Convenient Novel Method to Access N-Benzylated Isatoic Anhydride: Reaction Behavior of Isatoic Anhydride with 4-Chlorobenzyl Chloride in the Presence of Bases

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ABSTRACT: Sodium hydride, potassium carbonate, and other bases are commonly used for N-alkylation of heterocyclic compounds. This report reveals the problems associated with N-benzylation of isatoic anhydride and identifies the plausible byproduct structures formed during the reaction. Subsequently, a novel breakthrough methodology has been developed using diisopropylamine and tetra butyl ammonium bromide. It gives excellent yields >88% in a short reaction time (2 h) at 30 °C with no byproducts, saving on processes as the pure product is directly obtained.

INTRODUCTION

N-Alkylated and benzylated isatoic anhydride and their derivatives are the most expedient building blocks for the synthesis of numerous potent nitrogen-substituted heterocyclic compounds mainly N-substituted 4-hydroxyquinolinone esters, acetylenic quinazolinones, anilinamides, benzodiazepinediones, quinazolinones, quinolone derivatives, benzoazinone, N-sulfonyl-1,2,3-triazoles, tryptanthrin, and 2,3-dihydroquinazolin-4(1H)-ones. Therefore, in the global isatoic anhydride market, 30−40% isatoic anhydrides have been used as pharmaceutical and chemical intermediates. The isatoic anhydride derivatives find a variety of applications that include dyes, pigments, coupling agents, labeling, and functionalizing target materials.

Owing to the significant importance of N-alkylated/benzylated isatoic anhydride, various methodologies for its synthesis have been developed earlier. However, these methods have significant shortcomings and disadvantages of product conversion, time, excess energy and cost-intensive processes, nonrenewable, and usage of toxic chemicals. Hence, there is a pressing need to develop a simple, generic, time, energy, and cost-efficient eco-sustainable method for the synthesis of N-benzylated isatoic anhydride and its derivatives.

The existing methods for the synthesis of N-benzylated isatoic anhydride can be summarized into three categories (Figure 1):

- a Cyclization of anthranilic acid
- b Carbonylation of substituted anilines with CO in the presence of a Pd(II) catalyst
- c Direct alkylation/benzylation of isatoic anhydride in the presence of a base

In method a, anthranilic acid, phosgene, triphosgene, or ethyl chloroformate are used as a source of a carbonyl group. Because of high toxicity of phosgene and its analogs, this approach is inconvenient. The method b has been developed to overcome the problems for the synthesis of substituted isatoic anhydrides based on the Pd(II)-catalyst. Yields of 6−99% are reported in the literature. Numerous reagents like oxidants, bases, additives, Pd catalysts, carbon monoxide, and nonrenewable solvents are used in this method making it highly expensive and complex. Both the methods a and b produce the intended product, but they require elevated temperatures (60−100 °C), a long reaction time (10−16 h), usage of toxic solvents/metal, and are cost-intensive.

Direct alkylation/benzylation of isatoic anhydride is most commonly used (method c) for the preparation of a N-substituted isatoic anhydride derivative. In 1975, Hardtmann and co-workers reported the N-sodio derivative of isatoic anhydride that is easily formed with sodium hydride and potassium carbonate. The N-Sodio derivative is readily alkylated with alkenyl, propargyl, and benzyl halides. However, lower
yields were found in the case of benzylation with secondary alkyl halide with a reaction time of 18 h. In 2011, Wube and his team followed the same method for the synthesis of N-substituted isatoic anhydride derivatives with a slight modification in reagent quantity and solvent. Alkylation was completed in 24 h with an improved yield of 70−87%.5 Diisopropylethylamine (DIPEA) was also used for the formation of N-benzylated isatoic anhydride.1,17

