Heteroatom Chemistry
Volume 10, Number 4, 1999

PCl_3 Mediated Cyclization: Synthesis, at Room Temperature, of N-Alkenyl Derivatives of 1,4-Phthalazinedione

Graziano Baccolini, Carla Boga, and Umberto Negri

Dipartimento di Chimica Organica, Università, Viale Risorgimento 4, I-40136 Bologna, Italy

Received 6 November 1998; revised 22 December 1998

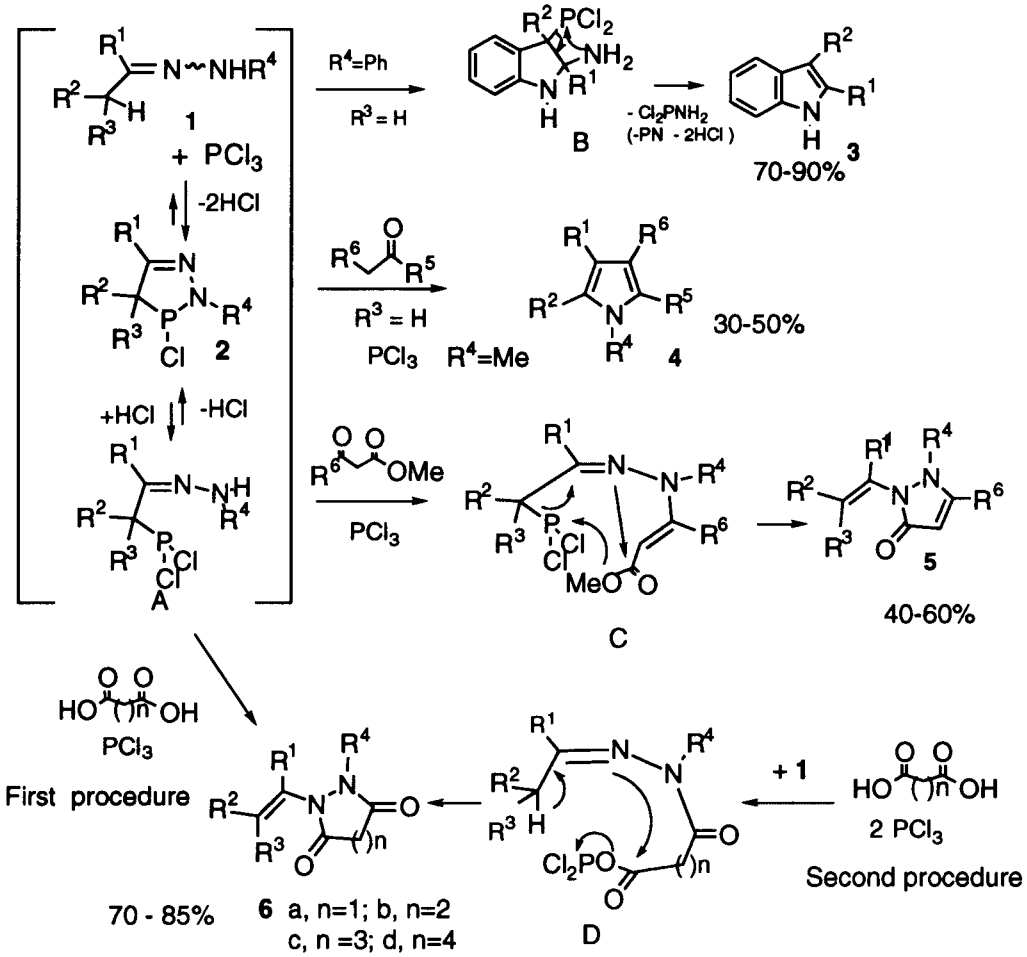
ABSTRACT: *The use of a PCl_3/hydrazone/dicarboxylic acid combination can be applied in an efficient one-pot procedure for the synthesis at room temperature of the title ring compounds that are also a new family of stable enamines. The phthalazinediones* **7** *were obtained in good yields by reaction of PCl_3 with phthalic acid and hydrazones* **1a,b,c** *containing hydrogen atoms only in one α position. Two structurally isomeric phthalazinediones (***7** *and* **8***) were obtained with hydrazones* **1d,e,f,g** *containing hydrogen atoms in the two different α positions. When we used a methyl ketone hydrazone* **1c,d,e,f,i**, *it was possible also to isolate the isomer containing an N-alkenyl group with two terminal hydrogen atoms. Where E,Z isomers are possible, the exclusive formation of the E isomer was always observed. As a rule, changing the order of addition of reagents gave almost identical results; however, in the case of phthalic acid, it is better to use the procedure in which PCl_3 is added last to prevent the formation of the corresponding anhydride.*
 Heteroatom Chem 10: 291–296, 1999

