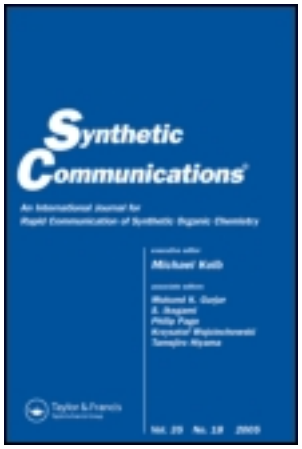

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Green and Catalyst-Free One-Pot Synthesis of Anthranilamide Schiff Bases: An Approach Toward Sirtinol

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GREEN AND CATALYST-FREE ONE-POT SYNTHESIS OF ANTHRANILAMIDE SCHIFF BASES: AN APPROACH TOWARD SIRTINOL

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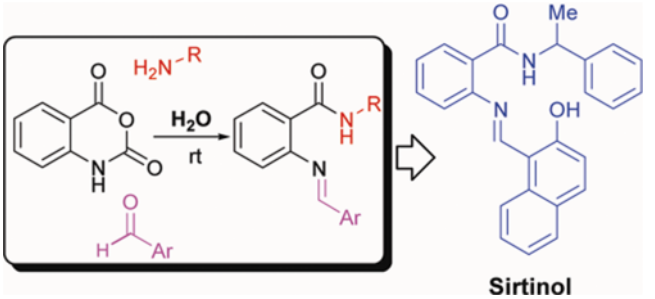
GRAPHICAL ABSTRACT



Abstract *A novel and simple method for the green one-pot synthesis of anthranilamide Schiff bases is described. The reported Schiff bases are obtained via the reaction of isatoic anhydride, amines, and aromatic aldehydes in water at room temperature, without using any catalysts. No cyclization toward 2,3-dihydro-4(1H)-quinazolinones occurred in this method and anthranilamide Schiff bases were produced exclusively. This approach offers a green method to prepare the medicinally important Schiff base sirtinol and other bioactive anthranilamide Schiff bases.*

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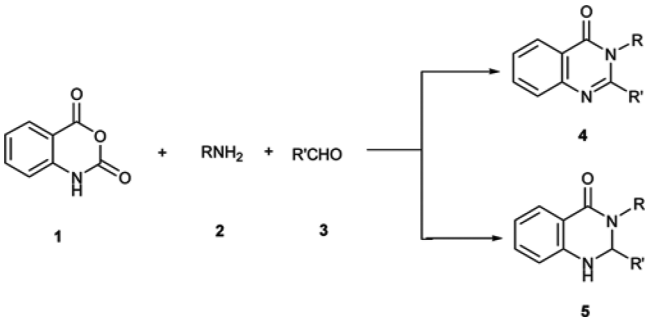
Keywords 2-Aryl-*N*-substituted-benzamides; isatoic anhydride; multicomponent reactions (MCRs); Schiff base

INTRODUCTION

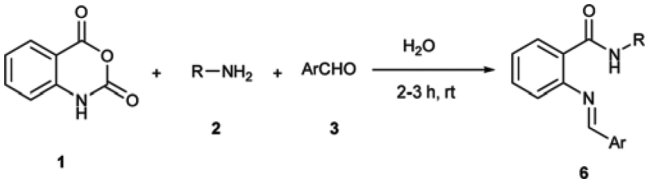
Isatoic anhydrides are generally used as useful building blocks in the synthesis of heterocyclic compounds such as quinazolinones, quinazolones, quinazolinediones, pyrroloquinazolones, benzimidazolones, and phthalimides with therapeutic interest.[1] Moreover, isatoic anhydrides are also used as intermediates in the synthesis of anthranilic acid and anthranilamide derivatives with various biological activities including anticancer,[2] VEGFR tyrosine kinase inhibitory,[3] factor Xa inhibitory,[4] and insecticidal activities.[5]

Multicomponent reactions (MCRs), because of their atom economy, simple procedures, straightforward reaction design, facile execution, and convergence, are some of the best tools in synthesis of organic compounds.[6] The utmost attribute of MCRs is the inherent formation of several bonds to construct complex molecules in one operation, ideally without isolation of intermediates.[7] These highly step-economical reactions are particularly appealing in the context of target-oriented synthesis. They also bear the promise of novelty in terms of process and compound-related intellectual property.[6]