In 1997, Coppola reported that the alkylation of N-substituted isatoic anhydride can be easily done with sodium hydride/potassium carbonate bases followed by the addition of an alkylating agent. However, direct substitution on nitrogen with an aryl moiety is not possible. It could be achieved by direct N-arylation of isatin with an aryl bromide in the presence of cupric oxide followed by oxidation. N-Arylation of isatins was completed in 5–8 h with 28−55% yield.18 Subsequent oxidation of N-aryl isatin was required to obtain the desired products. Chromic acid,19 chromium trioxide,20,21 glacial acetic acid with hydrogen peroxide and concentrated sulfuric acid,21 urea hydrogen peroxide complex with acetic acid and formic acid,22 m-chloroperbenzoic acid,1,23 and peroxyomonosulfate24 are frequently used for the oxidation of isatins. Despite these methods, it is still challenging to decide which base should be used for the synthesis of N-benzylated isatoic anhydride. Consequently, there is a significant need for the development of a methodology that is efficient, cost-effective, with a reduced time and temperature, free from a metal catalyst, uses a less-toxic solvent, and delivers a high yield with no side products.

### RESULTS AND DISCUSSION

Bases such as sodium hydride,5,11,15,25 cesium carbonate,26,27 sodium carbonate,28 potassium carbonate,11,29−31 DIPEA,3 potassium hydroxide,32 di-N-propylaniline, NN-diethylaniline, tri-N-butylamine, sodium hydroxide,33 triethylamine,34 potassium carbonate with potassium iodide,35 and 1,2,2,6,6-pentamethyl piperidine36 are commonly used for the N-alkylation/benzylation of heterocyclic compounds. Therefore, as part of the ongoing research program, a detailed analysis was carried out on different bases at varying temperatures and timeframes for the N-benzylation of isatoic anhydride with 4-chlorobenzyl chloride (Scheme 1, Table 1, and Figure 2: synthetic route 1).

The examination was initiated with sodium hydride (NaH) as the base at different temperatures (0, 30, and 80 °C). Multiple products were formed at 80 °C as evident from the thin layer chromatography (TLC) image (Figure S1) resulting in a complex mixture. Separation of these products became extremely difficult by column chromatography because of the formation of multiple byproducts. The plausible mechanism for the formation of these byproducts was explored with the help of the literature1 and spectroscopy data. It was found that several byproducts such as benzyl aldehyde (BP1), sodium 2-
isocyanatobenzoate (BP2), anthranilic acid (BP3), a double benzylation product (BP4), corresponding benzyl ester (BP5), and chloride salt of dimethylamine (BP6) were generated during the reaction with a plausible mechanism as illustrated in Figure 3.

At 30 °C, two compounds were obtained as the major products and the remaining compounds were of insignificantly low quantity as evident from the preparative TLC* image (Figure S2). The two major products were easily separated by TLC. The nuclear magnetic resonance (NMR) spectroscopy technique was used to identify the desired compound and to calculate its percentage yield (Figure 4). However, the desired compound could not be successfully obtained by column chromatography and flash chromatography. It may be because of the hydrolysis of anhydride functionality because the oxide beds (silica, alumina) of the column may work as a catalyst for the hydrolysis of anhydride, ester, and amide groups at room temperature.37 At 0 °C, the unreacted starting material was still over 50% and more than two byproducts were observed.

Furthermore, the role of other bases such as sodium hydroxide (NaOH), sodium carbonate (Na2CO3), potassium carbonate (K2CO3), and cesium carbonate (Cs2CO3) in benzylation of isatoic anhydride was explored at 0, 30, and 80 °C. However, they too were found to be ineffective during the reaction. Only 15−47% conversion of the desired product was achieved with major byproducts. These reactions were completed between 12 and 24 h at 30 °C. From the above reactions, it is inferred that the isatoic anhydride ring is very sensitive and gets opened in the presence of a strong base and under high-temperature conditions (Figure 5).

To overcome this disadvantage of a strong base and a high temperature, weak bases such as diisopropylamine (DIPA) and DIPEA were evaluated only at 0 and 30 °C. During this reaction, no byproducts were produced. However, the conversion was found to be reduced at 30 °C even after 24 h. Therefore, to enhance the conversion rate,30,38 the quaternary ammonium salts (phase transfer catalysts) were incorporated into the above reaction. This reaction was performed with a weak base (DIPA) at 30 °C (Scheme 2i).

