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1,3-Aminoalkoxylation and Phenolation/Dimerization of Maleimide-Derived Morita–Baylis–Hillman Adduct of Isatin via Domino Azidation–Michael Addition/Aza-Diels–Alder Reaction

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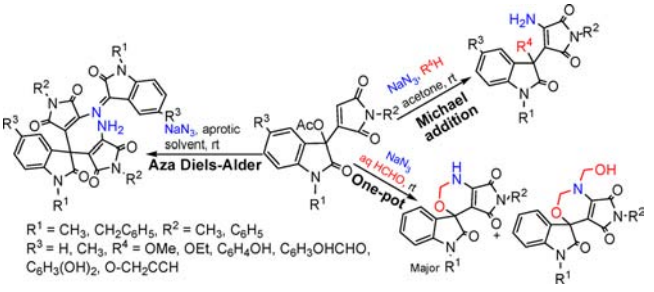
ABSTRACT



NaN_3–ROH/ArOH has been found to be an efficient reagent for 1,3-amino alkoxylation and 1,3-amino phenolation of a maleimide-derived MBH adduct of isatin via domino azidation–Michael addition. Following this protocol, with NaN_3–formalin, a one-pot synthesis of 3-spiro-1,2-dihydropyrrolooxazine-5,7-dione–oxindole has been achieved. In an aprotic medium, the reaction underwent an unusual amino dimerization via an aza-Diels–Alder reaction of a common allylic imine intermediate.

Functionalization at the C3 position of isatin via novel strategies has gained attention as the oxindole core has been found in a number of natural products and bioactive molecules.[1,2] The 3,4-disubstituted maleimide framework is also present in a number of natural products[3] and exhibits various biological activities.[4] The Morita–Baylis–Hillman (MBH) adducts[5] are well-known and have been used for the synthesis of multifunctional molecules.[6] The MBH adduct of isatin has served as a useful synthon for functionalized oxindole derivatives.[7] In general, nucleophilic

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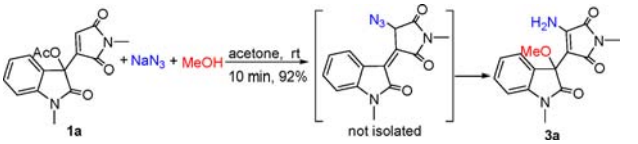
substitution of MBH adducts with sodium azide (NaN_3) resulted in allylic azide products.[8] In contrast to the previous reports, an unusual 1,3-amino alkoxylation/phenolation and 1,3-amino dimerization were observed with the maleimide derived MBH adduct, when reacted to NaN_3 with an alcohol/phenol and in an aprotic solvent, respectively. Organic azides are well-known as amine precursors where alcohols are converted into corresponding primary amines by a two-step process involving azidation and reduction of azide with various reducing agents[9] and catalysts.[10] Catalytic one-pot conversions of alcohols to amines are also known in the literature via azide intermediates.[11] An azide with adjacent oxo functionality possesses considerable synthetic value originated from the acidity of α-hydrogen.[12] Against this background, and also in continuation of our current interest in the functionalization of oxindoles via MBH adducts,[13] we report herein a catalyst-free one-pot transformation of maleimide derived MBH alcohol to amine along with simultaneous C3-functionalization of oxindole using NaN_3. The method has been successfully applied for synthesis of spiro-1,3-oxazine oxindole core. Various oxazine compounds have been found to show a range of bioactivities,[14] and methods for the synthesis of spiro-1,3-oxazine oxindoles are scarcely known in the literature.[15]

Initially, to perform the nucleophilic substitution reaction with azides, the maleimide-derived MBH adduct **1a** was treated with 1.2 equiv of NaN_3 in methanol at rt, forming a single amine with methoxylation at the C3 of oxindole **3a** in 92% yield in 10 min (Scheme 1). Thus, the reaction leads to amination of maleimide and simultaneous functionalization of C3 of oxindole. It should be noted that the amination–alkoxylation took place in a one-pot manner and in the absence of any catalyst or reducing agent.