Correspondence to: Graziano Baccolini
Contract Grant Sponsor: University of Bologna (funds for selected topics A.A 1997–1999)
Contract Grant Sponsor: Consiglio Nazionale delle Ricerche (CNR-Roma)
Contract Grant Sponsor: Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST)
 CCC 1042-7163/99/040291-06

INTRODUCTION

1,4-Phthalazinediones [1a,b] have been accorded increasing importance in the last few years owing to their application as medical substances [1c,d] and chemiluminescent tracers (luminol and related compounds) [1e,f,g]. A widely used approach for the synthesis of phthalazinediones is the condensation of phthalic anhydride (or diester or phthaloyl chlorides) with hydrazines. However, this reaction requires drastic conditions, and, with phenylhydrazine, it sometimes gives phthalimides as main products [1a,b,e,f,g]. Now we describe a convenient one-pot synthesis at room temperature of the title compounds (**7**,**8**) using a PCl_3/hydrazone/dicarboxylic acid combination. These compounds represent to date an unknown series of stable enamines [2] of 1,4-phthalazinediones.

For understanding the subsequent results, it is necessary to give a short introduction on how the idea to use the PCl_3/hydrazone/dicarboxylic acid combination was verified. Some years ago, we discovered [3] that the reaction between an arylhydrazone **1** (R^4 = Ph) and PCl_3 gives a 2,3-disubstituted indole **3** (see Scheme 1) in good yield after a few minutes at room temperature, while no formation of a monosubtituted indole was observed. Subsequently, we discovered [4] that a reaction between chlorodiazaphospholine **2** (R^4 = Me) [5], an enolizable ketone, and additional PCl_3 gives, at room temperature, an unsymmetrically substituted pyrrole **4**. To explain the formation of these aza-heterocycles, we have offered [3,4] a plausible interpretation that consists of an acid promoted cleavage of the P–N



SCHEME 1

bond of the first intermediate **2**, to give the ring-opened intermediate A (or its enehydrazine form). This intermediate A undergoes immediately a [3,3]sigmatropic rearrangement similarly to the accepted mechanism of Fischer indolization [6] (when R^4 = Ph R^3 = H) or a similar Piloty–Robinson pyrrolization [7]. Still later, we found, surprisingly [8], that on treating the reaction mixture containing **2** with a *β*-keto ester, a 1,2-dihydro-2-alkenyl-3*H*-pyrazol-3-one **5** was obtained at room temperature (see Scheme 1). In this case, the key intermediate might be C, which now cannot give the above mentioned sigmatropic rearrangement, but it gives instead a spontaneous intramolecular rearrangement forming a pyrazolone **5** [9]. From these results, it was clear that a new type of cyclization mediated by PCl_3 had been discovered, which permits us to obtain diaza-heterocycles, bearing an enamine group, which are probably very difficult to prepare by classic methods.