Screening of catalysts was started with 10−20 mol % tetra-n-butyl ammonium bromide (TBAB) and the Mukaiyama reagent (MR) with different equivalent millimoles of 4-chlorobenzyl chloride (2) at 30 °C (Table 2). The best result was obtained with 20 mol % TBAB catalyst and DIPA (2 equiv) having 1.5 mmol 4-chlorobenzyl chloride (2) within 2 h with 73.5% conversion (Figure 6). The reaction time was significantly reduced from 18 to 2 h with no requirement for higher temperature. Despite these advantages, the reaction yield was found to be less than 38%. With 20 mol % TBAB and 1.1 mmol 4-chlorobenzyl chloride, though 90% yield was obtained, conversion was merely 50%.

After studying the reaction behavior of isatoic anhydride in the presence of different catalysts and bases under different

### Table 1. Investigation of Bases for N-Benzylation of Isatoic Anhydride under Different Temperature Conditions for Scheme 1

| entry | base     | temp. (°C) | time (h) | conversion (%) |
|-------|----------|------------|----------|----------------|
| 1A1   | NaH      | 0          | 24       | 30             |
| 1A2   | NaH      | 30         | 12       | 48             |
| 1A3   | NaOH     | 80         | 06       | trace          |
| 1A4   | NaOH     | 0          | 24       | 16             |
| 1A5   | NaOH     | 30         | 12       | 18             |
| 1A6   | NaOH     | 80         | 06       | nil            |
| 1A7   | K2CO3    | 0          | 24       | 17             |
| 1A8   | K2CO3    | 30         | 12       | 43             |
| 1A9   | K2CO3    | 80         | 06       | trace          |
| 1A10  | Na2CO3   | 0          | 24       | 16             |
| 1A11  | Na2CO3   | 30         | 12       | 39             |
| 1A12  | Na2CO3   | 80         | 06       | trace          |
| 1A13  | Cs2CO3   | 0          | 24       | 15             |
| 1A14  | Cs2CO3   | 30         | 12       | 47             |
| 1A15  | Cs2CO3   | 80         | 06       | trace          |
| 1A16  | DIPA     | 0          | 24       | nil            |
| 1A17  | DIPA     | 30         | 24       | 13             |
| 1A18  | DIPEA    | 0          | 24       | nil            |
| 1A19  | DIPEA    | 30         | 24       | 13             |

isocyanatobenzoate (BP2), anthranilic acid (BP3), a double benzylation product (BP4), corresponding benzyl ester (BP5), and chloride salt of dimethylamine (BP6) were generated during the reaction with a plausible mechanism as illustrated in Figure 3.

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### Figure 2. Synthetic routes for the preparation of 1-(4-chlorobenzyl)-1,3-benzoazaine-2,4-dione. Synthetic route 1 shows the direct benzylation of isatoic anhydride (1) with 4-chlorobenzyl chloride (2) to obtain N-benzylated isatoic anhydride (3) and synthetic route 2 uses benzylation of isatin (4) in the presence of DIPA and TBAB catalysts (step 1) followed by the oxidation (step 2) to get N-benzylated isatoic anhydride (3).
temperature conditions, it is concluded that \( N \)-benzylation of isatoic anhydride cannot be achieved in its purest form. Therefore, keeping in view the above reaction problems, we performed a two-step reaction using isatin as the starting material instead of isatoic anhydride (Figure 2: synthetic route 2). The first step involves \( N \)-benzylation of isatin, which is followed by oxidation in the second step. Considering the advantages and trade-offs of TBAB and DIPA, the \( N \)-benzylation of isatin was performed under optimized conditions (Scheme 2ii). During step I, the substituted isatins at the 5th position gave excellent yields of \( N \)-benzylated isatins ranging from 76 to 88%. The purity of \( N \)-benzylated isatins was checked using \(^1\)H NMR. The reaction was found to be compatible with various functional groups; from electron-withdrawing to electron-donating groups such as fluoro, chloro, bromo, and methyl groups.

The second step involved the oxidation of \( N \)-benzylated isatin to obtain the desired compound \( N \)-benzylated isatoic anhydride. Various oxidizing agents such as peroxycids and peroxides (peracetic acid, performic acid, metachloroperbenzoic acid (MCPBA), and hydrogen peroxides with lewis acids) were used. First, peracetic acid was used because it is safe, cheap and easily available. Two spots were revealed after the completion of the reaction with peracetic acid and performic acid (Figure S6a, b,Figure 4. \(^1\)H NMR spectrum of the crude reaction mixture with sodium hydride.