In this context, three-component condensation of an isatoic anhydride, a primary amine, and an aromatic aldehyde has been widely investigated under a variety of catalysts such as *p*-TsOH,[8] silica sulfuric acid,[9] $Al(H_2PO_4)_3$,[10] $KAl(SO_4)_2 \cdot 12H_2O$ (alum),[11] $[bmim]BF_4$,[12] zinc perfluorooctanoate,[13] and gallium triflate.[14] Using these catalysts or other conditions[15] led to the formation of 4(3*H*)-quinazolinones **4** or 2,3-dihydro-4(1*H*)-quinazolinones **5** because of their stability (Scheme 1). To the best of our knowledge, there is no report for the production of another compound in this reaction. Following our research program on MCRs using isatoic anhydride as starting material,[16] we found that when the latter reaction is carried out at room temperature in water, surprisingly 4(3*H*)-quinazolinones **4** or 2,3-dihydro-4(1*H*)-quinazolinones **5** are not obtained, and instead the anthranilamide Schiff bases **6** are produced (Scheme 2).



Scheme 1. Three-component reaction of isatoic anhydride **1**, amines **2**, and aldehydes **3**.



Scheme 2. One-pot synthesis of anthranilamide Schiff bases **6**.

Accordingly, herein we present a novel synthetic method for the construction of anthranilamide Schiff bases **6** via a green three-component reaction involving commercially available starting materials.

RESULTS AND DISCUSSION

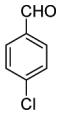
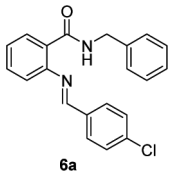
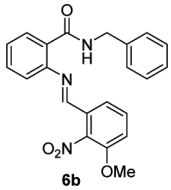
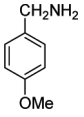
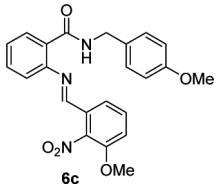
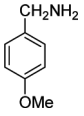
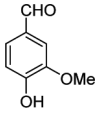
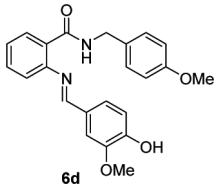
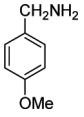
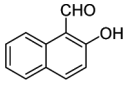
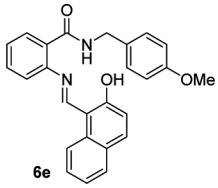
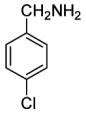
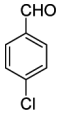
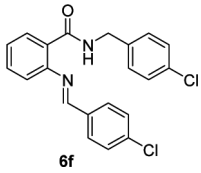
It is important to note that there is only one report for the synthesis of **6**, which is prepared by a multistep reaction from anthranilic acid using extensive and dangerous reagents such as thionyl chloride and pyridine.[17]

As shown in Scheme 2, a mixture of isatoic anhydride **1**, amine **2**, and aldehyde **3** undergoes a 1:1:1 addition reaction at ambient temperature in water to produce the corresponding anthranilamide Schiff bases **6a**–**m** in 65–92% yields (Table 1). All the reactions reached completion within 2–3 h. As shown in Table 1, the generality of the reaction toward various amines and benzaldehydes was explored. The results indicated that the direct three-component reactions worked well with aniline, benzylamine, furfurylamine, and substituted benzylamine. Also the reactions with a range of benzaldehydes carrying either electron-donating or withdrawing groups on the benzene ring afforded desired products in good yields.

The structures of the compounds **6** were deduced on the basis of infrared (IR), ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Representatively, the IR spectrum of **6h** showed absorptions at 3337 (NH), 1713 (strong, C=O) and 1633 (strong, C=N) cm^{-1}. The mass spectrum of **6h** displayed the molecular ion (M^{+}) peak at $m/z = 378$. The ^{1}H NMR spectrum of **6h** exhibited two singlet signals recognized as arising from CH of the imine and OMe groups ($\delta = 8.53$ and 3.56 ppm, respectively). One doublet signal at 4.50 ppm and one triplet signal at 9.34 ppm ($J = 5.5$ Hz) are due to the CH_2 and NH groups, respectively. Characteristic signals with appropriate chemical shifts and coupling constants for the 12 protons of the aromatic moieties were observed in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **6h** showed 18 distinct resonances, in agreement with the proposed structure.