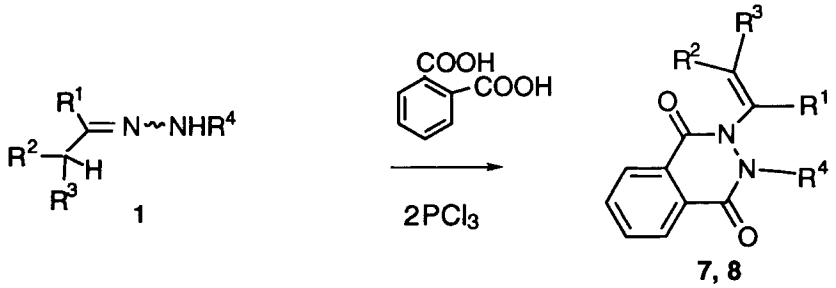
Recently, we tested this new cyclization using some dicarboxylic acids such as malonic, succinic, glutaric, and adipic acids obtaining, at room temperature and in good yields, new *N*-alkenyl five- [11], six-, seven-, and eight-membered [12] 1,2-diaza-heterocycles **6**. By use of these dicarboxylic acids, two additional interesting results were also observed. First, changing the order of addition of the reagents (first and second procedure as depicted in Scheme 1) gave almost identical yields. Second, the facile synthesis at room temperature of seven- and eight-membered rings occurs always by use of a high concentration of the reagents (0.2–0.5 M) [12]. These different procedures reveal that two pathways [11] may be operative.

It should be noted that in the first procedure (as depicted in Scheme 1), the addition of the product from the dicarboxylic acid and one equivalent of PCl_3 to the mixture containing **2** forms, presumably, an intermediate similar to D that intramolecularly cyclizes to give **6**. In contrast, in the second procedure, the product derived from the dicarboxylic acid and two equivalents of PCl_3, on reaction with **1** via the

hypothetical intermediate D, gives **6** without involving **2**. In a third procedure, where PCl_3 is added in a last step to a mixture of **1** and the dicarboxylic acid, both pathways are likely.

RESULTS AND DISCUSSION

Now, we have applied this type of cyclization using phthalic acid in order to obtain further information regarding the applicability, and eventually the limitations, of this new cyclocondensation when a benzo group is present in the final heterocycles. When we use phthalic acid with hydrazones **1a,b,c** containing hydrogen atoms only in one α position, phthalazinediones **7** are obtained (see Scheme 2). When we used hydrazones **1d,e,f,g** containing hydrogen atoms in both α positions, two structurally isomeric phthalazinediones, **7** and **8**, in a ratio that favors the isomer with minor overcrowding, were obtained. When we used methyl ketone hydrazones **1c,d,e,f,i**, it was also possible to obtain compounds **7c, 8d, 8e, 8f, 7i** containing the enamine double bond with two terminal hydrogen atoms. Only in the case of **8f**, it was not possible to isolate the product in pure form. In addition, the reaction of aldehyde hydrazone **1h** gave, in good yield, *E*-**7h** in which R^2 = H. Presumably, these types of disubstituted enamines are stabilized by the benzo group with its conjugating ability. In fact, by use of other dicarboxylic acids such as malonic acid, it was not possible to obtain a diaza ring **6** bearing this type of disubstituted enamine. It should be noted that when we used hydrazones **1a,b,f,g,h,** only the *E*-isomers were obtained. Traces of *Z* isomers were obtained only after workup and after a long time, indicating a slow isomerization in acidic medium. The configuration of the exocyclic double bond was deduced by NOE experiments. The best yields were performed with the third procedure because, in this manner, the formation of phthalic anhydride was minimized. It should be noted that the reaction of phthalic anhydride and hydrazones **1** did not give the corresponding phthalazinediones **7** and **8**, even if the reaction was carried out for several hours in refluxing THF. This fact is a further confirmation that phthalic anhydride is not the intermediate of this reaction, but presumably the true intermediate is D.



