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# Synthesis of different isoindolone embedded heterocycles with phenolic subunits from a common intermediate, 3-(2′-hydroxyaroyl)-2, 3-dihydroisoindol-1-ones

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**ABSTRACT**

A series of biologically important isoindolone embedded heterocycles such as tetracyclic 2,4-diamino-5-aryl-10-oxo-10*H*-1,10a-diazaindeno[2,1-*a*]indene-3-carbonitriles and tricyclic 1-aryl-3,5-dioxo-1*H*-imidazo-[3,4-*b*]isoindoles have been synthesized from an easily derived common intermediate, 3-(2′-hydroxyaroyl)-2,3-dihydroisoindol-1-ones. The significant advantages of the present methodologies are the use of simple and easily available starting materials and reagents, operational simplicity and good yields of the products with high atom-economy.

*Keywords:* Fused isoindolones, Ninhydrin adducts, Microwave heating, Condensation reactions, Heterocycles.

Isoindole and its derivatives are used as scaffolds for synthesis of diverse range of biologically active molecules.[1,2] Among these the isoindolone fused tetracyclic heterocycle **A**

possesses intrinsic anticancer activity[3] and heterocycle **B** shows high sub-nanomolar affinity for the melatonin binding site MT3[4] (Fig. 1). Moreover isoindolone fused heterocycle **C** shows the ability to bind to the nNK1 receptor[5] (Fig. 1). Heterocycle **C** can also be employed as a precursor for the synthesis of NorA efflux pump inhibitors.[6] Recently medicinal research on these tetracyclic heterocycles (**A**-**C**) reveals that they have antibacterial and antifungal activity.[7] Further studies also show that they have antiproliferative effects against HT-29 and L1210 cell lines.[8]

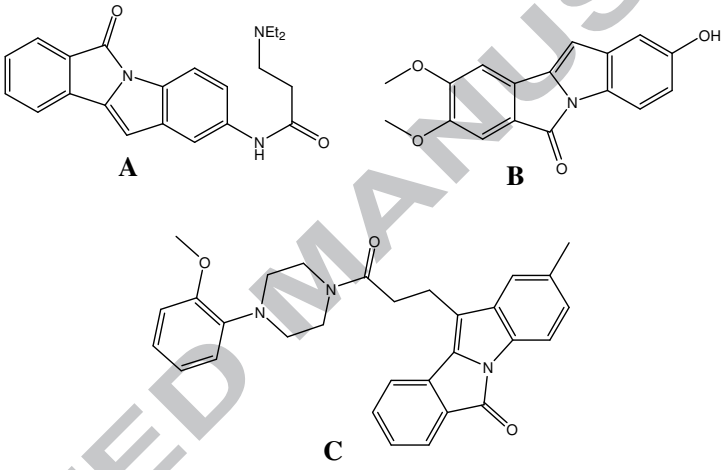


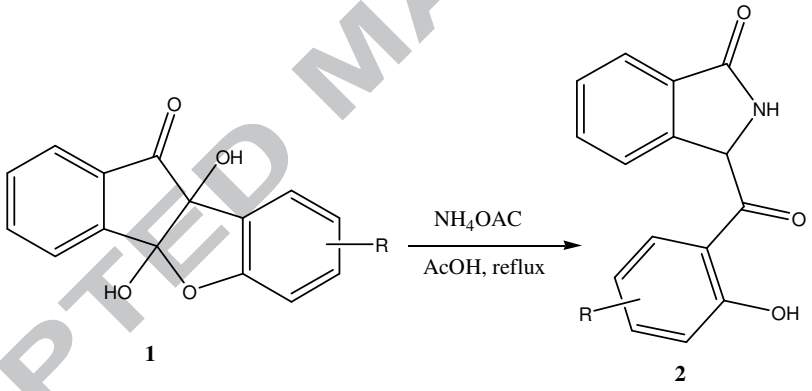

**Figure 1.** Biologically important heterocycles **A**-**C**

Imidazolone based heterocycles are prevalent in many natural products and also play an important role in various biochemical processes.[9] Generally they are used as building blocks in the development of various drugs such as COX-2 inhibitors,[10a] anti-inflammatory,[10b] anticancer,[10c,d] cardioactive agents[10e] and angiotensin II receptor antagonists[10f]. The use of imidazoisoindolone based orally active drugs for the treatment of respiratory syncytial virus (RSV) has been explored extensively.[11] Therefore, simple and efficient synthesis of isoindolone fused imidazolones and other heterocycles similar to tetracyclic **A**-**C** (Fig. 1), substituted with different functional groups is important for further biological evaluation. As part of our research

interest for the synthesis of bio-active compounds from ninhydrin,[12] we wish to report herein some general and efficient methodologies for the synthesis of isoindolone embedded heterocycles with diverse functional groups from easily available starting materials.

