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Nitroso-azomethine(ene) reaction enabled annulations of nitrosoarenes, azomethines and alkenes†

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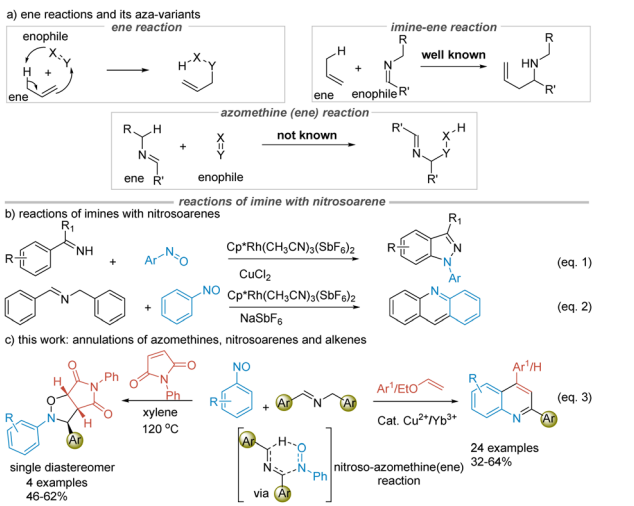
An unprecedented example of a nitroso-azomethine(ene) reaction is reported. Nitroso-azomethine(ene) reaction-mediated unprecedented annulation of nitrosoarenes, azomethines, and alkenes to furnish arylquinolines *via* arene functionalization of nitrosoarene has been developed. DFT studies provided mechanistic insights into the newly developed nitroso-azomethine(ene) reaction.

The ene reaction proceeds between an alkene having an allylic hydrogen (ene) and a compound containing a multiple bond (an enophile).[1] Since its discovery, the ene reaction, in particular, the imino-ene reaction, where azomethine acts as an enophile, has been widely used in organic synthesis.[2] Azomethine having hydrogen at the α-position of the nitrogen can, in principle, participate in ene-reactions with a suitable enophile. However, to the best of our knowledge, such an ene reaction where azomethine acts as an ene-component is not known (Scheme 1(a)).

Nitrosoarenes exhibit versatile reactivity, and thus, they are frequently used in various synthetic transformations to incorporate nitrogen and oxygen functionality into a molecule.[3] The nitroso group of nitrosoarenes has been extensively used as a dienophile, dipolarophile, and enophile in different pericyclic reactions.[4] In addition, nitrosoarenes participated in Aldol reactions and various annulation reactions for the synthesis of different heterocycles.[5] In the majority of cases, after the reactions, the arene moiety of the nitrosoarenes either remains as an unfunctionalized *N*-aryl group or is removed from the product afterward. The reactions that functionalize the arene moiety and incorporate it into the product are underdeveloped.[6] Mainly, aryne, alkyne, enone, and donor–acceptor cyclopropanes took part in the reaction with nitrosoarenes, forming various heterocycles *via* arene functionalization of nitrosoarenes.[6] However, the primary imine participates in a metal (Rh and Cu)-catalyzed annulation reaction to form a pyrazole ring having an unfunctionalized arene moiety of nitrosoarene (Scheme 1(b), eqn (1)).[7] On the other hand, the Rh-catalyzed reaction of azomethine with nitrosoarene led to the formation of acridines *via* arene functionalization of nitrosoarenes (eqn (2)).[8]

Herein, we report an unprecedented three-component annulation reaction of azomethine, nitrosoarene, and alkenes to obtain aryl quinolines *via* functionalization of the arene moiety of nitrosoarene. A nitroso-azomethine(ene) reaction, which was unknown to the best of our knowledge, mediated this annulation reaction (eqn (3)).

Quinoline derivatives are ubiquitous structural units of natural products, medicinal drugs, and unnatural compounds that possess important biological activities.[9] Therefore, various methods have been developed for their synthesis.[10] However, developing a new methodology for synthesizing quinoline derivatives



Scheme 1 Synthesis of heterocycles from the reaction of imines with nitrosoarenes.

