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Article

Conventional and Microwave-Assisted Reaction of *N*-Hydroxymethylphthalimide with Arylamines: Synthesis of *N*-(Arylaminomethyl)-phthalimides

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Uma síntese eficiente e fácil dos compostos: 2-fenillaminometil-isoindol-1,3-diona (**5a**), 2-[(*2*-Clorofenilamino)metil]-isoindol-1,3-diona (**5b**), 2-[(3-Clorofenilamino)methyl]-isoindol-1,3-diona (**5c**), 2-[(4-Clorofenilamino)metil)-isoindol-1,3-diona (**5d**), 2-[(*2*-Flúorfenilamino)metil]-isoindol-1,3-diona (**5e**), 2-[(3-flúorfenilamino)metil]-isoindol-1,3-diona (**5f**), 2-[(4-Flúorfenilamino)metil]-isoindol-1,3-diona (**5g**), 2-[(*2*-Nitrofenilamino)metil]-isoindol-1,3-diona (**5h**), 2-[(3-Nitrofenilamino)metil]-isoindol-1,3-diona (**5i**), 2-[(4-Nitrofenilamino)metil]-isoindol-1,3-diona (**5j**), 2-[1H-(1,2,4)Triazol-3-il-aminometil)-isoindol-1,3-diona (**5k**) e 2-([1,2,4]-Triazol-4-il-aminometil)-isoindol-1,3-diona (**5l**) está descrita. A síntese foi realizada partindo-se da *N*-hidróximetilftalimida **3** e de aril- e [1,2,4-triazol-3- e 4-il]-aminas **4a-l** através de procedimentos convencional e mediado por microondas. A reação de **3** com **4l** aconteceu rapidamente e com altos rendimentos. Está descrita uma comparação entre estes dois métodos. São propostos três prováveis mecanismos de formação das *N*-(arilaminometil)-ftalimidas (um em solução e os outros dois em condições de aceleração por microondas). As análises cristalográficas de **5d** forneceram as informações apropiadas sobre a conformação da mesma. Cálculos de orbitais moleculares *Ab initio* de **5d** empregando um conjunto de base 6-31G* foi realizado e os resultados concordaram com os dados de raio-X.

An efficient and easy synthesis of compounds: 2-Phenylaminomethyl-isoindole-1,3-dione (**5a**), 2-[(*2*-Clorophenylamino)methyl]-isoindole-1,3-dione (**5b**), 2-[(3-Clorophenylamino)methyl]-isoindole-1,3-dione (**5c**), 2-[(4-Clorophenylamino)methyl)-isoindole-1,3-dione (**5d**), 2-[(*2*-Fluorophenylamino)methyl]-isoindole-1,3-dione (**5e**), 2-[(3-fluorophenylamino)methyl]-isoindole-1,3-dione (**5f**), 2-[(4-Fluorophenylamino)methyl]-isoindole-1,3-dione (**5g**), 2-[(*2*-Nitrophenylamino)methyl]-isoindole-1,3-dione (**5h**), 2-[(3-Nitrophenylamino)methyl]-isoindole-1,3-dione (**5i**), 2-[(4-Nitrophenylamino)methyl]-isoindole-1,3-dione (**5j**), 2-[1H-(1,2,4)Triazol-3-yl-aminomethyl)-isoindole-1,3-dione (**5k**) and 2-([1,2,4]-Triazole-4-yl-aminomethyl)-isoindole-1,3-dione (**5l**), is described. The general synthesis procedure starts from *N*-hydroxymethylphthalimide **3** and aryl- and [1,2,4-triazol-3- and 4-yl]-amines **4a-*l*** by conventional and solvent-free microwave-mediated. The reaction of **3** with **4l** turned out to be a very rapid and high-yielding one. A comparison of these two methods has been made. Three probable mechanisms of formation of *N*-(arylaminomethyl)-phthalimides (one in the solution phase and two in the microwave-accelerated conditions are proposed. Crystallographic analyses of **5d** furnished the correct conformation of this molecule. *Ab initio* molecular orbital calculations of **5d** using 6-31G* basis set were performed and the results were comparable to the X-ray data.

Keywords: phthalimide, *N*-hydroxymethylphthalimide, spectroscopy, X-ray crystallography, M.O. calculations

Introduction

Phthalimide derivatives have been gaining considerable interest since 1979, when Chapman *et al.*[1] tested the hypolipidemic activity of 23 *N*-substituted phthalimide derivatives. Later on, Hall and co-workers [2,3] reported the antihyperlipidemic activity of phthalimide analogs in rodents and also the same activity was found by the administration of *ortho*-(*N*-phthalimido)acetophenone in sprague dawley rats. In

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2001, we reported hypolipidemic activity in α-D-mannopyranosides containing phthalimidomethyl function as aglycone.[4] There are other interesting biological aspects of these compounds which have been reviewed in 2003.[5] A recent paper cites the synthesis and anticonvulsant behavior of *N*-substituted phthalimides.[6] Besides, certain phthalimide derivatives are synthetically important and can be transformed to other useful products.[7]

A literature survey disclosed that only two compounds, i.e., *N*-(piperidinomethyl)phthalimide[8,9] and *N*-(morpholinomethyl)-phthalimide[8] were prepared initially. Later on, *N*-(phenylaminomethyl)-phthalimide was synthesized by Weaver *et al.*[10] In 1954, Winstead and Heine[11] published a note about the synthesis of *N*-(arylaminomethyl)-phthalimides by treating *N*-hydroxyphthalimide with aniline in an aqueous alcoholic solution and obtained 70% yield of *N*-(anilinomethyl)-phthalimide. These authors also refluxed a mixture of phthalimide **1**, 37% aqueous formaldehyde **2** and an aromatic amine **4** in ethanol to obtain the same product **5**. They suggested the following reaction sequence (scheme 1).

With this, it is obvious that these imides are potential candidates for biological evaluations and need further exploration. Therefore, the present contribution reports the conventional (solution as well as solid-phase) and microwave-accelerated syntheses of ten *N*-arylaminomethyl- **5a-j** and two [1,2,4-triazol-3- and 4-yl]phthalimides **5k**,**l** (Scheme 2).