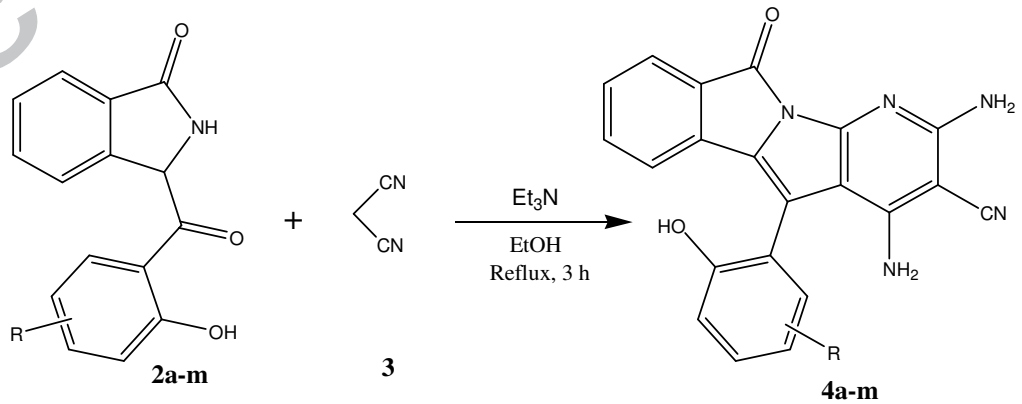
Recently we have reported that refluxing a mixture of ninhydrin adducts of phenols **1** and ammonium acetate in acetic acid produces 3-(2′-hydroxyaroyl)-2,3-dihydroisoindol-1-ones **2** in good yield (Scheme 1).[12a] Further it has been shown that the compound **2** can be utilized successfully in the synthesis of a series of novel spiro isoindoles.[12a] This result incited us for exploring the potential of adduct **2** as an intermediate in the synthesis of various isoindolone embedded heterocycles. Several examples show that both the active methylene group and cyano group of malononitrile (**3**) can participate in various reactions to form variety of addition products and heterocyclic compounds.[13] Therefore, considering the presence of electrophilic and nucleophilic functionalities in adduct **2** we choose malononitrile as a potential reactant for condensation with **2**. Interestingly when a mixture of compound **2d** (R = *p*-$CH_3$ with respect to phenolic –OH) and malononitrile was refluxed in ethanol in presence of base triethylamine, a new tetracyclic compound 2,4-diamino-5-aryl-10-oxo-10*H*-1,10a-diazaindeno[2,1-*a*]indene-3-carbonitrile **4d** was formed within 3 h (Scheme 2).[14] With the result in hand we then attempted to optimize the reaction condition to achieve maximum yield of the product. The reaction between compound **2d** and malononitrile **3** was chosen for the survey of the reaction. When the reaction was carried out under solvent-free condition without using any catalyst, no product was formed on heating (Table 1, entry 1). Subsequently the reaction was carried out in water with the base triethylamine, but still no desired product was formed (Table 1, entry 2). Probably the low solubility of **2d** in water hindered the reaction. However, refluxing a mixture of **2d** (1.0 mmol) and malononitrile (3.0 mmol) in ethanol (5.0 mL) in presence of triethylamine (0.5 equiv)

produced the desired product **4d** in good yield (Table 1, entry 3). After that we varied the amount of triethylamine in the reaction (Table 1, entry 4 and 5) and observed that minimum 0.5 equiv of triethylamine was required to get maximum yield of the product **4d**. Then we employed various other solvents like MeOH, $CH_3CN$ and DMF (Table 1, entries 6, 7 and 8), among which ethanol appeared to be the best solvent. We also used various organic bases like piperidine, pyridine, pyrrolidine and triethanolamine (Table 1, entries 9-12) but triethylamine produced the best result as a catalyst of the reaction (Table 1, entry 3). Various inorganic bases were also used in the reaction but it was observed that in presence of strong bases such as KOH and NaOH, the adduct **2d** totally decomposed without producing **4d** (Table 1, entries 13 and 14). Mild inorganic bases such as $Cs_2CO_3$ and $K_2CO_3$ produced **4d** in very low yield, 12-15% (Table 1, entries 15 and 16).




**1** **2**

**Scheme 1.** Synthesis of 3-(2′-hydroxyaroyl)-2,3-dihydroisoindol-1-ones **2** from adducts **1**.




**2a-m** **3** **4a-m**

**Scheme 2.** Synthesis of 2,4-diamino-5-aryl-10-oxo-10*H*-1,10a-diazaindeno[2,1-*a*]indene-3-carbonitriles **4** from intermediates **2**.