Figure 3. The plausible mechanism for the formation of byproducts during the reaction of synthesis of \( N \)-benzylated isatoic anhydride.
Table 3). These two compounds (1-(4-chlorobenzyl)-1,3-benzoazoxazine-2,4-dione and isomeric 1-(4-chlorobenzyl)-2,3-dioxo-1,4-benzoazines) might be produced by the rearrangement of the Criegee adduct (acts as the intermediate), which is produced by possible attack of peroxide at the C3 position (Figure 7). Separation of these isomeric compounds was not possible by ordinary chromatography.

Then, other peroxides were tested to achieve a regioselective synthesis of 1-(4-chlorobenzyl)-1,3-benzoazoxazine-2,4-dione. Ring opening was observed with peroxymonosulfuric acid (Scheme 3i, Figure 8). Lewis acid with hydrogen peroxide was also tried but no product was formed (Scheme 3ii, Table 3). Finally, the reaction was performed with metachloroperbenzoic acid (Scheme 3iii). The 95% yield of the regioselective compound 1-(4-chlorobenzyl)-1,3-benzoazoxazine-2,4-dione was obtained within 2−4 h. Purity of the compound was checked by using 1H NMR and the status of ring opening was checked by infrared (IR) spectroscopy where it was observed that the ring was quite stable (Figure 9).

Subsequently, the best solvent for this reaction, reagents, and conditions were identified and listed in Table 4. Dichloromethane (DCM), benzene, chloroform, ethanol, ethyl acetate, acetonitrile, and tetrahydrofuran (THF) were used as solvents. The product yield was found to be 95% with benzene. Benzene and DCM solvents were more compatible for oxidation with MCPBA.

## CONCLUSIONS

The direct N-benzylation of isatoic anhydride using the entire range of strong to weak bases led to the formation of many byproducts and proved to be ineffective and cost-intensive. The combination of conditions (2 equiv DIPA and 20% mol TBAB catalyst, at a normal temperature of 30°C and a reaction time of 2 h), though useful, results in an unstable anhydride ring of N-benzylated isatoic anhydride in silica and alumina columns. With 73% conversion of the desired product, the final yield was merely 35%. However, using the same combination for the N-benzylation of isatin with a hard nucleophile (4-chlorobenzyl chloride), the yield was increased to >88% with absolutely no byproducts. This combination is remarkably useful, for the N-benzylation of various N-containing heterocyclic nuclei except in the case of anhydride with a hard nucleophile in polar aprotic solvents. After N-benzylation of isatin, the insertion of oxygen with ring expansion was successfully achieved using MCPBA with 95% yield.

In view of the above, it can be concluded that direct benzylolation of isatoic anhydride cannot be achieved with a high yield without byproducts and accompanying high cost. The N-benzylated isatoic anhydride in the pure form with all the added advantages can be accomplished using this novel breakthrough methodology with isatin followed by oxidation. This methodology uses the green chemistry concept and is helpful for the scientific community as a whole.

## EXPERIMENTAL SECTION

### General Information.

All reagents, solvents, and TLC plates were procured from Sigma Aldrich, Himedia, LOBA, and Spectrochem. Reactions were carried out in oven-dried glasswares and solvents were dried using distillation followed by the addition of 3 Å activated (250°C for 2 h) molecular sieves. The progress of reactions was checked by silica gel G TLC plates with F-254 and spots were visualized under an UV chamber at 254 and 365 nm. The purification of the compounds was done by flash chromatography (EPCLC AL-580S & Yamazen Corporation) on the silica gel with hexane and ethyl acetate as a mobile phase. Melting points of the synthesized compounds were recorded using Thiele’s tube. The infrared spectra of the compounds were recorded on FT-IR-8400S (Shimadzu). Proton and carbon-13 nuclear magnetic resonance spectra were recorded on a Bruker DX 400/500 MHz spectrometer. CDCl₃ and DMSO-d₆ were used as a solvent. In 1H NMR, chemical shifts were reported in parts per million and tetramethylsilane was used as an internal standard.