	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
1a	Ph	H	Ph	Me	*E*-**7a**	Ph	H	Ph	Me
1b	Ph	H	Me	Me	*E*-**7b**	Ph	H	Me	Me
1c	Ph	H	H	Me	**7c**	Ph	H	H	Me
1d	Me	Me	Me	Me	**7d**	Me	Me	Me	Me
					8d	$CHMe_2$	H	H	Me
1e	Me	Ph	Ph	Me	**7e**	Me	Ph	Ph	Me
					8e	$CHPh_2$	H	H	Me
1f	Me	H	Ph	Me	*E*-**7f**	Me	H	Ph	Me
					8f	$PhCH_2$	H	H	Me
1g	Et	H	Ph	Me	*E*-**7g**	Et	H	Ph	Me
					E-**8g**	$PhCH_2$	H	Me	Me
1h	H	H	Ph	Me	*E*-**7h**	H	H	Ph	Me
1i	Ph	H	H	Ph	**7i**	Ph	H	H	Ph

SCHEME 2

Finally, the competition between the reaction of indolization (reported in Scheme 1) and formation of a diazaheterocycle containing the N–Ph group has been studied using phenylhydrazones with phthalic acid. In a previous work [10], it was reported that, when we used malonic acid with hydrazone **1** with $R^{1,2,4}$ = Ph, R^3 = H, a mixture (1:1) containing heterocycles **6** (n = 1) and 2,3-diphenylindole (**3**) was obtained using the second procedure. While using the first procedure, only the indole **3** was obtained. Now, by use of phthalic acid with the foregoing hydrazone, with all the procedures, only the indole **3** was obtained. In contrast, when we used phenylhydrazone **1i**, which is known [3] not to give the indolization reaction, the formation of the corresponding diazaheterocycle **7i** was also observed but with a longer reaction time being required. These facts indicate that the indolization reaction is faster than the diazaheterocycle formation and that the cyclization of malonic acid is faster than that of phthalic acid. This behavior may be explained by consideration of the greater conformational freedom of the aliphatic dicarboxylic acid, as against phthalic acid, that may favor the formation of the hyphothetical intermediate D and its ring closure. Then, with phthalic acid, it is possible to obtain phthalazinediones **7** containing the NPh group only when we use phenylhydrazones that cannot give the indolization reaction. It should be noted that, in the formation of **7i**, no trace of the corresponding phthalimide was detected.

In conclusion, by this reaction, we are now able to obtain, at room temperature, a new series of 1,4-phthalazinediones that are probably very difficult to prepare by other methods. It is obvious that it will be possible, using other derivatives of phthalic acid, to synthesize in this manner also several substituted phthalazinediones that might be useful as chemiluminescent tracers or drugs. In addition, after these results, we have a better knowledge of the factors that govern these new cyclocondensation reactions that make use of the PCl_3/hydrazone combination, and this might be of great utility in facilitating several organic transformations in which hydrazones or hydrazines are used to produce nitrogen heterocycles.

EXPERIMENTAL

All chemicals and solvents were of reagent grade. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ solution. Chemical shifts are given as δ values referred to Me_4Si. Mass spectra were recorded with a VG 7070 spectrometer or with an HP-5890 gas chromatograph equipped with a methyl silicone capillary column and by an HP-5970 mass detector. IR spectra were obtained in $CHCl_3$ by use of a Perkin Elmer 1600 spectrophotometer. Melting points were determined with a Buchi apparatus. Commercial PCl_3 was used without further purification. Yields are based on starting quantities of the phthalic acid. Flash chromatography was performed in a Gilson apparatus.

Hydrazones

These were obtained by heating the respective hydrazine and ketone (or aldehyde) together in equivalent amounts in benzene solution at reflux for ca. 2 hours under Dean–Stark acid catalytic conditions. After drying and removal of the solvent, the crude products were crystallized and used immediately to avoid their decomposition.

Typical Procedure

To a THF solution (65 mL) of phthalic acid (10 mmol) and hydrazone **1** (10 mmol) was added PCl_3 (20 mmol), and the reaction mixture was allowed to react at room temperature for about 2–10 hours. The course of the reaction was followed by GC-MS analysis and TLC. After removal of the solvent, the crude oil or solid was dissolved in dichloromethane and washed with saturated sodium carbonate solution and then with water and dried over sodium sulfate. The solvent was evaporated under reduced pressure to give crude products (**7,8**) which were purified by crystallization or by silica-gel column chromatography.

