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A Morita-Baylis-Hillman Pathway to Wittig Products: One-pot Transformation of Nitroalkylideneoxindoles to Oxindolylidene-carboxylates

Lakshminarayana Satham,[a] Chenikkayala Siva Sankara[a] and Irishi N. N. Namboothiri[a]*

Abstract: An unusual Morita-Baylis-Hillman (MBH) type reactivity of isatin-derived nitroalkenes with activated carbonyl compounds has been demonstrated for the first time. The unexpected 3-alkylideneoxindole esters were formed in moderate to excellent yields with complete stereoselectivity (only *E*-isomer). The proposed mechanism based on control experiments involves a hybrid MBH-Wittig pathway.

3-Alkylideneoxindoles exhibit a wide variety of biological properties and are also versatile building blocks for the synthesis of diverse heterocycles, especially spiro-heterocycles.[1] 3-Oxindolylidenecarboxylate, in particular, exists in bioactive indole alkaloids, e.g. costinone A,[2] and several other bioactive compounds, e.g. **A-D**, which exhibit anti-fouling (**A**),[3] anti-inflammatory (**B**)[4] and Cdc25A inhibitory (**C-D**)[5] activities (Figure 1).

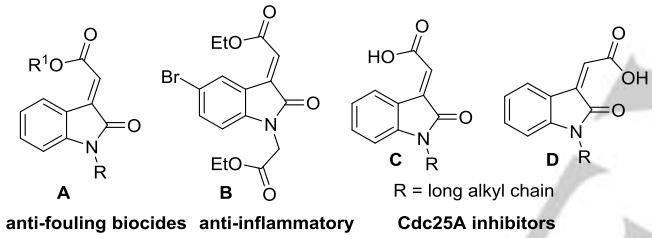
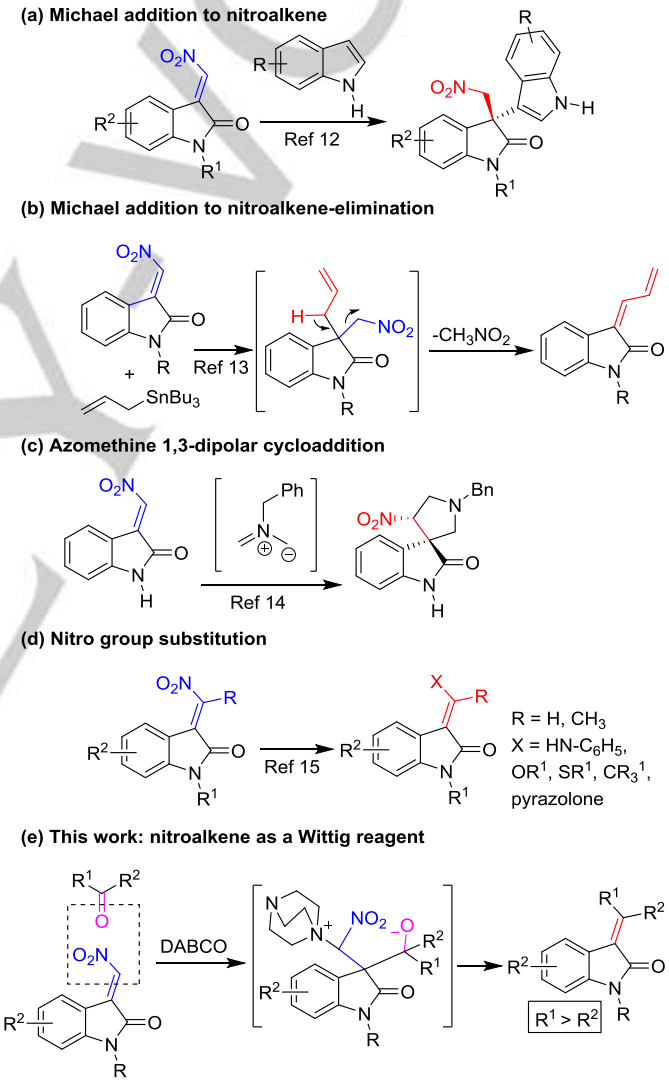


Figure 1. Selected bioactive compounds containing 3-alkylideneoxindole moiety.