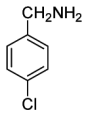
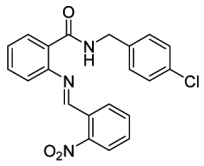
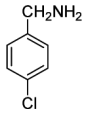
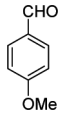
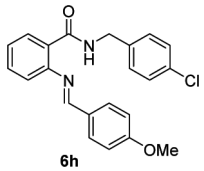
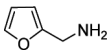
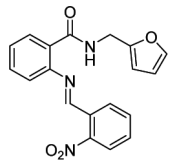
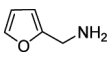
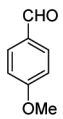
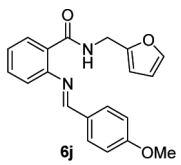
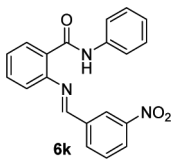
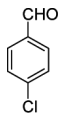
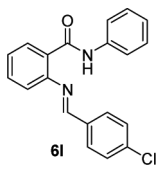
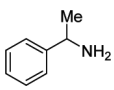
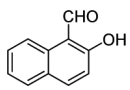
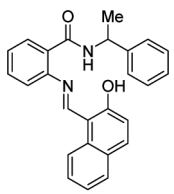
Among various Schiff bases reported here, sirtinol (Fig. 1) attracted our attention. Sirtinol, 2-((2-hydroxynaphthalen-1-yl)methyleneamino)-*N*-(1-phenylethyl)benzamide (**6m**), acts as a specific and a direct inhibitor of sirtuin class of histone deacetylase (HDAC) activity.[18] Synthesis of Schiff bases similar to sirtinol rarely has been discussed in the literature.[17,18] As shown in Table 1, when the reaction of an equimolar mixture of isatoic anhydride, 1-phenylethanamine, and 2-hydroxynaphthalene-1-carbaldehyde was conducted in water at room temperature, after 3 h the expected product, sirtinol (**6m**), was obtained in good yield (87%).

Table 1. Synthesis of anthranilamide Schiff bases **6a**–**h** by one-pot reaction of isatoic anhydride, an amine, and an aldehyde in water under catalyst-free conditions at room temperature

Entry	Amine **2**	Aldehyde **3**	Product **6**	Mp (°C)	Yield (%)
1			 **6a**	120–122	84
2			 **6b**	124–125	85
3			 **6c**	144–145	86
4			 **6d**	142–143	65
5			 **6e**	179–180	92
6			 **6f**	165–166	83

(*Continued*)

Table 1. Continued

Entry	Amine **2**	Aldehyde **3**	Product **6**	Mp (°C)	Yield (%)
7			 **6g**	113–114	83
8			 **6h**	156–157	70
9			 **6i**	112–113	80
10			 **6j**	131–132	75
11			 **6k**	144–146	75
12			 **6l**	167–168	82
13			 **6m (Sirtinol)**	220–222	87

[a]Isolated yields.

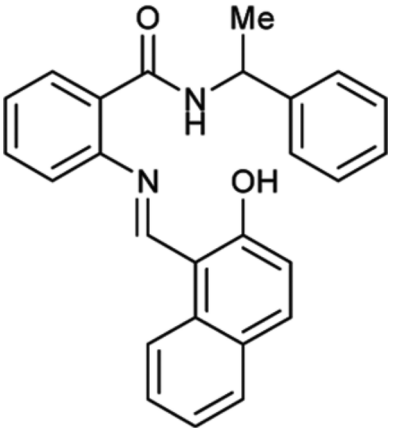
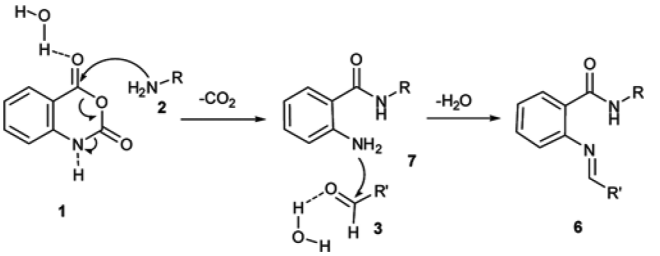


Figure 1. Structure of a medicinally important anthranilamide Schiff base, sirtinol.



