Indian Journal of Chemistry
Vol. 46B, August 2007, pp. 1361-1363

Note

Facile and efficient synthesis of 1,8-naphthyridinyl phthalazine-1,4-diones under microwave irradiation

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Received 6 November 2006; accepted (revised) 15 May 2007

Microwave irradiation of 3-aryl-2-hydrazino-1,8-naphthyridines **1** with phthalic anhydride **2** in the presence of a catalytic amount of DMF provides a fast, efficient and simple method for the synthesis of 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthalazine-1,4-diones **3** in excellent yields.

Keywords: Microwave irradiation, 3-aryl-2-hydrazino-1,8-naphthyridine, phthalic anhydride, 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthalazine-1, 4-diones

Microwave irradiation has been successfully applied in organic synthesis[1-4]. Recently reaction facilitated by microwaves under solvent-free[2,3] condition have attracted more attention because of their enhanced selectivity, reducing reaction time, easier work-up procedure. Phthalazine derivatives represent a heterocyclic system of remarkable pharmacological / biological efficiency[5,6]. There are several methods available in the literature for the synthesis of phthalazinones. However, some of these methods suffer from disadvantages such as long reaction times, lower yields and requirement of severe conditions. Therefore, the development of new methods with greater efficacy, straightforward procedures and better yields still is desirable. 1,8-Naphthyridine derivatives have attracted considerable attention owing to their effective biological activity[7-9]. Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and phthalazinone might result in compounds with interesting biological activity. In view of this, we report herein a new and efficient method for the synthesis of 1,8-naphthyridinyl phthalazinones under solvent-free microwave irradiation conditions.

Treatment of 3-aryl-2-hydrazino-1,8-naphthyridines **1** with phthalic anhydride **2** in the presence of catalytic amount of DMF without any solvent under microwave irradiation afforded the corresponding 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthalazine-1,4-diones **3** (**Scheme I**). The reactions proceed efficiently in excellent yields at ambient pressure within a few min. The products were obtained with a high degree of purity by this procedure and in most cases no further purification was needed. The process is environmentally friendly. The experimental procedure is very simple. Further, we observed that the neat mixture of **1** and **2** did not react on microwave irradiation, but the reaction completed within min on addition of few drops of high dielectric solvent such as DMF.

In a typical case, a mixture of 2-hydrazine-3-phenyl-1,8-naphthyridine **1** (Ar = C_6H_5), phthalic anhydride **2** and DMF (5 drops) was exposed to microwave irradiation at 400 W intermittently at 30 sec intervals for 3.0 min. After usual work-up 2-(3-phenyl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydro-phthalazine-1,4-dione **3a** (Ar – C_6H_5) was obtained in 92% yield.

The reaction is of general applicability and the various 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthtlazine-1,4-diones in **3b-f** synthesized are given **Table I**.

Alternatively, the same reaction was performed with specific example under thermal conditions in an oil-bath preheated to 120°C (temperature measured at the end of exposure during microwave experiment) and reaction was completed in 8 hr and the yield of **3a** was only 40%.

The structures of the compounds **3** were determined by spectral (IR, ^{1}H NMR and MS) data.

In conclusion, a simple and efficient method has been developed for the synthesis of phthalazine-1,4-diones in solvent-free conditions under microwave irradiation. Moreoever, short reaction times, simple experimental work-up procedure, high yields and excellent purities of the products are noteworthy advantages of this method.

