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Catalyst-Free One-Pot Tandem Reduction of Oxo and Ene/Yne Functionalities by Hydrazine: Synthesis of Substituted Oxindoles from Isatins

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An unprecedented one-pot tandem reduction of oxo and ene/yne functionalities of substituted isatins is disclosed for the synthesis of oxindole derivatives in excellent yields. The reaction is simply performed by treating *N*-(2-alkenyl)/propargylisatins with an excess amount of hydrazine hydrate (25 %) under catalyst-free refluxing conditions. The reduction process appears to be quite unique and proceeds quite efficiently without the aid of any catalyst at ambient pressure.

Introduction

The indolin-2-one or oxindole structural motif is considered to be an important ring system in heterocyclic chemistry owing to its presence in a wide variety of natural products and biologically active compounds.[1] Substituted and unsubstituted oxindoles also serve as crucial synthetic precursors for the synthesis of highly desirable indole-based heterocycles and alkaloids.[2] In the recent past, there has been considerable effort devoted to the development of an efficient and general synthesis of substituted oxindoles. Some of the synthetic strategies include cyclization of *o*-aminophenylacetic acid derivatives, oxidative *N*-heterocyclization of amino alcohols,[3] intramolecular amination,[4] oxidation of indoles,[5] radical cyclization,[6] intermolecular Heck reaction,[7] intramolecular arylation of amides[8] and amide enolates,[9] the Friedel–Crafts cyclization of α-halo[10] and α-hydroxy[11] acetanilides, and its modifications involving C–H functionalization.[12] However, the classical approach to access substituted oxindoles is based on the one-step derivatization of isatins under Wolff–Kishner reduction conditions involving hydrazine hydrate.[13–15] This strategy is still widely used and is quite appealing to synthetic chemists because several substituted isatins are commercially available and are relatively inexpensive. Moreover, the reductive transformation of isatins to oxindoles is generally a high-yielding process.

There have been previous reports describing the use of hydrazine hydrate in the selective reduction of unsaturated carbon–carbon bonds.[16] It is believed that hydrazine undergoes oxidation to produce diimide (N_2H_2) in situ, which acts as a transfer-hydrogenation agent in the reduction process.[17] Oxidants such as H_2O_2, $NaIO_4$, $K_3[(FeCN)_6]$, and even molecular oxygen have been shown to catalyze the selective reduction of unsaturated carbon–carbon bonds by using hydrazine.[17] The oxidation of hydrazine to diimide by using molecular oxygen typically requires a catalyst (e.g., copper, iron, and guanidine salts and various flavin derivatives) to promote the reaction.[17] Catalyst-free oxidation of hydrazine with molecular oxygen is rather inefficient, as it requires an excess amount of hydrazine and proceeds at a sluggish rate.[16] The reactive diimide intermediate is also prone to disproportionation (reformation to hydrazine) and over oxidation under these conditions.[16] In recent times, specialized reactors have been developed to perform the catalyst-free selective reduction of terminal olefins by using hydrazine hydrate and molecular oxygen at high temperature and pressure in continuous-flow mode.[17]

Since the first application of the Wolff–Kishner reaction in the synthesis of oxindoles from isatins,[13a] the chemistry community has used this methodology extensively. A SciFinder survey revealed a total of 120 references to date reporting the conversion of various substituted isatins into oxindoles under these conditions. To the best of our knowledge, there is only one report of a Wolff–Kishner reduction on a *N*-ene-/yne-substituted isatin in the chemical literature.[18] Recently, while describing the synthesis of the hodgkinsine and hodgkinsine B alkaloids, Willis et al. reported the synthesis of *N*-allyloxindole from *N*-allylisatin (**1a**) in only 20% yield (reported in the Supporting Information) by using hydrazine hydrate.[18] The reasons behind such a poor yield were not discussed in the paper. On the basis of our results (see below), we suspect the loss in yield could be caused by the reduction of the allyl group under these conditions. It is quite possible that other researchers may have faced a similar challenge while attempting to prepare

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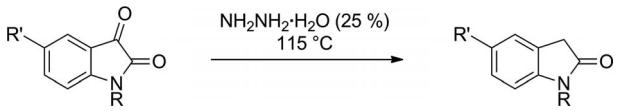
N-alkenyl/alkynyloxindoles from the corresponding isatins, and the undesired results were never reported. In this communication, we report the tandem reduction of oxo- and *N*-ene-/yne-substituted isatins to oxindole derivatives, which offers novel insight into the scope of the Wolff–Kishner procedure. The reaction is performed under catalyst-free refluxing conditions in the presence of hydrazine hydrate (25% in H_2O). We believe these counterintuitive results will be of significant importance to the synthetic and medicinal chemistry community.