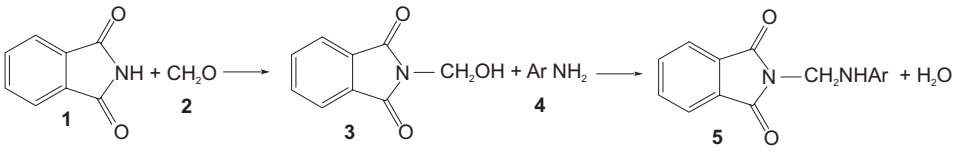
Results and Discussion

Synthesis

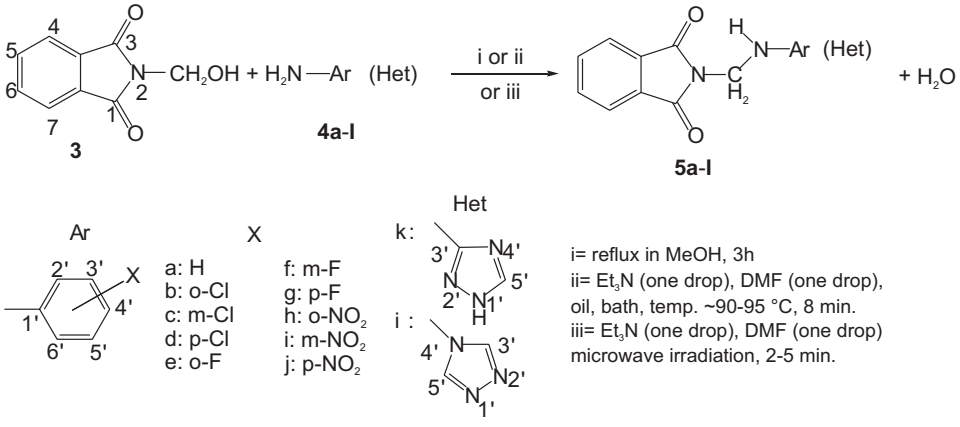
N-Hydroxymethylphthalimide **3** and an appropriate arylamine **4a-j** or triazolamines **4k**,**l** in methanol were refluxed for 3h. Work-up gave crystalline compounds **5a-l** where the yields ranged from 68-99% with the exception of *N*-(*ortho*-chlorophenylaminomethyl) and *N*-(*ortho*-nitrophenylamino-methyl) phthalimides which gave lower yields (49 and 64%, respectively). Compound **5d** was acetylated and ^{1}H-NMR spectra of **9d** supported the proposed structure of **5d**. The m.ps., crystallizing solvent and yields of these compounds are compiled in Table 1. The literature records the preparation of **5a-d** by the conventional procedure.[11]

Infrared Spectroscopy

The infrared spectra showed an absorption between 3392-3453 cm^{-1} for a secondary amine in each case. These are generally somewhat sharp signals. There are also two strong absorptions between 1747-1775 cm^{-1} for the symmetric and asymmetric stretching vibrations of the imide carbonyl functions.



Scheme 1. Reaction of phthalimide with formaldehyde followed by the reaction with arylamine.



Scheme 2. Reaction of *N*-hydroxymethylphthalimide with arylamines.

Table 1. Solvent of crystallization, reaction time, yields and melting points of compounds **5a-l** are given. The results of conventional heating as well as microwave irradiation are also provided

		Conventional				Microwave		mp (°C)		
		Reflux		Oil bath						
Comp.	Cryst. Solvent	time (min)	Yield (%)	time (min)	Yield (%)	time (min)	Yield (%)	Recorded	Lit.[10]	Yield (%)
5a	CH_3COCH_3	120	92	8	68	5	90	148.0-148.3	144.5-145	70
5b	$CHCl_3$	180	49	8	61	5	72	140.1-140.6	141-141.5	32
5c	$CHCl_3$	180	89	8	94	5	98	165.9-166.4	165	50
5d	$CHCl_3$	100	93	8	92	5	97	207.6-208.0	207-208	73
5e	$CHCl_3$	180	77	8	74	5	94	169.0-170.1	-	-
5f	$CHCl_3$	180	84	8	81	5	85	202.2-202.6	-	-
5g	$CHCl_3$	180	94	8	88	5	99	175.3-176.3	-	-
5h	CH_3COCH_3	180	64	8	58	5	60	160.2-161.8	-	-
5i	CH_3COCH_3	180	82	8	74	5	78	196.4-198.0	-	-
5j	CH_3COCH_3	180	82	8	78	5	86	285.2-287.1	-	-
5k	EtOH	180	79	8	75	3	86	229.9-230.7	-	-
5l	EtOH	180	83	8	86	2	95	167.0	-	-

^{1}H Nuclear Magnetic Resonance Spectroscopy

The ^{1}H NMR spectra of compounds **5a-j** presented a triplet around δ 5.0 ppm for the NH proton suggesting the existence of a CH_2 group in its vicinity. The methylene protons presented a doublet in the same region in each case supporting the proposed structure. The other two compounds of this series, viz., **5k** e **5l** also agreed with the structure but their chemical shifts apparently exhibited some difference compared to **5a-j**. For example, the NH proton of compound **5k** of the triazole ring appeared at low field (δ = 11.34 ppm) and the CH heterocyclic ring proton absorbed at δ 8.68 ppm, four aromatic protons of the phthalimide moiety gave a multiplet between 7.87-7.75 ppm and the CH_2 protons appeared at δ = 4.77 ppm. Compound **5l** gave a singlet at δ = 8.48 ppm representing H-3' and H-5' protons of the triazole portion. The aromatic protons of this compound presented a singlet at δ 7.87 ppm, CH_2 at δ 4.77 (2H, d, J = 4.8 Hz) and NH at 7.52 as a triplet (J = 4.8 Hz).

Structure Verification

Although the structures of **5a-l** appear reasonable, we considered other possibilities as well. In fact, there are three other isomers, besides **5a-l**, which need contemplation. These are: **6**, **7** and **8** (Figure 1), which have the same molecular formula, but are constitutional isomers.

In order to get more insight for the structures of the synthesized compounds, we acetylated one of these compounds, i.e., **5d** with acetic anhydride and pyridine at room temperature. The reaction occurs in 30 min. and only one product **9d** was isolated (Figure 2). The infrared

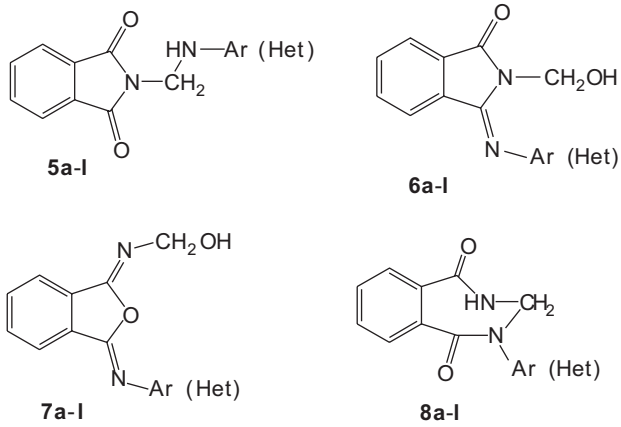


Figure 1. Possible isomeric structure of compounds **5a-l**.

spectrum of this compound didn't show any absorption for the ester carbonyl group; hence structures **6** and **7** are eliminated. Regarding isomer **8**, its acetylation under mild conditions is not possible because of the amide function. Besides, the *N*-acetylation of the amide function requires severe conditions; hence structure **8** is also excluded. Therefore, it appears appropriate to say that the structures proposed for **5a-l** are the correct ones.

