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# AN EXPEDIENT METHOD TO THE SYNTHESIS OF *N*-SUBSTITUTED 1*H*-ISOINDOLE-1,3(2*H*)-DIONES

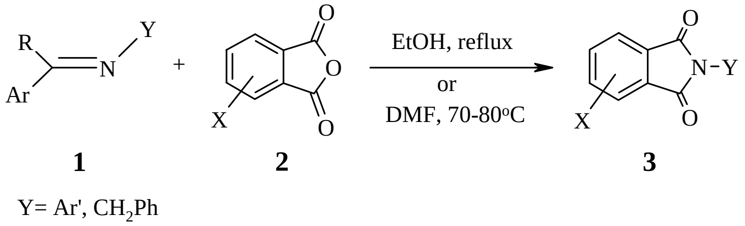
**Farzad Nikpour* and Baran Mohammadi Mogaddam**

Department of Chemistry, Faculty of Sciences, University of Kurdistan, P.O. Box 66315-416, Sanandaj, Iran

**Abstract** – The synthesis of *N*-substituted 1*H*-isoindole-1,3-(2*H*)-diones is described from the reaction of cyclic anhydrides with Schiff bases as suitable replacing substrates instead of the corresponding amines.

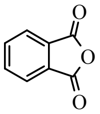
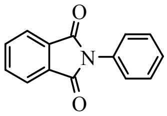
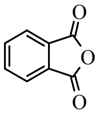
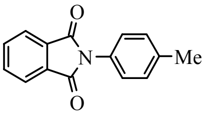
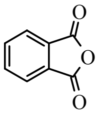
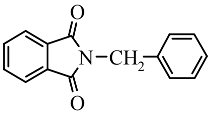
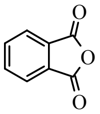
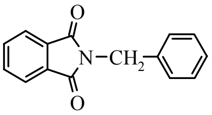
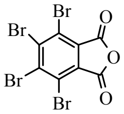
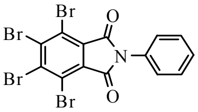
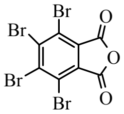
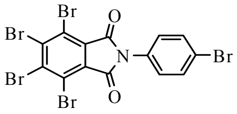
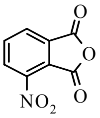
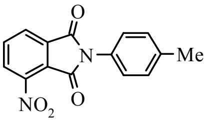
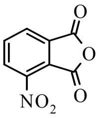
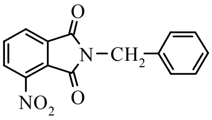
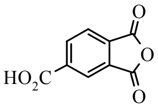
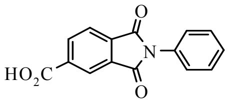
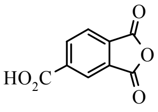
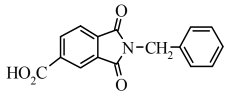
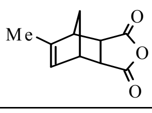
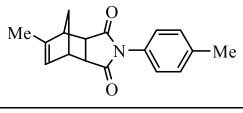
Imines with an aryl or a benzyl group on nitrogen (Schiff bases), are stable to oxygen and water. They are readily prepared and are promising starting materials in biologically important systems and hence attract broad interest. Due to their diverse reactivity, imines are common substrates in a wide variety of transformations. For example, they are used in synthesis of $\beta$-lactams,[1] aziridines,[2] 1,2-amino alcohols,[3] 1,3-oxazolidines[4] and cycloaddition reactions.[5]

It is possible to make the $\alpha$-carbon of the aldehyde adds to the carbonyl carbon of the ketone, by using an imine instead of an aldehyde.[6] Furthermore, the reaction of imines with a wide range of carbon nucleophiles[7] has been known. To extend our previous works on the synthesis of five member cyclic imides,[8] here, we wish to report the use of Schiff bases as expedient substrates in the preparation of *N*-substituted 1*H*-isoindole-1,3-(2*H*)-diones. We observed that in the presence of suitable electrophiles such as cyclic anhydrides, imines can react as amine functional groups, by removing of the aldehydes or the ketones *in-situ* without need to hydrolysis. The reaction procedure is simple, and the reaction conditions are mild.[9] The cyclic imides **3** are efficiently and rapidly formed from the reaction of cyclic anhydrides **2** with Schiff bases **1** in EtOH or DMF without need to use any catalyst (Scheme 1). Results are summarized in Table 1.