### Experimental Details for the Synthesis of N-Benzylated Isatoic Anhydride from Isatoic Anhydride.

**General Procedure for Scheme 1.** The base (Table 1, 1 mmol) was slowly added to a solution of isatoic anhydride (0.163 g, 1 mmol) in 1 mL N,N-dimethylacetamide with continuous stirring at different temperatures (0, 30, and 80°C). 4-Chlorobenzyl chloride (0.192 g, 1.1 mmol) was added to the
Scheme 2. (i) Benzylation of Isatoic Anhydride; (ii) Benzylation of Isatins

**i) Benzylation of isatoic anhydride**

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\text{Benzylation of isatoic anhydride}
\]

**ii) Benzylation of isatins**

\[
\text{Benzylation of isatins}
\]

"Reaction conditions: 2i 1 (1.0 mmol), 2 (1.1 mmol/1.5 mmol), DIPA (2 mmol), 2A (10 mol %/20 mol %), 2B (10/20 mol %), DMA (2 mL).
2ii 4 (1.0 mmol), 2 (1.1 mmol), DIPA (2 mmol), 2A. TBAB (20 mol %), and DMA (2 mL).

The precipitate was filtered off, washed with cold water, and dried.

**General Procedure for Scheme 2i.** Isatoic anhydride (0.163 g, 1 mmol) was dissolved in N,N-dimethylacetamide (2 mL) and then tetra butyl ammonium bromide (0.145 g; 10 mol %) and DIPA (2 mmol) were added to the reaction mixture with continuous stirring at 30 °C. After 5 min, 4-chlorobenzylchloride (0.192 g; 1.1 mmol/0.262 g; 1.5 mmol) was added to the reaction mixture. The reaction mixture was poured into the crushed ice. The precipitate was filtered off, washed with cold water, and dried.

**Experimental Details for the Synthesis of N-Benzylated Isatin.** General Procedure for Scheme 2ii. DIPA (0.28 mL, 2 mmol) and tetra butyl ammonium bromide (0.32 g, 20 mol %) were added to the solution of isatin (1 mmol) in N,N-dimethylacetamide and 4-chlorobenzyl-chloride (1.1 mmol) was added to the reaction mixture, the reaction mixture was poured into the crushed ice after 2 h mixing at 30 °C. The precipitate so obtained was filtered off and washed with water and dried. Completion of the reaction was checked by TLC.
Table 2. Optimization of the Catalyst (Percentage) and Reaction Time for the Synthesis of 1-(4-Chlorobenzyl)-1,3-Benzoxazine-2,4-dione in the N,N-Dimethylacetamide Solvent for Scheme 2i

| entry | catalyst | mol % | time (h) | 4-ClB$^a$ (equiv mm) | conversion (%) | yield (%) |
|-------|----------|-------|----------|-----------------------|----------------|-----------|
| 2A1   | TBAB     | 10    | 4        | 1.1                   | 48.0           | 88.0      |
| 2A2   |          | 20    | 2        | 1.1                   | 50.0           | 90.0      |
| 2A3   |          | 10    | 4        | 1.5                   | 71.0           | 32.0      |
| 2A4   |          | 20    | 2        | 1.5                   | 73.0           | 38.0      |
| 2B1   | MR       | 10    | 5        | 1.1                   | Nil            | Nil       |
| 2B2   |          | 20    | 2        | 1.1                   | Nil            | Nil       |

$^a$4-ClB = 4-chlorobenzyl chloride.

Table 3. Screening of Oxidizing Agents for the Conversion of N-Alkylated Isatin to N-Alkylated Isatoic Anhydride for Scheme 3iii

| entry | oxidizing agents | catalyst | $T$ (°C) | time (h) | yield (%) |
|-------|------------------|----------|----------|----------|-----------|
| 3A    | peracetic acid   |          | 30       | 24       | 70        |
| 3B    | performic acid   |          | 30       | 24       | 75        |
| 3C    | persulfuric acid |          | 30       | 24       | trace     |
| 4A    | hydrogen peroxide| bismuth nitrate | 60 | 48 | nil |
| 4B    | hydrogen peroxide| mercuric chloride | 60 | 48 | nil |

Figure 6. $^1$H NMR spectrum of the crude reaction mixture with DIPA.

