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Lewis Acid Catalyzed Reactivity Switch: Pseudo Three-Component Annulation of Nitrosoarenes and (Epoxy)styrenes

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Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Lewis acid catalyzed annulation reaction via arene functionalization of nitrosoarenes, and C-C cleavage of (epoxy)styrene to provide arylquinolines is reported. The Lewis acid catalyst altered the annulation pattern providing arylquinolines instead of oxazolidines. The reaction with styrene gave a mixture of 2,4diarylquinoline and 4-arylquinoline, while only 3-arylquinoline was formed from the reaction of epoxystyrene.

Annulation reaction involving two or more components is a powerful strategy for the synthesis of a cyclic compound.¹ Multiple numbers of bond breaking and bond making are achieved in a single operation, which makes this strategy advantageous in the context of step and atom economy as compared to the classical multistep reactions. Nitrosoarenes were used in a wide variety of reactions, such as Diels-Alder, ene, [3+2] cycloaddition, aldol reactions to install the amine and oxygen functionality in the organic molecules.² In addition, nitrosoarenes also participate in different annulation reactions to provide a variety of heterocycles.³ Primarily, the reactive nitroso functionality of the nitrosoarenes participates in the reactions. In most of the cases, the arene moiety is sacrificed after the reaction. Therefore, the development of reaction for the C-H functionalization of nitrosoarene that incorporates the arene moiety into the product is of great interest. In this context, a few examples of reactions of nitrosoarenes involving both nitroso and arene moiety have been developed recently.^{4,5} Highly reactive molecules, such as aryne, alkyne, enone and donor-acceptor cyclopropanes reacted with nitrosoarene acting as three atom unit (C-C-N) in the presence of suitable metal catalyst/reagents to provide the different heterocycles.⁵ In contrast, only the nitroso functionality participates in the reaction of nitrosoarene with styrene to provide the nitrone⁶ and oxazolidine derivatives (Scheme 1, eq 1).⁷ Nitrone, which is well known for their 1,3-dipolar cycloaddition reaction with the styrene/oliefin,8 formed in situ from nitrosoarene and the styrene reacted with another equivalent of the styrene to provide the corresponding oxazolidine derivative. We anticipated that the use of oxophilic lanthanide-based Lewis acid, such as Sc³⁺, Yb³⁺ could deactivate the dipole through

strong coordination with the anionic oxygen atom of the nitrone. This would open the possibility of a different mode of reactivity of nitrone with the olefin.⁹ For example, the desired C-H functionalization of nitrosoarene could be achieved if the nitrone reacts with the styrene via a Povarov type reaction. However, to the best of our knowledge, there is no report on the reaction of styrene or epoxystyrene with the nitrosoarene as a three atom unit known in the literature. Herein we report the first example of a Yb and Cu-catalyzed pseudo-three-component annulation reaction of nitrosoarenes and styrene or epoxystyrene providing a wide range of aryl quinolines (Scheme 1, eq 2).

a) known reaction: [3+2] cycloaddition involving nitroso moiety



Functionalized quinoline, particularly, arylquinoline are widely found as the key scaffold of many natural products and bioactive molecules.¹⁰ Therefore, the efforts are being devoted to the development of novel and more efficient synthetic methods for the synthesis of functionalized quinoline derivatives.¹¹ However, the development of novel synthetic methods to provide quinoline derivatives with wide structural diversity starting from readily available starting materials under simple reaction conditions still remains challenging and desirable.

To test our hypothesis, we started our investigation by performing a reaction of nitrone **1** with styrene **2** in the presence of a catalytic amount of $Sc(OTf)_3$. We were pleased to observe that the reaction of **1** and **2** provided quinoline **3** instead of classical product, oxazolidine (eq. 3).

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⁺ Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

nitrosoarenes

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Then the stage was ready for testing a pseudo-threecomponent reaction of nitrosoarene and styrene in the presence of $Sc(OTf)_3$. Accordingly, nitrosobenzene **4** was reacted with styrene **2** in the presence of 30 mol% of $Sc(OTf)_3$ in refluxing toluene for 24 h. As expected, the 2,4-diarylquinoline **5b** and 4-arylquinoline **5b'** were isolated as 3:1 ratio with a 47% combined yield (SI, Table S1). The best yield of the desired quinoline was observed when the reaction with reduced catalyst loading was carried out in refluxing DCE instead of refluxing toluene (entry 6).



2 | J. Name., 2012, **00**, 1-3

analogs.12 The reaction of substrate 6 having two styrene moiety was then investigated. Both mono-substituted 7b and 2,4-disubstituted 7a guinolines were formed under standard conditions (eq 4). Quinoline 7a derivative having two styrene units can serve as the potential crosslinking agent in polystyrene synthesis. The reactions with α -methylstyrene, stilbene and 1phenylbutadiene did not provide the desired quinolines (Scheme S2). Interestingly, the reaction of β -methylstyrene and nitrosobenzene under standard conditions provided 2-phenyl quinoline via a different reaction pathway (eq 5, Scheme S2).

The best reaction conditions were then used to investigate the substrate scope of this unprecedented annulation feacility.

