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A phosgene and peroxide-free one-pot tandem synthesis of isatoic anhydrides involving anthranilic acid, Boc anhydride, and 2-chloro-*N*-methyl pyridinium iodide

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ABSTRACT

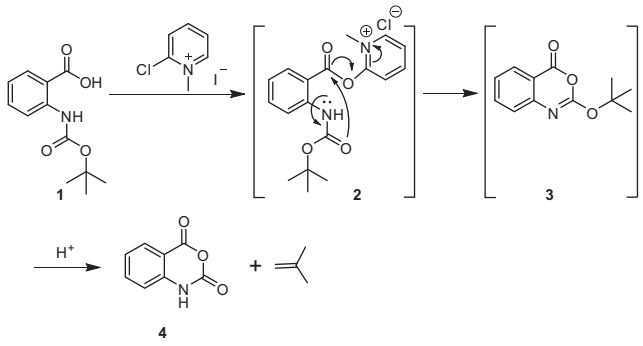
A phosgene and peroxide-free approach for the synthesis of isatoic anhydrides has been described. The synthesis involves the carbamate formation with Boc anhydride followed by in situ cyclization to afford the isatoic anhydride. The importance of this synthetic strategy is in the ease of operation, scalability, and preparation from readily available raw materials.

1*H*-Benzo[*d*][1,3]oxazine-2,4-dione commonly known as isatoic anhydride is a widely used intermediate in organic synthesis. It is used as a precursor for the synthesis of various five and six membered heterocyclic compounds such as quinazolinones, quinazolones, benzimidazolones, phthalimides, pyrroloquinazolones, quinazolinediones, oxazolones, indoles, and their derivatives.[1,2] The synthesis of isatoic anhydride relies mainly on following methods (i) cyclization of anthranilic acid with phosgene, alkylchloroformate or carbonyldiimidazole[3] (ii) oxidation of isatin with chromic acid or peroxy acid[4] and (iii) rearrangement of phthalic acid derivative.[5]

The other reported methods are transmetalation of *o*-bromophenyl isocyante with *n*-BuLi followed by reaction with carbon dioxide.[6] Although all these methods are widely used for the synthesis of isatoic anhydrides, they have some drawbacks due to the toxicity of reagents. Recently, green synthesis of isatoic anhydride from isatin has been described using ultrasound.[7] However, this method lacks the practical applicability at a bigger scale.

In this Letter, we report a one-pot two-step synthesis of isatoic anhydrides from anthranilic acid and Boc anhydride (di-*tert*-butyl dicarbonate) in the presence of 2-chloromethylpyridinium iodide (CMPI, Mukaiyama reagent) around the concept of enolization of carbamate (**2**) as illustrated in Scheme 1.

The formation of active esters like **2** is well documented with coupling reagents viz. dimethylimidazolidinium chloride (DMC), *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate imidazolidinium chloride (TBTU), propylphosphonic anhydride (T3P), benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) etc.[8] It was anticipated that Boc protected anthranilic acid (**1**) under basic condition will enolize and initiate in situ cyclization with active ester (**2**, Scheme 1).



Scheme 1. Plausible mechanism for the formation of isatoic anhydride.

The chemistry started with the synthesis of Boc anthranilic acid from anthranilic acid under standard condition (THF/H_2O/NaOH), which on treatment with coupling reagents led to the formation of intermediate **3** and subsequently to desired product **4** under acidic work-up (Scheme 2). All efforts to isolate intermediate **3** were unsuccessful.

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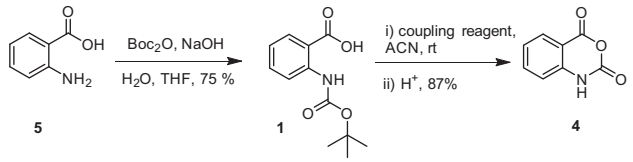
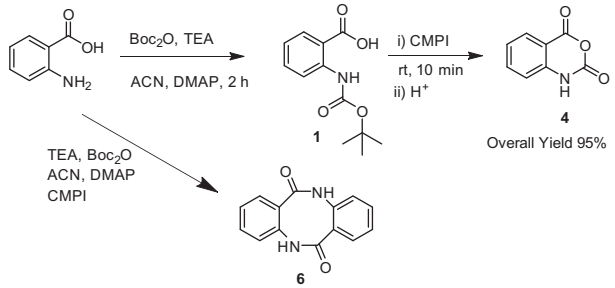


Scheme 2. Formation of isatoic anhydride and screening of coupling reagents.

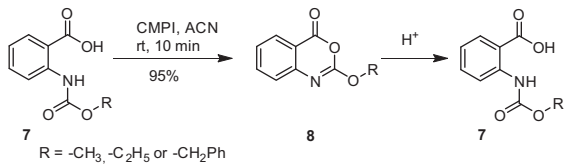
Table 1
Coupling reagents scope in cyclization

Entry	Coupling reagent	Time (h)	Yield[a] (%) of **4**
1	DMC	0.17	92
2	TBTU	5	58
3	BOP	12	27
4	T3P	24	No conversion
5	CMPI	0.17	93

[a] Yield based on crude LCMS.



Scheme 3. One pot two-step synthesis of isatoic anhydride.



Scheme 4. Mechanistic consideration of formation of isatoic anhydride.