The commonly used method for the synthesis of 3-oxindolylidenecarboxylates is the Wittig reaction of isatin with alkoxycarbonylmethylene(triphenyl)phosphoranes. However, the Wittig reaction suffers from poor and/or unpredictable *E*/*Z* selectivity due to its sensitivity to substituents and reaction conditions.[6] Other methods include Pd-catalyzed oxidative carbonylation of 2-ethynylanilines,[7] Ni-catalyzed cyclization of N-alkenyl-o-chloroanilines,[8] phenoxide cyclization followed by dehydrogenation[9] and a 1,3-dipolar-inverse 1,3-dipolar-olefination involving isatin and ethyl isocyanoacetate,[10] to name a few.

The isatin-derived nitroalkene possesses a 3-alkylideneoxindole moiety which is a skeleton of pharmacological importance.[11] As for the chemistry of such nitroalkenes, nucleophilic addition at the β-position of the nitro group (Scheme 1a-b),[12-13] 1,3-dipolar cycloaddition which also involves addition of the negative end of the dipole at the β-position of the nitro group (Scheme 1c)[14] and nucleophilic addition at the α-position followed by elimination of the nitro group (Scheme 1d)[15] are reported. However, a Morita-Baylis-Hillman[16] or Wittig type reactivity of isatin-derived nitroalkene (Scheme 1e) remains unreported, to our knowledge.



Scheme 1. Diverse reactivity of isatin-derived nitroalkene.

As a part of our ongoing interest in the Morita-Baylis-Hillman (MBH) reaction of *β*-substituted nitroalkenes and synthetic applications of their adducts,[17] we wished to investigate the reactivity of *β*-disubstituted nitroalkenes such as isatin-derived nitroalkenes as substrates in the MBH reaction. Although diverse reactivities of isatin-derived nitroalkenes have already been reported,[12-15] their total absence, and near absence of other *β*-disubstituted activated alkenes[18] from the MBH literature

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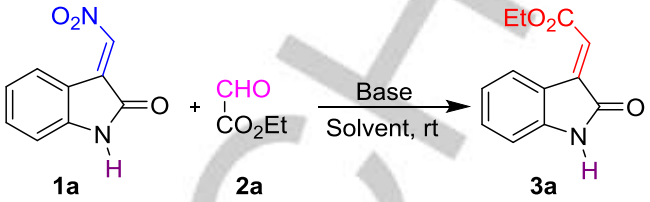
prompted us to utilize them as substrates in the MBH reaction with activated carbonyl compounds as electrophiles. In principle, these isatin-derived nitroalkenes could undergo α-hydroxyalkylation with carbonyl compounds *via* MBH reaction leading to the corresponding multifunctional adducts. However, much to our surprise, the reaction took an unexpected pathway via hydroxyalkylation of the β-position of the nitro group, in which the enamide acted as the Michael acceptor, providing 3-alkylideneoxindole esters as single geometrical isomers (Scheme 1e).

To demonstrate the use of nitroenamide **1** as the substrate in the MBH reaction, we started with the preparation of **1** by developing a convenient procedure which is different from that in the literature.[11,13,15] Thus, isatins were treated with nitromethane in the presence of catalytic amount of piperidine which resulted in nitroaldol adducts in almost quantitative yields within 15 min at room temperature. These adducts were further subjected to elimination by using thionyl chloride in the presence of triethylamine. The isatin-derived nitroalkenes **1** were formed in good yields with moderate to high *E*/*Z* ratios in 30 min in most cases (see the SI).