**Table 1** Optimization of reaction condition for the synthesis of **4d** from intermediate **2d**[a]

| Entry | Amount of catalyst load (equiv) | Catalyst | Solvent (5.0 ml) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | – | – | – | 12 | – |
| 2 | 0.5 | $Et_3N$ | $H_2O$ | 12 | – |
| **3** | **0.5** | **$Et_3N$** | **EtOH** | **3** | **75** |
| 4 | 0.2 | $Et_3N$ | EtOH | 3 | 28 |
| 5 | 1.0 | $Et_3N$ | EtOH | 3 | 75 |
| 6 | 0.5 | $Et_3N$ | MeOH | 3 | 62 |
| 7 | 0.5 | $Et_3N$ | $CH_3CN$ | 3 | 60 |
| 8 | 0.5 | $Et_3N$ | DMF | 3 | 57 |
| 9 | 0.5 | piperidine | EtOH | 3 | 67 |
| 10 | 0.5 | pyridine | EtOH | 3 | 59 |
| 11 | 0.5 | pyrrolidine | EtOH | 3 | 69 |
| 12 | 0.5 | triethanolamine | EtOH | 3 | 36 |
| 13 | 0.5 | KOH | EtOH | 3 | –[c] |
| 14 | 0.5 | NaOH | EtOH | 3 | –[c] |
| 15 | 0.5 | $Cs_2CO_3$ | EtOH | 3 | 15 |
| 16 | 0.5 | $K_2CO_3$ | EtOH | 3 | 12 |

[a] 1.0 mmol of **2d** and 3.0 mmol of malononitrile were used in all reactions.

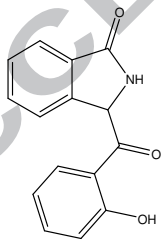
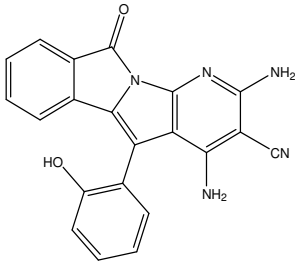
[b] isolated yield of **4d**.

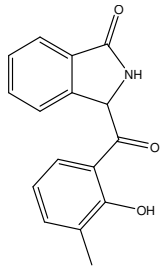
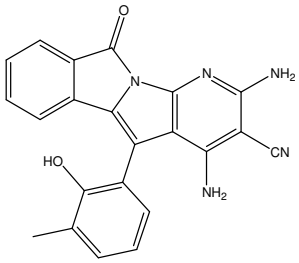
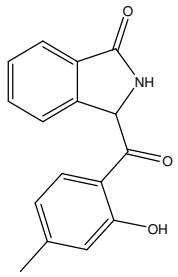
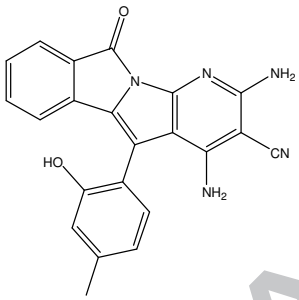
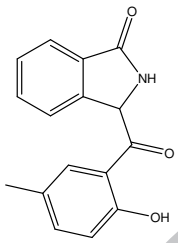
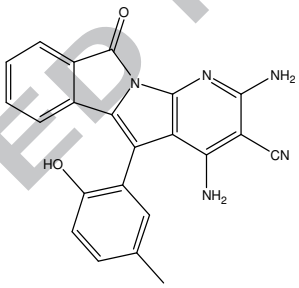
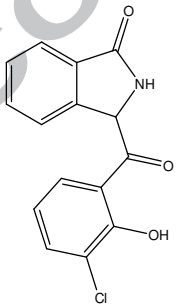
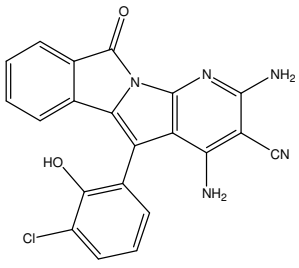
[c] decomposition of the adduct **2d** occurred.

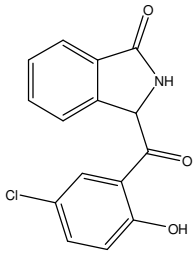
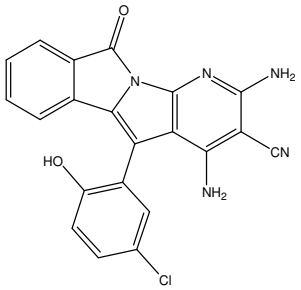
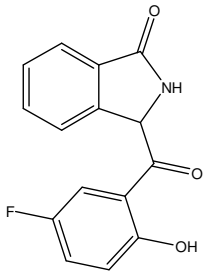
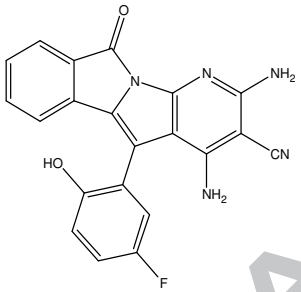
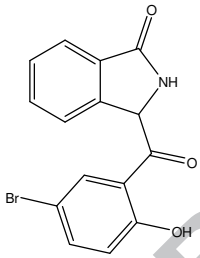
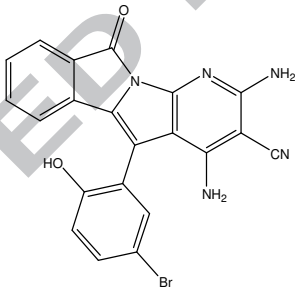
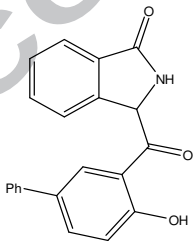
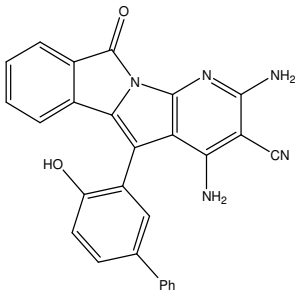
After optimization of the reaction condition, we assessed the scope and generality of the reaction by employing various adducts **2** with a variety of electron donating and electron