Results and Discussion

Several substituted isatins were obtained from commercial sources and were converted into *N*-(2-alkenyl)/propargyl derivatives **1a**–**n** in quantitative yields by using reagents such as allyl bromide, prenyl bromide, cinnamyl bromide, and propargyl bromide following a published procedure.[19] These substitutions are important as such and are also aptly suited for further chemical manipulations. Inspired by previous reports of the Wolff–Kishner procedure for the preparation of oxindoles from isatins, we initially subjected *N*-allylisatin (**1a**) to an excess amount of hydrazine hydrate at reflux temperature (115 °C).[14] Clean conversion of the reactant to the product was evidenced by TLC analysis. The NMR spectroscopic data of the isolated product revealed that along with the C3 oxo group of isatin the allyl group was also reduced efficiently to deliver 1-propyl-2-oxindole (**2a**). If the temperature of the reaction was lowered to 80 °C, the reaction did not go to completion. A significant amount of the starting material remained unreacted in the reaction mixture even after 48 h of heating. Subsequently, we settled with the reflux temperature and decided to investigate in detail the reduction of *N*-(2-alkenyl)/propargylisatins possessing differently substituted unsaturated carbon–carbon bonds by using hydrazine hydrate.

As shown in Table 1, the tandem reduction of the C3 ketone and the olefinic group proceeded quite smoothly for isatins bearing monosubstituted and disubstituted unsaturations. The yields of the isolated products in all cases were found to be high except for nitro-substituted isatin **1j**. Interestingly, the nitro group along with the oxo and olefin functionalities also underwent reduction to afford 5-amino-1-(3-phenylpropyl)indolin-2-one (**2j**) in 57% yield. Although the reduction of nitroarenes by using hydrazine hydrate has been previously reported, the use of an iron source appears to be a necessary condition to catalyze the reduction process.[20] Furthermore and quite surprisingly, selective reduction of the C3 oxo group was observed for *N*-prenylisatin (**1k**, a trisubstituted carbon–carbon unsaturation; Table 1, entry 11) to produce 1-prenyl-2-oxindole (**2k**). Even after 24 h of refluxing, the olefin group of **1k** was not reduced under these reaction conditions. The yield (20%) for the synthesis of related compound *N*-allyloxindole by Willis et al. was reported to be over two steps starting from isatin (*N*-allylation followed by hydrazine-mediated reduction of the C3 oxo group). Among the two steps, the *N*-allylation of isatin presumably proceeds in near-quantitative yield, and we suspect the bulk of the loss in the yield might occur in the reduction step, as our results show that the allyl group is prone to reduction under these conditions (Table 1, entry 1).

Table 1. Tandem reduction of oxo- and ene-/yne-substituted isatins by using hydrazine hydrate.[a]



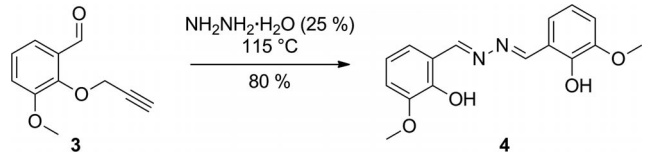
Entry	Substrate			Product			Time	Yield[b]
		R′	R		R′	R	[h]	[%]
1	**1a**	H	allyl	**2a**	H	propyl	4	83
2	**1b**	CH_3	allyl	**2b**	CH_3	propyl	4	81
3	**1c**	Cl	allyl	**2c**	Cl	propyl	4	80
4	**1d**	Br	allyl	**2d**	Br	propyl	5	78
5	**1e**	F	allyl	**2e**	F	propyl	4	80
6	**1f**	H	cinnamyl	**2f**	H	3-phenylpropyl	14	75
7	**1g**	CH_3	cinnamyl	**2g**	CH_3	3-phenylpropyl	14	73
8	**1h**	Cl	cinnamyl	**2h**	Cl	3-phenylpropyl	14	71
9	**1i**	F	cinnamyl	**2i**	F	3-phenylpropyl	14	71
10	**1j**	NO_2	cinnamyl	**2j**	NH_2	3-phenylpropyl	4	52
11	**1k**	H	prenyl	**2k**	H	prenyl	24	89
12	**1l**	H	propargyl	**2a**	H	propyl	4	71
13	**1m**	CH_3	propargyl	**2b**	CH_3	propyl	4	70
14	**1n**	Cl	propargyl	**2c**	Cl	propyl	4	68

