Synthesis of Substituted Isatins from the MBH Adduct of 1,5,6-Trisubstituted Isatins Using (2,4-Dinitrophenyl)hydrazine and K-10 Clay Explored as Protection–Deprotection Chemistry

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Supporting Information

ABSTRACT: An interesting synthetic transformation of protection–deprotection chemistry in an isatin molecule is achieved. Morita–Baylis–Hillman (MBH) adduct formation used as protection of the C-3 position in the isatin molecule is reported. C=C bond cleavage in the MBH adduct of isatin with the help of phenylhydrazone and C=N bond cleavage in the phenylhydrazone derivative of isatin with the help of K10 clay are studied systematically and reported as deprotection.

INTRODUCTION

The chemistry of indoline-2,3-dione (isatin)1–15 functionalization at the 1,3,4,5,6-positions leads to attractive applications among major classifications of chemical, biological, and medicinal fields of science. Functionalization of these positions is well established in the literature, such as Morita–Baylis–Hillman addition reaction16–32 (MBH adduct formation at C-3 position), substitution reactions (N-alkylation, aromatic electrophilic substitution), oxidation, and reduction. To conduct one particular reaction in the core structure of the isatin molecule, some of the positions have to be protected using protection–deprotection chemistry. For instance, substitution of the N-H position of the isatin molecule was done after protection of the C-3 position (carbonyl protection), which is reported in the literature as 1,2-diol protection.33 However, the protection of the C-3 position of isatin with the help of a well-known MBH adduct forming reaction was not explored as protection of the C-3 position of indoline-2,3-dione (isatin). Thus, the protection concept by means of adduct formation is untouched from 2005 to 2018. Hence, we planned to study and report such a methodology as a novel work in this paper.

RESULTS AND DISCUSSION

Our initial work started from MBH adduct formation. The reaction of simple isatin with methyl acrylate and DABCO afforded C-3-protected methyl 2-(3-hydroxy-2-oxoindolin-3-yl)acylate 1a.

The MBH adduct 1a was allowed to deprotect by means of C=C bond cleavage.34–48 An interesting approach employed is a reaction with phenylhydrazine hydrochloride.49 In that attempt, formation of a mixture of E/Z isomers of 3-(2-phenylhydrazono)indolin-2-one 1b (yield in a range of 35–56%) confirmed the C=C bond cleavage in 1a (Scheme 1). The generality for the C=C bond cleavage reaction was achieved using different MBH adducts of isatin 2a–7a and afforded the corresponding C=C bond cleaved products 2b–7b in good to excellent yields (55–88%). The reactions are shown in Figure 1. Consequently, starting materials 2a–4a for eqs 1, 2, and 3 were prepared by general N-alkylation of the isatin procedure. However, starting materials 5a–7a for eqs 4, 5, and 6 were prepared from our own previous procedures.50–53

For the improvement in the yield of the C=C bond cleavage reactions, different phenylhydrazines were tested as shown in Scheme 2. Thus, the C=C bond cleavage occurred very efficiently when the reagent was with either phenylhydrazine hydrochloride solid or phenylhydrazine liquid, and the formation of phenylhydrazone 2b in very good to excellent yields was found. However, while using 2,4-dinitrophenylhydrazine hydrochloride solid, the C–C bond cleaving product 2b* was formed in excellent yield (Scheme 2, eq iii). After...
finding a good result with 2,4-dinitrophenylhyrazine hydrochloride (DNP, colored reagent), further studies were performed with DNP itself for the C–C bond cleavage purpose.

