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One-Pot Au[III]-/Lewis Acid Catalyzed Cycloisomerization of Nitroalkynes and [3 + 3]Cycloaddition with Donor–Acceptor Cyclopropanes

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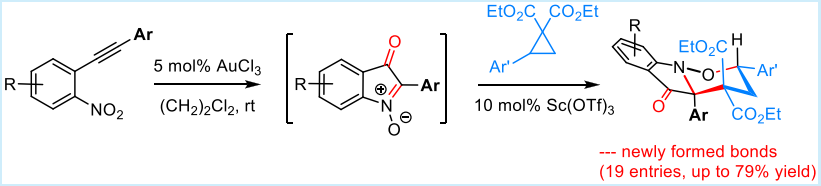
Supporting Information



ABSTRACT: A one-pot protocol for the synthesis of a tricyclic pseudoindoxyl scaffold from 2-nitroalkynylbenzenes, comprising of an Au(III)-catalyzed nitroalkyne cycloisomerization leading to isatogen and its [3 + 3]-cycloaddition with donor–acceptor cyclopropanes mediated by a suitable Lewis acid, has been developed.

Pseudoindoxyl natural products occupy a special place in the indole alkaloids family because of their fascinating molecular structures and promising biological activities (see Figure 1).[1] In general, the biosynthesis of these pseudoindoxyl

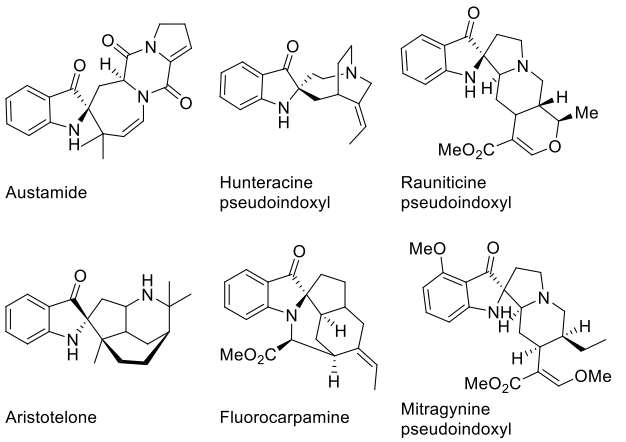


Figure 1. Representative pseudoindoxyl natural products.

natural products comprises of an oxidative rearrangement of the corresponding indole alkaloids.[2] Indeed, this is one of the key approaches employed in the synthesis of the pseudoindoxyl core.[3] However, the competing formation of 2-oxindole derivatives during the rearrangement and control over the stereochemistry of the newly generated quaternary carbon center are the major concerns.[4] In this regard, alternative approaches for constructing the pseudoindoxyl (2,2-disubstituted 1,2-dihydro-3*H*-indol-3-one) core have been explored.[5] Among these, the metal catalyzed cycloisomerization of *o*-nitrotolans[6] and *o*-azidotolans[7] and subsequent inter- and intramolecular transformations have emerged as simple and effective tools to create pseudoindoxyl cores. In this manuscript, we document a one-pot gold(III)-catalyzed nitroalkyne cycloisomerization of 2-nitrotolans and a Lewis acid catalyzed [3 + 3]-cycloaddition of the intermediate isatogen with donor–acceptor (DA) cyclopropanes leading to 2,2-spiro pseudoindoxyl derivatives. The cycloaddition reaction of DA-cyclopropanes is one of the important reactions unveiled during the past decade.[8] The (homo) cycloaddition reactions of DA-cyclopropanes with various dipolarophiles, in general,[9] and with nitrones,[10] in particular, have been well explored in natural products synthesis.[11] However, the same with isatogens has not yet been examined. Given the fact that the preparation of isatogens from nitroalkynes and the [3 + 3]-cycloaddition reaction of DA-cyclopropanes require Lewis acids, it was assumed that there is a chance of combining both the reactions in one-pot, which would lead to fused tricyclic pseudoindoxyl derivatives.[12]

With this intent, in order to identify the suitable Lewis acid for the [3 + 3]-cycloaddition, 2-phenyl- and 2-*n*pentyl isatogens **1a** and **1b**, respectively, as well as commonly employed DA-cyclopropane diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**2a**) have been selected as the suitable partners and screened with the commonly employed $Sc(OTf)_3$ and $Yb(OTf)_3$ for the projected [3 + 3]-cycloaddition.[10] With both Lewis acids, the cycloaddition reaction of **2a** with **1a** and **1b** was facile at rt and provided the corresponding cycloaddition products **3aa** and **3ba** with complete diastereoselectivity. The yields in general were also good and that with $Sc(OTf)_3$ were best. The relative

