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Clean and efficient microwave-solvent-free synthesis of 1-(2′,4′-dichlorophenacyl) azoles

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Abstract—Microwave induced *N*-alkylation of several azoles with 2,2′,4′-trichloroacetophenone (TCA) under solvent-free conditions allowed to obtain the corresponding 1-(2′,4′-dichlorophenacyl) azoles with satisfactory to good selectivities and yields. TGA and DSC measurements were achieved for the synthesized compounds and showed a close relationship between the thermal behavior and the reaction temperature under microwave heating. Non-purely thermal microwave effects were evidenced during the alkylation of pyrazole and 1H-indazole under the selected conditions. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Selective *N*-alkylation of azoles is a useful reaction commonly employed in the preparation of value intermediates of fungicides and other pharmacologically interesting compounds.[1] Classical procedures have been reported for the synthesis of *N*-alkylated azoles, most of which suffer long reaction times and yielding complex mixtures of products, which need further delicate separations. Moreover, they have shown low selectivity.[2–4]

N-alkylations of aromatic compounds involving nitrogen heterocycles with alkyl halides under phase transfer catalytic conditions (PTC) have been reported.[5,6] Thus, KOH and *t*-BuOK were employed as a base and crown ethers as phase transfer catalysts.[7] On an other hand, was reported the *N*-alkylation of nitrogen heterocycles with alkyl halides using aqueous or powdered potassium hydroxide as a base in the presence of polyethylene glycols (PEG) or their dialkyl ethers (PEG-ether) as phase transfer catalysts.[8]

Recently, several reports on microwave-assisted *N*-alkylation of azaheterocycles in dry media have appeared.[9] Thus, we want to report here the successful microwave-assisted *N*-alkylation of several azoles with 2,2′,4′-trichloroacetophenone (TCA) under solvent-free conditions and in the absence of any base. The choice of TCA as electrophile is based on the fungicidal activity exhibited by some pharmaceuticals containing the 2,4-dichlorobenzyl moiety in their structures.[10] The present clean protocol shows excellent selectivity, leading to the corresponding N_1-monoalkylated azoles in satisfactory to good yields (Table 1).

Table 1. Microwave-assisted *N*-alkylation of azoles (**1a–e**) with TCA (Molar ratio **1a–e**/TCA=2:1)

Compound	Output power[a] (W)	Reaction time (min)	Temperature (°C)	% Conversion[b]	% Regioselectivity[c]	% N_1 Yield[d]
2a	100–15	30	90	82	N_1	75
2b	150–15	15	100	>98	$N_1/N_{1,3}$=77/23	73
2c	150–15	30	140	>98	$N_1/N_{1,3}$=95/5	93
2d	240–15	30	140	>98	N_1/N_2=87/13	82
2e	240–15	10	170	>98	$N_1/N_{1,3}$=93/7	91

[a] Range of modulation of MW power between optimal and minimal values to maintain constancy of temperature.
[b] Based on% of consumed TCA.
[c] Determined by HRGC and ^{1}H NMR.
[d] Isolated product.

Keywords: azoles; *N*-alkylation; microwave irradiation; solvent-free; fungicides.
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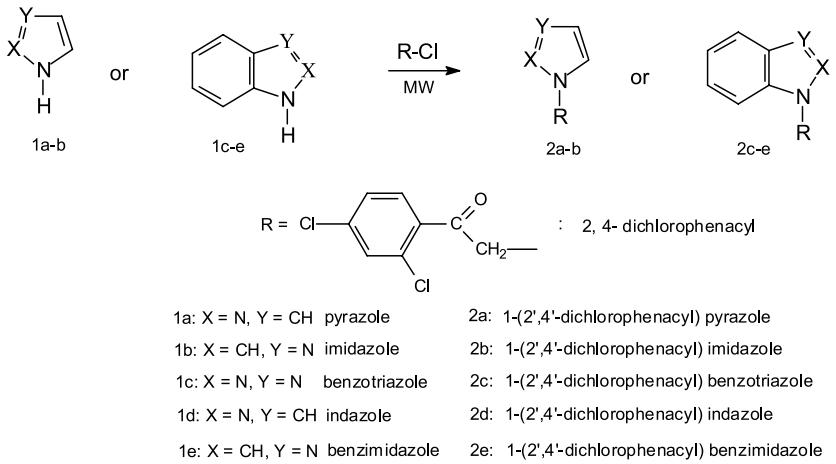


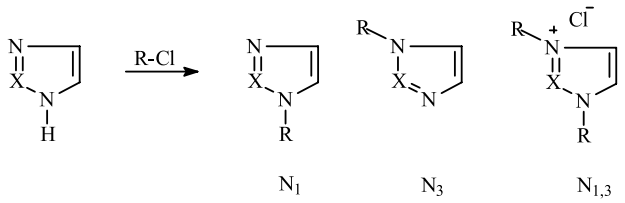
Scheme 1.

