Bulgarian Chemical Communications, Volume 41, Number 1 (pp. 84–88) 2009

Microwave assisted condensation of hydrazone derivatives with aldehydes

M. I. Marzouk

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

Received May 12, 2008; Revised November 6, 2008

3-(4-Chloro-3-methyl)benzoylpropionic acid and 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid reacted with hydrazine hydrate under conventional and microwave irradiation conditions in the absence of solvents to afford 6-(4-chloro-3-methyl)phenyl-(2H)-4,5-dihydropyridazine-3-one and 6-(4-chloro-3-methyl)phenyl-(2H)-pyridazine-3-one in good yields. The oxidation of dihydropyridazinone with Br_2/AcOH gave 6-(4-chloro-3-methyl)phenyl-(2H)-pyridazine-3-one. 6-(4-Chloro-3-methyl)phenyl-(2H)-4,5-dihydropyridazine-3-one reacted with ethyl bromoacetate under microwave irradiation in polyethyleneglycol to give 6-(4-chloro-3-methyl)phenyl-2-carbethoxymethyl dihydropyri-dazine-3-one, which further reacted with hydrazine hydrate under microwaves to give the corresponding hydrazide. The hydrazide reacted with certain aldehydes namely benzaldehyde, *p*-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, piperonal and 2-hydroxynaphthaldehyde in DMF under microwave irradiation to give the corresponding hydrazones.

Key words: pyridazinone, microwave, condensation reaction, hydrazones.

INTRODUCTION:

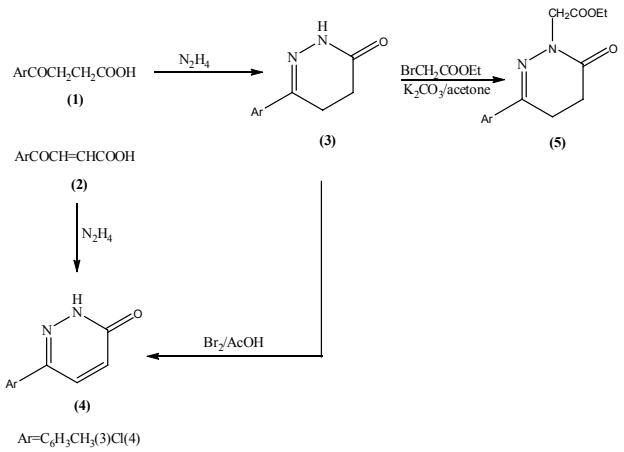
The present day industrialization has led to immense environmental quality deterioration. The increasing environmental consciousness throughout the world has put a pressing need to develop an alternative synthetic approach for biological and synthetic important compounds. This requires a new approach, which will reduce the material and energy consumption of chemical process and products, minimize or eliminate the emission of harmful chemicals in the environment in a way that improves the environmentally benign approach and meet the challenges of green chemistry [1]. There is a considerable current interest in organic reactions under microwave irradiation [2]; it provides advantage [3–6] with respect to reducing reaction time, and increasing product yields, when compared to conventional heating. Pyridazinones have anti-hypertensive activity [7, 8], analgesic and anti-inflammatory activity [9].

In this work, the author sought to investigate the effect of microwave irradiation on the synthesis of some pyridazinones and some hydrazones.

RESULTS AND DISCUSSION

Microwave irradiation using commercial domestic ovens in the absence of solvent is very efficient to synthesize 6-(4-chloro-3-methyl)phenyl-(2H)-4,5-dihydropyridazin-3-one **3** and 6-(4-chloro-3-methyl)phenyl-(2H)-pyridazin-3-one **4** from 3-(4-chloro-3-methyl)benzoylpropionic acid **1** and 3-(4-chloro-3-methyl)benzoylprop-2-enoic acid **2** and hydrazine hydrate, respectively, giving rise to remarkable rate enhancements (Table 1).

The authentic sample of the pyridazinone derivative **4** was prepared by the oxidation of the dihydropyridazinone **3** with Br_2/AcOH.



Scheme 1.