After the successful preparation of a variety of nitroenamides **1**, we have envisioned their reactivity with an activated carbonyl compound such as ethyl glyoxalate **2a**.[19] Our investigation started by stirring a mixture of representative nitroenamide **1a** and ethyl glyoxalate **2a** in acetonitrile in the presence of imidazole (1 equiv) at ambient temperature. Surprisingly, instead of the expected multifunctional MBH adduct, either of the nitroalkene moiety or of the enamide moiety, 3-alkylideneoxindole ester **3a** was formed as the sole product in 55% yield within 24 h (Table 1, entry 1). Since the unexpected product **3a** is a known compound, it could be easily characterized by comparing its physical and spectral data with those reported in the literature.[4] It is important to mention that ester **3a**, formed by the unexpected reactivity of nitroenamide **1a** and glyoxalate **2a**, was isomerically pure (exclusively the *E*-isomer). The above result encouraged us to further optimize the reaction conditions. When we employed 1 equiv of DMAP as the nucleophilic base, only traces of product **3a** were formed (entry 2). However, in the presence of 1 equiv of DABCO, the reaction was complete in 40 min and the product **3a** was formed in 70% yield (entry 3). Lower yield (55%) and longer reaction time (24 h) were encountered upon lowering the quantity of DABCO to 0.5 equiv (entry 4). There was no reaction when tricyclohexyl phosphine and triethylamine were used as the catalysts (entries 5, 6 and 17). Only trace amount of product **3a** was obtained upon decreasing the concentration of the reaction mixture to 0.05 M (entry 7). When the reaction was carried out at higher concentration (0.2 M), the yield dropped to 42% (entry 8). In order to further optimize the conditions, the amount of glyoxalate **2a** was varied. When 2.0 equiv of **2a** was employed, the yield further dropped to 32% and prolonged time was necessary to complete the reaction (entry 9). There was slight improvement in the yield with 6.0 equiv of glyoxalate **2a** (entry 10), but further increasing the amount of **2a** to 10.0 equiv resulted in decrease in the yield (entry 11). In subsequent attempts, we have screened few other solvents such as MeOH, DCM, HMPA and 1,4-dioxane. The product **3a** was isolated in moderate yield, when MeOH, DCM and 1,4-dioxane were used as solvents (entries 12-13 and 15). However, there was no reaction in HMPA (entry 14) and the reaction in 1,4-dioxane, in the presence of LiCl as additive, resulted in traces of the product **3a** (entry 16). From the above results, we selected conditions in entry 3 to study the substrate scope.

Table 1. Optimization of reaction conditions.[a]



1a **2a** **3a**

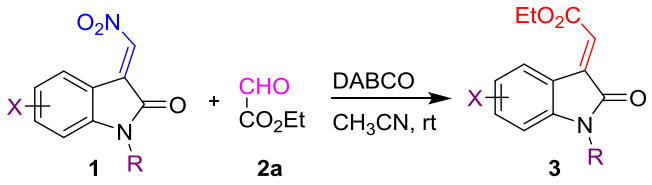
entry	**2a**/ equiv	base/equiv	solvent/mL	time	yield/%[b]
1	4	Imidazole (1.0)	CH_3CN/1.0	24 h	55
2	4	DMAP (1.0)	CH_3CN/1.0	2 h	Traces
3	**4**	**DABCO (1.0)**	**CH_3CN/1.0**	**40 min**	**70**
4	4	DABCO (0.5)	CH_3CN/1.0	24 h	55
5	4	$P(Cy)_3$ (1.0)	Toluene/1.0	48 h	No reaction
6	4	$P(Cy)_3$ (1.0)	CH_3CN/1.0	48 h	No reaction
7	4	DABCO (1.0)	CH_3CN/0.5	5 min	Traces
8	4	DABCO (1.0)	CH_3CN/2.0	24 h	42
9	2	DABCO (1.0)	CH_3CN/1.0	24 h	32
10	6	DABCO (1.0)	CH_3CN/1.0	40 min	71
11	10	DABCO (1.0)	CH_3CN/1.0	40 min	65
12	4	DABCO (1.0)	MeOH/1.0	30 min	55
13	4	DABCO (1.0)	DCM/1.0	1 h	50
14	4	DABCO (1.0)	HMPA/1.0	24 h	No reaction
15	4	DABCO (1.0)	1,4-dioxane/1.0	36 h	64
16	4	DABCO (1.0)	1,4-dioxane/1.0	48 h	Traces[c]
17	4	Et_3N (1.0)	CH_3CN/1.0	48 h	No reaction

[a] Reaction scale: nitroalkene **1a** (0.1 mmol), ethylglyoxalate **2a** (50% in toluene, 0.5-1.0 mmol, 2-10 equiv), base (0.5-1.0 equiv), solvent (0.5-2.0 mL). [b] After silica gel column chromatography. [c] 0.1 mmol of LiCl as additive.

