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Microwave Assistant Synthesis and Biological Activity of Some 2,4-Dichloroaryloxyacetyl hydrazones

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A series of 2,4-dichloroaryloxyacetyl hydrazones was synthesized from 2,4-dichlorophenol under microwave irradiation. Nine 2,4-dichloroaryloxyacetyl hydrazones were synthesized in excellent yields (83-94 %) and short reaction times. The fungicidal activities of some of these compounds were also investigated. The bioassay results indicated that some of these compound exhibit moderate fungicidal activities.

Key Words: 2,4-Dichloroaryloxyacetyl hydrazones, Microwave irradiation, Fungicidal activity.

INTRODUCTION

Hydrazones possess a diverse range of bioactivities in pharmaceutical and agrochemical field[1], such as anticonvulsant, antidepressant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumoral, vasodilator, antiviral and antischistosomiasis activities[2], herbicidal, fungicidal and insecticidal activity[3]. In addition, they are important intermediates in many reactions[4]. To date, many methods have been described for the preparation of acylhydrazides and acylhydrazones[5]. Usually, the synthetic method to produce acyl hydrazones involves the reaction between acyl hydrazides and aldehydes in ethanol at reflux temperature. However, traditional methods of synthesis of hydrazones suffer from disadvantages, such as long reaction time, low yield and inconvenience of handling.

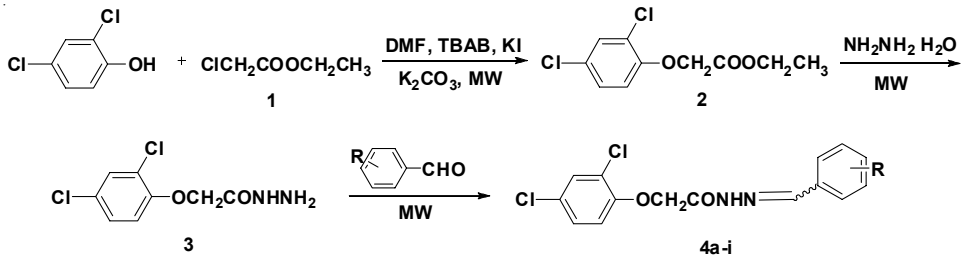
Microwave-assisted heating has been shown to be an invaluable method in synthesis[6], since it can often dramatically reduce reaction times. Meanwhile, microwave technique has been widely used for a variety of organic reactions[7], such as Claisen, cyclization, oxidation, Diels-Alder reaction, hydrolysis, esterification, etherification, *etc.* Many reviews[8] have been published in favour of its considerable accelerations of the reaction rates and satisfactory yields.

In view of these facts and as a part of our work on the synthesis and biological activity of 2,4-dichloroaryloxyacetyl acid derivatives, we now report a rapid, efficient and high yield method for the synthesis of 2,4-dichloroaryloxyacetyl hydrazones.

EXPERIMENTAL

Melting points were determined using a Yanaco MP-241 apparatus and were uncorrected. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using TMS as an internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyzer. LWMC-250 domestic microwave oven was used to do microwave reaction.

General procedure: 2,4-Dichlorophenol (5 mmol), KI (1 mmol), DMF (1 mL) and TBAB (0.5 mmol) were place in a dried round-bottomed flask and the mixture was irradiated by microwaves (200 W) for 4 min. On completion of the reaction, the mixture was cooled to room temperature and then added to ethanol (10 mL) with constant stirring. After filtering off the inorganic salts, the reaction mixture was added to 85 % hydrazine hydrate (5 mmol) and subjected to microwave irradiation (500 W) for an additional 1 min. Then, it was cooled to room temperature, allowed to settle for 1 h and the precipitates were filtered off and recrystallized from ethanol to afford the pure product **3**. Then **3** (1 mmol) and substituted aldehyde (1 mmol) were mixed in an agate mortar. The mixture was put into the microwave oven (495 W) and irradiated for 5 min to produce the crude solid, which on recrystallization with ethanol gave the pure product (**Scheme-I**).



Scheme-I: Synthetic route of title compounds

2-(2,4-Dichlorophenoxy)-N'-(2-nitrobenzylidene)acetohydrazide: White crystal, yield 94 %, m.p.178-179 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.74 (s, 2H, OCH_2), 6.82 (d, 1H, *J* = 8.81 Hz, Ar-H), 6.90 (d, 1H, *J* = 8.80 Hz, Ar-H), 7.45 (dd, 1H, J_1 = 2.45 Hz, J_2 = 2.32 Hz, Ar-H), 7.50-7.62 (m, 2H, Ar-H), 7.68-7.72 (m, 1H, Ar-H), 8.10 (d, 1H, *J* = 8.10 Hz, Ar-H), 8.74 (s, 1H, CH), 9.92 (s, 1H, NH); ESI-MS: 367 (M-1); Elemental anal. (%), calculated: C, 48.93; H, 3.01; N, 11.41; found: C, 48.66; H, 3.31; N, 11.35.