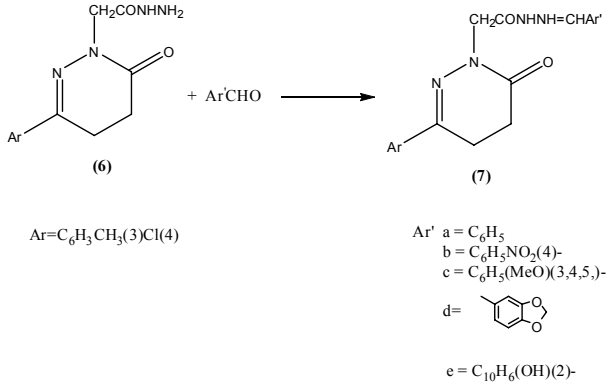
The microwave-assisted reaction was also examined in the absence of solvent and using various reaction media such as *n*-butanol and polyethyleneglycol (PEG) [10, 11] to prepare 6-(4-chloro-3-methyl)phenyl-2-carboethoxymethyl-4,5-dihydropyridazin-3-one **5** by the reaction of 6-(4-chloro-3-methyl)phenyl-(2H)-4,5-dihydropyridazine-3-one **3** with ethyl bromoacetate in the presence of K_2CO_3. The reaction in the absence of solvent and in *n*-butanol did not occur. The development of PEG eliminates the need of volatile organic solvents. This reaction [12] was also carried out by the conven-

* E-mail: douda56@yahoo.com

tional method in the presence of K_2CO_3 in acetone to yield the same compound **5**.

The reaction of the 6-(4-chloro-3-methyl)phenyl-2-carboethoxymethyl-4,5-dihydropyridazin-3-one **5** with hydrazine hydrate to afford 6-(4-chloro-3-methyl)phenyl hydrazinocarbomethyl-4,5-dihydropyridazin-3-one **6** was achieved under neat reaction conditions (solvent free) and it showed a yield improvement and a time saving with respect to the conventional method (Table 1).

N,N-Dimethylformamide was used as a reaction medium in the synthesis of the aldehyde hydrazones **7(a-e)** by the reaction of 6-(4-chloro-3-methyl)-phenyl hydrazinocarbomethyl-4,5-dihydropyridazin-3-one **6** with several aldehydes namely benzaldehyde, *p*-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, piperonal and 2-hydroxynaphthaldehyde. Irradiated by microwave, the reactions were completed at 360–630 W in 4–10 minutes, in contrast to the conventional method that needed 3–6 h.



Scheme 2.

The structures of all the compounds have been confirmed by spectroscopic studies.

EXPERIMENTAL

All microwave reactions were carried out in a domestic microwave oven. All melting points were uncorrected. The IR spectra were recorded in KBr on FTIR Matteson Spectrometers. The ^{1}H 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 instrument at 70 eV. TLC was run using TLC aluminium sheets silica gel F_{254} (Merck).

*Synthesis of 6-(4-chloro-3-methyl)phenyl-(2H)-4,5-dihydropyridazin-3-one (**3**) and 6-(4-chloro-3-methyl)phenyl-(2H)-pyridazin-3-one (**4**)*

(A) By conventional heating. A mixture of the acids **1** and/or **2** (0.01 mol) and hydrazine hydrate (0.01 mol, 99%) in ethanol (30 ml) was refluxed for 6 h. The solid that separated out after concentration and cooling down was filtered off and recrystallized from ethanol to give the expected pyridazinone **3** and **4,** respectively.

(B) By microwave irradiation. A mixture of the acids **1** and/or **2** (0.01 mol) and hydrazine hydrate (0.01 mol) was irradiated with microwaves at *P* = 540 W and time 2–5 min (Table 1). The solid that was obtained was recrystallized from ethanol to give the expected pyridazinone **3** and **4**, respectively.

(C) By oxidation. A stirred solution of **3** (0.01 mol) in glacial acetic acid was heated up to ~ 60–70°C and then treated portion wise with bromine (0.01 mol) for 15 min. The mixture was stirred further for 3 h and poured into ice water. The separated solid was filtered and recrystallized from ethanol.

