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MeOTf-induced carboannulation of arylnitriles and aromatic alkynes: a new metal-free strategy to construct indenones†

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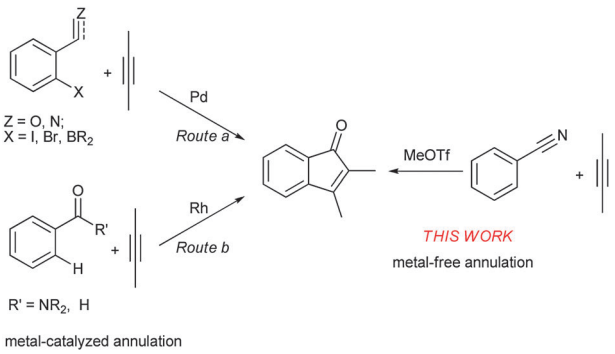
MeOTf-induced carboannulation of arylnitriles and aromatic alkynes for synthesis of indenones under metal-free conditions has been described. When *ortho*-substituted benzonitriles were used, indeno[1,2-c]-isoquinolines were formed.

Indenones are valuable frameworks in organic and bioorganic compounds.[1] In addition, they have also found applications in materials chemistry and medicinal chemistry.[2] Due to the importance of indenones, various synthetic methodologies for their synthesis have been reported. Traditional methods to yield indenones include intramolecular Friedel–Crafts acylation or addition of organometallic reagents to 1,3-indandiones. These methods usually require multiple steps and/or have a limited substrate scope.[3] Transition metal-catalyzed syntheses of indenones have been developed in recent years.[4–7] Among them, Pd-catalyzed annulation of alkynes with *ortho*-functionalized arylcarbonyl or arylnitrile compounds is a powerful strategy leading to the formation of indenones (Scheme 1, *route a*).[4,5] However, these approaches require prefunctionalized arenes, and this is both time and cost consuming in a synthetic sequence. Recently, direct construction of indenones *via* Rh-catalyzed annulation of benzimides or benzaldehydes with alkynes has been reported (*route b*).[6] Although significant advances have been made to date, new methods for the synthesis of diverse indenones with readily available starting materials and a simple reaction process under metal-free conditions are still highly desirable, particularly in the drug scanning process. Herein, we report the methyl triflate (MeOTf) induced annulation of arylnitriles and aromatic alkynes to afford indenones under metal-free conditions.



Scheme 1 Synthetic strategy leading to indenones.

Recently, Cu(II)-catalyzed cascade annulation of diaryliodoniums, nitriles, and alkynes afforded quinolines, in which phenylium (Ph^+) generated from Cu(II)-catalyzed decomposition of a diaryliodonium salt was thought to act as an electrophile to induce the formation of *N*-phenylnitrilium.[8] Inspired by this work, we envisioned whether a related process could be induced by MeOTf which is frequently used in the methylation reaction of heteroatomic compounds. In this process, MeOTf as an electrophile reacts with arylnitriles to give the *N*-methylnitrilium **A**,[9] which is a highly reactive species and could react with alkynes to afford intermediate **B**. Intermediate **B** undergoes an electrophilic annulation to form indenones after hydrolysis (Scheme 2).

In the preliminary experiment, upon heating the mixture of *p*-tolunitrile **1a**, MeOTf, and diphenylacetylene **2a** (1 : 1 : 1) in dichloroethane (DCE) at 150 °C for 12 h, the desired product indenone **3aa** was formed in 30% yield after hydrolysis. The by-product was pyrimidine which was produced by acid-catalyzed cyclotrimerization of alkynes and nitriles.[10] This side-reaction was inhibited upon increasing the amount of MeOTf. Then we tried different ratios of substrates, and found that the best result was obtained when the ratio of *p*-tolunitrile, MeOTf, and diphenylacetylene was 1.5 : 3 : 1 (Table 1, entries 2–5). Temperature screening experiments (entries 5–7) revealed that the best reaction temperature was 150 °C (entry 5). When the reaction was conducted in 6 h, the yield was 51% (entry 8).