Mechanism of formation of N-(arylaminomethyl)-phthalimides 5a-l from N-hydroxymethylphthalimide 3 and arylamines 4a-l by conventional method

According to Winstead and Heine,[11] phthalimide first reacts with formaldehyde to produce *N*-hydroxymethylphthalimide followed by its reaction with an arylamine to give *N*-arylaminomethylphthalimide. Alternatively, formaldehyde may first react with an amine to provide *N*-hydroxymethylamine which would

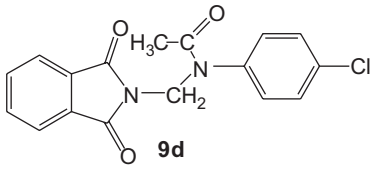


Figure 2. Structure of *N*-acetyl derivative of **5d**.

subsequently condense with phthalimide to give arylaminomethyl phthalimides. Besides this, the authors didn't elaborate about the reaction mechanism. Therefore, we are proposing a more probable mechanism starting from *N*-hydroxymethylphthalimide with an arylamine.

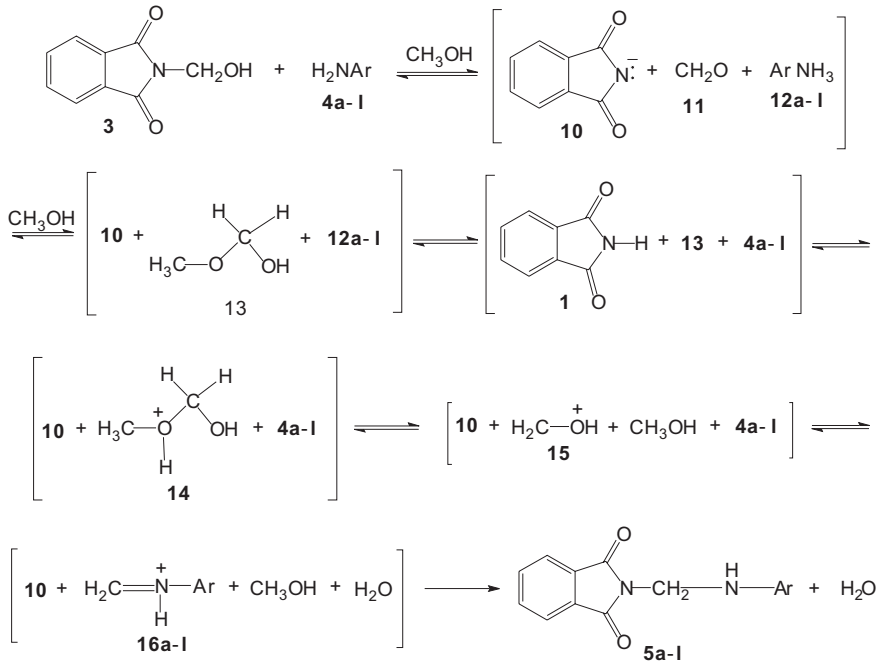
The mechanism which accommodates best in solution involves the formation of an intimate ion pair. The solvent-separated ion par is still an ion pair i.e., the cation and anion are not independent of each other, and may also yield products, or undergo internal return to give the starting reagents **3** and **4a-l**. The complete mechanism of formation of the product is described below and given in Scheme 3.

Initially, arylamine **4a-l** abstracts the proton from *N*-Hydroxymethylphthalimide **3** and generates phthalimide anion **10**, formaldehyde **11** and protonated amine **12a-l**. In methanol all three components are in a single solvation shell, where methanol immediately associates with formaldehyde forming a hemiacetal **13**. Anion **10** may abstract a proton from **12a-l** yielding phthalimide **1** and arylamine **4a-l**, or alternatively a proton may transfer from **1** to **13** to provide the protonated hemiacetal **14**, and phthalimide anion **10**. All species are in equilibrium and are closely fitted ion pairs. Then, the protonated hemiacetal can easily lose methanol to furnish a protonated formaldehyde molecule, which in turn reacts with 4 to give an iminium ion **16a-l**.

Finally the phthalimide anion **10** attacks the carbon atom of the iminium ion providing the product **5a-l**.

In order to test the possibility whether this reaction indeed involves general base catalysis, we added a few drops of triethylamine to the methanol solution containing *N*-Hydroxymethylphthalimide **3** and an arylamine **4d** and refluxed the contents. TLC monitoring showed that the reaction got completed in one hour instead of the normal reflux time of three hours without this base. Thus, we have been able to reduce the reaction time. The detection of phthalimide in one experiment by ^{1}H NMR spectroscopy in conjunction with the rate enhancement by the addition of Et_3N strongly supports that this is a general base catalysis reaction, where the rate determining step is the formation of the tight ion pair which in a few steps leads to the final product.

In order to get more perception about the mechanism of formation of the products **5a-l** from *N*-hydroxy-methylphthalimide **3** and an amine **4a-l**, we tried to do the reaction in a NMR tube. In a typical experiment, we dissolved compound **3** (0.017 mmol) and 4-chloroaniline **4d** (0.017 mmol) in DMSO-d_6 (1 mL) at room temperature and obtained the spectrum at 25, 35 and 45 °C, but did not find any significant change. At 55 °C, after 40 min, we observed a change in the spectrum. There was a weak



Scheme 3. Probable mechanism of formation of compounds **5a-l**.

broad signal at approximately 11.21 ppm. This signal corresponds to N-H proton of phthalimide. The literature shows such as hydrogen at ≈ 11.29 ppm in DMSO-d_6.[12] However, we didn't observe any hydrogen due to formaldehyde. It appears that the aldehyde remains as a hemiacetal in methanol solution. Although it was not possible to see an aldehyde signal in the spectrum, the formation of phthalimide **1** in the spectrum supports the mechanism of formation of the final products from **3** and an arylamine **4**. The following experiments were performed to have an idea about the formation of hemiacetal as well as phthalimide.

Initially, one mol equiv. of each *N*-hydroxymethylphthalimide **1** and *p*-chloroaniline **4d** were dissolved on methanol-d_4 in an NMR tube and the ^{1}H NMR spectrum recorded immediately at 20 °C . This produced the aromatic signals of compounds **3** and **4** as well. Besides, the –CH_2O- and -NH_2- of compounds **3** and **4** appeared at δ 5.13 and 4.92 ppm, respectively. After 5 min, two new signals at δ 4.65 and 4.57 ppm became visible. The former and the latter signal are presumably due to the methylene hydrogens of hemiacetal (CD_3OCH_2OH) and *N*-*p*-chlorophenylaminomethylphthalimide **5d**, respectively. Increasing the temperature to 30 °C caused the decrease of the signal at δ 5.13 ppm and modification of the aromatic hydrogen signals. Finally, at 40 °C, the signal at δ 5.13 ppm disappeared, but the signal at δ 4.58 ppm became stronger and the –CH_2– signal of the hemiacetal was visible at δ 4.65 ppm.

The interesting part was the aromatic region, which showed a narrow multiplet at δ 7.8 ppm similar to the aromatic hydrogens of phthalimide.

Further confirmation of the hemiacetal and phthalimide formation from *N*-hydroximethylphthalimide came when this compound was dissolved in CD_3OD and gradually heated to 45 °C and later to 58 °C in a NMR tube. The signal at δ 4.65 ppm as well as the aromatic signals were quite clear. The above variable temperature experiments in the NMR tube strongly supported that compound **3** is in equilibrium with formaldehyde and phthalimide.