[a] Reaction conditions: Isatin (30 mg), $NH_2NH_2·H_2O$ (25%, 2 mL), reflux. [b] Yield if isolated product.

Next, isatins **1l**–**n** possessing an alkyne group were exposed to similar conditions. Remarkably, these propargyl-substituted isatins also underwent a tandem reduction to produce 1-propyl-2-oxindoles quite efficiently (Table 1, entries 12–14). Encouraged by these results, we subsequently attempted to scale up the reaction from milligram scale to gram quantities. We were quite happy to find that the reaction could be scaled up without any difficulty. A typical example of scale-up conditions is the following: 1 g of *N*-allylisatin (**1a**) was heated at reflux in 30 mL of hydrazine hydrate (25%), which resulted in 0.81 g of 1-propyl-2-oxindole (**2a**, 87%) in 4 h.

We further proceeded to investigate the reduction of compounds having a substitution makeup of oxo– and carbon–carbon unsaturations, analogous to the isatins described above by using hydrazine hydrate (Scheme 1). Interestingly, such compounds, that is, 2-methoxy-6-(prop-2-ynyloxy)benzaldehyde (**3**), underwent condensation with hydrazine to produce aldazine **4** under the reaction conditions. Notably, the alkyne functionality of the propargyl group of **3** was not reduced under these conditions, but the entire group was lost during the process (Scheme 1). The spectroscopic data of **4** was found to be in agreement with the literature report.[21]

It appears from our results that the tandem reduction of the oxo and ene/yne functionalities by using hydrazine is unique to *N*-(2-alkenyl)/propargylisatins, for which the reduction of the C3 oxo group involves the well-known Wolff–Kishner mechanism, and the reduction of the olefinic



Scheme 1. Reaction of hydrazine hydrate with 2-methoxy-6-(prop-2-ynyloxy)benzaldehyde (**3**).

group is facilitated by the in situ formation of a diimide (created by the aerobic oxidation of hydrazine hydrate), which is consistent with the previously reported mechanism.[16] Currently, we are actively evaluating the full scope of this mechanism.

Conclusions

In conclusion, the reduction of *N*-(2-alkenyl)/propargylisatins by using hydrazine hydrate (25% in H_2O) led to *N*-alkyloxindoles. This is an unprecedented example of a tandem reduction of two functionalities (i.e., oxo group and alkene/alkyne) present in isatin under catalyst-free conditions at ambient pressure. The reaction offers clean conversion of the reactants into products in excellent yields, which can be easily scaled up to gram quantities. As an added advantage, the *N*-(2-alkenyl)/propargylisatins can potentially be further chemically manipulated (e.g., chain elongation by using the alkyne functionality) to prepare diversely substituted oxindoles. The observed counterintuitive double reduction provides further insight into the full scope of the Wolff–Kishner procedure to prepare substituted 2-oxindoles.

Experimental Section

General Procedure for the Synthesis of Substituted Oxindoles by using Hydrazine Hydrate: *N*-(2-Alkenyl)/propargylisatin **1** (0.03 g) was mixed with hydrazine hydrate (25%, 2 mL) and heated at 115 °C (see Table 1 for the reaction time). Upon completion of the reaction (as evidenced by TLC), the excess amount of hydrazine hydrate was evaporated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel; hexanes/ethyl acetate, 96:04) to give 1-alkyl-2-oxindole **2**.

Supporting Information (see footnote on the first page of this article): Spectroscopic data and the copies of the ^{1}H NMR and ^{13}C NMR spectra for products **1a**–**n**, **2a**–**k**, and **4**.

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