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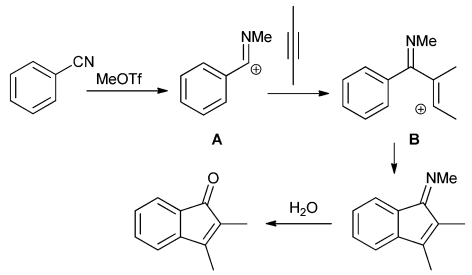
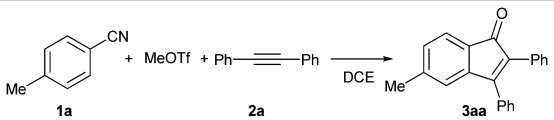
† Electronic supplementary information (ESI) available: Experimental procedures, full characterization including ^{1}H NMR and ^{13}C NMR data and spectra for all compounds. X-ray structure of **4a**. CCDC 965411. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00088a



Scheme 2 Design of the construction of indenones by MeOTf-induced carboannulation.

Table 1 Reaction optimization[a]

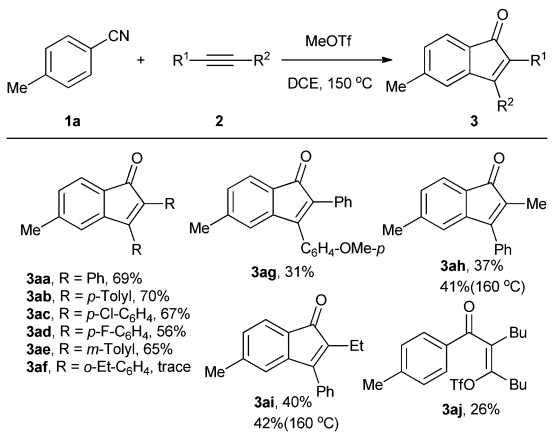


Entry	Ratio	Temperature (°C)	Yield[b] (%)
1	1 : 1 : 1	150	30
2	1.2 : 1.5 : 1	150	53
3	1.5 : 2.0 : 1	150	67
4	1.5 : 2.5 : 1	150	72
5	1.5 : 3 : 1	150	74 (69)
6	1.5 : 3 : 1	140	58
7	1.5 : 3 : 1	160	73
8[c]	1.5 : 3 : 1	150	51
9[d]	1.5 : 3 : 1	150	Trace

[a] The reaction was performed with 0.5 mmol diphenylacetylene in 2 mL DCE in a sealed tube for 12 h under nitrogen. [b] ^{1}H NMR yield, isolated yield is given in parentheses. [c] Reaction time of 6 h. [d] CCl_4 as the solvent.

When the reaction was carried out in CCl_4, only a trace amount of the product was obtained (entry 9).

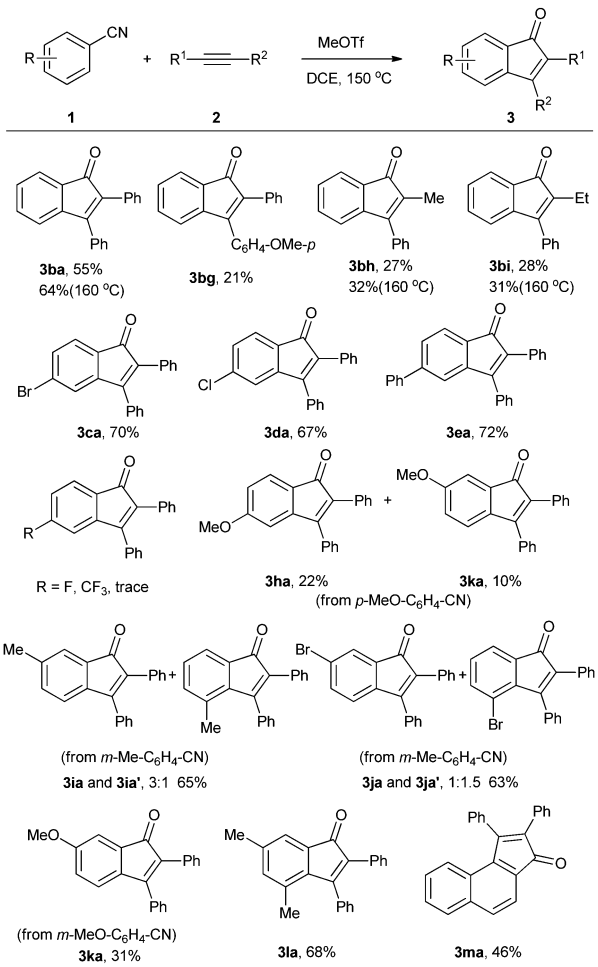
With the optimized reaction conditions, we tested various alkynes for the annulation reaction (Scheme 3). When symmetrical diarylacetylenes were used, the desired indenones (**3aa–3ae**) were formed in 56% to 70% isolated yields. Trace indenone product **3af** was obtained using 1,2-bis(2-ethylphenyl) acetylene, wherein the steric hindrance might have largely inhibited the reaction. It is noteworthy that when unsymmetrical 4-methoxyldiphenylacetylene was used, only one product **3ag** was formed. The yield was modest,