The same mechanism holds for dry conditions (without any solvent) like the reaction of **3** and **4a-l** by conventional heating or under microwave irradiation. In both cases, addition of triethylamine increased the reaction rate and completed the reaction. Here also a tight ion pair is formed followed by the proton transfers to formaldehyde. This way, all the reagents remain together and lead to the iminium ion and finally to the product. This can also be considered a general base-catalyzed reaction.

There is another important observation which requires attention. This is about dry heating the reagents **3** and **4** in an oil bath without microwave assistance. The reaction takes a little longer (8 min) compared to 5 min in a domestic microwave oven. In both cases, it is heating but in the latter the microwaves do accelerate the reaction.

X-ray Crystallographic Analysis

The bond distances in general are as expected. However, a quite fascinating phenomenon was observed; the N(2)"C(9) bond length is 1.427 Å, which is much shorter then the normal bond distance of simple N"C bond (~1.47 Å). This shortening can be attributed to the superposition of the lone pair of electrons of N(2) with the antibonding (σ^*) orbital of C(9). This is similar to the anomeric effect which is common in carbohydrates and also in 2-alkoxytetrahydropyran systems.[13]

The bond angle C(1)"N(1)"C(9) of 122.27 degrees clearly shows that N(1)"C(9) bond is coplanar with the imide ring. Another interesting observation is that the angle C(10)"N(2)"C(9) has 122.67 degrees. This deviation is due to interaction of the electron pair at N(2) and σ^* of C(9) discussed above. Only such an occurrence can be compatible with this value.

The torsion angles C(1)"N(1)"C(9)"N(2) and C(8)"N(1)"C(9)"N(2) are 69.7 and "114.42° clearly indicate that C(9)"N(2) bond is ~70° out of the phthalimide plane. This also supports the overlap of N(2) electron-pair and C(9)"N(2)"C(10)"C(11) is 14.9°, which is necessary to stabilize the conformation. An Ortep diagram is given in Figure 3.

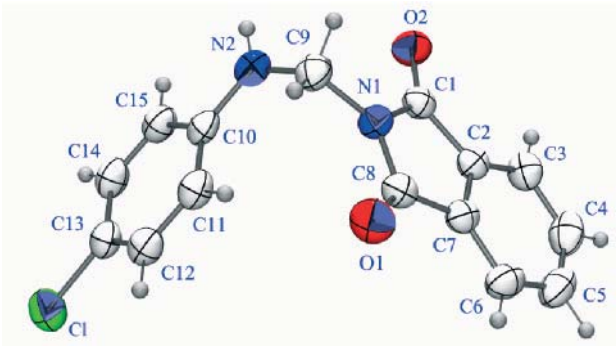


Figure 3. Ortep diagram of compound **5d**.

The unit cell diagram (Figure 4) contains two molecules of **5d**, where the phenyl ring of one molecule is arranged in a parallel fashion with the phenyl ring of the other molecule in the crystal packing; however the chlorine atoms of the two molecules are set in opposite direction.

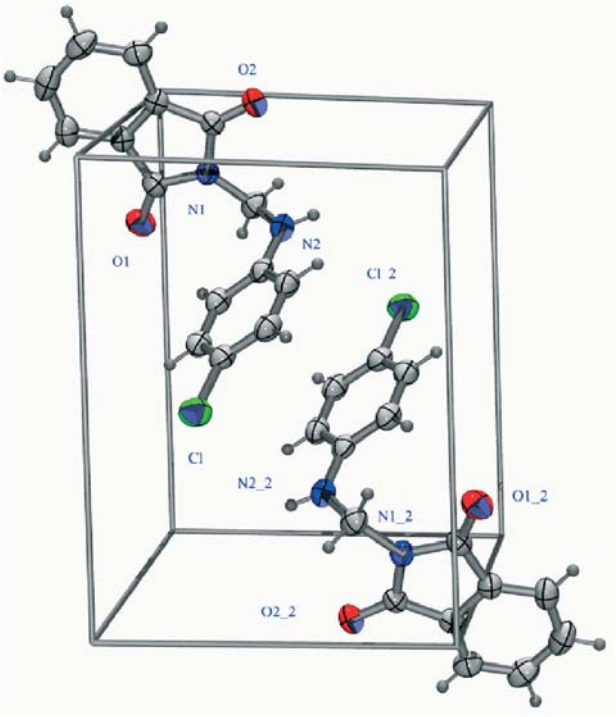


Figure 4. Unit cell diagram showing two molecules of **5d**.

It is fascinating to observe that the chlorine atom of one molecule attracts the oxygen atom of the other molecule which results in holding two molecules together in the unit cell (Figure 5).

Another interesting feature is that there is hydrogen bonding between the amino hydrogen atom of one molecule with the carbonyl oxygen atom of the other molecule, thus bringing both molecules closer. The bond distance between H-2 and 0-2 is 2.55 Å and the N(2)-H(2)-O(2) angle is 126° (Figure 6).

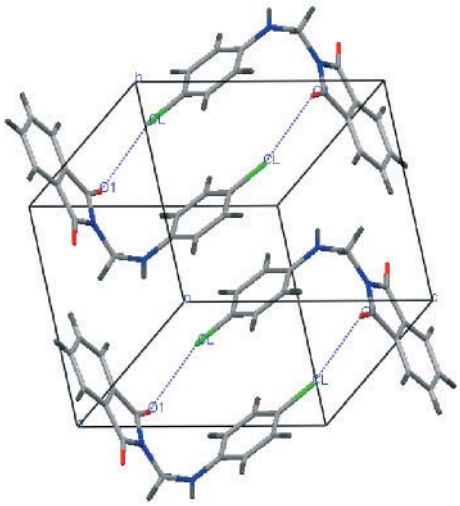


Figure 5. Unit cell structure showing the interaction between the chlorine atom of one molecule and the oxygen atom of the other molecule of phthalimide.

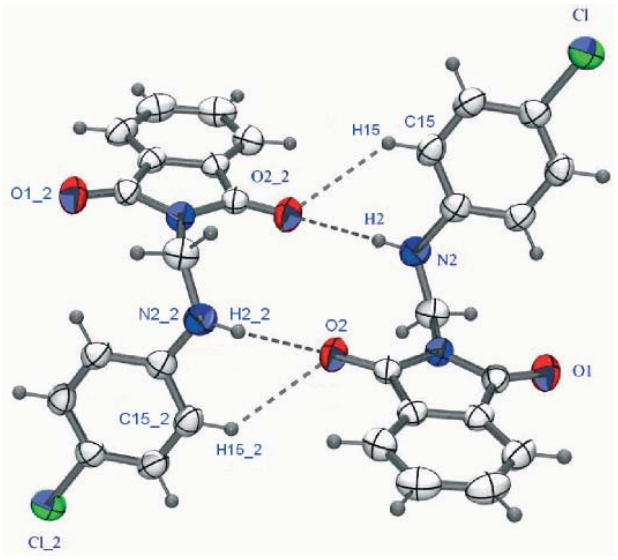


Figure 6. View of the crystal packing showing the N(2)-H(2)—O(2) and C(15)-H(15)—O(2) interactions.