With the optimized reaction conditions in hand, we decided to investigate the scope and generality of this unusual transformation. Initially, different substituents on ring nitrogen as well as substitution on benzo-group of nitroenamide **1** with ethyl glyoxalate **2a** were investigated (Table 2). Besides the *N*-unsubstituted nitroenamide **1a** which reacted very well and rendered ester **3a** in good yield (entry 1), nitroenamides **1b**-**1d** bearing methyl, allyl and propargyl substituents on ring nitrogen afforded the corresponding products **3b**-**d** in moderate yield (37-41%, entries 2-4). The *N*-benzyl and *N*-4-chlorobenzyl substituted nitroenamides **1e-f** also reacted well and afforded the corresponding products **3e**-**f** in moderate yields (44-49%, entries 5-6). Then the reactivity of nitroenamide **1** with different substituents on the benzo group, but devoid of any substituent

on ring *N* was evaluated. To our delight, substituents such as methoxy, chloro, bromo, and methyl at position 5 in nitroenamides **1g-j** were well tolerated and the corresponding products **3g-j** were formed in moderate to good yields (51-69%, entries 7-10). Quite remarkably, all the reactions were complete in an hour or less and all the products, 3-alkylideneoxindole esters **3**, were single geometrical isomers (*E*-isomers).

Table 2. Scope of nitroisatylidenes in the reaction with ethyl glyoxalate.[a]



entry	1	R	X	time/min	3	yield/%[b]
1	**1a**	H	H	40	**3a**	70
2	**1b**	Me	H	60	**3b**	37
3	**1c**	Allyl	H	45	**3c**	41
4	**1d**	Propargyl	H	60	**3d**	41
5	**1e**	Bn	H	60	**3e**	49
6	**1f**	4-Cl-Bn	H	60	**3f**	44
7	**1g**	H	5-OMe	45	**3g**	51[c]
8	**1h**	H	5-Cl	60	**3h**	64
9	**1i**	H	5-Br	30	**3i**	56
10	**1j**	H	5,7-Me_2	30	**3j**	69

[a] Reaction scale: nitroalkene **1** (0.2 mmol), ethyl glyoxalate **2a** (50% in toluene, 0.8 mmol, 4 equiv), DABCO (0.2 mmol, 1.0 equiv), CH_3CN (2.0 mL). [b] After silica gel column chromatography. [c] 30% 5-OMe-isatin was isolated.

Some of the 3-alkylideneoxindole esters **3** are known compounds and could be characterized by comparison of their physical and spectral data with those in the literature.[4] The structure and double bond geometry of the products **3** were further unambiguously confirmed by single crystal X-ray analysis of a representative compound **3h** (Figure 2).

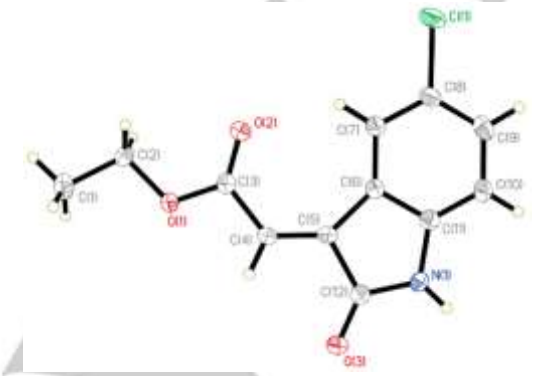
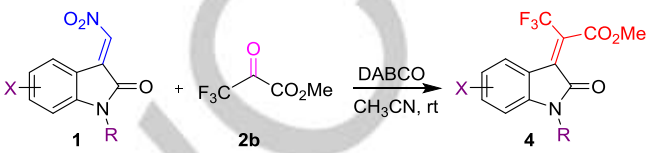


Figure 2. X-ray Crystal Structure of **3h** (CCDC 2001024).

After demonstrating the reactivity of isatin-derived nitroalkenes **1** with ethyl glyoxalate **2a**, we were interested in expanding the substrate scope by treating **1** with several other easily available activated carbonyl compounds. Our attempts to perform the reaction of nitroenamide **1a** with carbonyl compounds such as formaldehyde, ketomalonate, ninhydrin etc under the optimized conditions were unsuccessful (see the SI). However, methyl 3,3,3-trifluoropyruvate **2b** turned out to be a useful electrophile which reacted well with some of the nitroenamides **1** (Table 3).

Table 3. Scope of nitroisatylidenes in the reaction with methyl 3,3,3-trifluoropyruvate.[a]



entry	1	R	X	time/h	4	yield/%[b]
1	**1a**	H	H	24	**4a**	90[c]
2	**1b**	Me	H	24	**4b**	Traces
3	**1e**	Bn	H	15	**4c**	Traces
4	**1g**	H	5-OMe	48	**4d**	…[d]
5	**1h**	H	5-Cl	30	**4e**	69
6	**1i**	H	5-Br	30	**4f**	68
7	**1j**	H	5,7-Me_2	48	**4g**	…[d]

[a] Reaction scale: nitroisatylidenes **1** (0.2 mmol), trifluoropyruvate **2b** (0.2 mmol, 1.0 equiv), DABCO (0.2 mmol, 1.0 equiv), CH_3CN (2.0 mL). [b] After silica-gel column chromatography. [c] 3 mmol scale: 30 h, 85% yield. [d] 50-53% of corresponding isatins were isolated.