Table 1. Yield and reaction time interval in the synthesis of compounds **3**, **4, 5** and **6**.

Comp.	Yield A*	Microwave irradiation (neat conditions)		
No.	%	Time, min	Power, W	Yield B*, %
3	86.0	2	540	86.48
		5	540	99.00
4	95.9	2	540	79.59
		3	540	85.7
		5	540	99.00
5	80	30	360	90.00
6	65	4	450	15
		5	540	30
		10	540	80

* A - Conventional heating; B - Microwave irradiation.

Table 2. Yield and reaction time interval in the synthesis of compounds **7**(**a**–**e**).

Comp.	Yield A*	Microwave irradiation		
No.	%	Time, min	Power, W	Yield B*, %
7a	99	4	360	-
		5	450	-
		8	630	99
7b	83.3	4	360	33
		5	630	99
7c	60	4	360	-
		5	630	99
7d	83	4	360	-
		6	450	70
		10	450	78
7e	16	4	360	-
		8	630	40

* A - Conventional heating; B - Microwave irradiation.

6-(4-Chloro-3-methyl)phenyl-(2H)-4,5-dihydropyridazin-3-one (**3**): M.p. 159–62°C; ethanol. IRS cm^{-1}: 1590 (C=C), 1612 (C=N), 1683 (C=O), 3448 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, Me), 2.4–2.5 (t, 2H, CH_2 pyridazinone ring β- to C=O), 2.91–2.99 (t, 2H, CH_2 pyridazinone ring α- to C=O), 7.4–7.7 (m, 3H, Ar–H) and 10.9 (s, 1H, NH).

6-(4-Chloro-3-methyl)phenyl-(2H)-4,5-pyridazin-3-one (**4**): M.p. 228–30°C; ethanol; IRS cm^{-1}: 1590 (C=C), 1615 (C=N), 1664 (C=O), 3217 (NH), 3423 (OH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, Me), 6.94–6.96 (d, 1H, CH– β- to C=O), 6.99–7.0 (d, 1H, CH– α- to C=O), 7.4–8.0(m, 3ArH), 12.8 (s, 1H, NH).

*Synthesis of 6-(4-chloro-3-methyl)phenyl-2-carboethoxymethyl-4,5-dihydropyridazin-3-one (**5**).*

(A) By conventional heating. A mixture of the pyridazinone **3** (0.01 mol) ethyl bromoacetate (0.04 mol) anhydrous potassium carbonate (0.04 mol) and acetone (60 ml) was refluxed for 48 h on a water bath. The solvent was then evaporated and the reaction mixture was poured into water. The separated solid was filtered off, dried and recrystallized from petroleum ether (b.p. 40–60°C).

(B) By microwave irradiation. A mixture of the pyridazinone **3** (0.01mol), ethyl bromoacetate (0.04 mol) anhydrous potassium carbonate (0.04 mol) and PEG600 (2 ml) was mixed well and the contents were then heated in a microwave oven at *P* = 360 W for 30 min. After cooling down, the product was extracted with diethyl ether to afford compound **5** after evaporation. The separated solid was recrystallized from petroleum ether (b.p. 40–60°C).

Compound **5**: m.p. 98–100°C; petroleum ether b.p. 40–60°C. IRS cm^{-1}: 1230 (C–O), 1615 (C=C), 1630 (C=N), 1740 (C=O). ^{1}H NMR (DMSO) δ: 1.26–1.31 (t, 3H, $COOCH_2\underline{CH_3}$), 2.4 (s, 3H, CH_3 attached to the ring), 2.65–2.69 (t, 2H, CH_2– β- to C–O), 2.99–3.01(t, 2H, CH_2– α- to C–O), 4.21–4.23 (q, 2H, –COO–$\underline{CH_2}CH_3$), 4.59 (s, 2H, –$O\underline{CH_2}COOCH_2CH_3$) and 7.37–7.83 (m, 3Ar–H).