To reproduce the C-3 position as β-carbonyl (ketone functionality), the phenyldrazone part of intermediate products 2b and 2b’ should be worked up with an acid to perform C–N bond cleavage. To remove the phenyldrazone part from the isatin core, a systematic study was conducted as shown in Table 1. Two reactions were performed: one was by adding a solvent with dilute HCl (condition A) and the other was by adding solvents with and without K-10 clay (condition B). In this study, room temperature (RT) to high boiling chlorobenzene reflux

Table 1. Deprotection Optimization Study

| entry | R₁ | R₂ | R₃ | conditions (A) | conditions (B) | yield (%) (A) | yield (%) (B) |
|-------|----|----|----|----------------|----------------|---------------|---------------|
| 1     | Me | H  | H  | EtOH           | EtOH/conc HCl  | 78            | 85            |
| 2     | Me | H  | OMe| EtOH           | EtOH/dil HCl   | 77            | 85            |
| 3     | Me | Me | H  | Me₂CO         | Me₂CO/K-10 clay | 67            | 85            |
| 4     | Me | Me | OMe| CHCl₂         | CHCl₂/reflux   | 77            | 85            |
| 5     | Me | NO₂| H  | EtOH           | EtOH/K-10 clay | trace         | trace         |
| 6     | Me | NO₂| OMe| C₂H₅Cl (RT)   | C₂H₅Cl/reflux  | poor          | trace         |
| 7     | H  | H  | H  | C₂H₅O₂         | C₂H₅O₂/K-10 clay | 30            | 65            |
| 8     | H  | H  | OMe| C₂H₅N (1:1)   | C₂H₅N (1:2)    | 30            | 65            |
| 9     | H  | Me | H  | Me₂CO         | Me₂CO/K-10 clay | 30            | 65            |
| 10    | H  | Me | OMe| C₂H₅CH₃       | C₂H₅CH₃/K-10 clay | fair          | fair          |
| 11    | H  | NO₂| H  | Me₂CO         | Me₂CO/K-10 clay | 28            | 75            |
| 12    | H  | NO₂| OMe| CCl₄          | CCl₄/K-10 clay  | 28            | 75            |

*Based on TLC. †Based on a UV–vis lamp.
conditions were tested for phenylhydrazone cleavage (C≡N), and different adducts were also examined to know the electrochemical effect on the deprotection procedure. Hence, entries 1, 2, 4, 6, 8, and 12 in the Table 1 did not show the phenylhydrazone cleavage part, whereas entries 5, 7, and 10 showed a positive sign for the cleavage of the C≡N bond monitored by thin-layer chromatography (TLC).

Finally, the second step of the deprotection procedure was considered as the optimum condition where it uses acetone/K-10 clay (Table 1, entry 3). Moreover, a mixture of E/Z isomers in phenyhydrazone products 2b−7b was directly allowed to remove the phenylhydrazone part and get isatin back as a C-3 regenerated product. It was found that the C≡N cleavage occurred in one of the isomers of phenyhydrazone products. To find isomer selectivity, after column separation, both were tried for the C≡N cleavage reaction separately. Between the isomers, the E isomer gets the C≡N cleavage, whereas the H-bond-stabilized Z isomer does not undergo the C≡N bond cleavage (Scheme 3).

After finding this result, only E isomers of 2b−7b were allowed for the C≡N bond cleavage reaction and found 100% conversion in all cases monitored by TLC (Figure 2).

For the justification of protection−deprotection methodology in isatin molecules, careful stepwise reactions were conducted as shown in Figure 3. The C-3 position of isatin is protected by means of MBH adduct formation using methyl acrylate or acrylonitrile with DABCO to get the compound 2a/3a (30 min for the nitrile adduct; 3−6 days for the acrylate adduct). The MBH adduct 2a/3a is treated with CAN in a 1:1 methanol/acetonytrile solvent mixture to afford five formyl derivatives50 or one (N-methylene methylether)51,52 position of the functionalized MBH adduct of isatin 2a/3a'. Then, the adduct 2a'/3a' is treated with 1.2 equiv of 2,4-dinitrophenylhydrazine to afford the C−C bond-cleaved phenylhydrazone product 2b/3b. Removal of the phenyl-

Figure 2. Generality for the C≡N bond cleavage reaction from the E isomer.

Figure 3. Pictorial justification for the protection−deprotection methodology in isatin molecules.