2. Results and discussion

The general reaction representing *N*-alkylation of azoles with TCA under microwave irradiation is illustrated in Scheme 1.

The most relevant results obtained for the solvent-free microwave-assisted protocol are given in Table 1.

In some cases, several regioisomers can be formed as resulting from alkylation either in different positions involving the sites 1 (N_1) or 2 (N_2) for **2d** and 1 or 3 (N_3) or both successive sites ($N_{1,3}$) for **2b**, **2c** and **2e** (Scheme 2).



Scheme 2.

In preliminary experiments, we have observed a delicate compromise between the reaction temperatures and the yields in N_1-alkylazoles. Yields can be dramatically affected by rather small variations of temperature. For instance, unsatisfactory conversions and negligible yields of compounds **2c** and **2d** were obtained at temperatures lower than 120°C, whereas, on the other hand, significant decomposition occurred when the temperatures were higher than 140°C. In the same way, compound **2a** decomposes close to 120°C whereas nil conversion was detected below 90°C.

Consequently, we have performed some thermogravimetric analysis (TGA) for compounds **2a**, **2c** and **2d** to obtain information about their thermal stabilities (Table 2). The loss of weight in compounds were evaluated according to the heating temperature range.

The results given in Table 2 are in agreement with the observed behavior during the synthesis of compounds **2a**, **c** and **d** according to reaction temperature. Thus, main thermal decomposition of compound **2a** occurred at temperatures higher than 115°C, whereas bulky decomposition of compounds **2c**, **d** has been observed beyond 140°C.

As a consequence, reactions were carried out at temperature in the range of 75–90°C for compound **2a** and 130–140°C for **2c** and **2d**, by modulation of the output microwave power and reaction times. Quantitative conversions as well as satisfactory to good yields and regioselectivities were achieved for compounds **2c** and **2d** at 140°C under experimental conditions indicated in Table 1.

TGA analyses for compound **2a** revealed that no significant loss of weight occurred neither at 75 (0.47%) nor at 90°C (2.22%) within 30 min and the small differences observed from the sample weight could be only associated with loss of the crystallization solvent.

On isothermal TGA at 140°C for 30 min, compound **2c** shows a loss of weight corresponding to only 10% of the starting value. Compound **2d**, under the same TGA conditions, showed even smaller loss of weight (2%).

Compound **2c** has displayed the higher thermal stability from TGA (Table 2) among analyzed products. Thus, higher yield of **2c** under microwave irradiation could be correlated with its increased thermal stability.

Compound **2d** showed a small peak for the loss of weight starting from 80°C but, on examining differential scanning calorimetry (DSC) curves, any variation of heat was

Table 2. TGA for compounds **2a**, **2c** and **2d**

Compound	Sample weight (mg)	1st Loss of weight (mg; %)	2nd Loss of weight (mg; %)
2a	5.3050	70–115°C (0.0589; 1.1)	115–234°C (5.2290; 98.7)
2c	5.3980	138–400°C (3.7230; 68.9)	400–705°C (0.6923; 12.8)
2d	5.0810	50–153°C (0.5327; 10.4)	153–350°C (4.2620; 83.8)