*Synthesis of 6-(4-chloro-3-methyl)phenyl hydrazinocarbomethyl-4,5-dihydrazin-3-one **6**.*

(A) By conventional heating. 6-(4-Chloro-3-methyl)phenyl-N-carboethoxymethyl-4,5-dihydropyridazin-3-one **5** (0.01 mol) was dissolved in ethanol (30 ml), the hydrazine hydrate (0.01 mol, 99%) was added and then the reaction mixture was refluxed for 5 h. The separated solid after concentration was filtered off and recrystallized from ethanol.

(B) By microwave irradiation. A mixture of the ester **5** (0.01 mol) and hydrazine hydrate (0.01 mol) was irradiated with microwaves at *P* = 450 W, t = 4 min, *P* = 540 W, t = 5 min and t = 10 min (Table 1) to give the hydrazide **6** with different yields. The solid that obtained was crystallized from ethanol.

Compound **6**: m.p. 199–200°C; ethanol. IRS cm^{-1}: 1523 (C=C), 1648 (C=O), 1668 (C=O pyridazinone ring) and 3314 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, CH_3), 2.4 (s, 2H, NH_2), 2.50–2.59 (t, 2H, CH_2– β- to C=O), 2.9–3.0 (t, 2H, CH_2– α- to C=O), 4.3 (s, 2H, CH_2CO), 7.3–7.7 (m, 3 Ar–H) and 9.1 (s, 1H, NH). MS m/z: 294 ($M^{+\bullet}$ 16.7), 296 ($M^{+\bullet}$ + 2, 6.4), 263 (36.8), 235 (100), 236 (8.5), 208 (8.7), 206 (7.3), 172 (17.0), 89 (12.8), 82 (6.7), 55 (45.7).

*Synthesis of 6-(4-chloro-3-methyl)phenylarylidene hydrazinocarbomethyl-4,5-dihydropyridazin-3-one **7(a-e)***

(A) By conventional heating. A mixture of 6-(4-chloro-3-methyl)phenyl hydrazinocarbomethyl-4,5-dihydropyridazin-3-one **6** (0.01 mol) and aromatic aldehydes namely benzaldehyde, *p*-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, piperonal and 2-hydroxynaphthaldehyde (0.01 mol) in DMF or ethanol (30 ml) was refluxed for 3–6 h. The solid that separated out after concentration and cooling down was filtered off and recrystallized from the proper solvent.

(B) By microwave irradiation. A mixture of the hydrazide **6** (0.01 mol) and the aromatic aldehydes namely benzaldehyde, *p*-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, piperonal and 2-hydroxynaphthaldehyde (0.01 mol) was wetted with DMF and irradiated with microwaves at *P* = 360–630 W, t = 4–10 min (Table 2) to give the corresponding aldehyde hydrazones **7**(**a–e**), which were recrystallized from the proper solvent.

6-(4-Chloro-3-methyl)phenylbenzylidenehydrazinocarbomethyl-4,5-dihydropyridazin-3-one **7a**: m.p. 210–12°C; ethanol. IRS cm^{-1}: 1580 (C=C), 1610 (C=N), 1658 (C=O), 1692 (C=O, pyridazinone ring) and 3447 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, CH_3), 2.5–2.6 (t, 2H, CH_2β-to C=O), 2.9–3.0 (t, 2H, CH_2 α-to C=O), 4.8 (s, 2H, CH_2CON), 7.4–8.0 (m, 8Ar–H), 8.2 (s, 1H, N=CH) and 11.5 (s, 1H, NH). MS m/z: 382 ($M^{+\bullet}$, 18.6), 384 ($M^{+\bullet}$ + 2, 10.6), 263 (19.5), 265 (8.3), 264 (3.9), 235 (81.7), 237 (26.3), 236 (24.4), 208 (30.1), 207 (23.8), 206 (3.6), 172 (18.5), 120 (3.0), 89 (26.2), 82 (1.8), 55 (100), 57 (6.3), 56 (22.5), 54 (6.6) and 36 (17.2).