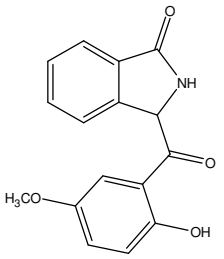
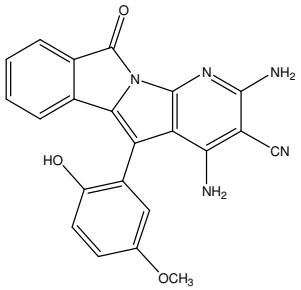
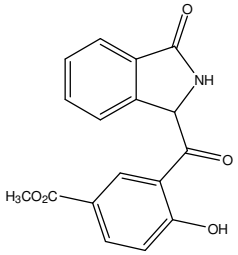
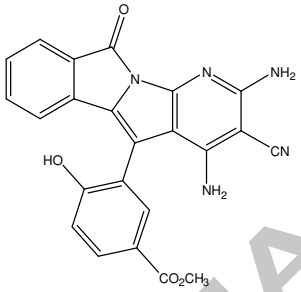
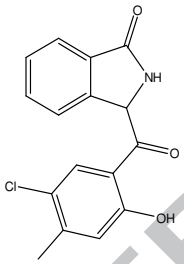
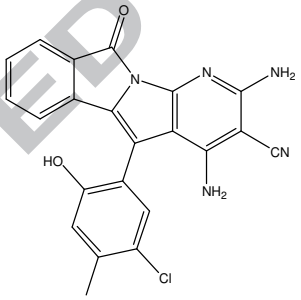
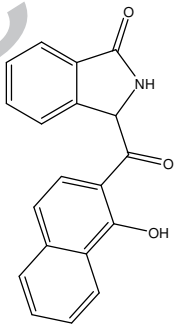
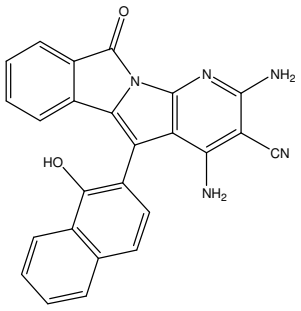
withdrawing substituents in the phenolic group. The results are summarized in Table 2 which shows that it is a very general reaction with high yields of products **4**. All the products were fully characterized by $^{1}H$ and $^{13}C$ NMR and elemental analyses. Further, elucidation of the crystal structure of compound **4l** confirmed the formation of isoindolone fused tetracyclic heterocycles substituted with consecutive donor(-$NH_2$)-acceptor(-CN)-donor(-$NH_2$) and various phenolic groups (Fig. S1).[15] On the basis of previous reports [16] a plausible mechanism for the formation of compound **4** is depicted in Scheme 3. The process comprises a cascade of reactions with an initial base catalyzed Knoevenagel condensation between compound **2** and malononitrile to furnish intermediate **5**. Subsequently another molecule of malononitrile attacks the nitrile group of intermediate **5** to produce intermediate **6**. Then intermediate **6** undergoes tandem cyclization followed by tautomerization and aromatization to furnish the final compound **4**. It was not possible to isolate any of the intermediates under the reaction conditions.

**Table 2** Synthesis of 2,4-diamino-5-aryl-10-oxo-10*H*-1,10a-diazaindeno[2,1-*a*]indene-3-carbonitriles **4** from intermediates **2**