Compounds **7,8** were characterized by ^{1}H NMR and mass spectrometry and by microanalysis. All compounds **7** and **8** give a very strong absortion in the infrared at ca. 1630–1650 cm^{-1}. The *E*-configuration of the exocyclic double bond was deduced from NOE experiments carried out on a *E,Z* mixture obtained by isomerization of the *E* isomer.

E-2,3-Dihydro-3-(1,2-diphenylvinyl)-2-methylphthalazine-1,4-dione (7a)

After 8 hours of reaction, ***E*-7a** was obtained as a pale yellow solid (68% yield), mp 141°C, R_F 0.41 (diethyl ether–dichloromethane–petrol ether 20:1:10 as eluent). Found: C, 77.7; H, 5.1; N, 7.8%; HRMS (EI) *m/z* 354.1366 (M^+) $C_{23}H_{18}N_2O_2$ requires C, 77.9; H, 5.1; N, 7.9%; M^+, 354.1368. δ_H 3.55 (3H, s, N-CH_3), 7.06 (1H, s, =C*H*), 7.23–7.25 (10H, m, =CPh), 7.88–7.75 (2H, m, Ph), 8.42–8.30 (2H, m, Ph).

E-2,3-Dihydro-2-methyl-3-(1-phenylprop-1-enyl)phthalazine-1,4-dione (7b)

After 7 hours of reaction, ***E*-7b** was obtained as white crystals (74% yield), mp 143°C, R_F 0.33 (diethyl

ether–dichloromethane–petrol ether 20:1:10 as eluent). Found: C, 73.7; H, 5.5; N, 9.5%; HRMS (EI) *m/z* 292.1209 (M^+) $C_{18}H_{16}N_2O_2$ requires C, 73.9; H, 5.5; N, 9.6%; M^+, 292.1212. δ_H, 2.19 (3H, d, J = 7.3 Hz, =C-C*H*$_3$), 3.57 (3H, s, N-C*H*$_3$), 6.39 (1H, q, J = 7.3 Hz, =C*H*), 7.30–7.50 (5H, m, =CPh), 7.80–7.95 (2H, m, Ph), 8.35–8.50 (2H, m, Ph).

2,3-Dihydro-2-methyl-3-(1-phenylvinyl)-phthalazine-1,4-dione (7c)

After 8 hours of reaction, ***E*-7b** was obtained as light yellow crystals (68% yield), mp 153–154°C, R_F 0.35 (diethyl ether–dichloromethane–*n*-hexane 1:1:1 as eluent). Found: C, 73.2; H, 5.1; N, 10.1%; HRMS (EI) *m/z* 278.0134 (M^+); $C_{17}H_{14}N_2O_2$ requires C, 73.4; H, 5.1; N, 10.1%; M^+, 278.1055. δ_H, 3.48 (3H, s, N-C*H*$_3$), 5.70 (1H, d, J = 1.0 Hz, =C*H*), 6.26 (1H, d, J = 1.0 Hz, =C*H*), 7.36 (5H, m, =CPh), 7.84–7.89 (2H, m, Ph), 8.37–8.42 (2H, m, Ph).

2,3-Dihydro-2-methyl-3-(1,2,2-trimethylvinyl)-phthalazine-1,4-dione (7d) *and 2,3-Dihydro-3-(1-isopropylvinyl)-2-methyl-phthalazine-1,4-dione* (8d)

After 8 hours, the reaction with **1d** gave **7d** and **8d** in the ratio of about 1:2. **7d** (impure of **8d**) was obtained as a white solid (28% yield), R_F 0.58 (diethyl ether–dichloromethane 2:1 as eluent). Found: C, 68.7; H, 6.6; N, 11.5%; HRMS (EI) *m/z* 244.0335 (M^+); $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%; M^+, 244.1218. δ_H, 1.73 (3H, s, =C-C*H*$_3$), 1.91 (3H, s, =C-C*H*$_3$), 1.95 (3H, s, =C-C*H*$_3$), 3.52 (3H, s, N-C*H*$_3$), 7.86–7.92 (2H, m, Ph), 8.29–8.48 (2H, m, Ph).