Scheme 3. Proposed mechanism for the formation of **6**.

A mechanistic rationalization for this reaction is provided in Scheme 3. It is conceivable that initially isatoic anhydride **1** can convert to compound **7** via ring opening by nucleophilic attack of amine **2** to the carbonyl group, which then undergoes a decarboxylation. This generated anthranilamide could convert to the titled product **6** by simple condensation with aldehyde **3**.

A literature survey indicates that condensation of the aromatic aldehyde with the amino group of type **7** compounds in the presence of *p*-TsOH/DDQ,[19] I_2,[20] $FeCl_3$,[21] $CuCl_2$,[22] $TiCl_4$/Zn,[23] chiral phosphoric acid,[24] and ionic liquid/water[25] undergoes cyclization to afford the dihydroquinazoline product **5**. In our method, no cyclization toward 2,3-dihydro-4(1*H*)-quinazolinones occurred and anthranilamide Schiff bases were produced exclusively.

CONCLUSION

In conclusion, we have described a simple, highly efficient, and straightforward protocol for the exclusive synthesis of anthranilamide Schiff bases **6** in water at ambient temperature without using any catalysts. Furthermore, the procedure offers several advantages including simple experimental procedure, excellent yields of the products, clean reactions, simple workup, and low cost, which make it a useful and attractive strategy in the synthesis of the medicinally important Schiff base sirtinol.

EXPERIMENTAL

Melting points were taken on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker FT-500, using tetramethylsilane (TMS) as an internal standard. The infrared (IR) spectra were obtained on a Nicolet Magna FT-IR 550 spectrophotometer (KBr disks). Mass spectra were recorded on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus.

Synthesis of Anthranilamide Schiff Bases 6a–m

A mixture of isatoic anhydride (1 mmol), amine (1 mmol), and aromatic aldehyde (1 mmol) in H_2O (5 mL) was stirred at room temperature for 2–3 h. After the completion of reaction (checked by thin-layer chromatography, TLC), the precipitate was filtered off and recrystallized from ethanol to give the pure compound **6**.

2-(4-Chlorobenzylideneamino)-*N*-benzylbenzamide (6a)

Yield: 84%; mp 120–122 °C; IR (KBr): 3251, 3055, 2950, 2862, 1646, 1620, 1566 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): $\delta_H = 9.09$ (t, $J = 5.6$ Hz, 1H, NH), 8.61 (s, 1H, NCH), 7.86 (dd, $J = 7.7$, 1.5 Hz, 1H, ArH), 7.78 (d, $J = 8.5$ Hz, 2H, ArH), 7.55 (dd, $J = 7.7$, 1.5 Hz, 1H, ArH), 7.52 (d, $J = 8.5$ Hz, 2H, ArH), 7.38 (dt, $J = 7.7$, 1.5 Hz, 1H, ArH), 7.35–7.25 (m, 6H, ArH), 4.50 (d, $J = 5.6$ Hz, 2H, NCH_2); ^{13}C NMR (DMSO-d_6, 125 MHz,): $\delta_C = 165.9$, 161.2, 148.7, 139.0, 136.6, 134.3, 131.6, 130.6, 129.4, 129.0, 128.9, 128.3, 127.5, 126.9, 126.2, 119.2, 42.9; MS m/z (%) = 350 ($[M]^+ + 2$], 10), 348 ($[M]^+$, 30), 257 (100), 237 (61), 214 (42), 180 (41), 152 (31), 106 (80), 77 (35), 51 (14). Anal. calcd. for $C_{21}H_{17}ClN_2O$: C, 72.31; H, 4.91; N, 8.03. Found: C, 72.05; H, 4.72; N, 8.28.

SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra are available via the Supplementary Content section of this article's Web page.

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