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Nucleophilic substitution reaction of Morita–Baylis–Hillman adducts of isatin with X, S, N, and O-nucleophiles: a facile and efficient synthesis of highly functionalized tetrasubstituted alkene appended oxindoles

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ABSTRACT

The Morita–Baylis–Hillman adducts derived from isatins and maleimides have undergone a facile and efficient allylic nucleophilic substitution reaction with X, S, N, and O-nucleophiles to afford functionalized tetrasubstituted alkene appended oxindoles in very good yield. The MBH adducts and their acetates on treatment with halides, saturated and unsaturated amines, thiols, and trialkyl orthoformates afforded allyl halide, allyl amine, allyl thio-ether and allyl ether derivatives of oxindole, respectively.

Development of novel methods to functionalize C-3 position of isatin is vital for the synthesis of 3-spirocarbocycle-2-oxindoles, 3-spiroheterocycle-2-oxindoles, 3-spirolactone-2-oxindoles, and 3-spirocyclicether-2-oxindoles that are elegant synthetic targets due to their significant biological activities.[1–3] The Morita–Baylis–Hillman (MBH) adducts[4] and their acetate derivatives have been used as synthons for the preparation of diverse and multifunctional molecules.[5] Isomerization of MBH adducts with catalysts such as H_2SO_4,[6] TFA[7] TMSOTf,[8] montmorillonite K10 clay,[9] and various nucleophiles provided highly functionalized trisubstituted alkenes.[10] They have also been served as versatile building blocks in the synthesis of natural products, heterocycles, and bio-active molecules.[11] We have exploited the MBH adduct of isatin for the synthesis of a number of 3-spiro-oxindole derivatives.[12,13] Recently, analogues synthesis of MBH adduct of isatin with maleimide has been reported.[14] However, except a lone [3+2]-cycloaddition reaction,[14,13c] no chemistry of this synthetically potential MBH adduct has been explored. Hence, we were intrigued to study the nucleophilic substitution reaction of MBH adducts with X, S, N, and O-nucleophiles, which in principle provide synthetically challenged, tetrasubstituted alkene appended oxindoles and to explore their synthetic use.

Initially, halogen as a nucleophile has been explored (Scheme 1). Thus, slurry prepared from MBH adduct of isatin **3a**, SiO_2, and aq HBr was irradiated in a microwave oven for 4 min.

The reaction afforded bromo allylic substituted product **5a** in a 43% yield as a major product and an unusual debrominated compound **6a** in a 11% yield as a minor product (Table 1, entry 1). Increase of irradiation time or 100% power level (PL) favored the debrominated product **6a** (Table 1, entries 2 and 3). Reactions under lower PL (50%), and reduced irradiation time (2 min) afforded only **5a**; however, in low yield (Table 1, entries 4 and 5). The reaction with extended irradiation time (10–15 min) with full 100% PL provided complex material.

It should be noted that under similar reaction conditions no debrominated products are formed from MBH adducts of isatin derived from activated alkenes such as acrylonitrile and methyl acrylate.[15] Thus, it is apparent that the debrominated product **6a** is formed from the allylic substituted product **5a**. A separate microwave irradiation reaction of bromo derivative **5a** with aq HBr/SiO_2 yielded only the eliminated product **6a** in a quantitative yield with the elimination of bromine, strengthening this observation. A plausible mechanism for the formation of **6a** from **5a** is shown in Scheme 2.

In order to increase the yield of **5a**, the reaction of **3a** in acetonitrile with other reagent system has been carried out, where the HBr gas has been generated in-situ (2 equiv of LiBr and 2.5 equiv of H_2SO_4), for 5 h at room temperature.[16] The reaction afforded

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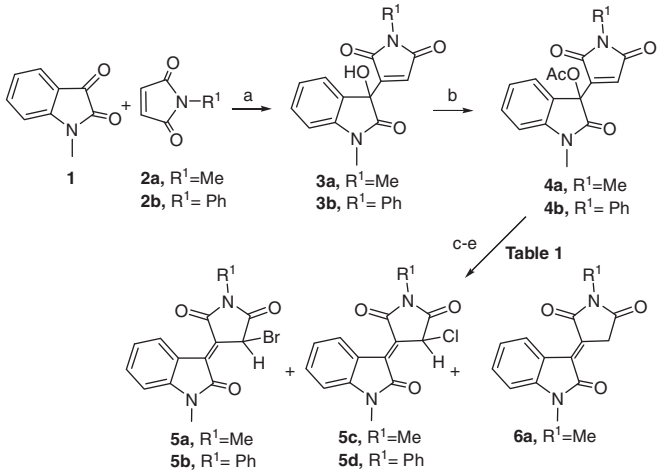


a. DABCO, CH_3CN, r.t., 24 h, 80%; b. AcCl, K_2CO_3, DCM, r.t.,12 h, 80%; c. aq.HBr, SiO_2, mW 70% PL, 4 min.; d. LiBr, H_2SO_4, CH_3CN, 0 °C-r.t.; e. LiCl, H_2SO_4,CH_3CN, 0 °C-r.t..

Scheme 1. Nucleophilic substitution reaction of MBH adducts **4a**/**4b** with halogen nucleophiles.