Figure 7. Rearrangement of the Criegee adduct formed during oxidation of isatins into two possible isomers.
Scheme 3

Reagent conditions:

i. PAA (3A) / 3B PFA (3B) / PSA (3C)  
ii. HgCl₂ (4A) / Bi(NO₃)₃ (4B),  
Urea hydrogen peroxide, Ethanol, 60 °C  
iii. MCPBA, DCM (5A1), 30 °C

Figure 8. IR spectrum of the reaction mixture with peroxymonosulfuric acid.

“Reagent conditions: iii. 5 (0.01 mol), 3A [urea H₂O₂ complex (0.015 mol), acetic anhydride (8 mL) and glacial acetic acid (1 mL)], 3B [urea H₂O₂ complex (0.015 mol) and acetic anhydride (8 mL)], 3C [30% H₂O₂ (2 mL) and 95% H₂SO₄ (6 mL)]. iii. 5 (0.01 mol) 4A (20 mol %), 4B (20 mol %), ethanol (4 mL), urea H₂O₂ complex (0.015 mol). iii. 5 (1 mmol), MPCBA (1.1 mmol), and DCM (13.5 mL)."
Figure 9. IR spectrum of 1-(4-chlorobenzyl)-2H benzo[de][1,3] oxazine-2,4(1H)-dione with MCPBA.

Table 4. Screening of Solvents for the Synthesis of N-Benzylated Isatoic Anhydrides for Scheme 3ii

| entry | solvent | time (h) | yield (%) |
|-------|---------|----------|-----------|
| 5A1   | DCM     | 24       | 85        |
| 5A2   | benzene | 4        | 95        |
| 5A3   | chloroform | 5    | 85        |
| 5A4   | ethanol | 6        | 55        |
| 5A5   | ethyl acetate | 6   | 50        |
| 5A6   | AcCN    | 12       | trace     |
| 5A7   | THF     | 12       | nil       |

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ASSOCIATED CONTENT

Supporting Information
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Compound characterization data and 1H NMR and 13C NMR spectral data (PDF)

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Notes
The authors declare no competing financial interest.

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REFERENCES

(1) Beutner, G. L.; Kuethe, J. T.; Yasuda, N. A practical method for preparation of 4-hydroxyquinolinone esters. J. Org. Chem. 2007, 72, 7058−7061.
(2) Usifoh, C. O.; Scriba, G. K. E. Synthesis and anticonvulsant activity of acetylenic quinazolinone derivatives. Arch. Pharm. 2000, 333, 261−266.
(3) Webb, R. R.; Barker, P. L.; Baier, M.; Reynolds, M. E.; Robarge, K. D.; Blackburn, B. K.; Tischler, M. H.; Weese, K. J. Mono-N-alkylation of anthranilamides via quinazolinones. An efficient synthesis of G5598, a benzodiazepine dionegpIIbIIIa antagonist. Tetrahedron Lett. 1994, 35, 2113−2116.
(4) Abbas, S. Y.; El-Bayouki, K. A. M.; Basyouni, W. M. Utilization of isatoic anhydride in the syntheses of various types of quinazoline and quinazolinone derivatives. Synth. Commun. 2016, 46, 993−1035.
(5) Wube, A. A.; Bucar, F.; Hochfellner, C.; Blunder, M.; Bauer, R.; Hüfner, A. Synthesis of N-substituted 2-[(1E)-alkenyl]-4-(1H)-quinolone derivatives as antimycobacterial agents against non-tubercular mycobacteria. Eur. J. Med. Chem. 2011, 46, 2091−2101.
(6) Rostkowski, H.; Lapinski, L.; Nowak, M. J. Photochemical Generation of Benzoazetinone by UV Excitation of Matrix-Isolated Precursors: Isatin or Isatoic Anhydride. J. Phys. Chem. A 2020, 124, 4106−4114.
(7) Pal, K.; Hoque, A.; Volla, C. M. R. Rh-Catalyzed Denitrogenative Reaction of N-Sulfonyl-1,2,3-triazoles with Isatoic Anhydrides and Oxadiazolones. Chem.—Eur. J. 2018, 24, 2558−2564.
(8) Hou, H.; Li, H.; Han, Y.; Yan, C. Synthesis of visible-light mediated tryptanthrin derivatives from isatin and isatoic anhydride under transition metal-free conditions. Org. Chem. Front. 2018, 5, 51−54.
(9) Zhang, Z.; Qin, Z.; Chang, W.; Li, J.; Fan, R.; Wu, X.; Guo, R.; Xie, X.; Zhou, L. Nickel-Catalyzed Decarboxylative Cyclization of Isatoic Anhydrides with Carbodiimides: Synthesis of 2,3-Dihydroquinazolin-4(1 H )-ones. Adv. Synth. Catal. 2020, 362, 2864−2869.
(10) Bogdanov, A. V.; Mironov, V. F. Synthesis of isatoic anhydride derivatives (microreview). Chem. Heterocycl. Compd. 2016, 52, 90−92.
(11) Hardtmann, G. E.; Kolter, G.; Pfister, O. R. The chemistry of 2H-3,1-benzoxazine-2,4(1H)ones (isatoic anhydrides) 1. The synthesis ofN-substituted 2H-3,1-benzoxazine-2,4(1H)ones. J. Heterocycl. Chem. 1975, 12, 565−572.
(12) Gao, S.; Chen, M.; Zhao, M.-N.; Du, W.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. Palladium-catalyzed carbonylation of o-iodoanilines for synthesis of isatoic anhydrides. *J. Org. Chem.* 2014, 79, 4196–4200.