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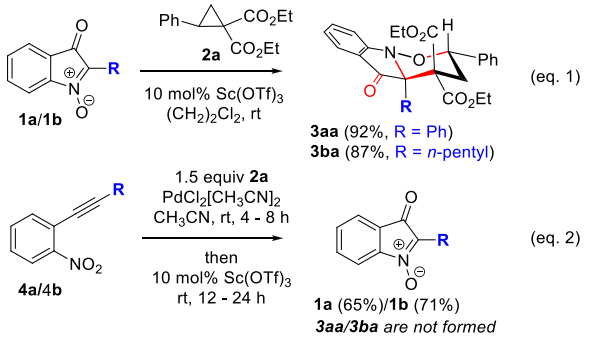
stereochemistry of the newly formed 1,2-oxazine ring has been proposed by considering the previous reports on the cycloaddition with cyclic nitrones where both experimental and theoretical calculations favored a single diastereomer having cis-orientation of the 1,4-phenyl substituents (see Figure S1, SI for the NOESY spectra of cycloaddition product **3eb** synthesized later and the representative nOes observed that support the assigned configuration/conformation).[10a,e,f] Nonetheless, this early success with the cycloaddition of isatogens with DA-cyclopropanes prompted us to proceed for the examination of the possibility of carrying out nitroalkyne cycloisomerization and cycloaddition in one-pot.

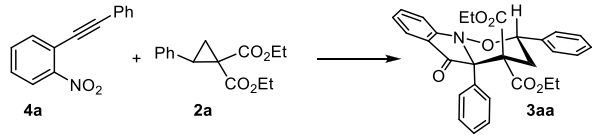
The nitroalkyne cycloisomerization leading to isatogens has been explored with [Au]- and [Pd]-complexes, though the former has a limitation of requirement of aryl substituent on the other side of alkyne (with simple alkyl substituents, it leads to isomeric anthranil derivatives).[6a] [Pd]-complexes generally lead to the isatogens.[6b] Keeping this in mind, the initial studies have been carried out by employing the nitroalkynes **4a**/**4b** and DA-cyclopropane **2a**. Initial experiments employing $PdCl_2[CH_3CN]_2$ for cycloisomerization and $Sc(OTf)_3$ for cycloaddition have been carried out in acetonitrile at rt. The procedure followed involved the stirring of a solution of nitroalkynes **4a**/**4b** along with 1.5 equiv of **2a** in the presence of 10 mol % [Pd]-complex in acetonitrile at rt (for 4−10 h), subsequent addition of 10 mol % of $Sc(OTf)_3$, and continued stirring for an additional 12−24 h. As shown in Scheme 1 (eq 2), in both cases, only corresponding isatogens were isolated. Changing the solvent to dichloromethane hampered the initial cycloisomerization itself. This led us to look at the [Au]-complexes, however, with due consideration of employing only aryl substituted derivatives such as **4a**.

Scheme 1. [3 + 3]-Cycloaddition of 2-Phenyl/*n*-Pentyl Isatogens 1a/1b with DA-Cyclopropane 2a



At the outset, $AuCl_3$ has been selected as a catalyst for the nitroalkynes cycloisomerization, given its superior selectivity to provide isatogens[12] over the initially discovered $AuBr_3$ by Yamamoto. Following the prescribed conditions, the cycloisomerization of **4a** has been carried out employing 5 mol % of $AuCl_3$ as a catalyst in CH_2Cl_2 as a solvent at rt. To our delight, we observed that both nitroalkyne **4a** and cyclopropane **2a** were getting consumed slowly and that the formation of product **3aa** along with the isatogen **1a** took place. The reaction was incomplete even after stirring for 24 h. The product **3aa** was isolated in 48% yield (Table 1, entry 1). Encouraged by this result, initially we looked at the possibility of bringing both cycloisomerization and cycloaddition with $AuCl_3$ alone as catalyst. In this regard, we screened different solvents, different [Au]-complexes, and some of the prescribed additives, changing the catalyst from gold to platinum and increasing the temperature to 60 °C. As shown in Table 1, the results are not encouraging (see Table S1, SI). Only when the solvent was switched from dichloromethane to dichloroethane, was the yield improved to 54% with $AuCl_3$, and there was no improvement when the solution was heated to 60 °C in the same solvent. To this end, considering the excellent cycloaddition yields of isatogen **1a** with **2a** that we had initially noticed, we looked at the possibility of carrying the [Au]-catalyzed cycloisomerization first and then adding cyclopropane **2a** and $Sc(OTf)_3$ to proceed for the cycloaddition. The results are promising, and we obtained the desired **3aa** in 65% yield. Increasing the temperature of the reaction did not improve the yield. The yield of **3aa** was improved to 71% when the reaction was carried out in the presence of 4 Å molecular sieves, at room temperature (Table 1).