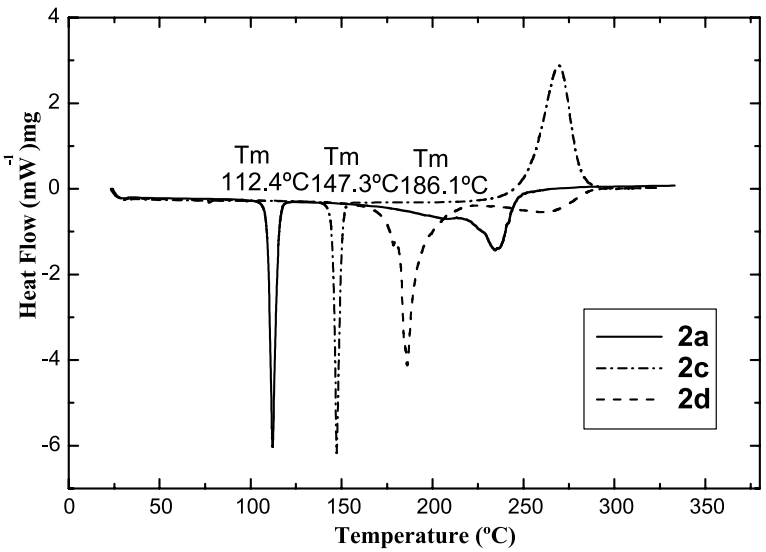


Figure 1. DSC curves for compounds **2a**, **2c** and **2d**.

detected at this temperature value. Hence, this could be due to loss of crystallization solvent (small peak at about 80°C on DSC curve in Fig. 1), since NMR and GC–MS analyses of the sample, previously heated up to 100°C, were in agreement with the **2d** proposed structure.

Results from thermal analysis are thus supporting the satisfactory to good yields obtained for the synthesis of compounds **2a**, **2c** and **2d** operating at reported temperatures (Table 1), and without significant thermal decomposition of products (Table 3).

Table 3. DSC results for compound **2a**, **2c** and **2d**

Compound	T_m (°C)	ΔH_m (J g^{-1})	Decomposition peak (°C)
2a	112.0	134.9	234.6
2c	147.3	121.7	269.0
2d	186.1	270.0	265.3

For sake of comparison with more classical reaction conditions, and to underline the interest of solvent-free microwave-assisted method, reactions were performed either in the presence or in the absence of solvent, under similar set of conditions (time, temperature, and profiles of raise in temperature), either under MW activation or conventional heating inside a thermostated oil bath. Results of this study are shown in Table 4 for the alkylation of benzotriazole **1c** with TCA as a model reaction.

Preparation of **2c** under microwave or reflux conditions in a non-polar solvent (therefore transparent to microwaves) was unsuccessful when temperature was kept below 140°C (entries 1 and 2). The best situation was achieved in the absence of any solvent where yields up to 90% (entries 5 and 6) were obtained irrespective of the mode of activation.

The use of *p*-xylene allows to reveal a noticeable MW effect (entries 3 and 4). This effect is masked under solvent-free conditions due to an increase in reactivity by higher concentration effect[11] as here yields are yet nearly quantitative under classical heating.

The influence of the activation mode was next studied for all compounds under experimental conditions described in Table 1. Results are summarized in Table 5.

Specific (purely thermal) MW effects were evidenced in the case of pyrazole **1a** and indazole **1d**. Under the conditions employed here, they disappeared with the other azoles **1b**, **1c** and **1e**. As yields are yet quantitative under conventional heating, in connection with a high temperature level, these possible effects can be necessarily masked. They can of course only appear in the case of less reactive systems when initial yields are limited (i.e. 65 and 60%, respectively, for **1a** and **1d**). It is now well known in a lot of cases that MW specific effects could only appear when lowering temperature and reaction time.[12]

Table 4. Influence of solvent and activation mode on the conversion and the yield in the synthesis of 1-(2′,4′-dichlorophenacyl) benzotriazole (**2c**) (**1c**/TCA=2:1, output power=150–15 W, reaction time=30 min)

Entry	Solvent	Activation	T (°C)	% Conversion	% Yield N_1	% Yield $N_{1,3}$
1	Toluene	MW	110	9	9	0
2	Toluene	Oil bath	110	5	5	0
3	*p*-Xylene	MW	140	79	71	4
4	*p*-Xylene	Oil bath	140	50	46	2
5	None	MW	140	98	94	2
6	None	Oil bath	140	91	83	4

Conversion and yield determined by ^{1}H NMR and GC–MS (based on% consumed TCA).