We have carried out *ab initio* molecular orbital calculations of *N*-(p-chlorophenylaminomethyl)phthalimide **5d** using 6-31G* (Figure 8) as the basis set. The purpose was to compare the calculated values of **5d** with the crystallographic data. Although the calculations are performed for a single molecule in vacuum, the experimental values are close with the calculated ones. These are described below:

The N(2)-C(9) bond distance is 1.427 Å and the experimental value is also the same, showing a decrease in the C-N bond length. As observed in the X-ray crystallography data, the calculated value is remarkably the same. This supports the Overlap of C(9) σ* orbital with N(2) nonbonded orbital.

The bond angle C(1)-N(1)-C(9) has been found as 122.46° which is extremely close to the experimental one (122.27 Å). Also, C(10)-N(2)-C(9) gives the value 122.92 degrees; the value is again close to the crystal data.

The remarkably close values of the experimental and calculated data show the effectiveness of the 6-31G* basis set (Figure 7).

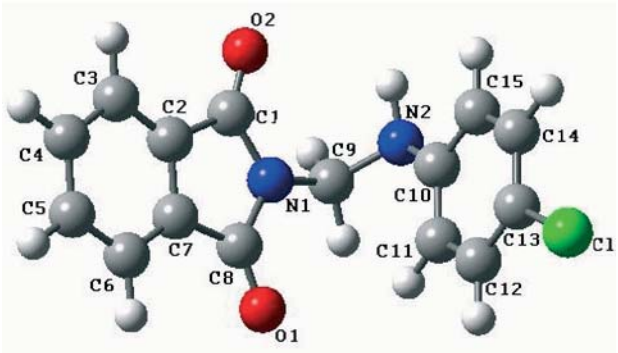


Figure 7. Molecular conformation obtained by *Ab initio* molecular orbital calculations using 6-31G* method.

Conclusions

We have accomplished the synthesis of twelve *N*-arylamino-methylphthalimides **5a-l** employing conventional, dry heating and microwave-accelerated procedures. The last method was the speediest one causing a drastic reduction of the reaction time. Tree reasonable mechanisms of formation of the final products have been proposed. The X-ray data analyses in conjunction with the molecular orbital calculations gave the correct conformation of the molecule particularly for compound **5d**.

Experimental

General

All compounds were checked for their structures by infrared (IR), UV, and ^{1}H NMR spectroscopy. Melting points were determined on a Digital Electrothermal serie IA 9100 melting point apparatus and are uncorrected. The microanalyses were performed in a Carlo Erba Mod. EA1110 equipment. UV spectra were recorded with a U-3200 Hitachi spectrometer. IR spectra were measured with a Bruker model IF S66 FTIR spectrometer using potassium bromide discs. NMR spectra were recorded in $CDCl_3$ (for compounds **5a-j**) or DMSO-d_6 (for compounds **5k**,**l**) using tetramethylsilane (TMS) as an internal standard, on Varian Unity Plus 300 MHz spectrometer. Assignments of 2-[(4-Fluorophenylamino)methyl]-isoindole-1,3-dione and 2-[(3-Fluorophenylamino)methyl]-isoindole-1,3-dione were made using ^{1}H homonuclear irradiation and gHMBC (gradient Heteronuclear Multi Bonds Correlation) NMR spectra. The reactions in microwave were realized in Oven Microwave Sanyo EM-3500B, 220V/1350W/2450MHz. Since we do not have any specific microwave oven, we did some experiments and located the correct heating place in the oven. Each experiment was repeated at least three times in order to obtain reproducible results. Therefore, we feel confident that these experiments can be repeated using any microwave oven.

*General procedure for the synthesis of compounds **5a-l** by heating*

Compounds **5a-l** were obtained by refluxing a mixture of *N*-hydroxymethylphthalimide **3** (0.6 mmol) and an appropriate aromatic amine **4a-l** (0.6 mmol) in MeOH (3.0 mL) for 3 hours under N_2 atmosphere. The progress of the reaction was accompanied by thin-layer chromatography. After solvent evaporation, the solid material was crystallized and recrystallized from an appropriate solvent, except the products **5k,1** which were filtered through a short column containing silica gel. This procedure removed the impurities and facilitated crystallization. Table 1 contains the crystallizing solvent, yields and melting points of compounds **5a-l**.

*2-Phenylaminomethyl-isoindole-1,3-dione (**5a**)*

Obtained from hydroxymethylphthalimide (100 mg, 0.56 mmol) and aniline (50 mg, 0.56 mmol). ^{1}H NMR (300 MHz, $CDCl_3$)- δ (ppm) 7.81 (dd, 2H, *J* 5.4 and 3.0 Hz; H-4 and H-7), 7.68 (dd, 2H, *J* 5.4 and 3.0 Hz; H-5 and H-6), 7.18 (ddd, 2H, *J* 7.5 and 1.2 Hz; H-3'and H-5'), 6.86 (ddd, 2H, *J* 7.5, 7.5 and 2.0 Hz; H-2'and H-6'), 6.76 (tt, 1H, *J* 7.5 and 0.9 Hz; H-4'), 5.18 (d, 2H, *J* 8.1 Hz, -CH_2), 4.84 (t, 1H, *J* 7.8 Hz, -NH). IR n_{max}/cm^{-1} (Nujol) – 3384, 2956, 2923, 2854, 1767, 1709, 1603, 1520, 1498, 1406, 1468 and 1405 cm^{-1}. UV (MeOH) – λ_{max} 286 nm, $\in_{max}$ 4843 L mol^{-1} cm^{-1}, transition n $\rightarrow \pi^*$; λ_{max} 218, 230 e 238 nm, $\in_{max}$ 46582, 27315 and 24212 L mol^{-1} cm^{-1} respectively, transition $\pi \rightarrow \pi^*$.

*2-[(2-Clorophenylamino)methyl]-isoindole-1,3-dione (**5b**)*

Obtained from hydroxymethylphthalimide (150 mg, 0.85 mmol) and 2-chloroaniline (108 mg, 0.85 mmol). Crystallized from $CHCl_3$, R_f = 0.57, mp 144-145 °C (48.5% yield); [lit.[11] mp 141-141.5 °C, yield 32%]. Calculated for $C_{15}H_{11}ClN_2O_2$ (286.72) – C, 62.84; H, 3.87; N, 9.77. Found: C, 62.48; H, 3.92; N, 9.58. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.83 (dd, 2H, *J* 5.4, 3.0 Hz; H-4 and H-7), 7.70 (dd, 2H, *J* 3.0, 5.1 Hz; H-5 and H-6), 7.24-7.18 (m, 2H, H-3'and H-5'), 7.14 (dd, 1H, *J* 8.1 and 1.5 Hz; H-6'), 6.66 (ddd, 1H, *J* 7.5, 7.5, and 1.8 Hz; H-4'), 5.45 (t, 1H, *J* 8.1 Hz, -NH), 5.24 (d, 2H, *J* 8.1 Hz, -CH_2). IR ν_{max}/cm^{-1} (Nujol) – 3421, 2952, 2921, 2852, 1767, 1712, 1596, 1517, 1458, 752, and 722 cm^{-1}. UV (MeOH) – λ_{max} 292 nm, $\in_{max}$ 2890, L mol^{-1} cm^{-1}, transition n $\rightarrow \pi^*$; λ_{max} 218, 231 and 239 nm, $\in_{max}$ 34430, 17037 and 15454L mol^{-1} cm^{-1} respectively, transition $\pi \rightarrow \pi^*$.