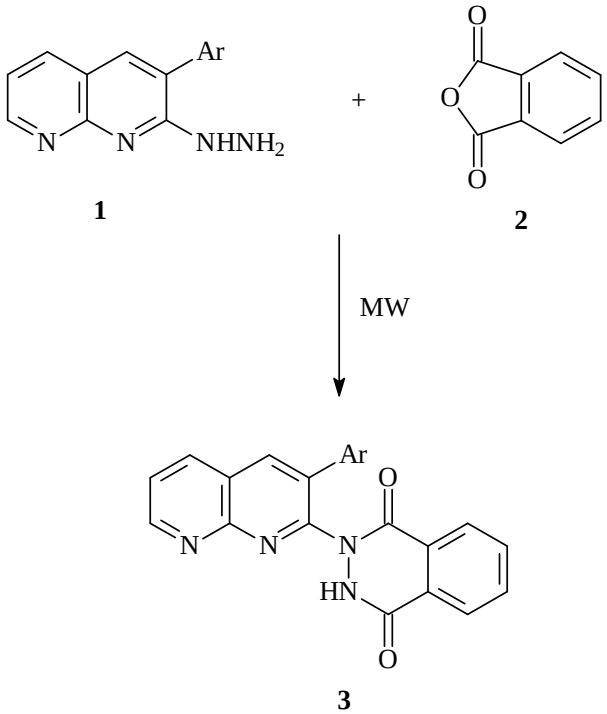
Experimental Section

All melting points were determined on a Cintex melting point apparatus and are uncorrected. The purity of the compounds was checked by TLC. IR spectra (KBr) were recorded on a Perkin-Elmer BX

Table I — Physical and spectral data of compounds **3a-f**

Compd*	Reaction Period (min)	m.p. °C	Yield (%)	^{1}H NMR ($CDCl_3$) δ, ppm
3a	3.0	300	92	7.90 (m, 2H, C_4-H, C_5-H), 8.05 (m, 1H, C_7-H), 7.20-7.80 (m, 10H, C_6-H, 9Ar-H), 8.85 (s, 1H, NH).
3b	4.0	225	94	3.92 (s, 3H, OCH_3), 7.70 (m, 2H, C_4-H, C_5-H), 7.95 (m, 1H, C_5-H), 8.10 (m, 1H, C_7-H), 7.02-7.60 (m, 8H, Ar-H), 8.20 (s, 1H, NH).
3c	3.5	290	93	8.10 (m, 2H, C_4-H, C_5-H), 7.95 (m, 1H, C_6-H), 8.25 (m, 1H, C_7-H), 7.40-7.88 (m, 8H, Ar-H), 9.05 (s, 1H, NH).
3d	4.0	280	92	7.85 (m, 2H, C_4-H, C_5-H), 7.70 (m, 1H, C_6-H), 8.06 (m, 1H, C_7-H), 7.20-7.62 (m, 8H, Ar-H), 8.78 (s, 1H, NH).
3e	4.0	284	96	7.87 (m, 2H, C_4-H, C_5-H), 8.07 (m, 1H, C_7-H), 7.18-7.80 (m, 9H, C_6-H, 8Ar-H), 8.80 (s, 1H, NH).
3f	3.5	272	93	7.92 (m, 2H, C_4-H, C_5-H), 8.15 (m, 1H, C_7-H), 7.15-7.74 (m, 9H, C_6-H, 8Ar-H), 8.87 (s, 1H, NH).

*All the compounds gave satisfactory C H N analyses.



Ar		Ar	
a,	C_6H_5	**d,**	*m*-ClC_6H_4
b,	*p*-$CH_3OC_6H_4$	**e,**	*p*-ClC_6H_4
c,	*o*-ClC_6H_4	**f,**	*p*-BrC_6H_4

Scheme I

series FT-IR spectrophotometer and ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS on internal standard. The reactions were carried out in LG MS 556P, 2450 MHz domestic microwave oven. The starting compounds **1** were prepared according to literature procedure[10-15].

General procedure for the synthesis of 2-(3-aryl-1,8-naphthyridin-2-yl)-1,2,3,4-tetrahydrophthalazine-1,4-diones 3a-f. A mixture of 3-aryl-3-hydrazino-1,8-naphthyridine **1** (0.01 mole) and phthalic anhydride **2** (0.01 mole) was thoroughly mixed in a 50 mL beaker and DMF (5 drops) was added to it. The beaker was covered with a watch glass and irradiated in a microwave oven at 400 W intermittently at 30 sec intervals for the appropriate time **(Table I)**. After completion of the reaction (monitored by TLC), the beaker was removed from the oven and the mixture was cooled to room temperature, 20 mL cold ethanol was added. The product obtained was filtered and recrystallized from methanol to give **3 (Table I)**.

Acknowledgements

The authors are thankful to the Director, IICT, Hyderabad for recording ^{1}H NMR spectra.

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