Table 5. Solvent-free synthesis of compounds **2a–e** under microwave irradiation or classical heating (thermostated oil bath) (conditions of Table 1)

Compound	Activation	Conditions	% Conversion	% Yield[a] N_1	N_1/N_2	$N_1/N_{1,3}$
2a	MW	30 min, 90°C	82	78 (75)	–	–
	Oil bath		65[b]	60	–	–
2b	MW	15 min, 100°C	98	77 (73)	–	77/23
	Oil bath		98	70	–	70/30
2c	MW	30 min, 140°C	98	95 (93)	–	95/5
	Oil bath		91	83	–	83/4
2d	MW	30 min, 140°C	98	85 (82)	87/13	–
	Oil bath		60	54	90/10	–
2e	MW	10 min, 170°C	100	93 (91)	–	93/7
	Oil bath		100	88	–	88/12

[a] Determined by ^{1}H NMR and GC–MS and yield of isolated product in parenthesis.
[b] Yield was improved to 66% (conversion=70%) when extending reaction time up to 2 h.

This case of reaction is propitious to the observation of specific MW effects when considering the mechanism.[13] The polarity of the system is increased during the reaction progress from the neutral ground state (GS) to the dipolar transition state (TS) for both N_1 and N_2 alkylation of **1a** (Scheme 3). Consequently, as MW stabilizing effects by dipole–dipole interactions with the electric field are increased with the polarity of materials[14], they are improved from GS to TS, leading therefore to a decrease in the energy of activation (Scheme 4). Such an explanation of MW effects[13] is supported by calculations suggesting a relation between MW irradiation and the polarity (or polarizability) of the transition state.[15]

The reactivity of the different azoles towards alkylation could be tentatively justified by considering some relevant parameters able to describe their nucleophilicities. They involved:—the pK_a of azolium ions[16] which can reflect an increased basicity (and possibly nucleoplilicity) when pK_a (NH^+) is increased,—the HOMO and *n* lone pairs energy levels[17] to take into account orbital control of the reaction,—the net atomic charge on the reactive nitrogen atoms (q_N)[17] under charge-controlled reactions. The main values are given in Table 6.

When considering the data indicated in the table, it appears that there is not one unique parameter able to justify the experimental sequence and that certainly a combination of factors is responsible for relative reactivities (**1a**>**1b**>**1c**, **1d**>**1e**). Charge control can be eliminated when considering the total reverse in the sequence in q_N when compared to relative reactivities one. Considering HOMO levels, **1d** and **1e** would appear as the most reactive azoles whereas pK_a values would indicate an enhanced reactivity for **1b** and **1e**. Certainly, to be more accurate in establishing the reactivity sequence would need strict comparisons under similar sets of conditions and determining half-time reaction.

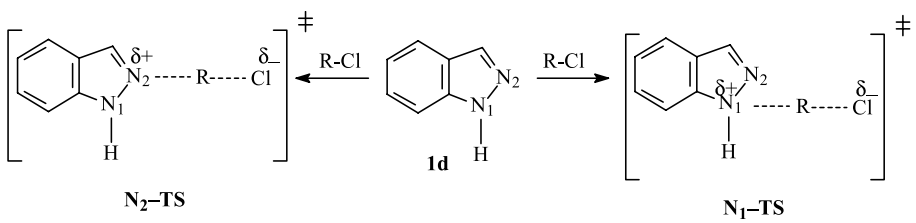
Table 6. Some relevant parameters for predicting relative azole reactivites

Compound	pK_a (azolium ions)	E_{HOMO}[a] (eV)	E_n[b] (eV)	q_N
Pyrazole **1a**	2.64	−9.71	−11.80	−0.147
Imidazole **1b**	7.11	−9.16	−11.25	−0.218
Benzotriazole **1c**		−9.43	−11.78	−0.350
Indazole **1d**	1.25	−8.86	−11.28	−0.324
Benzimidazole **1e**	5.68	−9.00	−11.16	−0.478

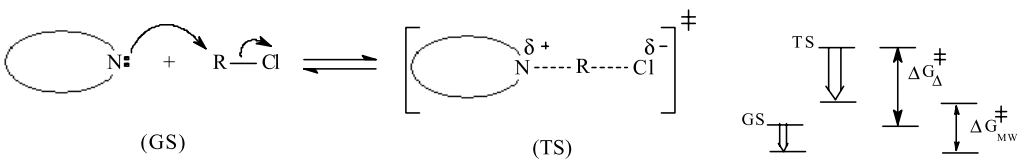
[a] Higher occupied molecular orbitals delocalized on aromatic ring (π-type)
[b] Energy level of n-type (non liant) orbital located on reactive N atom.

3. Experimental

The microwave reactor was a monomode system (Synthewave 402 from Société Prolabo)[18] with focused waves operating at 2.45 GHz. The temperature was controlled and evaluated by an infrared detector, previously calibrated with the use of an optical fiber. It was monitored by a computer and maintained constant at a constant value by a discrete



Scheme 3.