*2-[(3-Clorophenylamino)methyl]-isoindole-1,3-dione (**5c**)*

Synthesized from hydroxymethylphthalimide (150 mg, 0.85 mmol) and 3-chloroaniline (108 mg, 0.85 mmol). Calculated for $C_{15}H_{11}ClN_2O_2$ (286.7169) – C, 62.84; H, 3.87; N, 9.77. Found: C, 62.73; H, 3.57; N, 9.49. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.84 (dd, 2H, *J* 5.4 and 3.0 Hz; H-4 and H-7), 7.71 (dd, 2H, *J* 5.4 and 3.0 Hz; H-5 and H-6), 7.09 (t, 1H, *J* 8.1 Hz; H-5'), 6.86 (t, 1H, *J* 1.8

Hz; H-4'), 6.74 (ddd, 2H, *J* 8.4, 7.8 and 1.8 Hz; H-2' and H-6'), 5.15 (d, 2H, *J* 7.8 Hz, -CH_2), 5.24 (t, 1H, *J* 7.8 Hz, -NH). IR ν_{max}/cm^{-1} (Nujol) – 3384, 2922, 2853, 1764, 1707, 1594, 1485, 1460, 1407, 1173 and 1090 cm^{-1}. UV (MeOH) – λ_{max} 282 nm, $\in_{max}$ 1951 L mol^{-1} cm^{-1}, transition n → π*; λ_{max} 240, and 248 nm, $\in_{max}$ 6473, and 5751 L mol^{-1} cm^{-1} respectively, transition π → π*.

*2-[(4-Clorophenylamino)methyl)-isoindole-1,3-dione (**5d**)*

Hydroximethylphthalimide (150 mg, 0.85 mmol) and 4-cloroaniline (108 mg, 0.85 mmol), Crystallized from $CHCl_3$, R_f = 0.53, mp 208.5-209.3 °C (93.42% yield); [lit. 10] mp. 207-208 °C, 73% yield. Calculated for $C_{15}H_{11}ClN_2O_2$ (286.7169) – C, 62.84; H, 3.87; N, 9.77. Found: C, 62.92; H, 3.82; N, 9.94. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.83 (dd, 2H, *J* 5.4 and 3.0 Hz; H-4 and H-7), 7.16 (dd, 2H, *J* 5.7 and 3.0 Hz; H-5 and H-6), 7.12 (dd, 2H, *J* 6.6 and 2.1 Hz; H-3' and H-5'), 6.79 (dd, 2H, *J* 6.6 and 2.4 Hz; H-2' and H-6'), 5.15 (d, 2H, *J* 8.1 Hz, -CH_2), 4.82 (t, 1H, *J* 7.5 Hz, -NH). IR ν_{max}/cm^{-1} (Nujol) – 3380, 3055, 2960, 1768, 1712, 1597, 1515, 1489, 1406, 818, 726 cm^{-1}. UV (MeOH) – λ_{max} 296 nm, $\in_{max}$ 1821 L mol^{-1} cm^{-1}, transition n → π*; λ_{max} 218, 232, 240, and 250 nm, λ_{max} 26563, 12222, 12491 and 10842 L mol^{-1} cm^{-1} respectively, transition π → π*.

*2-[(2-Fluorophenylamino)methyl]-isoindole-1,3-dione (**5e**)*

Hydroximethylphthalimide (391 mg, 2.2 mmol) and 2-fluoroaniline (245 mg, 2.2 mmol), Crystallized from $CHCl_3$, R_f = 0.55, mp 176-176.6 °C (77.0%, yield). Calculated for $C_{15}H_{11}FN_2O_2$ (270.2585) – C, 66.66; H, 4.10; N, 10.37. Found: C, 66.42; H, 4.36; N, 10.65. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.83 (dd, 2H, *J* 5.4 and 3.3 Hz; H-4 and H-7), 7.70 (dd, 2H, *J* 5.4 and 3.0 Hz; H-5 and H-6), 7.20 (ddd, 1H, *J* 8.7, 8.4 and 1.5 Hz; H-5'), 7.01 (m, 1H, H-5'), 6.94 (ddd, 1H, *J* 8.7, 8.4 and 1.5 Hz; H-6'), 6.68 (m, 1H, H-4'), 5.21 (d, 2H, *J* 7.8 Hz, -CH_2), 5.09 (t, 1H, *J* 7.5 Hz, -NH). ^{13}C NMR (75 MHz, $CDCl_3$) – δ (ppm) 168.3 (s, 2C, C-1 and C-3), 151.9 (d, 1C, *J* 239.7 Hz, C-2'), 134.2 (s, 2C, C-5 and C-6), 132.9 (d, 1C, *J* 10.6 Hz, C-1'), 131.8 (s, 2C, C-8 and C-9), 124.6 (d, 1C, *J* 4.1 Hz, C-5'), 123.5 (s, 2C, C-4 and C-7), 118.9 (d, 1C, *J* 15.3 Hz, C-4'), 114.8 (d, 1C, *J* 18.6 Hz, C-6'), 113.4 (d, 1C, *J* 13.7 Hz, C-3') and 47.0 (s, 1C, CH_2). IR ν_{max}/cm^{-1} (Nujol) – 3434, 3063, 2924, 2854, 1767, 1713, 1621, 1526, 1460, 1360, 754 and 727 cm^{-1}. UV (MeOH) – λ_{max} 286 nm, $\in_{max}$ 1779 L mol^{-1} cm^{-1}, transition n → π*; λ_{max} 218, 232 and 239 nm, $\in_{max}$ 26321, 15607 and 12805 L mol^{-1} cm^{-1} respectively, transition π → π*.

