucleus, bearing a nucleoside moiety. Thus, when compound **5** was allowed to react with hydrazones of glucose and mannose in boiling butanol, it afforded **7a**, **b** respectively. These

products (**7a**, **b**) were also prepared under microwave conditions, which considerably reduced the time of the reaction (Table 2).



Figure(4)

It was reported that triazolo-pyridazines showed activity in tests indicative of anxiolytic activity [7]. So, the author sought to improve the yield of the reaction by using the microwave irradiation. The reaction of compound **5** with acylhydrazines, namely benzoylhydrazine, and salicyloylhydrazine in refluxing butanol gave triazolopyridazine **8** and **9**. Although the yield by the conventional method and the microwave irradiation was approximately the same, the microwave irradiation was saving time, whereas the reaction time was reduced from 48 hours for the conventional method down to 8–10 minutes for microwave irradiation (Table 2).



Figure(5)

Table 2. Observed yield and reaction time.

Comp. No.	Conventional heating		Microwave irradiation	
	Yield, %	Time, min	Power, W	Yield, %
2	49.2	20	180	75
3	28.8	4	540	57.6
4	50	3	540	98
5	62	5	540	82.8
6	96.8	—	—	—
7a	40	8	630	38
7b	52	8	630	47
8	63	10	720	67.4

CONCLUSION

In conclusion, the results demonstrate a simple and efficient synthesis method of spiro derivatives in almost excellent yields. While the conventional thermal methods require considerable reaction time, the microwave irradiation can substitute classical methods allowing easy and rapid access to spiro derivatives, reducing the reaction times from hours to minutes with improved yields.

EXPERIMENTAL

All microwave reactions were carried out in a domestic microwave oven (Galanz WP900AP23-2). All melting points were uncorrected. The IR spectra were recorded in KBr on FTIR Mattson Spectrometers. The ¹H NMR and ¹³C NMR spectra were measured on Varian Gemini 200 MHz instrument with chemical shift (δ) expressed in ppm downfield from TMS. The mass spectra were recorded on Shimadzu GC-MS-QP 1000 Ex and MS_5988 instruments at 70 eV. The TLC analysis was run using TLC aluminium sheets silica gel F₂₅₄ (Merck). The structures of all compounds have been confirmed by spectroscopic studies.

Synthesis of 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid 1. This compound has been prepared according to reference [9] as yellow crystals, m.p. 130–131°C.

Synthesis of 2,2'-(2,4,6-trioxohexahydropyrimidine-5,5-diyl)bis[3-(4-chloro-3-methyl)benzoylpropionic acid] 2. (A) *By conventional method.* To a mixture of 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid **1** (2 g) and barbituric acid (1.03 g) in 30 ml ethanol, 2 ml of aqueous NaOH (50%) were added. The mixture was left to stay at room temperature for 4 days. The solvent was evaporated; the solid that separated was dissolved in water and then poured onto ice/HCl, filtered, washed with water and recrystallized from benzene.

(B) *By microwave radiation.* A mixture of 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid **1** (2 g) and barbituric acid (1.03 g) in 10 ml of aqueous NaOH (50%) was irradiated with microwaves at *P* = 180 and 270 W for 20 min in subsequent intervals (5 min for each interval) (Table 2). The solid phase that separated was dissolved in water and then poured onto ice/HCl, filtered, washed with water and recrystallized from benzene.

The product was yellow crystals, m.p. 200–202°C; IR cm⁻¹: 1756–1683 (C=O), and 3316 (NH). ¹H NMR (DMSO) δ: 2.4 (s, 6H, CH₃), 3.47–3.49 (dd, 2H, 2CH), 3.6–4.0 (2dd, 4H, 2CH₂), 7.5–7.9

(m, 6ArH), 11.2 (s, 2H, 2NH) and 11.3 (s, 2H, 2COOH). MS *m/z*: 533 (18.75), 224 (8.19), 180 (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** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) 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). 1H NMR (DMSO) δ : 2.4 (s, 6H, 2CH₃), 4.1 (s, 4H, 2CH₂), 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). 1H NMR (DMSO) δ : 1.10–1.80 (m, 4H, 2CH₂), 2.19–2.39 (m, 2H, 2CH), 2.48, 2.49 (2s, 6H, 2CH₃), 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), 1H NMR (DMSO) δ : 2.10–2.13 (m, 4H, 2CH₂), 2.40–2.45 (m, 2H, 2CH), 2.45 (s, 6H, 2CH₃) 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 spiro-tetrazolo 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). 1H NMR (DMSO) δ : 2.38–2.39 (m, 4H, 2CH₂), 2.74, 2.88 (dd, 2H, 2CH), 2.49 (s, 6H, 2CH₃), 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). ^1H NMR (DMSO) δ : 1.30–1.50 (m, 4H, 2CH₂), 2.34–2.36 (m, 2H, 2CH), 2.40 (s, 6H, 2CH₃), 3.75 (d, 2H, 2-CHOH-CH-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 C₃₈H₄₀Cl₂N₁₀O₁₀: 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). ^1H NMR (DMSO) δ : 1.22 (m, 4H, 2CH₂), 2.3–2.40 (m, 2H, 2CH), 2.49 (s, 6H, 2CH₃), 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 C₄₀H₂₈Cl₂N₁₀O₂: 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). ^1H NMR (DMSO) δ : 1.23 (m, 4H, 2CH₂), 2.43–2.46 (m, 2H, 2CH), 2.46 (s, 6H, 2CH₃), 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 C₄₀H₂₈Cl₂N₁₀O₄: 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

М. И. Марзук

Департамент по химия, Факултет по науки, Университет Аин Шамс, Абасия, Кайро, Египет

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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 $\text{PCl}_5/\text{POCl}_3$ 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.

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