Initially, the *N*-unprotected nitroalkene **1a** was treated with trifluoropyruvate **2b**. The reaction proceeded well and the corresponding ester **4a** was isolated in excellent yield (entry 1). Unfortunately, the *N*-methyl and *N*-benzyl substituted nitroalkenes **1b** and **1e** afforded only trace amounts of the products **4b** and **4c** (entries 2-3). Subsequently, the efficacy of benzo-substituted, *N*-unprotected nitroenamides **1g**-**1j** in their reaction with trifluoropyruvate **2b** was evaluated. Notably, nitroenamides **1h-i**, bearing weakly electron withdrawing substituents such as chloro and bromo, reacted with trifluoropyruvate **2b** under the optimized conditions and furnished the corresponding products **4e** and **4f** in good yields (entries 5-6). But, nitroenamides **1g** and **1j**, bearing electron donating substituents such as methoxy and methyl on the benzo group, did not afford the expected products **4d** and **4g**, instead, underwent hydrolysis to the corresponding isatins (entries 4 and 7). As in the case of glyoxalates, the trifluoropyruvate adducts **4a**, **4e** and **4f** were obtained as single geometrical isomers (*E*-isomers) though the reaction times were much longer.[20]

The preparative usefulness of this unusual reactivity of isatin-derived nitroalkene **1** with carbonyl compounds **2** in the presence of DABCO as the nucleophilic base was later investigated by performing the reaction of **1a** with **2b** on a gram scale. Pleasingly, the reaction was complete in 30 h and the product **4a** was isolated in high (85%) yield.

The structure and the double bond geometry of the products **4a**, **4e** and **4f** were confirmed by detailed analysis of their spectral characteristics, particularly, ^{1}H–^{1}H 2D-COSY and ^{1}H–^{1}H 2D-NOESY analysis. Further unambiguous assignment was carried out by single crystal X-ray analysis of a representative compound **4a** (Figure 3).

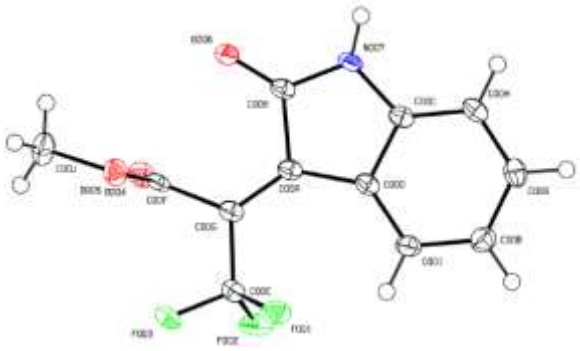


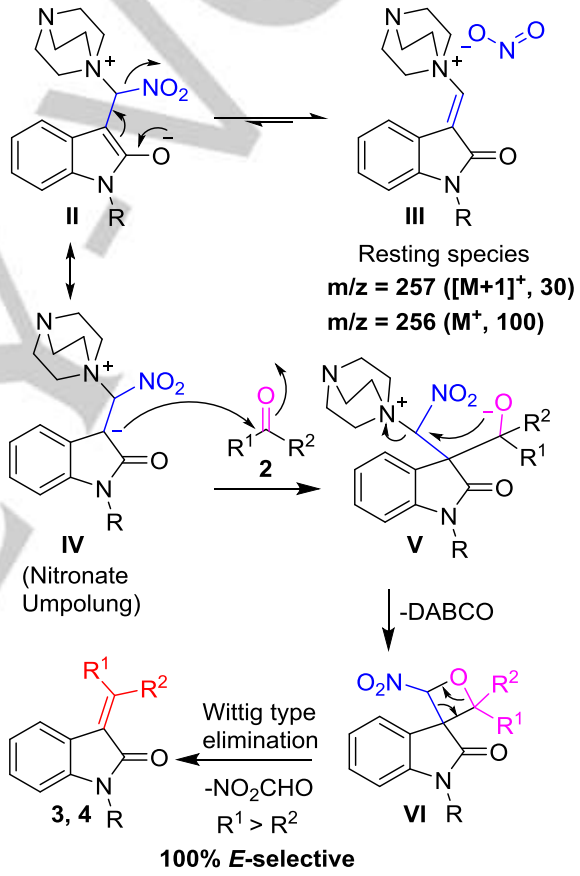
Figure 3. X-ray Crystal Structure of **4a** (CCDC 2002891).