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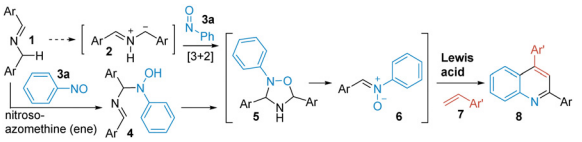


Scheme 2 Reaction design for arene functionalization of nitrosoarenes.

starting from readily available starting materials under simple reaction conditions would be advantageous.

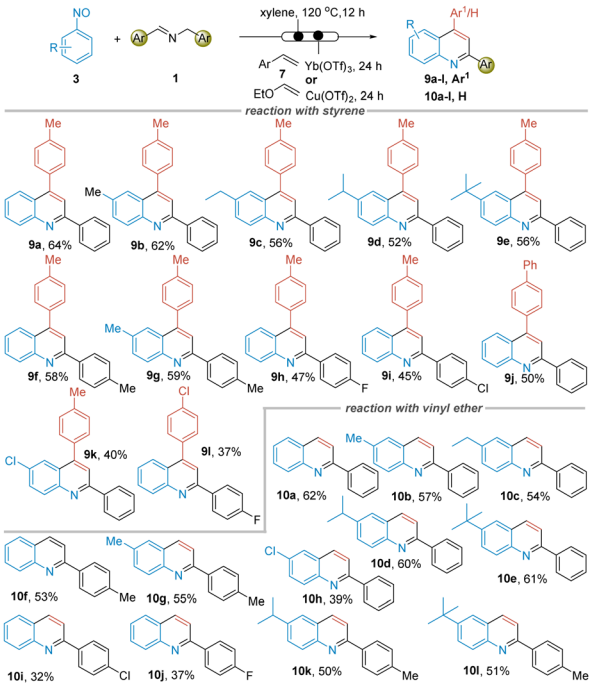
Nitrosoarene participates in [3+2] cycloaddition reaction with the azomethine ylides.[11] During our ongoing studies on the synthesis of heterocycles *via* arene functionalization of nitrosoarene, we thought that the 1,3-dipolar cycloaddition reaction of nitrosobenzene **3a** with azomethine ylides **2** generated from azomethine **1** would lead to nitrone intermediate **6** (*via* oxadiazolidine **5**, Scheme 2). The subsequent one-pot reaction of nitrone **6** with alkenes **7** in the presence of a suitable Lewis acid would provide arylquinoline **8** with two different aryl moieties *via* arene functionalization of nitrosoarene.[6m] However, the generation of azomethine ylide **2** from imine **1** is hard due to the low acidity of the benzylic hydrogen. Therefore, these imines do not participate in 1,3-dipolar cycloaddition reaction with dipolarophiles under standard reaction conditions. Suitable activating groups need to be installed at the α-position of the nitrogen to enable them to participate in 1,3-dipolar cycloaddition reaction.[12] Along the same line, the reaction of nitrosoarene with azomethine derived from aryl aldehyde and benzylamine was also not known. Nitrosoarene is known to participate in a variety of ene-reactions. Therefore, we thought that the nitroso azomethine(ene) reaction between nitrosoarene and azomethine would lead to the formation of nitrone **6** through the intermediacy of a hydroxyl amine **4** and oxadiazolidine **5**.

We have started our investigation by reacting nitrosobenzene **3a**, imine **1** (Ar = Ph) and 4-methyl styrene in the presence of a Lewis acid. After screening different reaction conditions (Table S1, ESI†), the best yield of quinoline **9a** was found from the reaction of **3a** (1 equiv.), imine **1** (1.5 equiv.), and 4-methyl styrene (2 equiv.) in the presence of 15 mol% of $Yb(OTf)_3$.