(13) Guan, Z.-H.; Chen, M.; Ren, Z.-H. Palladium-catalyzed regioselective carbonylation of C–H bonds of N-alkyl anilines for synthesis of isatoic anhydrides. *J. Am. Chem. Soc.* 2012, 134, 17490–17493.

(14) Wang, S.; Li, X.; Zhang, J.; Liu, M.; Zhang, S.; Jiang, G.; Ji, F. Palladium-Catalyzed Multistep Tandem Carbonylation/N-Dealkylation/Carbonation Reaction: Access to Isatoic Anhydrides. *J. Org. Chem.* 2019, 85, 2672–2679.

(15) Coppola, G. M. A new scavenger resin for amines. *Tetrahedron Lett.* 1998, 39, 8233–8236.

(16) Kappe, T.; Stadlbauer, W. Isatoic anhydrides and their uses in heterocyclic synthesis. *Adv. Heterocycl. Chem.* 1981, 28, 127–182.

(17) Khalifa, M. M.; Philkhana, S. C.; Golden, J. E. Synthesis of Ring-Fused, N-Substituted 4-Quinolinones Using pKa-Guided, Base-Promoted Annulations with Isatoic Anhydrides: Total Synthesis of Penicinotam. *J. Org. Chem.* 2020, 85, 464–481.

(18) Coppola, G. M. N-Arylation of isatins. A direct route toN-arylisoatoic anhydrides. *J. Heterocycl. Chem.* 1987, 24, 1249–1251.

(19) Sumpter, W. C. The chemistry of isatin. *Chem. Rev.* 1944, 34, 393–434.

(20) Coppola, G. M. The chemistry of isatoic anhydride. *Synth. 1980, 1980, 505–536.

(21) Reissenweber, G.; Mangold, D. Oxidation of Isatins to Isatoic Anhydrides and 2,3-Dioxo-1,4-benzoxazines. *Angew. Chem., Int. Ed.* 1980, 19, 222–223.

(22) Deligeorgiev, T.; Vasiliev, A.; Vaquero, J. J.; Alvarez-Builla, J. A green synthesis of isatoic anhydrides from isatins with urea–hydrogen peroxide complex and ultrasound. *Ultrason. Sonochem.* 2007, 14, 497–501.

(23) Bogdanov, A. V.; Sadykov, T. I.; Musin, L. I.; Khamatgalimov, A. R.; Krivolapov, D. B.; Dobrynin, A. B.; Mironov, V. F. Chemoselective oxidation of 1-alkenylisatins with m-chloroperbenzoic acid. Synthesis of new derivatives of isatoic anhydride. *Russ. J. Gen. Chem.* 2015, 85, 2030–2036.

(24) Kavery, M.; Govindsamy, C.; Johnson, S. A Kinetic Study on the Oxidation of Indole by Peroxomonomosulphate in Acetonitrile Solvent. *J. Korean Chem. Soc.* 2013, 57, 210–215.