In order to gain insights into the mechanism of the serendipitous formation of 3-alkylideneoxindole esters **3** and **4** by the reaction of isatin-derived nitroalkene **1** with activated carbonyl compounds **2** in the presence of DABCO as the nucleophilic base, we have performed multiple control experiments (see the SI). On the basis of the control experiments, a plausible mechanism was proposed as illustrated in Scheme 2. At first, DABCO adds to *α*-position of nitroalkene **1** (the enamide part of the alkylideneoxindole moiety behaves as the Michael acceptor) resulting reactive enolate **II** or **IV**. This site selectivity is consistent with the previously observed reactivity of 'hard' heteroatom centered nucleophiles with nitroalkene **1** (see Scheme 1d).[15] Steric factors also appear to favor the attack of DABCO at the *α*-position of nitroalkene **1**. In this case, DABCO converts an electrophilic carbon into a nucleophilic carbon (umpolung).

The transient intermediates **II** and **IV**, which are resonance structures with less charge separation in **IV**, could be in equilibrium with the relatively stable enaminium intermediate **III** (resting species). However, since the DABCO attached carbon in **III** is highly electrophilic, even the weakly nucleophilic nitrite (NO_2^-) could counter-attack to regenerate intermediate **II** or **IV** (reactive species) which adds to the carbonyl compound **2** resulting in the zwitterionic intermediate **V**. In the presence of less reactive electrophiles (*vide supra* and also the SI), a retro-Michael addition appears to be the probable pathway.

The above Michael addition-aldol reaction steps are identical to the first two steps in the classical MBH reaction, considering that the enamide moiety is the Michael acceptor. But since there is no hydrogen present at the *α*-position of the carbonyl group in adduct **V**, elimination of DABCO would be possible only via its intramolecular displacement by the alkoxide. Such a displacement would generate a spiro-oxetane intermediate **VI**. Wittig type elimination of NO_2CHO from intermediate **VI** provides 3-alkylideneoxindole ester **3** or **4**.

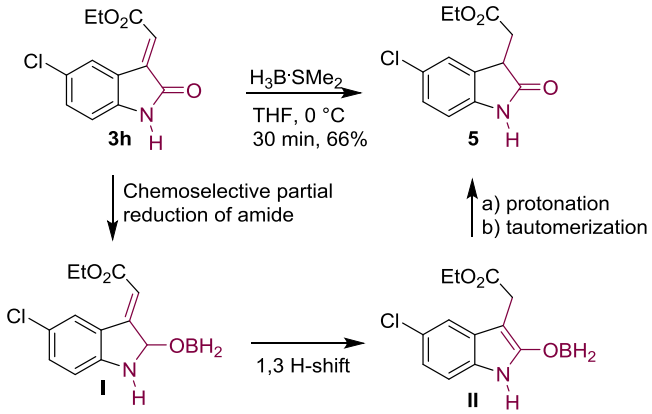
As shown in the mechanism (Scheme 2), the formation of product **3** or **4** appears to be taking place *via* intermediates **II**-**VI**. In order to characterize one or more of these intermediates during this unusual transformation, we have performed NMR (^{1}H and ^{13}C) and Mass analysis of a mixture of nitroalkene **1a** and DABCO. While the NMR experiments, though conducted in deuterated acetonitrile, was inconclusive due to the complex nature of the spectra, Mass analysis enabled us to detect the intermediate **III** (resting species). Then trifluoropyruvate **2b** was added to the reaction mixture. The formation of product **4a** was observed without sufficient evidence for intermediates **V** or **VI** or the elimination product NO_2CHO proposed above (Scheme 2). These results prompted us to conclude that the stable intermediate **III** was formed in the reaction mixture, but it spontaneously reacted through intermediates **II** and **IV** with the carbonyl electrophile **2** leading to the formation of product **4a**. The intermediates **II** and **IV**-**VI** as well as the elimination product NO_2CHO[21] were not detected by NMR or Mass due to their transient nature.