Table 1. Optimization of the One-Pot Nitroalkynes Cycloisomerization/[3 + 3]-Cycloaddition Reaction[a]



entry	cat.1	additive or cat.2	solvent	*T* (°C)	yield[b]
1	$AuCl_3$		DCM	rt	48%[c]
2	$AuCl_3$		1,2-DCE	rt	54%[c]
3	AuCl		1,2-DCE	rt	50%[c]
4	$PtCl_2$		1,2-DCE	rt	23%[c]
5	$PtCl_4$		1,2-DCE	rt	43%[c]
6	$AuCl_3$		1,2-DCE	60	55%
7	$AuCl_3$	$AgSbF_6$	1,2-DCE	60	no reaction
8	$AuCl_3$	AgOAc	1,2-DCE	60	42%[c]
9[d]	$AuCl_3$	$Sc(OTf)_3$	1,2-DCE	rt	65%
10[d]	$AuCl_3$	$Sc(OTf)_3$	1,2-DCE	60	68%
11[d,e]	$AuCl_3$	$Sc(OTf)_3$	1,2-DCE	rt	71%

[a]*Reaction conditions*: **4a** (0.1 mmol), **2a** (0.15 mmol), catalyst (5 mol %), and additive (10 mol %) in 1.0 mL of distilled solvent for 16 h. [b]Isolated yield after column chromatography. [c]10−35% isatogen recovered. [d]Stepwise addition of DAC and additive or *cat* 2. [e]In presence of 4 Å molecular sieves.

Having optimal conditions in hand, the substrate scope of this one-pot cycloisomerization/cycloaddition protocol has been examined by employing different nitroalkynes and DA-cyclopropanes with varying substituents on the aryl rings (Scheme 2). The reactions with substrates having electron-donating groups like -Me and -OMe *meta* to the nitro group are smooth, giving the corresponding cycloaddition products **3ca** and **3da** in moderate yields 56% and 74%, respectively. Even when there is an electron withdrawing group $-CO_2Me$, the reaction was facile and provided **3ea** in 75% yield. Next, the nitrotolans having -OMe and -^{t}Bu substituents *para* to the alkyne of pendant aryl ring have been subjected for this one-pot protocol and obtained the corresponding products **3fa** and **3ga** in moderate yields. Later, the scope of DA-cyclopropanes has been explored by employing DA-cyclopropanes **2b**−**2d** that bear different *para*-substituents and the dimethyl 2-(naphthalen-2-yl)cyclopropane-1,1-dicarboxylate (**2e**). In general, the reactions with these four cyclopropanes are smooth and provided the corresponding cycloaddition products in moderate to good yields. In addition, the cycloaddition reactions of 2-^{n}pentylisatogen **1b** have been carried with DA-

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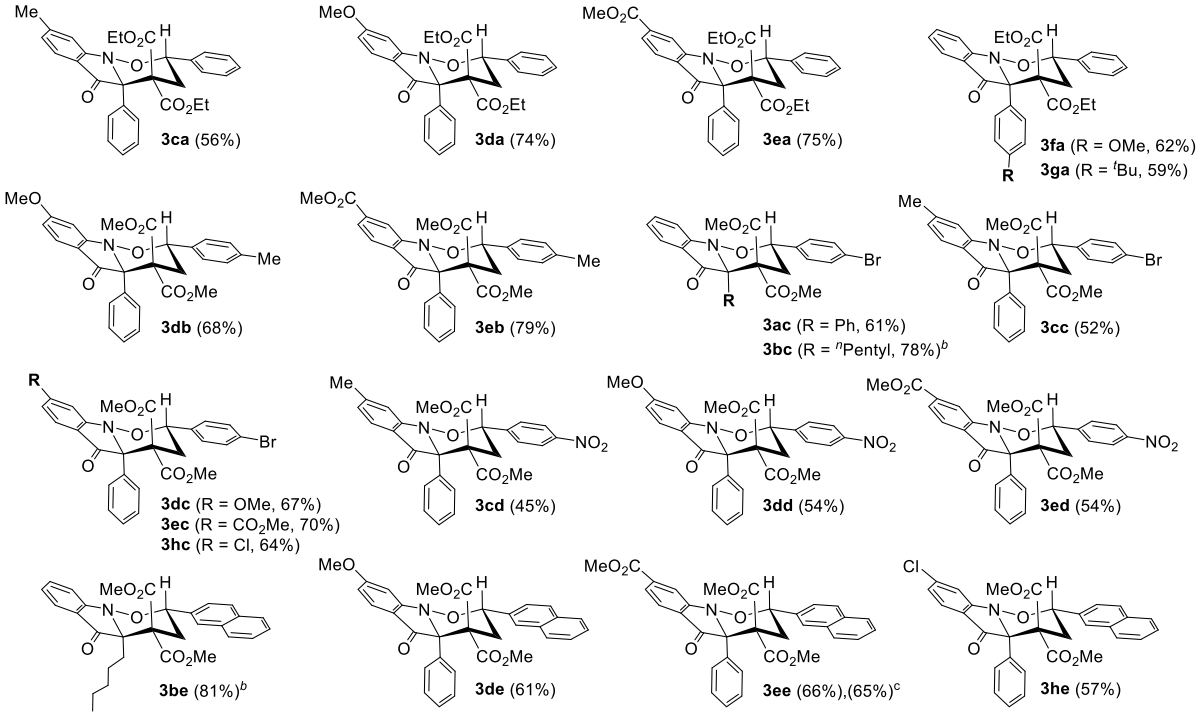
Scheme 2. Scope for Nitroalkynes and DA-Cyclopropane in the One-Pot Cycloisomerization/Cycloaddition Reaction[a]