A variety of nitrosoarenes **3** and imines **1** were reacted with different styrene derivatives under the optimized conditions to obtain structurally diverse quinoline derivatives **9a–l** with moderate to good yields (Scheme 3). Electron donating alkyl substitution at the *p*-position on the nitrosoarene provided quinolines **9b–e** with a better yield. The quinolines **9k–l** derived from the nitrosoarene and styrene containing electron withdrawing group were isolated with lower yields.

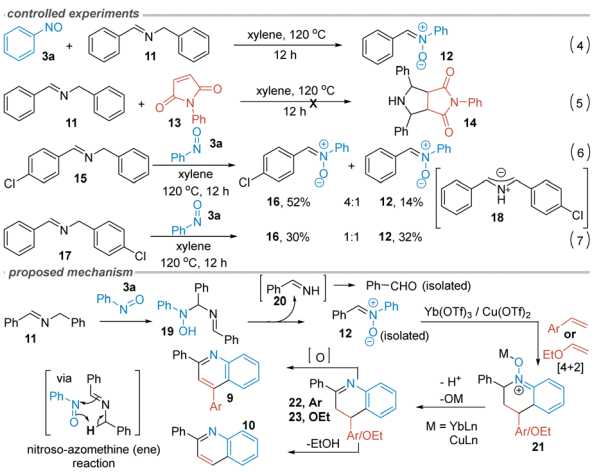
Similarly, 2-aryl quinoline **10a** was obtained from the $Yb(OTf)_3$ catalyzed three-component reaction of nitrosoarene, imine, and ethyl vinyl ether instead of styrene. This reaction could also be catalyzed with $Cu(OTf)_2$ to obtain the 2-aryl quinoline with a comparable yield. A variety of nitrosoarenes were reacted with different imines and ethyl vinyl ether to obtain 2-aryl quinolines **10a–l** with good yields. However, aliphatic alkenes and imine derived from aliphatic aldehyde failed to provide the desired quinoline (ESI,† Scheme S1).

Controlled experiments have been carried out to understand the reaction mechanism of this three-component annulation



Scheme 3 Substrate scopes. Conditions: **3** (1 equiv.), **1** (1.5 equiv.), and styrene (2 equiv.) in the presence of 15 mol% of $Yb(OTf)_3$ in xylene at 120 °C.

reaction. The nitrone **12** was isolated with a 73% yield from the reaction of **3a** with imine **11** under standard conditions (Scheme 4, eqn (4)). This indicates that nitrone is the possible reaction intermediate. Further experiments were carried out to probe the possible reaction mechanism for the formation of nitrone from the reaction of nitrosobenzene and imine. *N*-Phenyl maleimide **13**, a well-known dipolarophile, was reacted with imine **11** under standard conditions. The expected [3+2] cycloadduct **14** was not detected (eqn (5)). Unsymmetrical imines **15** and **17** were separately reacted with nitrosobenzene **3a** (eqn (6) and (7)). The reaction of imine **15** gave a mixture of nitrones **16**



Scheme 4 Controlled experiments and plausible mechanism for the annulation.

and **12** with a 4 : 1 ratio. On the other hand, the mixture of **16** and **12** with 1 : 1 ratio was observed from the reaction of imine **17** under the same conditions. The same azomethine ylide **18** would be formed from both the imine **15** and **17**. Therefore, both the reaction of imines **15** and **17** and nitrosoarene *via* [3+2] cycloaddition of species **18** would provide the same ratio of nitrone **16** and **12**. Thus, these results suggest that the reaction of imine and nitrosoarene did not proceed *via* [3+2] cycloaddition.

Based on the experimental results, we propose that **3a** reacted with imine **11** *via* nitroso-azomethine(ene) reaction to provide hydroxyl amine derivative **19.** Then **19** dissociated into the expected nitrone **12** and imine **20**, which ultimately provided aldehyde. Metal coordinated nitrone **12** underwent [4+2] cycloaddition with styrene to afford the quinoline **9** *via* the intermediates **21** and **22**.[6m] Similar cycloaddition of **12** with ethyl vinyl ether provided quinoline **10**.

