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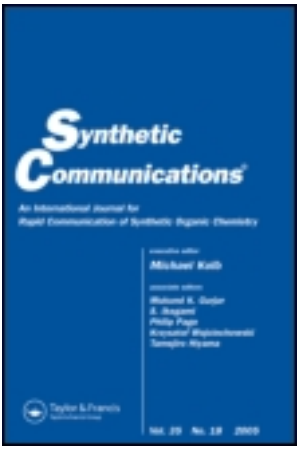

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MICROWAVE ASSISTED SYNTHESIS OF 4,6-DIARYLPYRIDAZIN-3(2H)-ONES IN SOLID STATE

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MICROWAVE ASSISTED SYNTHESIS OF 4,6-DIARYLPYRIDAZIN-3(2*H*)-ONES IN SOLID STATE

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ABSTRACT

Microwave assisted synthesis of dihydropyridazin-3(2*H*)-ones and the subsequent dehydrogenation using selenium dioxide are described.

Microwave initiated reactions, being an unconventional way of carrying out the reactions – especially in a solvent free condition, are becoming popular and a number of papers are appearing towards the end of the last millenium. Several heterocyclic compounds have been synthesized using this technique.[1] Dehydrogenation under microwave conditions is an area where much work has not been carried out. Reports on the reactions of selenium dioxide under microwave conditions are also meagre.[2] This paper describes the microwave initiated dehydrogenation of 4,6-diaryl-4,5-dihydropyridazin-3(2*H*)-ones with selenium dioxide in the solid state.

Many pyridazine derivatives exhibit biological activity and some are used as drugs.[3,4] 4,6-Diaryl-4,5-dihydropyridazin-3(2*H*)-ones have been synthesized from β-aroyl-α-arylpropionic acids obtained either from β-aroyl acrylic acids[5] or from chalcones.[6] They can be easily dehydrogenated

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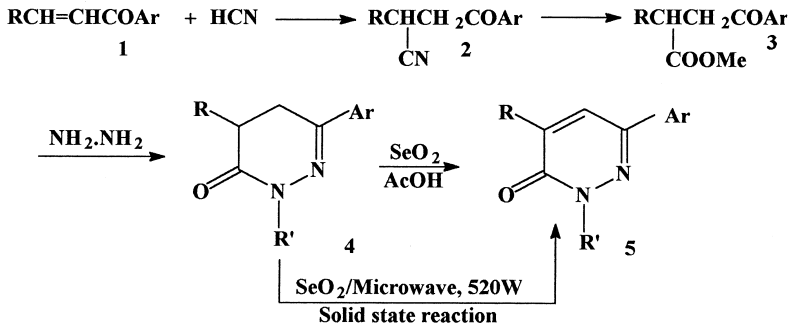
to give 4,6-diaryl-3-(2H)-pyridazinones[6] by bromination followed by dehydrohalogenation or using copper chloride.[7] Dehydrogenation using selenium dioxide both under conventional and microwave conditions are described here. It should be noted that selenium dioxide has been used for dehydrogenation in some selective compounds of this type.[8]

Different substituted chalcones **1**, prepared by the conventional method,[9] were converted to the γ-ketocyanides **2** either by the addition of the potassium cyanide in acetic acid[10] or of acetone cyanohydrin.[11] The γ-ketocyanides were then converted to the respective methyl esters (**3a–f**) with methanol and sulfuric acid. Condensation of hydrazine or phenylhydrazine with the methyl esters (**3**) afforded 4,6-diaryl-4,5-dihydropyridazin-3(2*H*)-ones. The treatment of these dihydropyridazin-3(2*H*)-ones with selenium dioxide in acetic acid effected the dehydrogenation resulting in 4,6-diarylpyridazin-3(2*H*)-ones (**5a–f**). The yields, physical constants and the ^{1}H NMR spectral data of the compounds are presented in Table 1. It should be mentioned that this sequence of synthesizing 4,6-diarylpyridazin-3(2*H*)-ones from chalcones has the ester **3** as the intermediate instead of the corresponding acid as reported in a previous work.[6] We have used selenium dioxide in acetic acid medium requiring only 90 min in some cases but require more time in some other cases (Table 1).