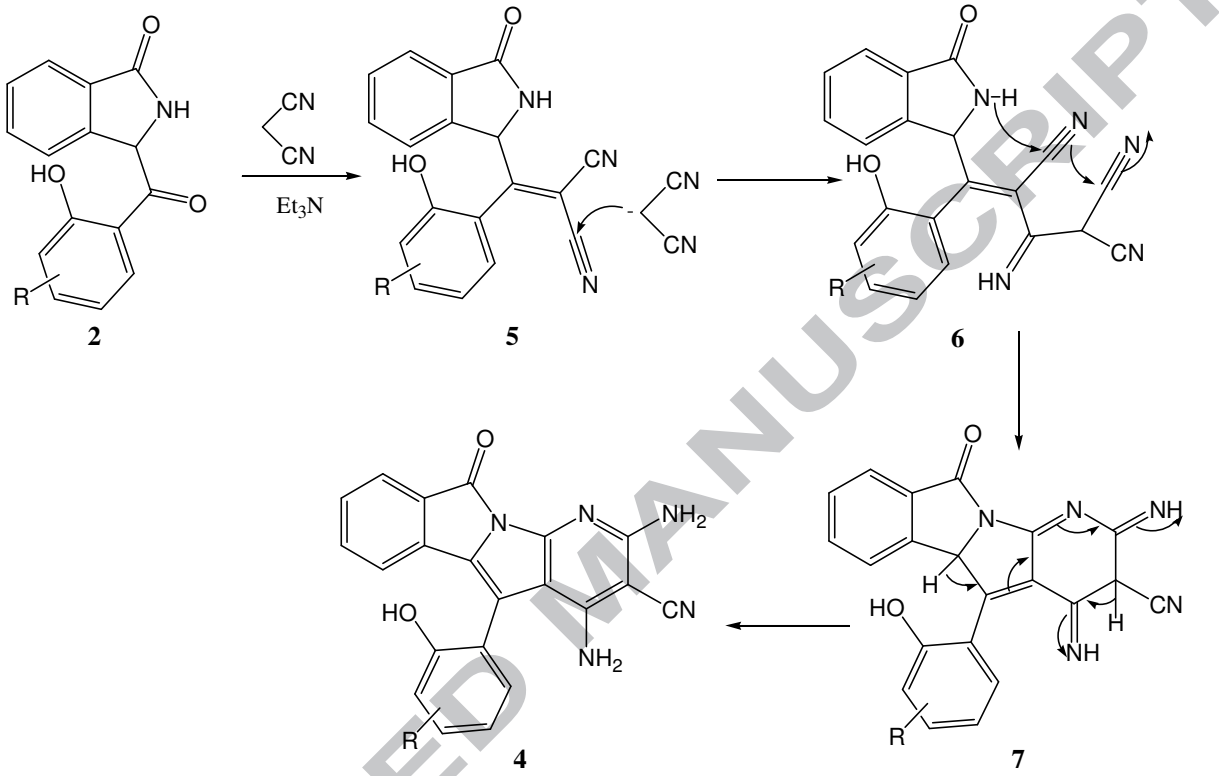
| Entry | Adduct (**2**)[a] | Product (**4**) | Time (h) | Yield (%)[b] | Melting Point (°C) |
|---|---|---|---|---|---|
| 1 |  **2a** |  **4a** | 3 | 78 | > 320 |

| | | | | | |
|---|---|---|---|---|---|
| 2 |  **2b** |  **4b** | 3 | 73 | > 320 |
| 3 |  **2c** |  **4c** | 3 | 71 | > 320 |
| 4 |  **2d** |  **4d** | 3 | 75 | > 320 |
| 5 |  **2e** |  **4e** | 3 | 70 | > 320 |

| | | | | | |
|---|---|---|---|---|---|
| 6 |  **2f** |  **4f** | 3 | 72 | > 320 |
| 7 |  **2g** |  **4g** | 3 | 75 | > 320 |
| 8 |  **2h** |  **4h** | 3 | 73 | > 320 |
| 9 |  **2i** |  **4i** | 3 | 75 | > 320 |

| | | | | | |
|---|---|---|---|---|---|
| 10 |  **2j** |  **4j** | 3 | 71 | > 320 |
| 11 |  **2k** |  **4k** | 3 | 74 | > 320 |
| 12 |  **2l** |  **4l** | 3 | 73 | > 320 |
| 13 |  **2m** |  **4m** | 3 | 70 | > 320 |

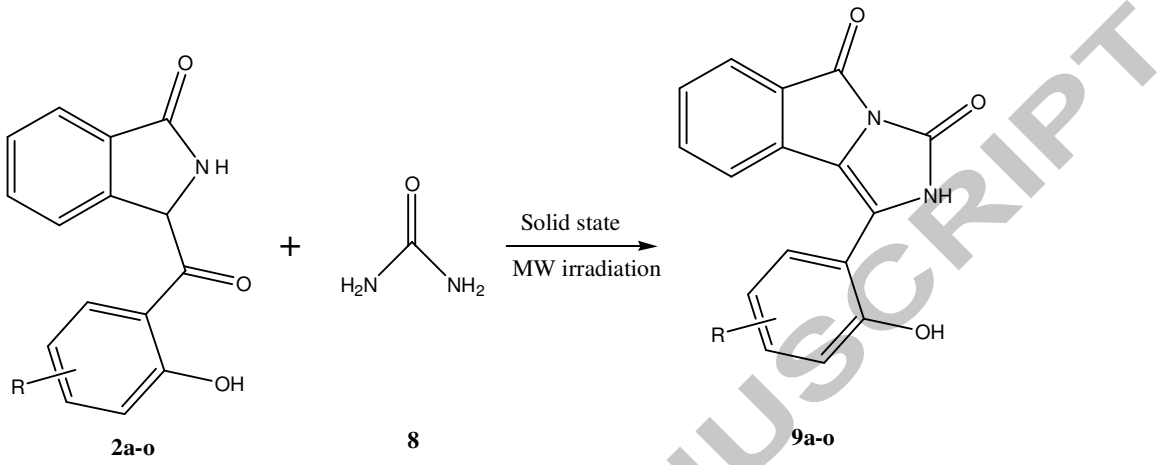
[a] unpurified compounds **2** were used in all reactions.[12a]
[b] isolated yields w. r. t. adducts **1**.




