

## A NEW METHOD FOR THE SYNTHESIS OF N-ARYLPHTHALISOIMIDES

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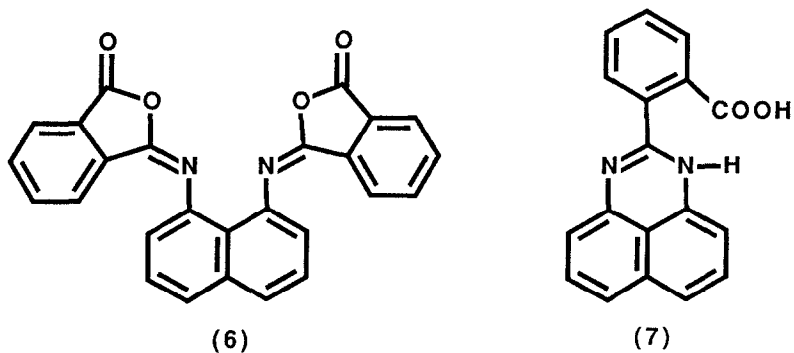
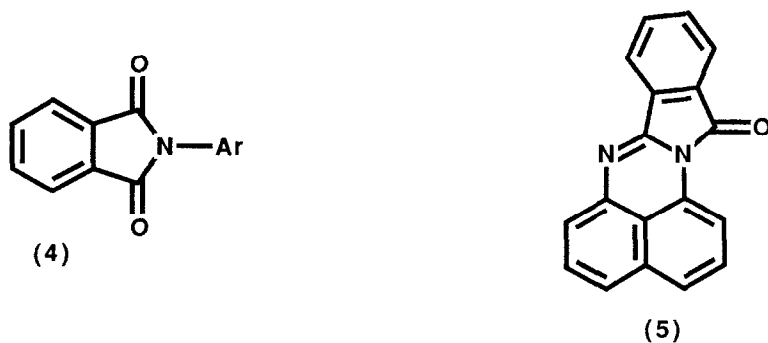
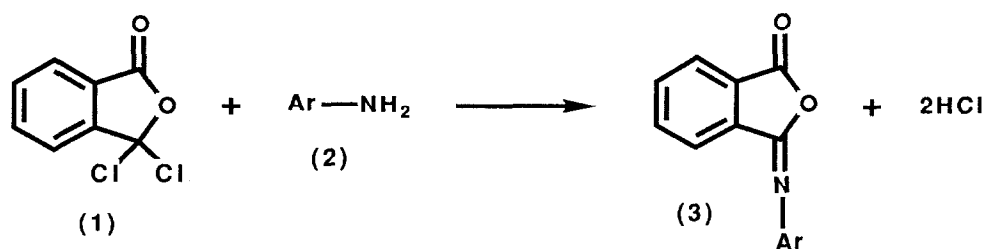
**Summary:** N-arylphthalisoimides have been synthesized in almost quantitative yields by the reaction, under very mild conditions, of 3,3-dichlorophthalide with aromatic amines.

The majority of the procedures to synthesize N-arylphthalisoimides (3) are based on cyclization processes by dehydration of N-substituted phthalamic acids<sup>1</sup>, but for many reactions the formation of the isomer phthalimides (4) is a competitive process. Either simple heating or a wide variety of reagents have been used for dehydration of phthalamic acids under different conditions<sup>2</sup>. However, the reagents most frequently reported for performing efficient dehydrations giving phthalisoimides are fewer in number: ethyl chloroformate, trifluoroacetic anhydride and N,N'-dicyclohexylcarbodiimide but, judging from the literature, they would appear not to be general in their action<sup>2-5</sup>. A comparative study of these three dehydration reagents and acetic anhydride have been reported, showing N,N'-dicyclohexylcarbodiimide as the most general to yield phthalisoimides<sup>4</sup>.

There is considerable evidence to suggest that dehydration to give either phthalimides or phthalisoimides, could proceed by intramolecular interaction of the amide function with suitably disposed activated acyl groups<sup>4,6-8</sup>. Thus, phthalimide formation would take place by ring closure with nucleophilic participation of the nitrogen of the amide group, while participation of the oxygen would lead to phthalisoimides. On the other hand, phthalisoimides undergo facile isomerization to the corresponding phthalimides by thermal or catalysed rearrangement processes<sup>2,8-10</sup>. Thus, it is possible that after a kinetically favoured formation of isoimide, the imide however could be the isolated product, especially if the reaction temperature is relatively high as well as if nucleophilic catalysts are present in the reaction medium. In short, three main factors are involved in the formation of the final products: (i) the activation type of the acyl group, which depends on the

dehydration reagent used, (ii) the electronic effects of functional groups attached to the N-aromatic ring, which are implicated in the nucleophilicity of the amide group and (iii) the experimental conditions, which in some cases could cause the isomerization of the isoimide to the imide. An effective control of these variables is difficult and erratic results can be observed<sup>11</sup>.

We herein report a new, general and simple method for the synthesis of N-arylphtalisoimides (3), starting from 3,3-dichlorophthalide (1), which is easily available from phthalic acid in high yield<sup>12</sup>.



Reaction of (1) with aromatic amines (2) gives the phthalisoimides (3) in nearly quantitative yields. In contrast with dehydration reactions, this method shows several advantages. Thus, the reaction products can be predicted without ambiguity since the arylimino group is linked to the previously formed ring system of (1), which because is not involved along the reaction process is retained. Consequently competitive formation of phthalimides does not take place. Moreover, the reaction is fast under mild conditions and therefore the isomerization of phthalisoimides is not favoured. It is also to be noticed that this method provides a valuable entry to substituted phthalisoimides bearing functional groups reactive toward dehydration reagents. The reactivity of this reagent and its synthetic usefulness remain little known.