Scheme 4.

modulation of delivered MW power. Mechanical stirring was used to provide homogeneity of temperature inside the reaction medium.

Thermal analyses were performed using a TA Instruments TGA 2950 DSC 2910 apparatus (dynamic flow of N_2: 90 and 80 mL min^{-1} for TGA and DSC respectively, heating rate for the TGA and DSC=10°C min^{-1}, temperature range: 25–710°C for TGA and 25–350°C for DSC, weight of sample: 5 mg for TGA and DSC, internal calibration with In for DSC, sample support was Platinum for TGA and Aluminum for DSC).

^1H and ^{13}C NMR spectra were recorded using a Bruker AC 250 apparatus. GC–MS analyses were carried out using the HP 5890 gas chromatograph coupled to a HP 5970 Series Mass Selective Detector. A HP-1 column (50 mm×0.20 mm×0.33 mm) was used. The temperature, of both the injector and the interface, was set at 300°C. Infrared spectra were recorded with a Perkin–Elmer 1310 apparatus. The elementary analyses were performed on an EA 1110 CE Instruments apparatus.

Syntheses of the compounds **2a–e** were carried out either under microwave irradiation or conventional heating. In a Pyrex open vessel adapted to the Synthewave reactor, 6 mmol of the azolic compound (**1a–e**) were mixed with 3 mmol of 2,2′,4′-trichloroacetophenone (TCA). The mixture was irradiated under conditions described in Table 1. Reactions in classical heating (thermostated oil bath) were carried out under similar experimental conditions (weight of reactants, time and temperature) as determined in microwave-assisted experiments. To ensure independence from the thermal effects, in experiments under conventional heating, the temperature was measured by insertion of a Quick digital thermometer into the reaction mixture and the profile of temperature rise was adjusted to be similar to that registered under microwave irradiation. Physical properties and structural characterization of the products are as follows:

3.1. 1-(2′,4′-Dichlorophenacyl) pyrazole 2a

White crystals; mp (DSC) 112.0°C (ethyl ether); ^1H NMR (250 MHz, DMSO-d_6): δ 5.66 (s, CH_2, 2H), 6.28 (dd, J= 1.6, 2.2 Hz, 1H), 7.45 (d, J=1.6 Hz, 1H), 7.58 (dd, J=2.0, 8.4 Hz, 1H), 7.73 (d, J=2.2 Hz, 1H), 7.76 (d, J=2.2 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H); ^{13}C NMR (62.50 MHz, DMSO-d_6): δ 59.6 (CH_2, C-6), 105.7 (C-4), 127.5 (C-3), 130.3 (C-12), 131.0 (C-5), 131.5 (C-10), 131.6 (C-8), 134.3 (C-9), 136.9 (C-11), 139.3 (C-13), 195.0 (C-7); MS (EI, 70 eV): m/z 254 (M^+, 1), 256 (M+2), 173 (100), 175 (64), 177 (11), 145 (20), 147 (13), 149 (2), 109, 81; IR (KBr): cm^{-1} 1690 (C=O), 1580–1540 (C aromatics). Anal. calcd for $C_{11}H_8Cl_2N_2O$: C, 51.76; H, 3.13; N, 10.90. Found: C, 51.42; H, 3.01; N, 10.67.

3.2. 1-(2′,4′-Dichlorophenacyl) imidazole 2b

White crystals; mp 76–78°C (ethyl ether), lit.[19] 76–78°C; ^1H NMR (250 MHz, DMSO-d_6): δ 5.60 (s, CH_2, 2H), 6.96 (d, J=2.2 Hz, 1H), 7.15 (d, J=2.2 Hz, 1H), 7.63 (dd, J=2.0, 8.4 Hz, 1H), 7.67 (s, 1H), 7.80 (d, J=2.0 Hz, 1H), 7.95 (d, J=8.4 Hz, 1H); ^{13}C NMR (62.50 MHz, DMSO-d_6): δ 55.2 (CH_2, C-6), 121.3 (C-4+C-5), 128.0 (C-12), 130.3 (C-2), 130.6 (C-10), 132.7 (C-13), 134.3 (C-8), 137.7 (C-9), 138.6 (C-11), 195.1 (C-7); MS (EI, 70 eV): m/z 254 (M^+), 256 (M+2), 173 (100), 175, 177, 145, 147, 149, 109, 81; IR (KBr): cm^{-1} 1690 (C=O), 1590–1530 (C aromatics).