Table 2
CMPI-catalyzed synthesis of substituted isatoic anhydrides (**9–22**)

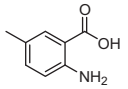
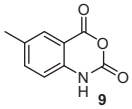
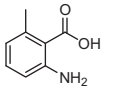
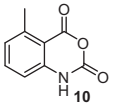
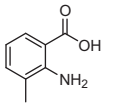
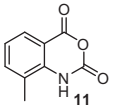
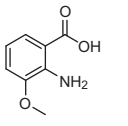
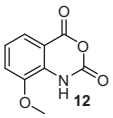
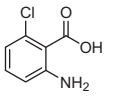
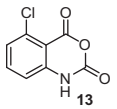
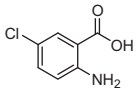
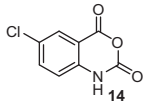
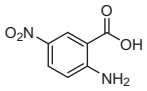
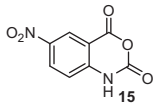
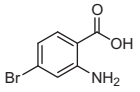
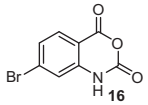
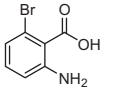
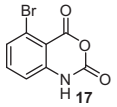
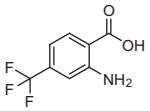
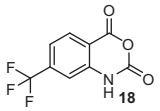
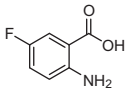
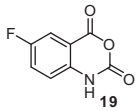
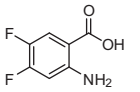
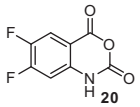
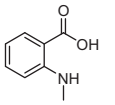
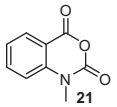
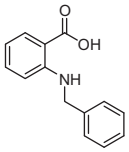
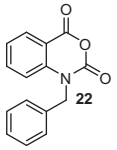
Entry	Anthranilic acid	Product	Yield[a] (%)
1			77[b]
2			94[c]
3			55[d]
4			58[e]

Table 2 (*continued*)

Entry	Anthranilic acid	Product	Yield[a] (%)
5			72[f]
6			71[b]
7			90[b]
8			62[c]
9			67[c]
10			56[g]
11			72[b]
12			80
13			75[h,i]
14			96[h,i]

[a] Isolated yield (calculated over 2 steps).
[b] Ref. 7.
[c] Ref. 10a.
[d] Ref. 10b.
[e] Ref. 10c.
[f] Ref. 10d.
[g] Ref. 10e.
[h] Ref. 10f.
[i] Boc protection in 2 h.

For optimization of the cyclization step, five coupling reagents were explored as depicted in Table 1. We were delighted to observe the efficient formation of isatoic anhydride in excellent yield in the case of DMC and CMPI (Table 1, entries 1 and 5). However, we chose CMPI as a reagent of preference for further exploration due to its chemical stability, cost, and ease of handling.

With the successful outcome of these results, we thought of doing one-pot two-step conversion of anthranilic acid to isatoic anhydride by adding CMPI to the same reaction mixture. However, there was no product formation observed. This might be due to the hydrolysis of active ester (**2**) under strong aqueous basic condition.

Then, the formation of carbamate (**1**) was optimized under anhydrous basic condition (Scheme 3). To this reaction mass (without isolation of **1**) was added CMPI, and subsequent acidic work-up afforded isatoic anhydride in good yield.[9]

On the success of this result, we tried to develop one pot one step strategy by adding all reagents (Boc anhydride, DMAP, CMPI, and TEA) in one shot; however, it led to the formation of undesired product **6**.

To understand the mechanism of the reaction, we prepared methoxy, ethoxy, and benzyloxy carbamates of anthranilic acid (Scheme 4).

On treatment with CMPI, the cyclized intermediates (**8**) formed were quite stable in comparison to **3** (Scheme 1). These on acidic work-up were converted to starting material (**7**) instead to isatoic anhydride, reflecting the preference of cyclic ester hydrolysis over acidolysis of the alkoxy group in intermediate **8**. These results support the proposed plausible mechanism in Scheme 1, where the protonation of *t*-butoxy group leads to the formation of isatoic anhydride.

Finally, we evaluated the versatility of this approach by synthesizing substituted isatoic anhydrides under optimized conditions (Table 2).

These examples clearly demonstrate the applicability of this strategy for the synthesis of substituted isatoic anhydrides. The key advantage of this convergent approach is the use of Boc anhydride (a cheap, readily available, and less toxic raw material), ease of operation and great scalability potential with no hazardous effect.

In conclusion, we have developed an efficient and work-friendly method for the synthesis of substituted and *N*-alkylated isatoic anhydrides.

Acknowledgment

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Supplementary data

Supplementary data associated (experimental detail, reaction conditions and characterisation of products depicted in Table 2) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.034.

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9. *General experimental procedure:* to a solution of anthranilic acid (0.5 g, 3.64 mmol) in acetonitrile (10 mL) were added TEA (0.73 g, 7.28 mmol), Boc anhydride (0.95 g, 4.37 mmol), and DMAP (0.044 g, 0.36 mmol). The mixture was stirred at rt for 2.0 h. CMPI (1.1 g, 4.36 mmol) was added in one lot to the reaction mixture. The reaction mixture was stirred at rt for 10 min. 1 N HCl (20 mL) was added to the reaction and the mixture was extracted two times with EtOAc. The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting solid was crystallized in DCM and MeOH to afford 0.56 g (95%) of 1*H*-benzo[*d*][1,3]oxazine-2,4-dione as an off white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.14–7.16 (d, J = 8 Hz, 1H), 7.23–7.27 (t, J = 16 Hz,1H), 7.72–7.74 (t, J = 8 Hz, 1H), 7.90–7.92 (d, J = 8 Hz,1H), 11.72 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 110.6, 115.7, 123.9, 129.3, 137.3, 141.8, 147.5, 160.3. IR (thin film) 3461, 3173, 2937, 1984, 1753, 1604, 1486, 1358, 1258, 1138, 1009, 765, 673, 492. ES–MS (m/z): 161.8 (M^+-H). MP (°C): 236°.
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