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Improved Synthesis of Pyridazinediones Under Microwave Irradiation

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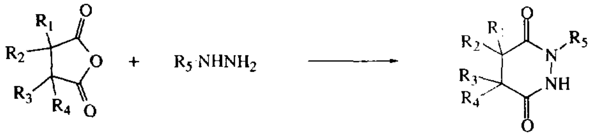
***Abstract**: Pyridazinediones have been synthesized with good to excellent yields under microwave irradiation. The results were compared with traditional stirring.*

Although the pyridazine moiety was known for a century [1] and the first synthesis reported as early as 1895 [2], its high development only emerged recently [3]. This heterocycle is now encountered in various therapeutic classes such as anti-inflammatories [4], antidepressants [5], neuroleptics,...

The most usual method for the synthesis of substituted pyridazinediones is the condensation of cyclic anhydrides with hydrazines (scheme 1). This reaction is classically performed in acetic acid. Depending upon the nature of the anhydride [6], reaction conditions can vary from 1 hour at room temperature to 24 hours at solvent reflux. As these conditions may induce significant degradation of sensitive hydrazines, we have attempted to define milder conditions. Microwave irradiation is particularly suitable to perform reactions in which elimination of a water molecule is involved. As this was the case here, we have investivated the synthesis of pyridazinediones using this method.



scheme 1

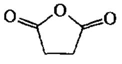
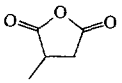
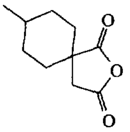
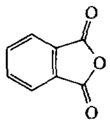
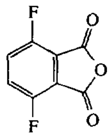
Initial trials were performed by reacting succinic anhydride and phenylhydrazine in acetic acid in various conditions. Microwave irradiation allowed a drastic reduction of reaction times : comparable yields were obtained using 2 min irradiation time in a domestic microwave oven, 4 min with a power of 500 W in a laboratory oven, while in classical conditions, the reaction requires 4 hours stirring at room temperature.

Assay	Method	Concentration (M)	Conditions	Reaction time	Yield (%)
1	T	0.2	r.t.	4 h	85%
2	domestic MW	0.2	power 2	2 min	86-88%
3	laboratory MW	0.2	315 W	6 min	86%
4	laboratory MW	0.2	500 W	2 min	85%
5	laboratory MW	0.05	500 W	4 min	87%

T: traditional stirring at r.t.. MW : microwave

Table 1: Reaction between succinic anhydride and phenylhydrazine

In order to extend the scope of this method, the reaction of phenylhydrazine with various anhydrides was then investigated [7]. In this case, a laboratory oven [8] in which power can be precisely adjusted was used. As can be seen in table 2, using short irradiation periods (2 to 4 min), the corresponding pyridazinediones were obtained in similar (assay 2 and 4) or higher (assay 6) yields than using the classical method. Moreover, in two cases (assay 8 and 10), microwave irradiation was the only method leading to the expected derivates. Increasing reaction times with the classical method led only to an extensive formation of degradation products (assay 7 and 9).

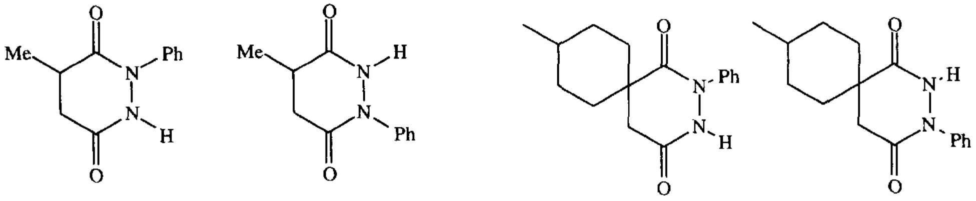
Assay	Anhydride	Method	Time	Yield (%) (a)
1		T	4 h	85
2		MW	4 min	87
3		T	24 h	80 (b)
4		MW	4 min	80
5		T	24 h	45 (c)
6		MW	4 min	74
7		T	48 h	0
8		MW	2 min	72
9		T	48 h	0
10		MW	2 min	87

T: traditional stirring at r.t.. MW : 500W microwave irradiation. (a) products isolated by flash chromatography. (b) mixture of the two regioisomers: 65 / 35. (c) mixture of the two regioisomers: 60 / 40.

Table 2 : Reaction of phenylhydrazine with various anhydrides

2-Anilinophtalimide was also obtained in assay 8, but as a by-product (23%). It could not be detected in assay 7, even if it was often the major product of the reaction according to the litterature [9].