(25) Vintonyak, V. V.; Warburg, K.; Over, B.; Hübel, K.; Rauh, D.; Waldmann, H. Identification and further development of thiazolidinones spiro-fused to indolin-2-ones as potent and selective inhibitors of Mycobacterium tuberculosis protein tyrosine phosphatase B. *Tetrahedron* 2011, 67, 6713–6729.

(26) Fink, D. M. Cesium carbonate promoted N-alkylation of indoles. *Synlett* 2004, 13, 2394–2396.

(27) Zanzoul, A.; Chollet, A.; Piedra-arroni, E.; Stigliani, J.-L.; Bernardes-Génisson, V.; Essassi, E. M.; Pratviel, G. Synthesis of an Indoloquinoxaline Derivative as Potential Inhibitor of InhA enzyme of Mycobacterium tuberculosis. *Lett. Org. Chem.* 2015, 12, 727–733.

(28) Sobiak, S. Tetrabutyl ammonium bromide as a catalyst for reaction of 5-(4-bromo-2-methyl-4(S)-nitroimidazol-2-yl)phenacyl bromides. *Acta Pol. Pharm.* 1999, 56, 155–158.

(29) Badul, O. M.; Zhungietu, G. I.; Rekhter, M. A.; Bukhanyuk, S. M. Simple method for the preparation of 1-substituted isatins. *Chem. Heterocycl. Compd.* 1983, 19, 286–288.

(30) Jaskowska, J.; Kowalski, P. N-Alkylation of imides using phase transfer catalysts under solvent-free conditions. *J. Heterocycl. Chem.* 2008, 45, 1371–1375.

(31) Lobe, M. M. M.; Efange, S. M. N. 3′,4′-Dihydro-2′H-spiro[indoline-3,1′-isooquinolin]-2-ones as potential anti-cancer agents: synthesis and preliminary screening. *R. Soc. Open Sci.* 2020, 7, 191316.

(32) Mijin, D.; Misić-Vuković, M.; Petrović, S. Alkylation of N-substituted-2-phenylacetamides. *J. Serb. Chem. Soc.* 2004, 69, 711–736.

(33) Abdallah, M.; Magaldi, D.; Hijazi, A.; Graff, B.; Dumur, F.; Fouassier, J. P.; Bui, T. T.; Goubard, F.; Lalevée, J. Development of new high-performance visible light photoinitiators based on carbazole scaffold and their applications in 3d printing and photocomposite synthesis. *J. Polym. Sci., Part A: Polym. Chem.* 2019, 57, 2081–2092.

(34) Sultana, N.; Sarfraz, M.; Tanoli, S. T.; Akram, M. S.; Sadiq, A.; Rashid, U.; Tariq, M. I. Synthesis, crystal structure determination, biological screening and docking studies of N1-substituted derivatives of 2, 3-dihydroquinoxalin-4-(1H)-one as inhibitors of cholinesterases. *Bioorg. Chem.* 2017, 72, 256–267.

(35) Abo-Ashour, M. F.; Eldehna, W. M.; Nocentini, A.; Bonardi, A.; Bua, S.; Ibrahim, H. S.; Elaesser, M. M.; Kryštof, V.; Jorda, R.; Gratteri, P.; Abou-Seri, S. M.; Supuran, C. T. 3-Hydrainosino-based benzene sulphonamides as novel carbonic anhydrase inhibitors endowed with anticancer activity: Synthesis, in vitro biological evaluation and in silico insights. *Eur. J. Med. Chem.* 2019, 184, 111768.

(36) Sommer, H. Z.; Lipp, H. I.; Jackson, L. L. Alkylation of amines. General exhaustive alkylation method for the synthesis of quaternary ammonium compounds. *J. Org. Chem.* 1971, 36, 824–828.

(37) Regen, S. L.; Mehrotra, A. K. Alumina-Assisted Basic Hydrolysis of Esters I. *Synth. Commun.* 1981, 11, 413–417.

(38) Keglevich, G.; Grün, A.; Balint, E. Microwave irradiation and phase transfer catalysis in C–O and N-alkylation reactions. *Curr. Org. Synth.* 2013, 10, 751–763.