2-(2,4-Dichlorophenoxy)-N'-(2-flurobenzylidene)acetohydrazide: White crystal, yield 92 %, m.p.173-174 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.72 (s, 2H, OCH_2), 6.89 (d, 1H, *J* = 8.82 Hz, Ar-H), 7.10 (d, 1H, *J* = 9.15Hz, Ar-H), 7.20(t, 1H, *J* = 7.75Hz, Ar-H), 7.39-7.43 (m, 2H, Ar-H), 7.46 (d, *J* = 2.15 Hz, 1H, Ar-H), 8.12-8.16 (m, 1H, Ar-H), 8.41 (s, 1H, CH), 9.75 (s, 1H, NH); ESI-MS: 340 (M-1); Elemental anal. (%), calculated: C, 52.81; H, 3.25; N, 8.21; found: C, 52.98; H, 3.31; N, 8.34.

N'-(2-Bromobenzylidene)-2-(2,4-dichlorophenoxy)acetohydrazide: White crystal, yield 91 %, m.p. 182-183 ºC; ^{1}H NMR ($CDCl_3$) δ: 4.71 (s, 2H, OCH_2), 6.89 (q, 1H, *J* = 8.04 Hz, Ar-H), 7.14-7.45 (m, 4H, Ar-H), 7.58 (t, 1H, *J* = 6.81 Hz, Ar-H), 7.81 (d, 1H, *J* = 6.11 Hz, Ar-H), 8.54 (s, 1H, CH), 9.25 (s, 1H, NH); ESI-MS: 401 (M-1); Elemental anal. (%), calculated: C, 44.81; H, 2.76; N, 6.97; found: C, 44.65; H, 2.98; N, 7.03.

2-(2,4-Dichlorophenoxy)-N'-(2-methoxybenzylidene)acetohydrazide: White crystal, yield 88 %, m.p.179-180 ºC; ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 3H, OMe), 4.70 (s, 2H, OCH_2), 6.85 (q, 1H, *J* = 8.79 Hz, Ar-H), 6.96-7.30 (m, 4H, Ar-H), 7.45 (d, 1H, *J* = 2.41 Hz, Ar-H), 7.76 (s, 1H, Ar-H), 8.14 (s, 1H, CH), 9.66 (s, 1H, NH); ESI-MS: 352 (M-1); Elemental anal. (%), calculated: C, 54.41; H, 4.00; N, 7.93; found: C, 54.23; H, 3.98; N, 7.99.

2-(2,4-Dichlorophenoxy)-N'-(3,4-dimethylbenzylidene)acetohydrazide: White crystal, yield 89 %, m.p.199-200 ºC; ^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 6H, Me), 4.69 (s, 2H, OCH_2), 6.82-6.91 (m, 1H, Ar-H), 7.16 (d, 1H, *J* = 8.02 Hz, Ar-H), 7.33-7.46 (m, 4H, Ar-H), 8.06 (s, 1H, CH), 9.07 (s, 1H, NH); ESI-MS: 350 (M-1); Elemental anal. (%), calculated: C, 58.13; H, 4.59; N, 7.98; found: C, 58.45; H, 4.78; N, 7.77.

N'-(3-Bromobenzylidene)-2-(2,4-dichlorophenoxy)acetohydrazide: White crystal, yield 92 %, m.p. 178-179 °C; ^{1}H NMR ($CDCl_3$) δ: 4.70 (s, 2H, OCH_2), 6.88 (d, 1H, *J* = 8.77 Hz, Ar-H), 7.41-7.50 (m, 2H, Ar-H), 7.54 (d, 2H, *J* = 8.40 Hz, Ar-H), 7.65 (d, 2H, *J* = 8.49 Hz, Ar-H), 8.14 (s, 1H, CH), 9.67 (s, 1H, NH); ESI-MS: 401 (M-1); Elemental anal. (%), calculated: C, 44.81; H, 2.76; N, 6.97; found: C, 44.99; H, 2.54; N, 7.23.