Figure 4. UV spectroscopic proof for protection−deprotection in isatin.
The material (SM) taken for the final conclusion was 1,5-dimethylisatin, and its UV absorption ($\lambda_{\text{max}}$) is 253 nm. The first step was to form an adduct in a duration of 3 days for C-3 protection (converting the SM to the MBH adduct with methyl acrylate and a catalytic amount of DABCO in ethanol). The second step was to deprotect, which was achieved in two stages: (i) C–C bond cleavage using 2,4-dinitrophenylhydrazine hydrochloride and (ii) treatment of phenylhydrazone with acetone/K10 clay to get C-3 ketone in the isatin molecule. After reaching these steps, the resulting product (isatin) showed a sharp UV absorption band ($\lambda_{\text{max}}$) at 253 nm, more clear and similar with purchased isatin.

The UV spectral comparison study was found general with different isatins (for instance, N-methylisatin, 1-methyl-5-nitroisatin, 1-methyl-5-formylisatin, and 1-propargylisatin). The result is shown in Figure 5.

This is to emphasize that our method is short and simple and that there is no need for column purification. A comparative experiment was conducted as in Scheme 4. Thus, the traditional protection of the isatin molecule with 1,2-diol formed the acetonide followed by hydrolysis using the condition of 1.18 N HClO4-THF, 25 °C, and 8 days, which afforded the isatin derivative and byproduct. However, our method needs only 3 h to get pure and crystalline isatin without any side products.

**CONCLUSIONS**

As a conclusion, a systematic and elaborate study has been conducted to demonstrate protection (MBH adduct formation) followed by deprotection (phenylhydrazone formation and its removal; C–C, C═N bond cleavage) aspects. It is noteworthy that the methodology can be applied in the alkaloid natural product intermediate synthesis and biological and medicinal areas of isatin derivatives.

**EXPERIMENTAL DETAILS**

**General Experimental Procedure for N-Alkylation of Isatin.** A mixture of isatin (1 mmol), alkyl bromide/iodide (1.5 mmol), and calcium hydride (3 mmol) in DMF was stirred at 60 °C for 1 h. After completing the reaction (monitored by TLC), the reaction mixture was poured into water, neutralized with 2 N HCl, and then extracted using ethyl acetate. The crude product obtained was purified by silica gel column chromatography using EtOAc/hexane (20:80) as eluent to afford the desired N-alkylisatin.

**General Experimental Procedure for the Preparation of MBH Adducts of Isatin (Protection of the C-3 Position of Isatin).** A mixture of N-alkylisatin (1 mol), 1.5 equiv of ethyl acrylate (1.5 mmol), and 0.02 equiv of DABCO (0.02 mmol) in ethanol (5 mL) was stirred at RT for 3–6 days. After completing the reaction (monitored by TLC), the
reaction mixture was diluted with ethyl acetate. The organic layer was washed successively with 0.2 N HCl. The organic layer was separated, dried (Na₂SO₄), and concentrated in vacuo. The crude product obtained was purified by silica gel column chromatography using EtOAc/hexane (20:80) as eluent to afford the desired MBH adduct of N-alkylisatin.

**General Procedure for the C–C Bond Cleavage (Deprotection of the MBH Adduct to Phenylhydrazone Followed by Isatin Formation).**

(i) A mixture of the MBH adduct (50 mg, 0.20 mmol) and 1.5 equiv of 2,4-dinitrophenylhydrazine was made as a paste and ground in a mortar and pestle in solvent-free conditions at room temperature (30 min). The crude reaction mixture was purified by silica gel column chromatography using EtOAc/hexane (20:80) as the eluent to afford 3-(2-(2,4-dinitrophenyl)hydrazono)-1,5-dimethylindolin-2-one.

(ii) A mixture of 2,4-dinitrophenylhydrazone of the MBH adduct of 1,5-dimethylisatin (0.05 g, 0.20 mmol) and 100% (w/w) K-10 clay was added with acetone (2.5 mL) and stirred at RT for 30 min. After completing the reaction (monitored by TLC), the reaction mixture was filtered to remove the clay, and the filtrate was evaporated to get the pure crystalline product 1,5-dimethylisatin (85%, 0.0376 g).

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01002.

1H NMR, 13C NMR, and UV–vis spectra of the synthesized compounds (PDF)

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Notes
The authors declare no competing financial interest.

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