DFT studies were carried out to understand the mechanistic insight for the formation of nitrone from the reaction of nitrosoarene and azomethine. Initially, the possibility of the formation of azomethine ylide **2** and its subsequent [3+2] cycloaddition reaction has been investigated. Analysis of the computed energy profile revealed a higher concerted transition state (TSp-1) energy of 61.1 kcal mol^{-1} for the formation of the desired azomethine ylide **2** from the corresponding azomethine (Fig. 1). Therefore, the possibility of nitrone formation *via* [3+2] cycloaddition of the ylide has not been investigated further.

Then, we studied the formation of nitrone **12** from nitrosoarene **3** and **11** *via* azomethine(ene)-reaction (Fig. 1). The ene reaction between **3** and **11** was found to proceed through a concerted pathway, without involving stepwise or radical intermediates,[13] as determined from detailed potential energy surface scans. The key steps in the reaction mechanism involved TS-1, a six-membered transition state ($\Delta G^{\dagger}$ of 26.5 kcal mol^{-1}), leading to N-nitroso ene adduct **19** (ΔG of −8.7 kcal mol^{-1}). In the subsequent step, an intramolecular proton transfer from the hydroxy to imine nitrogen and C–N bond cleavage of **19** occurred through a five-membered transition state TS-2 ($\Delta G^{\dagger}$; 28.8 kcal mol^{-1}) to provide the desired nitrone **12**. The reaction energy profile revealed that the formation of nitrone from **19** is the rate-determining step. A similar concerted transition state TS-1^{O} ($\Delta G^{\dagger}$; 23.3 kcal mol^{-1}) for the O-nitroso ene reaction was found. However, further reaction of intermediate **24** (ΔG; −21.0 kcal mol^{-1}), which was formed from the O-nitroso ene reaction, corresponding to the transfer of H from the NH to the imine N-center could not be tracked. Attempts to identify the reaction pathway of nitrone formation from intermediate **24**, which always led back to the starting materials, were unsuccessful.

Then we looked into the experimental observation of the formation of two nitrones from the reaction of azomethine (**15** & **17**) containing two different aryl moieties with nitrosoarene. Depending on the electronic factor of the aryl moiety, two nitrones were formed with different ratios. The formation of two nitrones could be explained by the formation of two different oxazolidines from the corresponding N-nitroso ene and O-nitroso ene adducts (ESI,† Scheme S2). However, the theoretical studies showed that the reaction proceeds *via* TS-2 instead of oxazolidine derivative **5** (Fig. 1). Moreover, the O-nitroso ene adducts did not yield the product. Therefore, further investigation was carried out to understand the reaction pathway for the formation of a mixture of nitrones from **15** & **17** (Fig. 2 and Scheme S2, ESI†).

The N-nitroso ene-adduct **25** (ΔG; −16 kcal mol^{-1}) from the imine **15** was formed through a six-membered cyclic transition state TS-1$_{Cl}$ ($\Delta G^{\dagger}$; 26.7 kcal mol^{-1}, Fig. 2). Hydroxyl amine **25** reacted *via* a five-membered transition state TS-2$_{Cl}$ ($\Delta G^{\dagger}$; 29.5 kcal mol^{-1}), for the formation of nitrone **16**. In contrast, a four-membered transition state TS-2′$_{Cl}$ ($\Delta G^{\dagger}$; 33.2 kcal mol^{-1}) was involved in the formation of an isomeric hydroxylamine derivative **26** from **25**. Participation of **26** in an intramolecular proton transfer and C–N cleavage through TS-3$_{Cl}$ ($\Delta G^{\dagger}$; 30.4 kcal mol^{-1}) lead to the formation of **12**. The small difference in the reaction energies for the formation of nitrones **16** and **12** (ΔΔGrxn = −0.1 kcal mol^{-1}) indicates that the regioselectivity in the product formation is solely controlled by kinetics. A significantly higher activation barrier for the formation of **12** through four-membered transition states, as opposed to **16**, was observed. This result is in accordance with the experimental observation of preference for the formation of nitrone **16** over **12** with a 4 : 1 ratio. In contrast, for imine **17**, the small activation energy difference for the formation of **16** and **12** leads to an equal ratio (Fig. S2, ESI†).

