Tetrahedron Letters 55 (2014) 4466–4474

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Ashis Kundu, Animesh Pramanik *

Department of Chemistry, University of Calcutta, 92, A.P.C. Road, Kolkata 700 009, India

ARTICLE INFO

Article history:
Received 5 May 2014
Revised 13 June 2014
Accepted 14 June 2014
Available online 20 June 2014

Keywords:
Fused isoindolones
Ninhydrin adducts
Microwave heating
Condensation reactions
Heterocycles

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.

Isoindole and its derivatives are used as scaffolds for the synthesis of a 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 subnanomolar 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]

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.

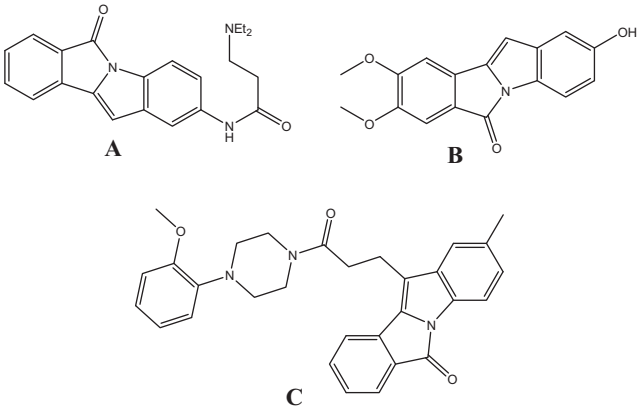
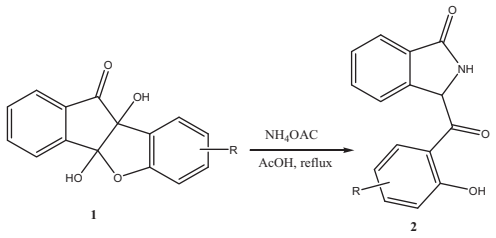


Figure 1. Biologically important heterocycles **A**–**C**.

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

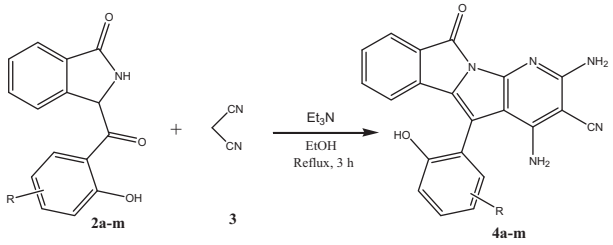
* Corresponding author. Tel.: +91 33 2484 1647; fax: +91 33 2351 9755.
E-mail address: animesh_in2001@yahoo.co.in (A. Pramanik).

http://dx.doi.org/10.1016/j.tetlet.2014.06.064
0040-4039/



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

yield (Scheme 1).[12a] Further it has been shown that 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 a 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 the 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



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**.

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 the 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, entries 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 6–8), 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 the 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).

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 ^1H 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 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

The bold value signifies the optimized reaction condition.
[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.