8d was obtained as a white solid (40% yield), mp 230°C, R_F 0.80 (diethyl ether–dichloromethane 2:1 as eluent). Found: C, 68.4; H, 6.5; N, 11.3%; HRMS (EI) *m/z* 244.0128 (M^+); $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.5%; M^+, 244.1218. δ_H, 1.12 [6H, d, J = 6.9 Hz, -CH(C*H*$_3$)$_2$], 2.60 [1H, sept, J = 6.9 Hz, -C*H*(CH$_3$)$_2$], 3.53 (3H, s, N-C*H*$_3$), 5.46 (1H, d, J = 0.9 Hz, =C*H*), 5.66 (1H, d, J = 0.9 Hz, =C*H*), 7.80–7.85 (2H, m, Ph), 8.31–8.35 (2H, m, Ph).

2,3-Dihydro-2-methyl-3-(1-methyl-2,2-diphenylvinyl)-phthalazine-1,4-dione (7e) *and 2,3-Dihydro-3-(1-diphenylmethylvinyl)-2-methylphthalazine-1,4-dione* (8e)

After 10 hours, the reaction with **1e** gave **7e** and **8e** in the ratio of about 1:1. **7e** was obtained as a white solid (18% yield), mp 119–120°C, R_F 0.36 (diethyl ether–*n*-hexane 3:1 as eluent). Found: C, 78.1; H, 5.4; N, 7.6%; HRMS (EI) *m/z* 368.0742 (M^+); $C_{24}H_{20}N_2O_2$ requires C, 78.2; H, 5.5; N, 7.6%; M^+, 368.1525. δ_H, 2.21 (3H, s, =C-C*H*$_3$), 3.58 (3H, s, N-C*H*$_3$), 7.11–7.40 (10H, m, =CPh$_2$), 7.75–7.80 (2H, m, Ph), 8.08–8.10 (2H, m, Ph).

8e was obtained (20% yield) as colorless crystals, mp 170–171°C; R_F 0.44 (diethyl ether–*n*-hexane 3:1 as eluent). Found: C, 78.1; H, 5.4; N, 7.6%; HRMS (EI) *m/z* 368.0892; $C_{24}H_{20}N_2O_2$ requires C, 78.2; H, 5.5; N, 7.6%; M^+, 368.1525. δ_H 3.51 (3H, s, N-C*H*$_3$), 5.01 (1H, s, C*H* Ph$_2$), 5.39 (1H, dd, J = 1.4 Hz, J = 0.6 Hz, =C*H*), 5.73 (1H, dd, J = 1.4 Hz, J = 1.0 Hz, =C*H*), 7.10–7.32 (10H, m, C*H*Ph$_2$), 7.64–7.69 (2H, m, Ph), 8.08–8.10 (2H, m, Ph).

E-2,3-Dihydro-2-methyl-3-(1-methyl-2-phenylvinyl)-phthalazine-1,4-dione (*E*-7f)

After 9 hours, the reaction with **1f** gave **7f** and **8f** in the ratio of about 7:3. ***E*-7f** was obtained as white crystals (60% yield), mp 143–144°C; R_F 0.44 (diethyl ether–petrol ether 2:1 as eluent). Found: C, 73.7; H, 5.5; N, 9.5%; HRMS (EI) *m/z* 292.0414 (M^+); $C_{18}H_{16}N_2O_2$ requires C, 73.9; H, 5.5; N, 9.6%; M^+, 292.1212. δ_H, 2.23 (3H, s, =C-C*H*$_3$), 3.63 (3H, s, N-C*H*$_3$), 6.83 (1H, s, =C*H*-Ph), 7.40–7.44 (5H, m, =C-Ph), 7.80–7.83 (2H, m, Ph), 8.32–8.39 (2H, m, Ph).