**Scheme 3.** Plausible mechanism for the formation of compounds **4**

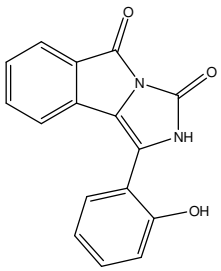
Microwave assisted organic synthesis (MAOS) under solvent-free condition is a popular methodology which serves the purpose of green chemistry.[17] Therefore after successful synthesis of compounds **4a-m** we attempted to carry out another condensation reaction by heating a solid mixture of compound **2** and urea (**8**) under microwave irradiation (Scheme 4). Interestingly a series of yellow solid products were isolated from these reactions in good yield within 20-35 min. The products were characterized by $^{1}$H and $^{13}$C NMR spectroscopy and found to be 1-aryl-3,5-dioxo-1*H*-imidazo-[3,4-*b*]isoindoles **9a**-**o**, the condensation products of intermediates **2** and

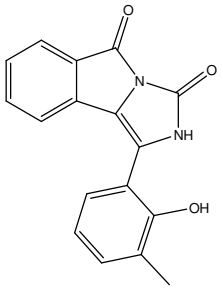
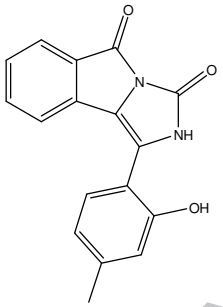
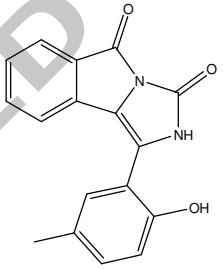
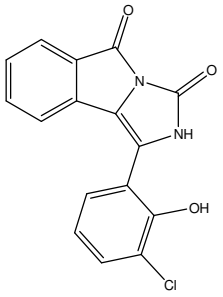
urea (Scheme 4, Table 3).[14] Determination of the X-ray crystal structure further confirmed the formation of product **9d** (Fig. S2).[15]

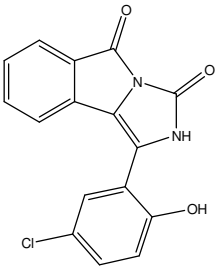
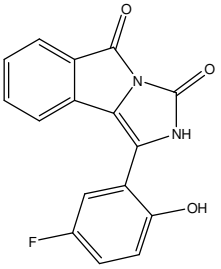
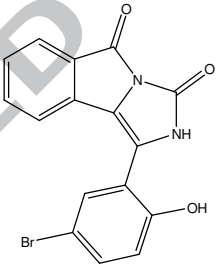
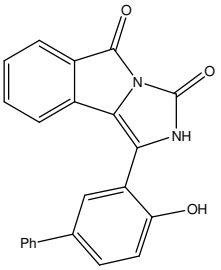


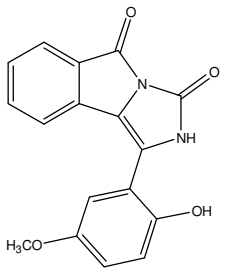
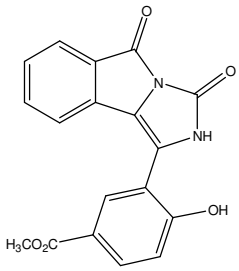
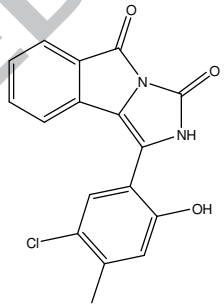
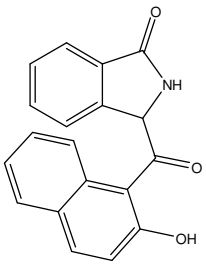
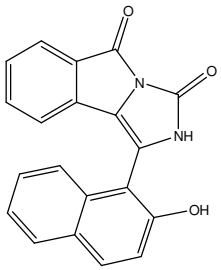