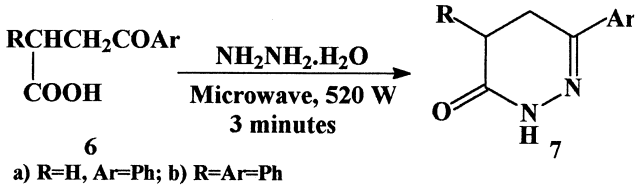
To investigate the dehydrogenation ability of selenium dioxide under microwave conditions, the conversion of **4** to **5** was carried out in a solvent free solid state in a domestic microwave oven. It is interesting to note that dehydrogenation takes place effectively with relatively high yields in short duration under these conditions. The time required, power of microwave used and the yields obtained are presented in Table 1.



a) R = Ar = C_6H_5; R' = H; b) R = C_6H_5; Ar = p-Cl-C_6H_4; R' = H; c) R = OMe.C_6H_4; Ar = C_6H_5; R' = H; d) R = p-Me.C_6H_4; Ar = C_6H_5; R' = H; e) R = p-Me.C_6H_4; Ar = p.Cl.C_6H_4; R' = H; f) R = OMe.C_6H_4; Ar = p.Cl.C_6H_4; R' = H; g) Ar = C_6H_5; R = R' = H; h) R = Ar = R' = C_6H_5; i) R = H; Ar = R' = C_6H_5;

Scheme 1.

4,6-Diaryl-4,5-dihydropyridazin-3(2*H*)-ones have also been obtained within 3 min from the respective acids and hydrazine under microwave conditions as given in Scheme 2.



Scheme 2.

EXPERIMENTAL

Melting points were uncorrected. The ^{1}H NMR spectra were recorded on a Perkin-Elmer R32 spectrometer with TMS as the internal standard and $CDCl_3$ (Compounds 4) or DMSO-d_6 (Compounds **5**) as the solvent, while IR spectra were recorded in a Perkin-Elmer 575 instrument by mounting the samples as KBr discs. Domestic microwave oven (LG, 1300 W, 28L capacity) was used. Chalcones **1** were prepared by literature method.[9] **1a**, **c** and **f** were converted to γ-ketocyanides using potassium cyanide and acetic acid[10] while **1** was converted to **2b**, **d** and **e** respectively with acetone cyanohydrin.[9] The γ-ketocyanides **2** (0.01 mol) were taken in methanol (sufficient to dissolve the compound) and sulfuric acid (0.377 g) and refluxed (the reaction time is indicated in Table 1). The reaction mixture was cooled well, diluted with water and the solid obtained was filtered, and crystallized from ethanol to give **3**. Compound **4g** was obtained from β-benzoylpropionic acid by hydrazine addition. The N-phenyl compounds **4h** and **4i** were prepared by the reaction of phenylhydrazine with β-benzoyl-nzoylpropionic acid and α-phenyl-β-benzoyl Propionic acid respectively. Compounds **2f**, **3b**, **3c**, **3e** and **3f** show satisfactory C,H,N analysis and spectral features.

4,6-Diaryl-4,5-dihydropyridazin-3(2*H*)-ones: Typical Procedure – A mixture of 0.5 g of ester **3a**, (1.8 mmol), 1 ml of hydrazine hydrate (100%) and 15 ml of diethylene glycol was heated over a steam bath for the period of time specified in the table. The reaction mixture was poured into crushed ice. The solid obtained was collected, washed repeatedly with water and dried to give 4,6-diphenyl-4,5-dihydropyridazin-3(2*H*)-ones (**4a**).

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Table 1. Physical Constants, Yields and the ^{1}H NMR Data of Pyridazinones Prepared by Conventional and Microwave Method (520 W Power)