*2-[(3-fluorophenylamino)methyl]-isoindole-1,3-dione (**5f**)*

Hydroxymethylphthalimide (391 mg, 2.2 mmol) and 3-fluoroaniline (245 mg, 2.2 mmol). Crystallized from $CHCl_3$, R_f = 0.50, mp 200-201 °C (84.42% yield). Calculated for $C_{15}H_{11}FN_2O_2$ (270,2585) – C, 66.66; H, 4.10; N, 10.37. Found: C, 66.57; H, 4.37; N, 10.57. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.84 (dd, 2H, *J* 5.7 and 3.0 Hz; H-4 and H-7), 7.71 (dd, 2H, *J* 5.7 and 3.0 Hz; H-5 and H-6), 7.11 (ddd, 1H, *J* 8.1, 8.1 and 5.1 Hz; H-5'), 6.62 (m, 1H, H-2'), 6.66 (m, 1H, H-6'), 6.47 (m, 1H, H-4'), 5.16 (d, 2H, *J* 7.8 Hz, -CH_2), 4.94 (t, 1H, *J* 7.5 Hz, -NH). ^{13}C NMR (75 MHz, $CDCl_3$) – δ (ppm) 168.2 (s, 2C, C-1 and C-3), 163.8 (d, 1C, J 244.7 Hz, C-3'), 145.6 (d, 1C, C-1'), 134.3 (s, 2C, C-5 and C-6), 131.8 (s, 2C, C-8 and C-9), 130.6 (d, 1C, *J* 10.1 Hz, C-5'), 123.6 (s, 2C, C-4 and C-7), 110.1 (s, 1C, C-6'), 106.6 (d, 1C, *J* 21.2 Hz, C-4'), 101.6 (d, 1C, *J* 25.7 Hz, C-2') and 47.8 (s, 1C, CH_2). IR ν_{max}/cm^{-1} (Nujol) – 3389, 2956, 2925, 2855, 1767, 1710, 1618, 1591, 1499, 1461, 853, 774 and 729 cm^{-1}. UV (MeOH) – λ_{max} 287 nm, $\in_{max}$ 1316 L mol^{-1} cm^{-1}, transition n → π*; λ_{max} 213, 218, 231 and 239 nm, $\in_{max}$ 16481, 17490, 9211 and 8778 L mol^{-1} cm^{-1} respectively, transition π → π*.

*2-[(4-Fluorophenylamino)methyl]-isoindole-1,3-dione (**5g**)*

Hydroxymethylphthalimide (391 mg, 2.2 mmol) and 3-fluoroaniline (245 mg, 2.2 mmol). Crystallized from $CHCl_3$, R_f = 0.49; mp 177.3-178 °C (93.62% yield). Calculated for $C_{15}H_{11}FN_2O_2$ (270.2585) – C, 66.66; H, 4.10; N, 10.37 Found: C, 66.37; H, 4.39; N, 10.53. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.82 (dd, 2H, *J* 5.7 and 3.0 Hz; H-4 and H-7), 7.70 (dd, 2H, *J* 5.4 and 3.0 Hz; H-5 and H-6), 6.87 (m, 2H, H-2' and H-6'), 6.79 (m, 2H, H-5' and H-3'), 5.14 (d, 2H, *J* 7.8 Hz, -CH_2), 4.71 (t, 1H, *J* 8.1 Hz, -NH). IR ν_{max}/cm^{-1} (Nujol) – 3394, 2923, 1763, 1709, 1515, 1460, 1406, 1082 and 831 cm^{-1}. UV (MeOH) – λ_{max} 297 nm, $\in_{max}$ 2077 L mol^{-1} cm^{-1}, transition n → π*; λ_{max} 218, 230 and 238 nm, $\in_{max}$ 26232, 14187 and 11781 L mol^{-1} cm^{-1} respectively, transition π → π*.

*2-[(2-Nitrophenylamino)methyl]-isoindole-1,3-dione (**5h**)*

Hydroxymethylphthalimide (257 mg, 1.45 mmol) and *2*-nitroaniline (200 mg, 1.45 mmol), refluxed in toluene for 3 h. Crystallized from acetone, R_f = 0.55; mp 162.3-163.1 °C (64.04% yield). Calculated for $C_{15}H_{11}N_3O_4$ (297.2657) – C, 60.61; H, 3.73; N, 14.14. Found: C, 60.68;

H, 3.51; N, 14.38. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 8.21 (dd, 1H, *J* 8.7, 1.8 Hz; H-5'), 7.90 (dd, 2H, *J* 5.4 and 3.0 Hz; H-4 and H-7), 7.76 (dd, 2H, *J* 5.4 and 3.0 Hz; H-5 and H-6), 7.52 (ddd, 1H, *J* 8.7, 7.2 and 1.5 Hz; H-3'), 7.00 (dd, 1H, *J* 8.7 and 1.2 Hz; H-2'), 6.80 (ddd, 1H, *J* 8.7, 7.2 and 1.2 Hz; H-4'), 5.26, (d, 2H, *J* 8.1 Hz, -CH_2), 5.02 (t, 1H, *J* 5.7 Hz, -NH). IR ν_{max}/cm^{-1} (Nujol) – 3486, 3445, 2955, 2923, 2853, 1779, 1770, 1705, 1608, 1460, 1426, 1406, 1328 and 732 cm^{-1}. UV (MeOH) – λ_{max} 286 nm, $\in_{max}$ 2905 L mol^{-1} cm^{-1}, transition n $\rightarrow$ π*; λ_{max} 217, 229 and 238 nm, $\in_{max}$ 48284, 24487 and 14878 L mol^{-1} cm^{-1} respectively, transition $\pi \rightarrow \pi$*.

2-[(3-Nitrophenylamino)methyl]-isoindole-1,3-dione ***(5i)***

Hydroxymethylphthalimide (257 mg, 1.45 mmol) and *3*-nitroaniline (200 mg, 1.45 mmol), reflux in toluene, 3 h of reaction. Crystallized in acetone, R_f = 0.7, mp 194.4-195.2 °C, (81.67%, yield). Calculated for $C_{15}H_{11}N_3O_4$ (297.2657) – C, 60.61; H, 3.73; N, 14.14; found: C, 60.36; H, 3.94; N, 14.32. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.87 (dd, 2H, *J* 5.7 and 3.0 Hz; H-4 and H-7), 7.73 (dd, 2H, *J* 5.4 and 3.0; H-5 and H-6), 7.72 (t, 1H, *J* 2.4 Hz; H-6') 7.60 (ddd, 1H, *J* 8.1, 2.4 and 2.1 Hz; H-4'), 7.32 (t, 1H, 8.1 Hz; H-3'), 7.18 (ddd, 1H, *J* 8.1, 2.4 and 2.1 Hz; H-2'), 5.21, (s, 2H, -CH_2), 5.16 (b, 1H, -NH). IR $\nu_{máx}$/cm^{-1} (Nujol) – 3416, 2954, 2923, 2853, 1773, 1709, 1625, 1536, 1521, 1314 and 729 cm^{-1}. UV (MeOH) – λ_{max} 372 and 282 nm, $\in_{max}$ 1331 and 4797 L mol^{-1} cm^{-1} respectively, transition n $\rightarrow$ π*; λ_{max} 218, 231, 239 and 250 nm, λ_{max} 46068, 34297, 28076 and 17042 L mol^{-1} cm^{-1} respectively, transition $\pi \rightarrow \pi$*.