**Scheme 4.** Synthesis of 1-aryl-3,5-dioxo-1*H*-imidazo-[3,4-*b*]isoindoles **9** from intermediates **2**

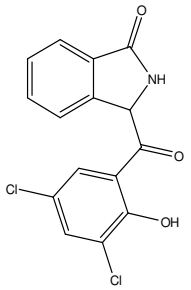
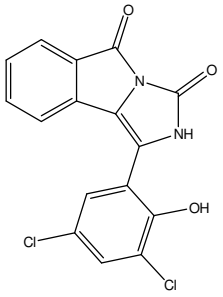
**Table 3** Synthesis of 1-aryl-3,5-dioxo-1*H*-imidazo-[3,4-*b*]isoindoles **9** from intermediates **2**

| Entry | Adduct (**2**)[a] | Product (**9**) | Time (min) | Yield (%)[b] | Literature m.p[12i] / Observed mp (ºC) |
|---|---|---|---|---|---|
| 1 | **2a** |  **9a** | 20 | 75 | 305-307 /302-304 |
| | | | | | 254-256 |

| | | | | | |
|---|---|---|---|---|---|
| 2 | **2b** |  **9b** | 20 | 77 | /252-253 |
| 3 | **2c** |  **9c** | 20 | 71 | 221-222 /219-221 |
| 4 | **2d** |  **9d** | 20 | 73 | 289-291 /287-288 |
| 5 | **2e** |  **9e** | 25 | 75 | 274-275 /270-272 |

| | | | | | |
|---|---|---|---|---|---|
| 6 | **2f** |  **9f** | 25 | 69 | 308-310 /303-305 |
| 7 | **2g** |  **9g** | 25 | 70 | >320 |
| 8 | **2h** |  **9h** | 20 | 68 | 306-307 /302-304 |
| 9 | **2i** |  **9i** | 20 | 67 | 310-311 |

| | | | | | |
|---|---|---|---|---|---|
| 10 | **2j** |  **9j** | 35 | 64 | 298-300 /295-297 |
| 11 | **2k** |  **9k** | 30 | 67 | 314-316 /311-313 |
| 12 | **2l** |  **9l** | 30 | 65 | 316-318 /313-315 |
| 13 |  **2n** |  **9n** | 30 | 64 | 295-297 |

| | | | | | |
|---|---|---|---|---|---|
| 14 |  **2o** |  **9o** | 35 | 67 | >320 |

[a] unpurified compounds **2** were used in all reactions.[12a]
[b] isolated yields w. r. t. adducts **1**.

Previously the series of compounds **9a**-**o** were also synthesized in our laboratory by refluxing the ninhydrin adducts of phenols **1** and urea in acetic acid for 2.5-8 h.[12i] The present method produces compounds **9** in comparable yield to that of the previous method[12i] within a shorter period of time (~ 2.0 h) in two steps starting from ninhydrin adducts of phenols **1** via intermediate **2**. Further isolation and charaterization of intermediate **2**[12a] and direct condensation of **2** with urea under solvent-free condition provide insights about the mechanistic pathway for the formation of compound **9**, which was not possible previously. Compounds **9** show interesting photophysical property and are being used as fluorescence marker in various biochemical and photochemical processes.[12i, 18]

In conclusion, we have successfully developed some simple and efficient methodologies for the synthesis of potentially bioactive isoindolone embedded heterocycles such as tetracyclic 2,4-diamino-5-aryl-10-oxo-10*H*-1,10a-diazaindeno[2,1-*a*]indene-3-carbonitriles and tricyclic 1-aryl-3,5-dioxo-1*H*-imidazo-[3,4-*b*]isoindoles from an easily derived common intermediate. The microwave assisted synthesis of tricyclic heterocycles through the condensation of this intermediate with urea under solvent-free condition is environmentally friendly. The present

methodologies will be useful to organic and pharmaceutical chemists due to simple and easily available starting materials and reagents, good yields of the products, high atom-economy and operational simplicity.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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14. **Typical procedure for the preparation of compound 4d from adduct 2d:** A mixture of crude adduct **2d** (obtained from 1.0 mmol of ninhydrin adduct of *p*-cresol, **1d**)[12a], malononitrile (3.0 mmol w. r. t. **1d**) and triethylamine (0.5 mmol w. r. t. **1d**) in ethanol (5

mL) was refluxed for 3 h. The yellow solid was precipitated out from the reaction mixture on cooling. The solid was filtered and washed with cold alcohol to get the pure compound **4d**.