First, nitrosobenzene was reacted with diversely substituted

styrene derivatives. The desired quinolines **5a-g** and **5a'-g'** were isolated with good combined yields. Styrene derivatives with

substituents at *p*-positions provided better yields as compared to the substrates having *m*-substituents. The reaction of styrene having a strong electron withdrawing group reacted slowly to

provide the desired quinolines with moderate yields (SI, Scheme

S1). Then the scope of the reaction using different

nitrosoarenes reacted smoothly with different styrene

derivatives to provide the quinoline derivatives 5h-s and 5h'-s'

with good combined yields. Interestingly, it was observed that

the guinolines which are originated from the unsubstituted

nitrones were obtained with a little lower yields as compared to

the guinolines that are formed from the substituted nitrone.

The observation can be rationalized based on the lower stability of the unsubstituted nitrones as compared to its substituted

Accordingly,

tested.

was



Subsequently, we explored the possibility of the annulation reaction of nitrosobenzene with epoxy-styrene. Therefore, nitrosobenzene was reacted with styrene oxide in place styrene. Interestingly, only 3-phenyl quinoline was isolated with 53% yield. This interesting observation led us to investigate the reaction further. Various reaction conditions were screened to maximize the yield of 3-phenyl quinoline (Table S2). Sc(OTf)₃ was found to be the best catalyst for this reaction in refluxing dichloroethane. However, a similar result was obtained when Cu(OTf)₂ was used as the catalyst under the same conditions.

Optimized conditions using cost-effective catalyst $Cu(OTf)_2$ was used to study the substrate scope of the reaction. Differently substituted styrene oxides were reacted with various

substituted

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nitrosoarene to obtain a series of structurally diverse 3-aryl quinolines **9a-o** with good yields (Scheme 3). Substrates containing both the electron-donating and electron-withdrawing groups provided the desired quinolines with good yields. The reaction of 4-oxiranylpyridine did not provide the desired quinoline. However, alkyl epoxide participated in the reaction to provide 3-alkylquinoline **9p**.



On the basis of our experimental results and literature reports, a plausible mechanism for the formal [3+2+1] annulation of nitrosoarene and styrene is depicted in Scheme 4a. The nitrones **1 (11)** and **10 (12)** were formed from the reaction of nitrosoarene and styrene involving azodioxy dimer **A1**¹³ and diazetidine derivative **D1**¹⁴ (Scheme S4, see SI).⁶ The nitrones could also be formed from nitrosoarene **4** and styrene following a radical pathway.^{6,7} Both the metal coordinated nitrone derivatives **11** and **12** reacted with another equivalent of styrene through the Povarov type reaction to provide the tetrahydroquinoline derivatives **14** and **13** produced respective dihydroquinoline **16** and **15**, which upon oxidation in the presence of oxygen or nitrosoarene provided the observed aryl quinolines **5** and **5'**.

To understand the mechanism of annulation reaction of epoxy styrene and nitrosoarene, epoxy styrene **8** was reacted with pre-formed nitrone **10** from nitroarene and formaldehyde (Scheme 4, eq 5). Under standard conditions, the 3-aryl quinoline **9a** was isolated with 73 % yield. This indicates the intermediacy of nitrone **10** in the annulation reaction of epoxy styrene and nitrosoarene. Moreover, the formation of aryl aldehyde (**19**) corresponding to the styrene oxide was observed in the reaction (Scheme S3). Based on these results, a plausible reaction mechanism has been depicted in Scheme 4c. Nucleophilic nitrosoarene **4** added to the least hindered site of styrene oxide **8**, which is activated by the coordination with the

Cu^{II}. C-C bond cleavage of the resulting ionic intermediate **18** occurred to provide the nitrone **12** and a Wehyde **19** The metal coordinated nitrone **12** reacted with the enolate **21**, which was generated *in situ* from styrene oxide **8** via Meinwald rearrangement, ¹⁵ either via a concerted or stepwise pathway involving Friedel-Crafts reaction (Scheme S5) to provide the N-oxide **20**. A reaction of pre-formed nitrone **10** with aldehyde **17**, which is capable of generating enolate related to **21**, producing desired quinolines (**9a**, **9q**) supports the intermediacy of **21** in the reaction. Fast aromatization followed by dehydration yielded observed 3-aryl quinoline as the single regioisomer. (a) Proposed mechanism for annulation of nitrosoarene and styrene





In summary, we have developed an unprecedented annulation reaction of nitrosoarenes and epoxy(styrene) providing arylquinolines with wide structural diversity. The cleavage across C=C of styrene and epoxide of epoxystyrene provided the nitrone intermediate. The use of the Lewis acid catalyst switched the reaction of nitrone and styrene from [3+2] to [4+2] cycloaddition and thus allowed to form quinoline derivatives instead of oxazolidines. The nitrones reacted with styrene to give a mixture of 2,4-diarylquinoline and 4-arylquinoline. On the other hand, 3-arylquinoline was formed selectively from the reaction of nitrone via cycloaddition of nitrone and

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enol/metal-enolate derived from epoxystyrene through Meinwald rearrangement.

We acknowledge Science and Engineering Research Board (SERB), New Delhi (CRG/2019/000330) for funding.

Conflicts of interest

"There are no conflicts to declare".

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TOC: Lewis acid alters the annulation pattern to construct arylquinolines via C-H functionalization of nitrosoarenes, and C-C cleavage of (epoxy)styrene.

Ņ^{∞O} _H <u>R</u>/Ar Ar/R Ar′ N [⊥]R Cu²⁺ (cat.) ^ℓ_R Yb³⁺ (cat.) Ar/H Ŕ

20 examples 45%-76%

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[4+2] of nitrone with olefin arene functionalization 37%-70% cleavage acros C=C and epoxide

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