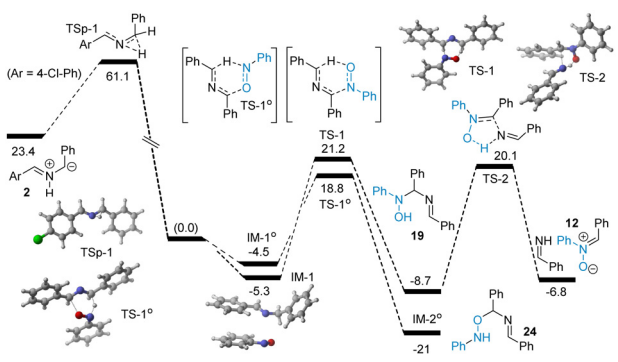


Fig. 1 Computed (M06-2X/6-31+G(d,p); with the SMD solvation model) energy profile (energy (ΔG) in kcal mol^{-1}) and the optimized structures of the transition states.

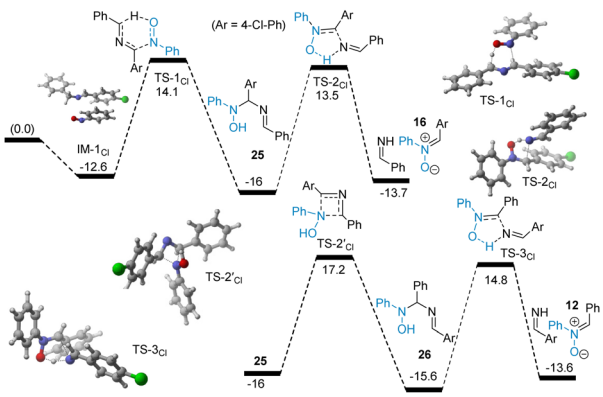
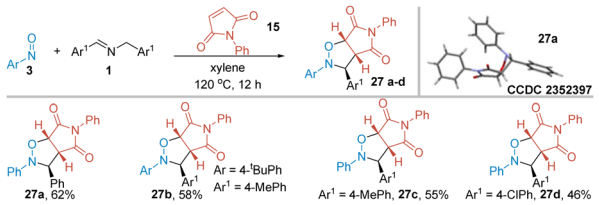


Fig. 2 Plausible mechanism for the formation of nitrons **16** and **12** from **15**.



Scheme 5 Scope for the synthesis of oxazolidines from imines, and nitrosoarenes.

Then, we wanted to explore the possibility of synthesis of oxazolidines from the annulation of imines, nitrosoarenes and alkenes. Accordingly, the nitrosoarene **3**, imine **1**, and *N*-phenyl maleimide **13** were reacted in the absence of Lewis acid to obtain the oxazolidines **27a–d** with good yields as a single isomer (Scheme 5). The relative stereochemistry of the oxazolidine derivative **27a** was confirmed by X-ray crystallographic analysis.

In summary, azomethine, which is well known to act as an enophile, is shown, for the first time, to act as an ene-component in nitroso-azomethine(ene) reaction. An unprecedented three-component annulation reaction of azomethine, nitrosoarene, and alkenes in the presence of a Lewis acid catalyst provided access to aryl quinolines. However, oxazolidines were obtained from the reactions that were carried out without any Lewis acid. The mechanistic studies showed that both reactions proceed *via* nitrone, which is formed *in situ* by a unique nitroso-azomethine(ene) reaction instead of a 1,3-dipolar cycloaddition reaction. DFT studies revealed that the nitroso-azomethine(ene) reaction follows a concerted pathway in contrast to the predominantly stepwise mechanisms observed in other nitroso-ene reactions. Interestingly, isomerization of the ene-adduct is found to be responsible for the formation of a mixture of nitrones from the reaction of imine with two different aryl moieties.

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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