**Scheme 1**

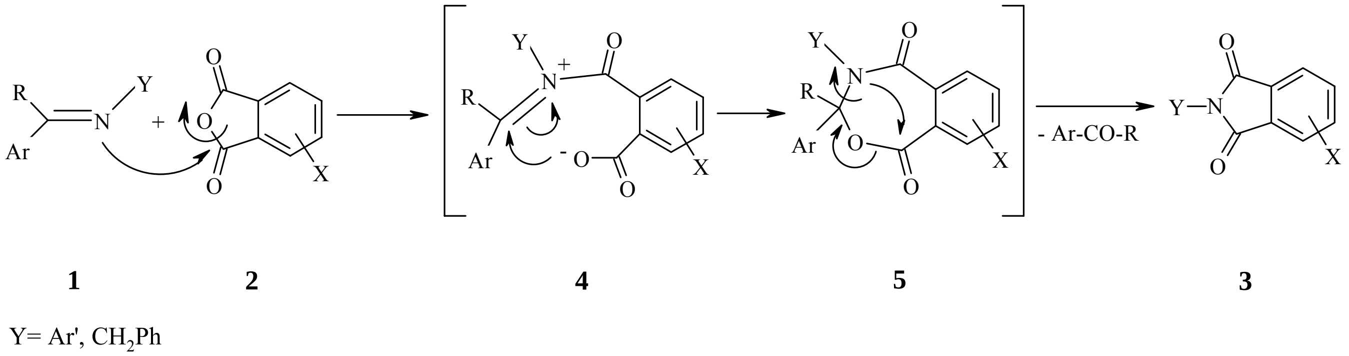
**Table 1.** Reaction of Schiff bases **1** with cyclic anhydrides **2** in EtOH

| | Ar | Y | R | **2** | Time/h | **3** | Yield /%[a,b] | Mp/°C (lit.) |
|---|---|---|---|---|---|---|---|---|
| **a** | *p*-ClPh | Ph | H |  | 3 |  | 95 | 205-207<br>(205-206[10]) |
| **b** | Ph | *p*-MePh | H |  | 3 |  | 90 | 201-203<br>(201-203[11]) |
| **c** | Ph | $PhCH_2$ | H |  | 3 |  | 90 | 116-118<br>(118.5-119.5[12]) |
| **d** | Ph | $PhCH_2$ | Me |  | 3 |  | 85 | 115-118<br>(118.5-119.5[12]) |
| **e** | *p*-ClPh | Ph | H |  | 1.5 |  | 85 | 277-279<br>(280[13]) |
| **f** | *p*-MePh | *p*-BrPh | Me |  | 1 |  | 92 | >250<br>(>380[13]) |
| **g** | Ph | *p*-MePh | H |  | 3 |  | 80 | 152-154<br>(155-156[14]) |
| **h** | Ph | $PhCH_2$ | H |  | 3 |  | 85 | 140-142<br>(142-143[14]) |
| **i** | Ph | Ph | H |  | 1.5 |  | 75 | >250<br>(>260[15]) |
| **j** | Ph | $PhCH_2$ | H |  | 3 |  | 80 | 198-201<br>(200-202[15]) |
| **k** | Ph | *p*-MePh | H |  | 4 |  | 95 | - |

[a] The products were identified and characterized by their physical and spectral data and comparison of them with those of authentic samples. [b] Isolated yield.

This strategy can be suitable, particularly, in the presence of sensitive substituents which may react with amines (Table 1, **2i** and **2j**). Also, some aromatic amines, especially those containing electron donating substituents are unstable and are easily oxidized or polymerized and purification of them is a tedious effort. However, the use of Schiff bases instead of the mentioned amines is more suitable.

The proposed mechanism is shown in Scheme 2. It is reasonable to assume that **3** results from an initial addition of Schiff base **1** to the anhydride **2** and subsequent cyclization of the unstable intermediate **4** to the intermediate **5**. Recyclization of **5** under the reaction conditions employed leads to the cyclic imides **3** with removing of the corresponding aryl aldehyde or aryl ketone.



**Scheme 2**

In conclusion, stable imines to hydrolysis (Schiff bases) are proposed as masked amines in the synthesis of *N*-substituted 1*H*-isoindole-1,3-(2*H*)-diones. The reactions are carried out under mild reaction condition without need to use any catalysts. Good to high yields of the products are obtained with easy work-up. The use of Schiff bases as suitable replacing substrates instead of the corresponding amines is an improvement over previous methods.

## ACKNOWLEDGEMENTS

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9. *General reaction procedure:* In a 10 mL round flask, 1 mmol of **1** was dissolved in 2 mL of EtOH. To this solution, 1 mmol of cyclic anhydrides **2** was added and the mixture was refluxed for the times as indicated in Table 1. Then, the solvent was removed under reduced pressure and the residue was washed with cold MeOH and dried in air. For more purification, the products were crystallized from MeOH or EtOH.

   *Note:* Because of the imine-enamine equilibrium, the aldehydes that are used in the synthesis of the imines **1** (Ar groups) should not have C-$H_\alpha$, therefore, aliphatic aldehydes are not suitable here. Also, due to the steric hindrance and the enamine formation, the R groups larger than methyl, are not suitable in this synthesis route.

   **Compound 3k:** IR (Liquid film): $\bar{\nu}$ ($cm^{-1}$) = 1772, 1704; $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$(ppm) = 7.12 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar-H), 6.97 (d, $^3J_{HH}$ = 8.2 Hz, 2H, Ar-H), 5.83 (bs, 1H, =CH), 3.43-3.40 (m, 2H, 2CH), 2.88-2.85 (m, 2H, 2CH), 1.83 and 1.81 (2s, 6H, $2CH_3$), 1.65-1.43 (m, 2H, $CH_2$); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): $\delta$(ppm) = 178.6, 177.5, 148.0, 132.1, 129.8, 127.1, 126.4, 126.2, 50.2, 49.6, 47.2, 45.7, 42.5, 16.6, 15.3; EI-MS (70 eV): *m/z* (%) = 267 ($M^{+\cdot}$, 18).

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