For asymmetric anhydrides (assay 3 to 6), the two methodologies provide differents results. Using the traditional methodology (assay 3 and 5), the two possible regioisomers were obtained (1a, 1b and 2a, 2b) as shown by reverse phase HPLC of the reaction medium. On the contrary, in both cases, only one isomer was obtained with MW irradiation (assay 4 and 6), identified as the minor isomer of previous experiments. Study of the 2D-NMR HSQC and HMBC spectra [10] allowed us to establish their structure as corresponding to the most hindered isomers **1a** and **2a**. This high regioselectivity is not a microwave effect since it was also observed when the reaction was conducted traditionally in refluxing acetic acid (concentration = 0.2M, reflux 1h, 58% yield) instead of room temperature. The lower yield can be explained by a slower rise in temperature leading to the degradation of phenylhydrazine in acetic acid, which does not occur by microwave irradiation.



1a **1b** **2a** **2b**

scheme 2

In order to further extend the usefullness of this method, the reaction of succinic anhydride with various hydrazines was investigated (Table 3). One of the problems encountered with the classical method is that hydrazine hydrochlorides (which are generally the commercially available form) are not soluble in acetic acid. Although the use of other solvents such as a DMF / AcOH mixture overcomes this problem, the corresponding yields were significantly lower. In fact, reaction of succinic anhydride with phenylhydrazine chlorhydrate in a DMF/AcOH : 3/1 solution provided the corresponding pyridazine with a 80% yield after a 24 hours reaction time at room temperature (instead of a yield of 84% after 4h stirring).

Again, in these experiments, microwave irradiation improved yields and shortened reaction times. In the case of benzylhydrazine, we could isolate the desired derivative in a moderate yield (assay 18) using MW methodology whereas no product could be identified from the complex mixture obtained with a traditional room temperature stirring (assay 17).

In conclusion, microwave irradiation provides a simple and versatile method to prepare various pyridazinediones in high yield. The short reaction times minimize the alteration of sensitive compounds which often lead to complex mixtures following the traditional methods.

Assay	Hydrazine	Method	Reaction time	Yield (%)
11	$2\text{-MePhNHNH}_2 \cdot \text{HCl}$	T$^{(a)}$	48 h	50
12		MW	4 min	70
13	$3\text{-ClPhNHNH}_2 \cdot \text{HCl}$	T$^{(a)}$	6 h	64
14		MW	4 min	82
15	$4\text{-BrPhNHNH}_2 \cdot \text{HCl}$	T$^{(a)}$	6 h	70
16		MW	4 min	76
17	$\text{PhCH}_2\text{NHNH}_2 \cdot 2\ \text{HCl}$	T$^{(a)}$	48 h	0$^{(b)}$
18		MW	2 min	40$^{(c)}$

T: traditional stirring at r.t.. MW : 500W microwave irradiation. (a) 0.05 M in a DMF / AcOH : 3/1 solution.(b) little evolution of the reaction media, a lot of products appeared. (c) degradation of benzylhydrazine with microwave irradiation.

Table 3 : Reaction of succinic anhydride with various hydrazines

Acknowledgments

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(2) Taüber, E. *Ber.* **1895**, *28*, 451-469.
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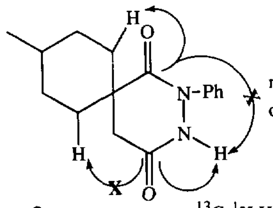
(4) Negwer, M. *Organic Chemical Drugs and Synonyms* (Akademie - Verlag Berlin) **1987**, I-III.
(5) Wermuth, C. G. *Actual. Chim. Thér.* **1985**, *12*, 3-35.
(6) Pilleboue-Melnyk, P. Doctorat de l'Université Paris VI (the 26th january 1993).
(7) Typical procedure: To a solution of anhydride (0.1 mmol) in glacial acetic acid (2 ml) was added hydrazine (0.1 mmol). The resulting mixture was irradiated in a CEM SAM 155 microwave oven (500 W) for 2 - 6 min. and evaporated. The solid was purified by flash chromatography (pentane / EtOAc) to provide the desired compound which was analyzed (TLC, HPLC) and characterized (NMR).
(8) Domestic microwave oven: Arthur Martin 506 25. Laboratory microwave oven : CEM SAM 155.
(9) Katritzky, A.R.; Rees, C.W. *Comprehensive Heterocyclic Chemistry* (Pergamon Press - Oxford) **1984**, vol. 3, 47.
(10) HSQC (Hetero Single Quantum Coherence): ^{13}C-^{1}H shift-correlation experiment in reverse mode (^{1}J), HMBC (Heteronuclear Multiple Bond Correlation): ^{13}C-^{1}H long range shift-correlation experiment in reverse mode (^{1}J, ^{2}J, ^{3}J, ^{4}J). HMBC correlation spots between C and H were reported below, the same correlation systems were observed for compound **1a**.



no ^{13}C - ^{1}H HMBC correlation observed

2a

^{13}C-^{1}H HMBC correlation observed

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