Scheme 1. Reaction of MBH Adduct **1a** with NaN_3–MeOH



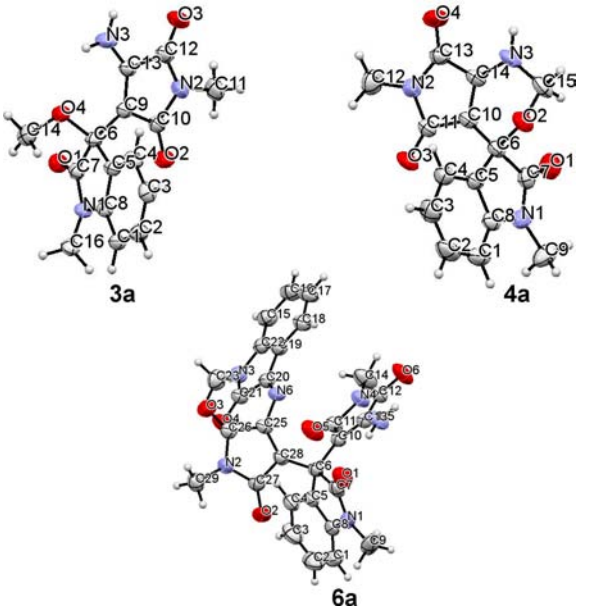


Figure 1. ORTEP diagram of compounds **3a**, **4a**, and **6a**.[16]

The structure of **3a** was assigned on the basis of spectroscopic data and single-crystal X-ray analyses (Figure 1).

The reaction holds with 1 equiv of MeOH in acetone as solvent. Reactions with EtOH and propargyl alcohol also resulted in 1,3-amino alkoxylation forming **3b** and **3c**, respectively (Scheme 2, Table 1, entries 2 and 3). The method was extended to phenol as the nucleophile, and the reaction led both ortho and para phenolation at the C3 of oxindole with amination at the maleimide core (Table 1, entry 4). The method has been found to be versatile for the substituted phenols, such as salicylaldehyde and resorcinol with 85% and 88% yields, respectively (Table 1, entries 5 and 6). The MBH adduct and the alcohol/phenol partner can be flexibly varied to produce a range of amino ether/amino-phenolated derivatives. The reaction was further generalized with various MBH adducts **1b**–**e** of isatin (Table 1, entries 7–14). As the O,C-nucleophiles were found to provide novel products, reactions with amines and thiols as nucleophiles were examined. However, the reactions ended only in allylic nucleophilic substitution with amines and thiols, respectively. The expected reaction with azide was not observed.

A plausible mechanism for the formation of **3** by invoking a domino azidation–Michael addition–tautomerism

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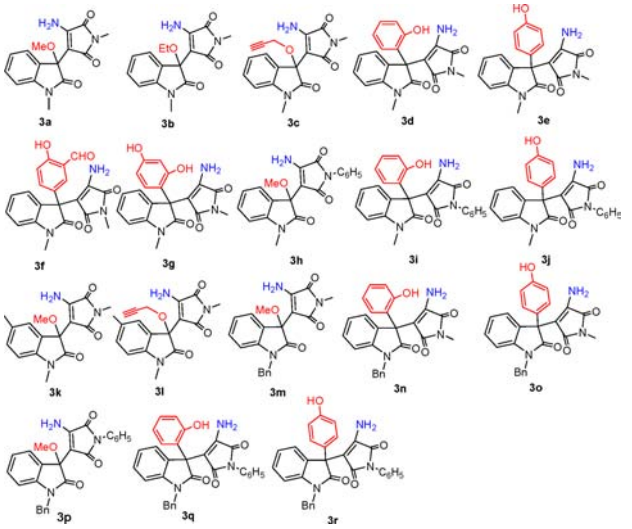
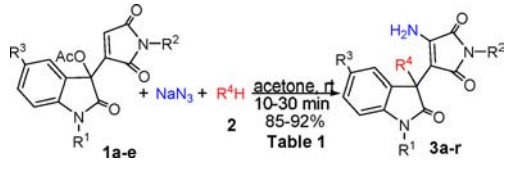
Table 1. Synthesis of **3a**–**r** from MBH Adducts **1a**–**e**[a]