Scheme 2. Proposed mechanism for the unusual reactivity of nitroisatylidene.

As part of our efforts to develop synthetic applications of the products, BH_3.DMS reduction of a representative ester **3h** was carried out. Although an electrophilic reducing agent such as BH_3.DMS was expected to selectively reduce the amide carbonyl group in the presence of a conjugated ester,[22] in our hands, selective reduction of the double bond (conjugate reduction) took place to afford product **5** in decent yield. This transformation appears to be taking place via partial reduction of amide to intermediate **I**, followed by a 1,3-proton transfer to form intermediate **II**. Protonation of intermediate **II** and tautomerization would deliver product **5**. Although product **5** could be more reactive than starting conjugated amide **3h** towards BH_3.DMS, we have been able to isolate amide **5** in

decent yield (66%) under our controlled conditions (0 °C, 30 min and immediate workup).



Scheme 3. Unusual reduction of electron deficient double bond with electrophilic borane.

In summary, we have demonstrated an unusual Morita-Baylis-Hillman type reactivity of isatin-derived nitroalkenes with different activated carbonyl compounds leading to Wittig olefination products. The unexpected products, 3-alkylideneoxindole esters, were formed in moderate to excellent yields and as single geometrical isomers (*E*-isomers). The control experiments performed provided valuable insights into the mechanism of this unexpected Wittig type olefination of isatin-derived nitroalkenes with activated carbonyl compounds in the presence of DABCO as the nucleophilic amine catalyst. Interestingly, the activated alkene in this case is the enamide rather than nitroalkene. Our future efforts will be focused on expanding the scope and applications of this unusual transformation.

Acknowledgements

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Keywords: Nitroalkenes • Morita-Baylis-Hillman Reaction • Wittig olefination • Isatin • Oxindole

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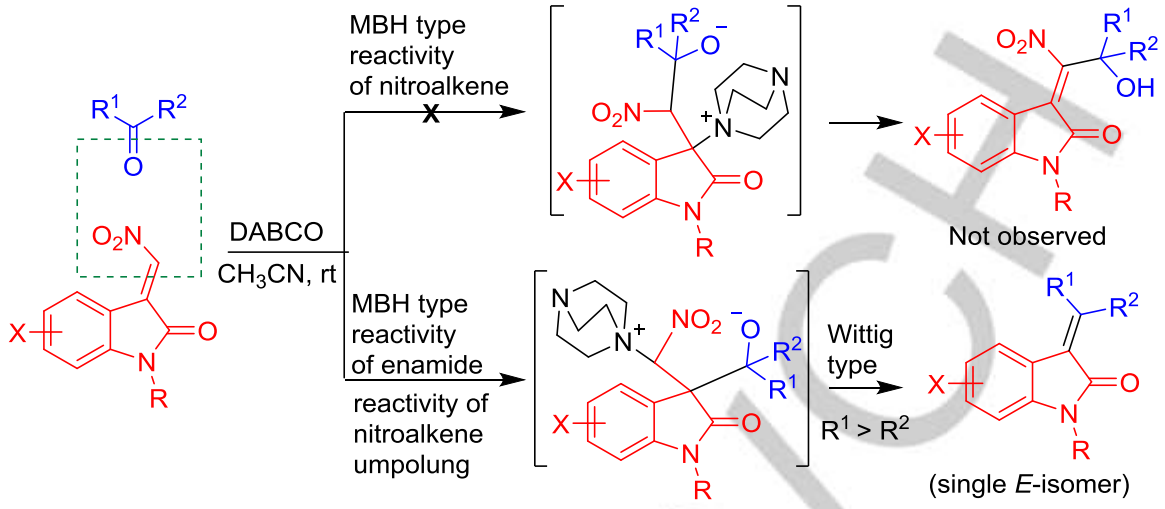

> Reactivity of nitroalkene with reversal of polarity
> Metal free coupling of two electrophilic synthons
> Nitroalkene reacts like a Wittig reagent
> 95% *E*-selective

Key Topic: Oxindolylidenecarboxylate Synthesis

Reaction of nitroalkylideneoxindoles with selected activated carbonyl compounds under Morita-Baylis-Hillman (MBH) conditions (DABCO/CH_3CN) led to unexpected formation of Wittig type products. While the first two steps involve MBH pathway (Michael addition and aldol reaction), the subsequent steps in this one-pot process presumably are intramolecular substitution and elimination.

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