Table 1. Preparation of N-Arylphthalisoimides by Reaction of 3,3-Dichlorophthalide with Aromatic Amines.

Entry	amine	yield (%) <sup>a</sup>	m.p. (°C)	Molecular Formula or Lit. m.p. (°C)
1	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	88	121-122	120-122 <sup>b</sup>
2	4-MeOC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	85	135-136	134 <sup>c</sup>
3	4-BrC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	87	165-167	166-167 <sup>d</sup>
4	2-MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	86	136-137	136 <sup>c</sup>
5	4-MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	79	123-125	123 <sup>c</sup>
6	2-IC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	87	146-148	C <sub>14</sub> H <sub>8</sub> INO <sub>2</sub>
7	4-ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	84	159-160	160 <sup>c</sup>
8	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	87	118-120	C <sub>14</sub> H <sub>7</sub> Cl <sub>2</sub> NO <sub>2</sub>
9	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	83	172-173	172 <sup>c</sup>
10	2-HOCH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	78	178-179	C <sub>15</sub> H <sub>11</sub> NO <sub>3</sub>
11	2-C <sub>10</sub> H <sub>7</sub> NH <sub>2</sub>	91	151-152	C <sub>18</sub> H <sub>11</sub> NO <sub>2</sub>

<sup>a</sup>yields in crystallized products. All compounds gave satisfactory IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectra, and elemental analyses. <sup>b</sup>Ref. 16; <sup>c</sup>Ref. 2; <sup>d</sup>Ref. 15.

**Typical Experimental Procedure.** A solution of 3,3-dichlorophthalide (1) (10 mmol) in acetonitrile (20 ml) was cooled to -10°C. Then, a solution of the appropriate amine(2) (10 mmol) and triethylamine (20 mmol), in acetonitrile (20 mL), was added from a compensated pressure addition funnel during 10 min under vigorous stirring. The temperature was maintained between -10 °C and -5 °C. A precipitate was formed after a few drops of mixture were added. The suspension was allowed to warm up to room temperature with continued stirring for 5 min. After removal of the solvent under

reduced pressure, the solid crude product was shaken twice with cold water and collected and dried by vacuum filtration. High purity crude reaction products were isolated in nearly quantitative yields<sup>13</sup> which were crystallized from acetone-water. The results are summarized in Table 1. Entry numbers 6,8,10, and 11 correspond to new phthalisoimides.

We have also studied the reaction with 1,8-diaminonaphthalene. In this case it was carried out according to the above experimental procedure, but adding 5 mmol of 1,8-diaminonaphthalene and 20 mmol of triethylamine to 10 mmol of (3). Phthaloperinone<sup>14</sup> (5) (32% yield) and 1,8-diphthalisoimidonaphthalene (6) (65% yield), m.p. 255-256 °C, a previously unknown substance, were the products. This reaction provides a useful entry to (6). In contrast, this compound cannot be obtained by the amic acid dehydration method since the reaction of phthalic acid anhydride with 1,8-diaminonaphthalene leads to 2-(2-perimidyl)benzoic acid<sup>14</sup> (7) which dehydrates to phthaloperinone(5).

**Acknowledgements:** We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica (project number PB89-0442).

#### REFERENCES AND NOTES.

- Further N-arylphthalisoimides formation reactions having less usefulness for synthesis are found in the literature: Howe, R.K. *J. Org. Chem.* **1973**, 38, 4164.; Ganin, E.V; Makarov, V.F.; Kikitin, V.I. *Ukr. Khim. Zh.* **1987**, 53, 964.; Takeuchi, H.; Eguchi, H. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2149.
- See for example: Roderick, W.R; Bhatia, P.L. *J. Org. Chem.* **1963**, 28, 2018., and references cited therein.
- Kukolja, S.; Lammer, S.R. *J. Am. Chem. Soc.* **1975**, 97, 5582.
- Awad, W.I.; Wasfi, A.S.; Ewad, M.J. *J. Iraqi Chem. Soc.* **1977**, 2, 5.
- Pyriadi, M.; Hadi, S. *Arab. Gulf. J. Sci. Res. A.* **1987**, 5, 341.
- Roderick, W.R. *J. Org. Chem.* **1964**, 29, 745.
- Sauers, C.K.; Gould, C.L.; Ioannou, E.S. *J. Am. Chem. Soc.* **1972**, 94, 8156.
- Au, T.K.; Baydar, A.E.; Boyd, G.V. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 2884.
- Cotter, R.J.; Sauers, C.K.; Wheland, J.M. *J. Org. Chem.* **1961**, 26, 10.
- Ernst, M.L.; Schmir, G.L. *J. Am. Chem. Soc.* **1966**, 88, 5001.
- Curtin, D.Y.; Miller, L.L. *J. Am. Chem. Soc.* **1967**, 89, 637.
- Erwin, O. *Organic Syntheses; Coll. Vol. II*, Blatt, A.H. Ed.; John Wiley and Sons, Inc.: London, **1946**; p.528.
- I.R and high field <sup>1</sup>H NMR spectra for crude and crystalline products were recorded showing negligible differences.
- Elsevier's Encyclopaedia of Organic Chemistry*, Radt, F. Ed.; Series III, Vol. 12B, Elsevier Publishing Company: New York. **1949**; p.830.
- Bhatia, P.L.; Gupta, S.N. *Indian J. Chem.* **1964**, 2, 295.
- Hoogenwerff, S.; van Drop, W.A. *Rec. Trav. Chim.* **1902**, 21, 339.

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