	MBH adduct					
entry	R^1	R^2	**1**	R^4H **2**	time (min)	product(s)[b] **3** (%)
1	Me	Me	**1a**	MeOH	10	**3a** (92)
2[c]	Me	Me	**1a**	EtOH	10	**3b** (90)
3	Me	Me	**1a**	propargyl alcohol	20	**3c** (90)
4	Me	Me	**1a**	phenol	10	**3d** (55) **3e** (30)
5	Me	Me	**1a**	salicylaldehyde	30	**3f** (85)
6	Me	Me	**1a**	resorcinol	30	**3g** (88)
7	Me	C_6H_5	**1b**	MeOH	10	**3h** (90)
8	Me	C_6H_5	**1b**	phenol	10	**3i** (52) **3j** (33)
9[d]	Me	Me	**1c**	MeOH	10	**3k** (90)
10[d]	Me	Me	**1c**	propargyl alcohol	20	**3l** (90)
11	Bn	Me	**1d**	MeOH	10	**3m** (92)
12	Bn	Me	**1d**	phenol	10	**3n** (52) **3o**(30)
13	Bn	C_6H_5	**1e**	MeOH	10	**3p** (90)
14	Bn	C_6H_5	**1e**	phenol	10	**3q** (52) **3r** (34)

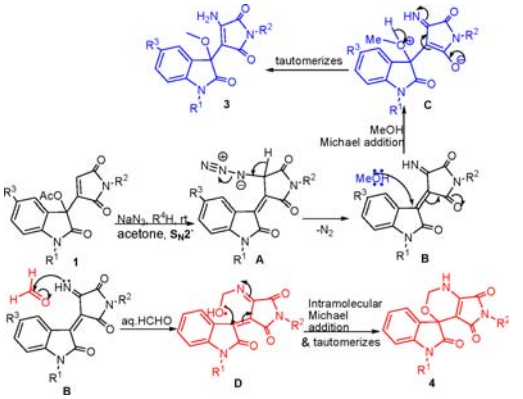
[a] All reactions were performed with 1.2 equiv of NaN_3 and 1.0 equiv of R^4H in acetone at rt. [b] Isolated yield. [c] Reaction was performed at 0–5 °C. [d] R^3 = Me.

Scheme 2. Reaction of MBH Adduct **1a** with NaN_3–ROH/PhOH



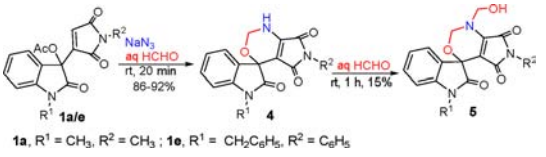
pathway is outlined in Scheme 3. In the initial step, nucleophilic displacement of acetate in the MBH adduct **1** with azide affords allylic azide **A** with neighboring oxo functionality. The increased C–H acidity of the α-hydrogen in the α-azido amide renders the expulsion of nitrogen molecule forming an α-imino amide **B**.[12a] Subsequent Michael addition of alcohols or phenols at the C3 of oxindole nucleus followed by tautomerism of resulted α-imino amide **C** provided resonance-stabilized α-enamino amide **3.**

Scheme 3. Plausible Mechanism of Formation of **3** and **4**



To demonstrate the synthetic diversity of the method, it has been successfully applied for the synthesis of novel 3-spiro-1,2-dihydropyrrolooxazine-5,7-dione–oxindoles by treating the MBH acetate **1a** with NaN_3 and formalin at rt for 20 min (Scheme 4). The 3-spiro oxazine oxindole derivative **4a** was formed in 92% yield and the structure was established based on spectroscopic and single crystal X-ray analyses.[16] When the reaction is allowed for 1 h, the free NH in **4a** got hydroxy methylated with excess formalin forming **5a** in 15% yield. Analogous formation of oxazine **4b** was observed from the adduct **1e** in 86% yield.

Scheme 4. One-Pot Synthesis of 3-Spiro-1,2-dihydropyrrolooxazine-5,7-dione–Oxindole **4** and **5**

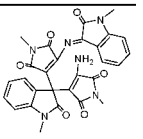
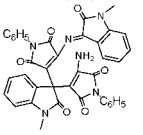
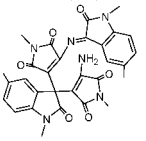
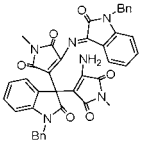


The formation of spiro-1,3-oxazine oxindole **4** could be explained by the nucleophilic addition of the allylic imine **B**, with formaldehyde forming a methanol amine intermediate **D**. An intramolecular Michael addition, followed by tautomerism of α-imino amide into resonance-stabilized α-enamino amide gives product **4** (Scheme 3).