Compound **8f** was not isolated in pure form, and it was characterized only by mass spectroscopy.

E-2,3-Dihydro-3-(1-ethyl-2-phenylvinyl)-2-methylphthalazine-1,4-dione (*E*-7g) *and E-2,3-Dihydro-3-(1-benzylprop-enyl)-2-methylphthalazine-1,4-dione* (*E*-8g)

After 10 hours, the reaction with **1g** gave **7g** and **8g** in the ratio of about 6:4. ***E*-7g** was obtained as a white solid (40% yield), mp 116–117°C, R_F 0.55 (diethyl ether–dichloromethane–*n*-hexane 1:1:1 as eluent). Found: C, 74.3; H, 5.8; N, 9.0%; HRMS (EI) *m/z* 306.1309 (M^+); $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.1%; M^+, 306.1368. δ_H, 1.03 (3H, t, J = 7.7 Hz, C*H*$_3$-CH$_2$-), 2.68 (2H, q, J = 7.7 Hz, CH$_3$-C*H*$_2$-), 3.62 (3H, s, N-C*H*$_3$), 6.85 (1H, s, =C*H*), 7.33–7.43 (5H, m, =CPh), 7.78–7.88 (2H, m, Ph), 8.33–8.39 (2H, m, Ph).

***E*-8g** (contaminated with **7g**) was obtained as a greasy oil (32% yield); R_F 0.42 (diethyl ether–dichloromethane–*n*-hexane 1:1:1 as eluent). Found: C, 74.3; H, 5.8; N, 9.0%; HRMS (EI) *m/z* 306.1309 (M^+); $C_{19}H_{18}N_2O_2$ requires C, 74.5; H, 5.9; N, 9.1%; M^+, 306.1368. δ_H, 2.05 (3H, d, J = 7.2 Hz, =C-C*H*$_3$), 3.17 (3H, s, N-C*H*$_3$), 3.77 (2H, s, C*H*$_2$-Ph), 5.96 (1H, q, J = 7.2 Hz, =C*H*), 7.72–7.78 (5H, m, =CPh), 7.82–7.87 (2H, m, Ph), 8.17–8.24 (2H, m, Ph).

E-2,3-Dihydro-3-(1,2-diphenylvinyl)-2-methylphthalazine-1,4-dione (*E*-7h)

After 10 hours, *E*-**7h** was obtained (60% yield) as yellow crystals, mp 122–123°C; R_F 0.55 (diethyl ether–dichloromethane 1:2 as eluent). Found: C, 73.3; H, 5.1; N, 10.1%; HRMS (EI) *m/z* 278.1009 (M^+); $C_{17}H_{14}N_2O_2$ requires C, 73.4; H, 5.1; N, 10.1%; M^+, 278.1055. δ_H, 3.63 (3H, s, N-CH_3), 6.63 (1H, d, J = 14.5 Hz, =C*H*), 7.26–7.46 (5H, m, =CPh), 7.50 (1H, d, J = 14.5 Hz, =C*H*), 7.81–7.84 (2H, m, Ph), 8.30–8.34 (2H, m, Ph).

2,3-Dihydro-2-phenyl-3-(1-phenylvinyl)phthalazine-1,4-dione (7i)

After 12 hours, **7i** was obtained (60% yield) as a white solid, mp 157–158°C; R_F 0.61 (diethyl ether–dichloromethane 1:1 as eluent). Found: C, 77.1; H, 4.8; N, 8.3%; HRMS (EI) *m/z* 340.1215 (M^+); $C_{22}H_{16}N_2O_2$ requires C, 77.6; H, 4.7; N, 8.2%; M^+, 340.1211. δ_H 5.54 (1H, d, J = 0.9 Hz, =C*H*), 5.83 (1H, d, J = 0.9 Hz, =C*H*), 6.9–7.3 (10H, m, Ph), 7.8–7.9 (2H, m, Ph), 8.35–8.56 (2H, m, Ph).

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