3.3. 1-(2′,4′-Dichlorophenacyl) benzotriazole 2c

White crystals; mp (DSC) 147.1°C (ethyl ether), lit.[20] 145°C; ^1H NMR (250 MHz, DMSO-d_6): δ 6.45 (s, CH_2, 2H), 7.45 (dd, J=8.5, 18 Hz, 1H), 7.59 (dd, J=8.5, 18 Hz, 1H), 7.72 (dd, J=1.6, 8.5 Hz, 1H), 7.83 (d, J=8.5 Hz, 1H), 7.88 (d, J=1.6 Hz, 1H), 8.11 (d, J=18 Hz, 1H), 8.18 (d, J=18 Hz, 1H); ^{13}C NMR (62.50 MHz, DMSO-d_6): δ 55.9 (CH_2, C-10), 110.7 (C-6), 119.1 (C-7), 123.9 (C-16), 127.4 (C-17), 127.6 (C-14), 130.5 (C-5), 131.5 (C-8), 132.1 (C-12), 133.4 (C-4), 133.5 (C-9), 137.4 (13), 145.0 (C-15), 193.1 (C-11); MS (EI, 70 eV): m/z 305 (M^+, 4), 307 (M+2), 214 (13), 216 (5), 173 (42), 175 (27), 177 (5), 145 (17), 147 (11), 149 (2), 132, 104, 77 (100); IR (KBr): cm^{-1} 1690 (C=O), 1570–1520 (C aromatics).

3.4. 1-(2′,4′-Dichlorophenacyl) indazole 2d

White crystals; mp (DSC) 186.3°C (after chromatography on silica G 60 and elution with 8:2 EtOAc/n-pentane); ^1H NMR (250 MHz, DMSO-d_6): δ 6.06 (s, CH_2, 2H), 7.04 (dd, J= 8.0, 8.3 Hz, 1H), 7.24 (d, J=8.3 Hz, 1H), 7.58 (d, J=8.3 Hz, 1H), 7.62 (dd, J=1.6, 8.4 Hz, 1H), 7.74 (d, J=8.3 Hz, 1H), 7.80 (d, J=1.6 Hz, 1H), 8.01 (d, J=8.4 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR (62.50 MHz, DMSO-d_6): δ 61.1 (CH_2, C-10), 116.3 (C-6), 121.0 (C-7), 121.4 (C-4+C-9), 121.6 (C-5), 126.6 (C-16), 127.6 (C-8), 130.4 (C-14), 131.5 (C-17), 132.1 (C-12), 133.7 (C-13), 137.4 (C-15), 147.3 (C-3), 193.3 (C-11); MS (EI, 70 eV): m/z 304 (M+, 18), 306 (M+2, 11), 308 (M+4, 2), 275, 277, 279, 173 (100), 175 (61), 177 (11), 145, 147, 149, 131, 103, 77; IR (KBr): cm^{-1} 1675 (C=O), 1570–1510 (C aromatics). Anal. calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.21; H, 3.28; N, 9.21. Found: C, 58.59; H, 3.07; N, 8.97.

3.5. 1-(2′,4′-Dichlorophenacyl) benzimidazole 2e

White crystals; mp dec. (ethyl ether); ^1H NMR (250 MHz, DMSO-d_6): δ 5.93 (s, CH_2, 2H), 7.23–7.29 (m, 1H), 7.36–7.41 (m, 1H), 7.55–7.59 (m, 1H), 7.68 (dd, J=2.0, 8.4 Hz, 1H), 7.67–7.75 (m, 1H), 7.84 (d, J=2.0 Hz, 1H), 8.08 (d, J= 8.4 Hz, 1H), 8.32 (s, 1H); MS (EI, 70 eV): m/z 304 (M+), 306 (M+2), 308 (M+4), 275, 277, 279, 173 (100), 175 (60), 177 (10%), 145, 147, 149, 131, 103, 77; IR (KBr): cm^{-1} 1660 (C=O), 1610–1540 (C aromatics). Anal. calcd for $C_{15}H_{10}Cl_2N_2O$: C, 59.10; H, 3.20; N, 9.11. Found: C, 58.62; H, 3.02; N, 8.83.

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