6-(4-Chloro-3-methyl)phenyl-p-nitrobenzylidenecarbomethyl-4,5-dihydropyridazin-3-one **7b**: m.p. 260–62°C; DMF. IRS cm^{-1}: 1586 (C=C), 1615 (C=N), 1660 (C=O), 1693 (C=O, pyridazinone ring) and 3448 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, CH_3), 2.5–2.6 (t, 2H, CH_2 β- to C=O), 2.8–3.0 (t, 2H, CH_2 α- to C=O), 4.9 (s, 2H, CH_2CON), 7.4–8.2

(m, 7 Ar–H), 8.3 (s, 1H, N=CH) and 11.9 (s, 1H, NH). MS m/z: 427 ($M^{+\bullet}$ 9.3), 429 ($M^{+\bullet}$ + 2, 4.9), 264 (6.2), 263 (14.9), 235 (70.9), 236 (34.9), 234 (85.9), 208 (25.0), 206 (21.8), 171 (18.1), 172 (15.9), 82 (4.9), 89 (25.6), 63 (25.9), 55 (100), 57 (10.6), 56 (31.9) and 54 (99.4).

6-(4-Chloro-3-methyl)phenyl-2,3,5-trimethoxybenzylidenehydrazinocarbomethyl-4,5-dihydropyridazin-3-one **7c**: m.p. 216–18°C; acetic acid. IRS cm^{-1}: 1581 (C=C), 1615 (C=N), 1661 (C=O), 1687 (C=O, pyridazinone ring) and 3270 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, CH_3), 2.4–2.5 (t, 2H, CH_2 β- to C=O), 2.9–3.0 (t, 2H, CH_2 α- to C=O), 3.6 (s, 3H, OCH_3 *p*-), 3.8 (s, 6H, OCH_3 *m*-), 4.9 (s, 2H, CH_2CON), 7.0–7.9 (m, 5Ar–H), 8.1 (s, 1H, N=CH) and 11.5 (s, 1H, NH). MS m/z: 472 ($M^{+\bullet}$ 16.8), 474 ($M^{+\bullet}$ + 2, 7.0), 263 (13.5), 235 (71.4), 236 (20.9), 208 (27.4), 206 (6.2), 172 (17.7), 82 (5.3), 55 (100) and 54 (6.1).

6-(4-Chloro-3-methyl)phenylpiperonylidenehydrazinocarbomethyl-4,5-dihydropyridazin-3-one **7d**: m.p. 228–230°C; acetic acid. IRS cm^{-1}: 1580 (C=O), 1600 (C=N), 1670 (C=C), 1692 (C=O, pyridazinone ring) and 3443 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, CH_3), 2.3–2.5 (t, 2H, CH_2– β- to C=O), 2.9–3.1 (t, 2H, CH_2– α- to C=O), 4.8 (s, 2H, CH_2CON), 6.0 (s, 2H, O–CH_2–O), 6.9–7.9 (m, 6 Ar–H), 8.4 (s, 1H, N=CH) and 11.4 (s, 1H, NH). MS m/z: 426 ($M^{+\bullet}$ 16.8), 306 (11.9), 235 (62.7), 236 (29.8), 208 (32.9), 84 (9.6), 55 (100) and 54 (15.9).

6-(4-Chloro-3-methyl)phenyl-2-hydroxynaphthylidenehydrazinocarbomethyl-4,5-dihydropyridazin-3-one **7e**: m.p. 220–22°C; ethanol. IRS cm^{-1}: 1599 (C=C), 1624 (C=N), 1665 (C=O), 1693 (C=O pyridazinone ring) and 3426 (NH). ^{1}H NMR (DMSO) δ: 2.3 (s, 3H, CH_3), 2.4–2.5 (t, 2H, CH_2 β- to C=O), 2.57–2.65 (t, 2H, CH_2 α- to C=O), 4.9 (s, 2H, CH_2CON), 7.1–9.2 (m, 9 Ar–H), 8.0 (s, 1H, N=CH), 11.5 (s, 1H, NH) and 12.4 (s, 1H, OH). MS m/z: 448 ($M^{+\bullet}$ 29.5), 450 ($M^{+\bullet}$ + 2, 13.8), 263 (19.3), 235 (87.9), 236 (17.9), 208 (36.3), 207 (21.2), 172 (21.3), 55 (100), 57 (14.2), 56 (22.2) and 54 (8.9).