*2,4-diamino-5-(2'-hydroxy-5'-methylphenyl)-10-oxo-10H-1,10a-diazaindeno[2,1-a] indene-3-carbonitrile* (**4d**): Yellow solid, mp > 320°C; IR (KBr): 1643, 2206, 3341 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 9.78 (s, 1H), 7.73 (d, *J* =7.5 Hz, 1H), 7.50 (t, *J* =7.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.21-7.16 (m, 2H), 6.99-6.97 (m, 2H), 6.81 (s, 2H), 5.83 (s, 2H), 2.27 (s, 3H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 161.2, 161.0, 153.2, 153.1, 149.1, 134.9, 134.5, 131.8, 131.6, 131.5, 128.9, 128.6, 128.1, 125.7, 121.2, 120.7, 118.3, 116.8, 115.3, 104.0, 71.0, 20.4; Anal. calcd for $C_{22}H_{15}N_5O_2$: C, 69.28; H, 3.96; N, 18.36 % found C, 69.12; H, 3.89; N, 18.28 %.

*2,4-diamino-5-(3'-chloro-2'-hydroxyphenyl)-10-oxo-10H-1,10a-diazaindeno[2,1-a] indene-3-carbonitrile* (**4e**): Yellow solid, mp > 320°C; IR (KBr): 1634, 2202, 3396 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) δ: 9.72 (s, 1H), 7.67 (d, *J* =7.5 Hz, 1H), 7.51-7.42 (m, 2H), 7.35-7.24 (m, 2H), 6.97 (t, *J* =7.8 Hz, 1H), 6.83 (d, *J* =7.8 Hz, 1H), 6.76 (s, 2H), 5.67 (s, 2H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 161.2, 161.0, 152.8, 151.2, 149.2, 135.1, 134.2, 131.8, 131.4, 130.1, 129.5, 128.4, 125.8, 122.2, 121.4, 121.1, 120.7, 116.8, 113.4, 103.7, 71.0; Anal. calcd for $C_{21}H_{12}N_5O_2Cl$: C, 62.77; H, 3.01; N, 17.43 % found C, 62.59; H, 2.94; N, 17.34 %.

**Typical procedure for the preparation of compound 9g from adduct 2g:** A solid mixture of crude adduct **2g** (obtained from 1.0 mmol of ninhydrin adduct of *p*-fluoro-phenol, **1g**)[12a] and urea (5.0 mmol w. r. t. **1g**) was heated under MW irradiation at 150 watt (temp. 123 $^oC$) for 25 min in an open vial (a BPL oven, Model No. BMO 800 TS

was used). After the completion of the reaction (monitored by TLC) cold water was added to the reaction mixture, extracted with ethylacetate and concentrated under reduced pressure. The crude mass obtained was purified through column chromatography (EtOAc/Hexane) to get the pure compound **9g**.

*1-(5'-fluoro-2'-hydroxyphenyl)-3,5-dioxo-1H-imidazo[3,4-b]isoindole* (**9g**): Yellow solid, mp > 320°C; IR (KBr): 1670, 1750, 3274 $cm^{-1}$; $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.90 (bs, 1H), 10.45 (bs, 1H), 7.81 (d, J=7.5 Hz, 1H), 7.68 (t, J=7.5 Hz, 1H), 7.44-7.39 (m, 2H), 7.31-7.17 (m, 2H), 7.07-7.02 (m, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$, F coupled $^{13}C$) δ: 160.7, 157.0, 153.9, 151.9, 147.7, 134.6, 132.3, 131.2, 127.8, 125.7, 122.9, 119.4, 118.3, 117.9, 117.8, 115.9, 115.8, 115.6; Anal. calcd for $C_{16}H_9N_2O_3F$: C, 64.87; H, 3.06; N, 9.46 % found C, 64.69; H, 2.98; N, 9.35 %.

*1-(3',5'-dichloro-2'-hydroxyphenyl)-3,5-dioxo-1H-imidazo[3,4-b]isoindole* (**9o**): Yellow solid, mp > 320 °C; IR (KBr): 1690, 1761, 3279 $cm^{-1}$; $^{1}H$ NMR (300 MHz, DMSO-$d_6$) δ: 10.93 (bs, 1H), 10.46 (bs, 1H), 7.83 (d, J=7.5 Hz, 1H), 7.71-7.67 (m, 2H), 7.56 (s, 1H), 7.51-7.46 (m, 1H), 7.30 (d, J=7.8 Hz, 1H); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) δ: 160.7, 150.2, 147.6, 134.9, 131.9, 131.2, 130.8, 128.5, 128.1, 125.8, 124.0, 123.5, 122.5, 119.3, 118.8, 118.0; Anal. calcd for $C_{16}H_8N_2O_3Cl_2$: C, 55.36; H, 2.32; N, 8.07 % found C, 55.19; H, 2.25; N, 7.98 %.

15. Crystallographic data for the structure **4l** and **9d** in this Letter have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 962749 and CCDC 972301, respectively. Copies of the data can be obtained, free of charge via the website www.ccdc.cam.ac.uk/data_request/cif.

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## Graphical Abstract

# Synthesis of different isoindolone embedded heterocycles with phenolic subunits from a common intermediate, 3-(2′-hydroxyaroyl)-2, 3-dihydroisoindol-1-ones

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