2-[(4-Nitrophenylamino)methyl]-isoindole-1,3-dione ***(5j)***

Hydroxymethylphthalimide (257 mg, 1.45 mmol) and *4*-nitroaniline (200 mg, 1.45 mmol), refluxed in toluene for 3 h. Crystallized from acetone R_f = 0.64, mp 228.6-229.1 °C (81.67%, yield). Calculated for $C_{15}H_{11}N_3O_4$ (297.2657) – C, 60.61; H, 3.73; N, 14.14. Found: C, 60.35; H, 3.72; N, 14.21. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 8.10 (dd, 2H, *J* 2.1 and 7.2 Hz; H-3' and H-5'), 7.87 (dd, 2H, *J* 5.7, and 3.0 Hz; H-4 and H-7), 7.75 (dd, 2H, *J* 5.7 and 3.0 Hz; H-5 and H-6), 6.88 (dd, 2H, *J* 7.2 and 2.1 Hz; H-2' and H-6'), 5.45 (t, 1H, *J* 8.0 Hz, -NH), 5.22 (d, 2H, *J* 7.5 Hz, -CH_2). IR ν_{max}/cm^{-1} (Nujol) – 3357, 3096, 2954, 2923, 2853, 1768, 1707, 1604, 1477, 1465, 1308 and 850 cm^{-1}. UV (MeOH) – λ_{max} 364 and 304 nm, $\in_{max}$ 15148 and 3916 L mol^{-1} cm^{-1} respectively, transition n $\rightarrow$ π*; λ_{max} 218 and 239 nm, $\in_{max}$ 38944 and 13704 L mol^{-1} cm^{-1} respectively, transition $\pi \rightarrow \pi$*.

2-[1H-(1,2,4)Triazol-3-yl-aminomethyl)-isoindole-1,3-dione ***(5k)***

Hydroxymethylphthalimide (257 mg, 1.13 mmol) and *3*-aminotriazole (95 mg, 1.13 mmol). Crystallized from EtOH as fine colorless crystals, R_f 0.6, mp 229.9-230.7 °C (79.24% yield). Calculated for $C_{11}H_9N_5O_2$ (243.08) – C, 54.32; H, 3.73; N, 28.79. Found: C, 54.27; H, 3.91; N, 28.85. ^{1}H NMR (300 MHz, DMSO-d_6) - δ (ppm) 11.34 (b, 1H, -NH Het), 8.68 (s, 1H, C-5´ Het), 7.89-7.47 (m, 4H, H-4, H-5, H-6 and H-7, -CH_2). IR ν_{max}/cm^{-1} (KBr) – 3392, 3040, 2851, 1792, 1770, 1747, 1712, 1527, 1492, 1467, 1374, 1354, 1232, 1117, 1085 and 718. UV – λ_{max} 293 nm, transition n $\rightarrow$ π*; λ_{max} 258 nm, transition $\pi \rightarrow \pi$*. MS – 243 (1%), 149 (1.46%), 148 (14.73%), 147 (100%), 104 (53.38%), 103 (92.43%), 76 (5.73%), 75 (1034), 74 (22.85%) and 50 (40.80%).

2-([1,2,4]-Triazole-4-ylaminomethyl)-isoindole-1,3-dione ***(5l)***

Hydroxymethylphthalimide (257 mg, 1.13 mmol) and *4*-aminotriazole (95 mg, 1.13 mmol). Crystallized from EtOH as fine crystals, R_f 0.5, mp 232.9-233.8 °C (82.99% yield). Calculated from $C_{11}H_9N_5O_2$ (243.08) – C, 54.32; H, 3.73; N, 28.79. Found: C, 54.44; H, 3.51; N, 28.92. ^{1}H NMR (300 MHz, DMSO-d_6) - δ (ppm) 8.48 (s, 2H, H-3´and H-5´), 7.87 (s, 4H, H-4, H-5, H-6 and H-7), 7.52 (t, 1H, *J* 7.20 Hz, -NH), 4.77 (d, 2H, *J* 4.80 Hz, -CH_2). IR ν_{max}/cm^{-1} (KBr) – 3459, 3200, 3061, 2718, 1775, 1752, 1604, 1468, 1388, 1308, 1288, 1184, 1140, 1090, 1071, 1053 and 716. UV – λ_{max} 293 nm, transition n $\rightarrow$ π*; λ_{max} 246 nm, transition $\pi \rightarrow \pi$*.

N-Acetyl derivative of N-(4-chlorophenylaminomethyl) isoindole-1,3-dione ***(9d)***

(100 mg, 0,35 mmol), dry pyridine (1.0 mL) and acetic anhydride (0.3 mL), agitation, r.t., 0.5 h; R_f= 0.7; (98.99% yield). Calculated for $C_{17}H_{13}N_2O_3$ (328.75) – C, 62.11; H, 3.99; N, 8.52. Found: C, 62.22; H, 4.19; N, 8.64. ^{1}H NMR (300 MHz, $CDCl_3$) - δ (ppm) 7.82 (dd, 2H, *J* 3.0 and 6.0 Hz; H-4 and H-7), 7.73 (dd, 2H, *J* 3.0 and 5.7 Hz; H-5 and H-6), 7.33 (d, 2H, *J* 8.4 Hz; H-3' and H-5'), 7.13 (d, 2H, *J* 8.4; Hz; H-2' and H-6'), 5.64 (s, 2H, -CH_2), 1.85 (s, 3H, -CH_3). IR ν_{max}/cm^{-1} (KBr) – 3200, 3061, 1780, 1724, 1669, 1651, 1489, 1467, 1431, 1410, 1384, 1356, 1299, 1083, 1011, 912, 757, 729 and 714. UV – λ_{max} 293 nm, transition n $\rightarrow$ π*, λ_{max} 221 nm, transition $\pi \rightarrow \pi$*.

Compounds **5a-l**, were also obtained by mixing equimolar quantities of **3** and an amine **4a-l** in the tube and adding one drop each of Et_3N and DMF followed by heating for 8 min. in an oil bath at 90 °C without any solvent. The solid material obtained was crystallized and the products were compared with the ones prepared by refluxing in methanol (Table 1).

*Microwave-assisted reaction of **3** and **4a-l***

N-Hydroxymethylphthalimide (0.85 mmol), arylamine (0.85 mmol), one drop each of triethylamine and *N*,*N*-dimethylformamide were well triturated in a porcelain dish and kept in a domestic microwave oven for 2-5 min operating at 1350 Watts and 2450 MHz. Thin-layer chromatogram showed the disappearance of the starting reagents and the formation of the product. The solid was washed with cyclohexane and dried. Direct crystallization from an appropriate solvent furnished the product (see Table 1 for details).

Crystallographic Study

The programs used were: cell determination and data collection: Kappa-CCD-Enraf-Nonius, (1999);[14] data reduction: HKL Denzo and Scalepack (1997);[15] data collection: Collect (1997);[16] structure solution: SHELXS-97 (Sheldrick, 1997a);[17] refinement: SHELXL-97 (Sheldrick, 1997b);[18] graphic presentation: ORTEP3 for Windows (Farrugia, 1997);[19] material to publication: WinGX-Routine (Farrugia, 1999).[20]

Computational Details

The *ab initio* Hartree-Fock Self-Consistent Field (HF-SCF) molecular orbital calculations were carried out using Gaussian 2003 program,[21] employing HF/6-31G* and 6-31G** method for geometry optimization and determining the electron densities.

Supplementary Information

The crystallographic data were deposited at the Cambridge Structural Data Base (deposition number: CCDC 285302). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).

The data collection and refinement procedures, crystal parameters, atom coordinates, thermal parameters, bond lengths and angles for compound **5d** are available free of charge via http://pubs.acs.org. Cartesian coordinates; Standard orientation: HF/6-31G(d).

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