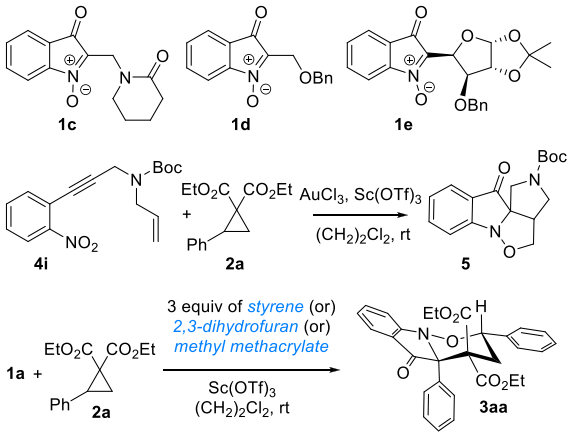


[a]*Reaction conditions*: **4** (1 equiv), **2** (1.5 equiv), $AuCl_3$ (5 mol %), and $Sc(OTf)_3$ (10 mol %). [b]Isatogen **2b** was used as the substrate. [c]2 mmol scale, employed 15 mol % $Sc(OTf)_3$.

cyclopropanes **2c** and **2e** to obtain the corresponding cycloaddition products **3bc** and **3be** in 78% and 81% yields.

As part of expanding the scope of this one-pot protocol, the compatibility of isatogens **1c**−**1e** having functional groups at the propargylic position has been examined (Scheme 3). All

Scheme 3. Limitation of Substituents at C2 and Competition between DA-Cyclopropane and Olefins



three substrates failed to undergo cycloaddition with DA-cyclopropane **2a** under established conditions. The lack of reactivity of substrates **1c**−**1e** may probably be due to the bulky C2-substituent that hinders the approaching dipolarophile. Interestingly, when the *N*-allyl propargylamide derived nitroakyne **4i** was treated with a gold complex along with the **2a**, it was found that after the cycloisomerization, the intermediate isatogen underwent an intramolecular [3 + 2]-cycloaddition with the pendant allyl group over the intermolecular [3 + 3]-cycloaddition. On the other hand, when the intermolecular completion experiments were conducted employing equal amounts of electron rich/electron deficient olefins along with DA-cyclopropane **2a**, the [3 + 3]-cycloaddition dominated the classical [3 + 2]-cycloaddition of isatogens.

In conclusion, the [3 + 3]-cycloaddition of DA-cyclopropanes with isatogens has been examined. In general, the cycloaddition reaction is highly diastereoselective and facile with 2-arylisatogens and also with 2-alkylisatogens. In the case of 2-arylisatogens, the preceding Au(III)-catalyzed nitroalkyne cycloisomerization has been successfully combined with the cycloaddition step in one-pot. On the other hand, with 2-alkylisatogens these steps have to be separately conducted, and also the cycloaddition is not facile. The functionalized alkyl groups are present at the C2 position of isatogen. Currently, work in the direction of employing this protocol in the synthesis of pseudoindoxyl natural products is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02035.

Characterization data, ^1H, ^{13}C NMR/DEPT, and HRMS spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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