CONCLUSION

Microwave irradiation is very efficient energy source and it can be used to reduce significantly the reaction times of numerous organic reactions. Moreover, microwaves can lead to improvement of isolated yields compared to conventional technology.

REFERENCES

1. W. Xie; Y. Jin; P. G. Wang, *Chemtech.,* **29**, 23 (1999).
2. D. Michael, P. Mingos, *Chem. Soc. Rev.,* **20**, 1 (1991).
3. (a) C. O. Kappe, *Angew. Chem., Int. Ed*., **43**, 6250 (2004); (b) B. L. Hayes, *Aldrichim. Acta X*, **37**, 66 (2004).
4. G. Bram, A. Loupy; M. Majdoub; E. Guetierrez, E. Ruiz-Hitzsky, *Tetrahedron,* **46**, 5167 (1990).
5. L. Baozhi, Z. Jinsong, L. Yufeng, *http://www.chemistrymag.org/cji/2003/059074ne.htm*
6. V. A. Monge, I. Aldana, P. Parrado, P. Daries, E. Fernandez-Alvarez, *An. Quim. Ser.*, **C79 (3, Suppl. 1)** 462 (1983); *Chem. Abstr*., **102**, 95598 (1985).
7. V. A. Monge, I. Aldana, M. Font; P. Parrado, E. Fernandez-Alvarez, J. A. Fuentes, *An. Quim. Ser.* **C79(2),** 242(1983), *Chem. Abstr*., **102**, 6363 (1985).
8. G. Nannimi, G. Biasoli, E. Perrone, A. Forgione, A. Buttinoni, M. Ferrari, *Eur. J. Med. Chem. Chim. Ther.,* **4**, 53 (1979).
9. G. H. Tamman, E. A. Soliman; A. M. El-Gendy, A. Y. El-Kady, *J. Chem. Soc. Pak.,* **9,** 1 (1987).
10. V. V.Namboodiri, R. S. Varma, *Green Chem.,* **3**, 146 (2001).
11. Y. Ju, R. S. Varma, *Tetrahedron Lett.*, **46,** 6011 (2005).
12. M. A.Salem, N. S. Harb, M. A. El-Hashash, M. I. Marzouk, *Ain Shams Sci. Bull.*, **29A**, 427 (1991).

КОНДЕНЗАЦИЯ НА ХИДРАЗОНОВИ ПРОИЗВОДНИ С АЛДЕХИДИ ПОД ДЕЙСТВИЕ НА МИКРОВЪЛНИ

М. И. Марзук

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

Постъпила на 12 март 2008 г.; Преработена на 6 ноември 2008 г.

(Резюме)

При реакцията на 3-(4-хлоро-3-метил)бензоилпропионова киселина и 3-(4-хлор-3-метил)бензоилпроп-2-енова киселина с хидразинхидрат в обикновени условия и при микровълново облъчване в отсъствие на разтворители са получени 6-(4-хлоро-3-метил)фенил-(2H)-4,5-дихидропиридазин-3-он и 6-(4-хлор-3-метил)-фенил-(2H)-пиридазин-3-он с добри добиви. Чрез окисление на дихидропиридазинона с Br_2/AcOH е получен 6-(4-хлор-3-метил)фенил-(2H)-пиридазин-3-он. Реакцията на 6-(4-хлоро-3-метил)фенил-(2H)-4,5-дихидропиридазин-3-он с етилбромацетат в среда от полиетиленгликол при облъчване с микровълни води до получаване на 6-(4-хлоро-3-метил)фенил-2-карбетоксиметилдихидропиридазин-3-он, който реагира с хидразинхидрат при облъчване с микровълни до съответния хидразид. В среда от диметилформамид и при микровълново облъчване хидразидът реагира с определени алдехиди, а именно бензалдехид, *p*-нитробензалдехид, 3,4,5-триметоксибензалдехид, пиперонал и 2-хидроксинафталдехид до съответните хидразони.