During the course of the investigation, an obvious query arose about the reaction in aprotic medium, and that led to an unexpected amino dimerization product **6a**. Thus, the adduct **1a** was treated with NaN_3 in aprotic solvent acetone, and the reaction resulted in the formation of an unusual compound **6a** in 90% yield in 2 h (Scheme 5). The structure of the product **6a** was assigned by spectroscopic

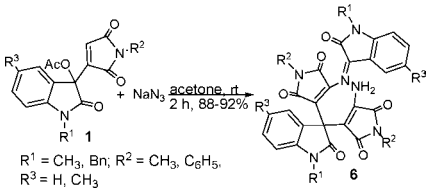
(16) CCDC 952979, 954486, and 952980 contains the supplementary crystallographic data of compounds **3a**, **4a** and **6a**, respectively. A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

Table 2. Synthesis of **6a**–**d** from MBH Adducts **1a**–**d**[a]

entry	MBH adduct			time (h)	yield of **6** (%)[b]
	R^1	R^2	**1**		
1	Me	Me	**1a**	2	 **6a** (90)
2	Me	C_6H_5	**1b**	2.5	 **6b** (88)
3[c]	Me	Me	**1c**	2.5	 **6c** (90)
4	Bn	Me	**1d**	2	 **6d** (88)

[a] All of the reactions were performed with 1.2 equiv of NaN_3 and 0.5 mL of acetone at rt. [b] Isolated yield. [c] R^3 = Me.

Scheme 5. Reaction of MBH Adduct **1a** with NaN_3 in Aprotic Medium



data analyses (IR, ^1H, ^{13}C NMR, and HRMS) and single-crystal X-ray analysis (Figure 1). A similar reaction was observed with other aprotic solvents such as DMF, DMSO, and acetonitrile. The analogous products **6b**, **6c**, and **6d** were formed from MBH adducts of 5-substituted, N-substituted isatin and N-substituted maleimide (Table 2, entries 2–4) generalizing the method.

In an aprotic medium, an aza Diels–Alder reaction[17] of intermediate **B** with itself, forming α-imino amide **E** followed by a skeletal rearrangement of α-imino amide **E** into

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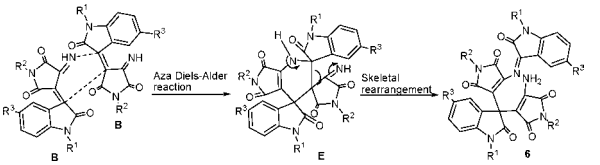
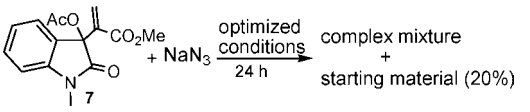
Scheme 6. Plausible Mechanism of Formation of **6** from the Common Intermediate **B**



Scheme 7. Reaction of MBH Adduct **7** with NaN_3



resonance-stabilized α-enamino amide, could probably explain the formation of amino-dimerized product **6** (Scheme 6).

However, experiments with the acrylate-derived MBH adduct of isatin **7**, under the above reaction conditions and also over longer reaction time (24 h), resulted a complex mixture with unreacted starting material (Scheme 7). The unusual reactivity of **7**, in comparison with the reactiviy of MBH adduct of bezaldehyde, may be due to the presence of the amide carbonyl of oxindole core adjacent to tertiary alcohol.

In conclusion, a facile method for a 1,3-aminoalkoxylation/phenolation of maleimide-derived MBH adduct has been developed using sodium azide and alcohols/phenols, and this method has been applied for the synthesis of 3-spirooxazine oxindole. An unusual amino dimerization product was noticed in an aprotic medium. The method features a simple experimental procedure under benign conditions. Further studies with utilization of these β-amino oxindoles for functionalization of a maleimide appended oxindole core are underway.

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Supporting Information Available. Detailed experimental procedure, spectroscopic data of new compounds, copies of spectra, and crystallographic data of compounds **3a**, **4a**, and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.