Compound[a]	Time h	mp (°C)	Lit[a] mp (°C)	Yield (%)	Microwave conditions		^{1}H NMR Data (δ)
					Time (min)	Yield (%)	
4a	1.5	162	163[6]	70	–	–	9.0(1H,b,NH); 6.8–7.6 (10H,m,Ar-H); 3.6(1H,m); 3.1(2H,m)
4b	12	160	165[6]	68	–	–	9.3(1H,b,NH); 7–7.4(9H,m,Ar-H); 3.6(1H,m); 3.1(2H,m)
4c	4	145		63	–	–	9.2(1H,b,NH); 6.6–7.6(m,9H,Ar-H); 3.6(1H,m); 3.1(2H,m); 3.6(s,OMe)
4d	10	Viscous liquid		24	–	–	9.4(1H,b,NH); 7.1–7.6(m,9H,Ar-H); 3.8(1H,m); 3.1(2H,m); 2.3(s,Me)
4e	4	145–147		68	–	–	9.2(1H,b,NH); 7.1–7.7(m,8H,Ar-H); 3.85(1H,m); 3.5(2H,m); 2.5(s,Me)
4f	8	130		70	–	–	9.5(1H,b,NH); 6.7–7.8(m,8H,Ar-H); 3.6(1H,m); 3.1(2H,m); 3.6(s,3H,OMe)
4g	2	146–148	151[12]	69	–	–	9.15(1H,b,NH); 2.9(t,2H); 2.6(t,2H); 7.3–7.5(5H,m,Ar-H)
4h	4	122	121–123[13]	68	–	–	6.9–7.7(15H,m,Ar-H); 3.9(1H,t);3.2(2H,d)
4i	2.5	Viscous liquid	94,[12] 201[14]	69	–	–	7.1–7.6(10H,m,Ar-H); 2.85(t,2H); 2.5(t,2H)

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5a	3	170	186–187[15]	68	7	82	12.5(1H,NH); 7.1–7.8(11H,m,Ar-H)
5b	3	212	224[6]	69	3	81	13.5(1H,NH); 7.4–8.0(10H,m,Ar-H)
5c	3	213		67	3	84	12.8(1H,NH); 6.6–7.8(10H,m,Ar-H); 3.5 (s,3H,OMe)
5d	3	205		66	2	79	13.5(1H,NH); 7.15–7.8(10H,m,Ar-H); 2.4(s,3H,Me)
5e	3	225–227		70	3	80	13.5(1H,NH); 7.15–7.8 (9H,m,Ar-H); 2.4(s,3H,Me)
5f	8	195–197		67	5	79	13.5(1H,NH); 6.7–7.8(9H,m,Ar-H); 3.5(s,3H,OMe)
5g	3	185–186	199–200[15]	68	1	81	13.5(1H,NH); 7.5–7.7(5H,m,Ar-H)
5h	6	145	179–181[16]	69	4	83	7.1–8.0(m,Ar-H)
5i	9	149	150–151[17]	70	4	79	6.9–7.9(m,Ar-H)

Microwave Assisted Preparation of Dihydropyridazine-3(2*H*)-ones

A mixture of 0.5 g of acid (**6**) and 1 ml of hydrazine hydrate (100%) was heated in a microwave oven (540 W) for 3 min. The solid 4,6-diaryl/4-aryl-4,5-dihydropyridazin-3(2*H*)-ones (**7**) obtained was collected. The yields of **7a** and **7b** were 82% and 80% respectively.

4,6-Diarylpyridazin-3(2*H*)-ones: Typical Procedure – A mixture of 0.5 g of 4,6-diphenyl-4,5-dihydropyridazin-3(2*H*)-ones (**4a**), (2 mmol), 1 g of selenium dioxide (9 mmol) and 15 ml of acetic acid was heated over a steam bath for the period of time specified in Table 1. The mixture was filtered to remove selenium and the filtrate was poured into crushed ice. The solid 4,6-diphenylpyridazin-3(2*H*)-ones obtained was collected, washed thoroughly with water to remove any adhering acetic acid and dried in air to give **5a**.

Microwave Assisted Dehydrogenation of Dihydropyridazin-3(2*H*)-ones with Selenium Dioxide

A mixture of 0.5 g of 4,6-dihenyl-4,5-dihydropyridazin-3(2*H*)-ones (**4a**), (2 mmol), 1 g of selenium dioxide (9.0 mmol) was ground well in a mortar and placed in a petri dish. It was placed in the microwave oven for the period of time specified in Table 1. The progress of the reaction was monitored by TLC. After the completion of the reaction, the contents were dissolved in chloroform, boiled well for 10 min and the precipitated selenium was removed by filtration. Evaporation of solvent gave pure solid 4,6-diphenylpyridazin-3(2*H*)-ones.

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