Table 1
Optimization of nucleophilic substitution reaction of **3a** with bromide as a nucleophile

Entry	Condition	Product(s) (% Yield)
1	aq HBr, SiO_2, μW, 70% PL, 4 min	**5a**(43), **6a**(11)
2	aq HBr, SiO_2, μW, 70% PL, 7 min	**5a**(20), **6a**(30)
3	aq HBr, SiO_2, μW, 100% PL, 4 min	**5a**(10), **6a**(40)
4	aq HBr, SiO_2, μW, 50% PL, 4 min	**5a**(20)
5	aq HBr, SiO_2, μW, 70% PL, 2 min	**5a**(16)
6	2 equiv LiBr, 2.5 equiv H_2SO_4, CH_3CN, 0 °C to rt, 5 h	**5a**(60)
7	2 equiv LiBr, CH_3CN, 0 °C to rt, 48 h	**5a**(15)
8	2 equiv LiBr, cat. H_2SO_4, CH_3CN, 0 °C to rt, 5 h	**5a**(76)

Table 2
Synthesis of allyl halides **5a–d** from MBH adducts **4a**/**b**

Entry	Substrate	Condition	Product	Yield (%)
1	**4a**/**b**	2 equiv LiBr, cat. H_2SO_4, CH_3CN, 0 °C to rt, 3 h	**5a**/**b**	82/80
2	**4a**/**b**	2 equiv LiCl, cat. H_2SO_4, CH_3CN, 0 °C to rt, 3.5 h	**5c**/**d**	82/81
3	**3a**/**4a**	KI, H_2SO_4, CH_3CN, rt, 3 h	—	—

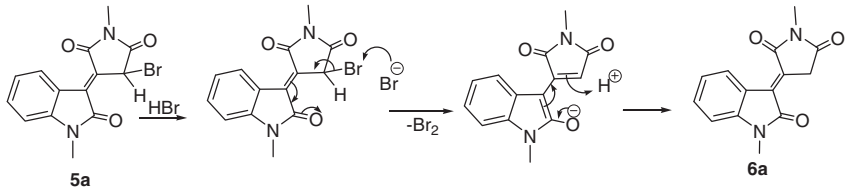
exclusively the bromo allylic substituted product **5a** in a 60% yield (Table 1, entry 6) with remaining charred material. To avoid charring due to excess of acid, an experiment with LiBr alone yielded bromo allylic substituted product **5a** only in 15% yield (Table 1, entry 7). However, reaction with 2 equiv of LiBr and a catalytic amount of H_2SO_4, **5a** was obtained in a 76% yield (Table 1, entry 8).

The observed moderate yield of **5a** under the conditions described above is perhaps due to the availability of free 3°-hydroxyl groups (Table 1, entries 1–8). Hence, to improve the yield, the hydroxyl group has been protected as acetate and the nucleophilic substitution reaction was studied. Thus, MBH adducts **3a** and **3b** were acylated using acetyl chloride and K_2CO_3 to yield protected adducts **4a** and **4b**, respectively, in excellent yield. Further nucleophilic substitution of acetates **4a** and **4b** under optimized condition described above (Table 1, entry 8) furnished bromo allylic substituted products **5a** and **5b** in 82% and 80% yields, respectively (Table 2, entry 1).

Extending the procedure to chloride as nucleophile, reactions of **4a** and **4b** with 2 equiv LiCl and catalytic amount of H_2SO_4 in CH_3CN yielded the chloro derivatives **5c** and **5d,** respectively, in excellent yield (Table 2, entry 2). However, attempts to use iodide as nucleophile with KI and H_2SO_4 for adducts **3a** and **4a** failed to provide desired products (Table 2, entry 3). The structure of the new compounds was arrived from spectroscopic data analysis (FTIR, ^{1}H NMR, ^{13}C NMR, DEPT-135, mass spectra, NOESY and single crystal X-ray data.). Z-geometry has been assigned for the double bond of compound **5c** as evidenced from single crystal XRD data[17] as shown in Figure 1. Further, the structure of debrominated product **7a** was confirmed from ^{1}H NMR spectrum as the presence of two methylene protons at δ 3.97 and a negative methylene carbon peak at δ 35.9 seen in the DEPT-135 spectrum.

Encouraged by the preliminary results, we were interested in studying the substitution reaction with sulfur nucleophiles although nucleophilic substitution of MBH adduct with sulfur nucleophile is less known (Scheme 3). Thus, acetate adduct **4a** in methanol was treated with *p*-thiocresol at room temperature afforded the allyl thio ether derivative **7a** in an 81% yield (Table 3, entry 1). Similarly, the α-toluenethiol and cyclohexanethiol with adduct **4b** also furnished corresponding thio allylic substituted products **7b** and **7c** in excellent yields (Table 3, entries 2 and 3). Appreciably, no catalyst was required for this transformation. The structure of compound **7a** was established from spectroscopic data analysis. Analysis of NOESY spectrum revealed the stereochemistry of double bond which is similar to that of compound **5c**.

To bring in diverse nucleophiles in the substitution reaction, nitrogen as nucleophile[18] was chosen. Therefore, the reaction of adduct **4a** in methanol with aryl amines and unsaturated aliphatic amine such as propargyl amine has been carried out (Scheme 4). Significantly, substitution reaction with propargyl amine afforded highly functionalized substituted *N*-propargylated secondary amine product **8a** in an 82% yield via an allylic substitution followed by 1,3-proton shift (Table 4, entry 1) and such type of allylic proton shift is facile under basic condition.[12c] Similarly, aniline and *p*-toluidine also acted as good nitrogen nucleophiles toward MBH adducts **4a** and **4b** to yield corresponding substituted products **8c/d** and **8e/f** in excellent yield, respectively (Table 4, entries 2 and 3). It should be noted that here also no catalyst was required for this transformation.



Scheme 2. Plausible mechanism for the formation of **6a**.