N'-(2-Chlorobenzylidene)-2-(2,4-dichlorophenoxy)acetohydrazide: White crystal, yield 89 %, m.p. 167-168 º; ^{1}H NMR ($CDCl_3$) δ: 4.71 (s, 2H, OCH_2), 6.88 (d, 1H, *J* = 8.77 Hz, Ar-H), 7.25-7.41 (m, 4H, Ar-H), 7.44 (d, 1H, *J* = 2.44 Hz, Ar-H), 8.18(t, 1H, *J* = 9.01 Hz, Ar-H), 8.56 (s, 1H, CH), 9.83(s, 1H, NH); ESI-MS: 356 (M-1); Elemental anal. (%), calculated: C, 50.38; H, 3.10; N, 7.83; found: C, 50.31; H, 2.89; N, 7.45.

2-(2,4-dichlorophenoxy)-N'-(4-hydroxy-2-methoxybenzylidene)acetohydrazide: White crystal, yield 83 %, m.p.174-175 ºC; ^{1}H NMR ($CDCl_3$) δ: 3.97 (s, 3H, OMe), 4.70 (s, 2H, OCH_2), 6.89(d, 1H, *J* = 8.82 Hz, Ar-H), 6.93 (d, 1H, *J* = 8.09 Hz, Ar-H), 7.08 (d, 1H, *J* = 6.56 Hz, Ar-H), 7.28 (s, 1H, Ar-H), 7.45 (d, 1H, *J* = 2.48 Hz, Ar-H), 7.52 (d, 1H, *J* = 1.14 Hz, Ar-H), 8.04 (s, 1H, CH), 9.56 (s, 1H, NH); ESI-MS: 368(M-1); Elemental anal. (%), calculated: C, 52.05; H, 3.82; N, 7.59; found: C, 52.23; H, 3.88; N, 7.45.

Bioassay of fungicidal activities: Fungicidal activities of compounds **4** against *Cladosporium cucumerinum, Corynespora cassiicola, Sclerotinia sclerotiorum* (Lib.) de Bary, *Erysiphe cichoracearum, Colletotrichum orbiculare* (Berk aLMont) Arx. were evaluated according to reference. The culture plates were cultivated at (24 ± 1 ºC). The relative inhibition rate of the circle mycelium compared to blank assay was calculated *via* the following equation:

$$\text{Relative inhibition rate (\%)} = \frac{d_{ex} - d_{ex'}}{d_{ex}} \times 100\ \%$$

where d_{ex} is the extended diameter of the circle mycelium during the blank assay; and $d_{ex'}$, is the extended diameter of the circle mycelium during testing.

RESULTS AND DISCUSSION

2,4-Dichloroaryloxyacetyl hydrazines reacted with 9 aldehydes, respectively, to produce 12 corresponding 2,4-dichloroaryloxyacetyl hydrazones (**Scheme-I**). Several experiments were carried out at various reaction times, power levels and different ratios of the reactants to establish the optimum reaction conditions. The products were analyzed using NMR spectroscopy, MS and elemental analysis. All products were obtained in excellent yields (83-94 %) and within 5 min.

Fungicidal activities: Fungicidal activities of compounds **4a**, **4c**, **4e**, **4h** against *Cladosporium cucumerinum, Corynespora cassiicola, Sclerotinia sclerotiorum*(Lib.) de Bary, *Erysiphe cichoracearum, Colletotrichum orbiculare* (Berk aLMont) Arx. were determined. The results were shown in Table-1. It was also found that some of these compounds displayed excellent fungicidal activity. For example, the biological activity of compound **4a** against *Corynespora cassiicola* and *Colletotrichum orbiculare* (Berk aLMont) Arx. to reach 86.0 and 81.22 %, respectively. The compound **4e** can inhibit *Erysiphe cichoracearum* to reach 75.14 %.

TABLE-1
FUNGICIDAL ACTIVITY OF TESTED COMPOUNDS *in vivo* AT 500 ppm

Compd.	*Corynespora cassiicola*	*Cladosporium cucumerinum*	*Erysiphe cichoracearum*	*Sclerotinia sclerotiorum* (Lib.)de Bary	*Colletotrichum orbiculare* (Berk aLMont) Arx.
4a	86.00	13.00	47.40	4.89	81.22
4c	43.00	10.00	44.16	33.75	56.18
4e	46.00	59.00	75.14	6.08	69.33
4h	-0.05	4.00	1.83	16.34	12.99

In conclusion, the use of microwave synthesis for the synthesis of 2,4-dichloroaryloxyacetyl hydrazones proved to be a fast, efficient, safe and environmentally benign technique with excellent yields.

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