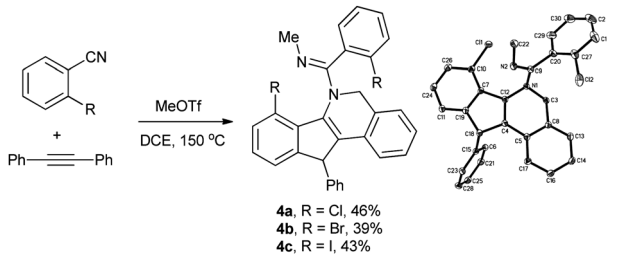
Scheme 3 Substrate scope of alkynes.

which may be due to the interaction of MeOTf and the methoxyl group. When 1-phenylpropyne and 1-phenylbutyne were employed, indenones **3ah** and **3ai** were formed in 45% and 50% isolated yields, respectively. In these cases, the alkyl group was located at the 2-position of the indenone ring and the phenyl group was located at the 3-position, which was totally different from transition-metal-catalyzed annulation of arenes with aryl alkyl acetylenes.[6] This regioselectivity may be due to the more stabilized effect of the phenyl group in intermediate **B**. When dialkylacetylene such as 5-decyne was used under the same reaction conditions, the cyclized product was not obtained and vinylketone **3aj** was formed as the final product, which indicates that **B** is an intermediate in this reaction.

Next, we investigated the scope of the arylnitriles (Scheme 4). Simple benzonitrile **1b** afforded indenones **3ba–3bi** in lower yields compared with *p*-tolunitrile. When benzonitriles with *para*-substituents such as bromo, chloro, and phenyl groups were employed, the corresponding indenones **3ca–3da** were formed in 67% to 72% isolated yields. It is noteworthy that utilization of *p*-methoxylbenzonitrile afforded not only the desired indenone **3ha** in 22% yield, but also the rearrangement isomer **3ka** in 10% yield (for possible formation of this isomer, see ESI†). Again, the low yield may be attributed to the interaction of MeOTf and the methoxyl group. Benzonitriles with strong electron-withdrawing groups, such as fluoro and trifluoromethyl groups, in the



Scheme 4 Substrate scope of arylnitriles.

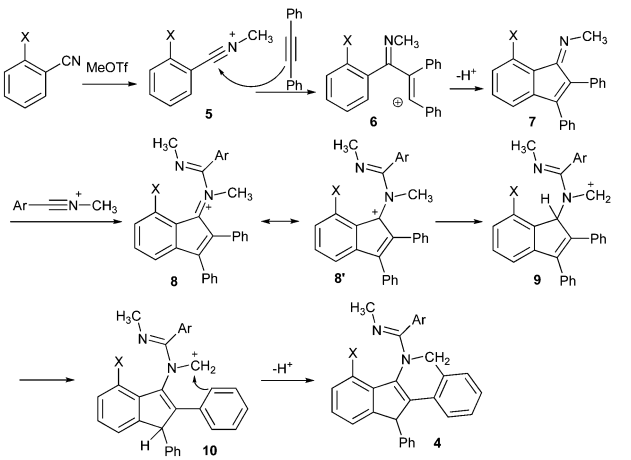


Scheme 5 Reaction of *ortho*-substituted benzonitrile, MeOTf, and diphenylacetylene and the X-ray structure of **4a**.

para-position afforded the corresponding indenones in trace amounts and the alkynes remained. Benzonitriles with a *meta*-substituted methyl or bromo group afforded the corresponding indenones as two isomers (**3ia** and **3ia′**, **3ja** and **3ja′**), respectively. Notably, when *m*-methoxylbenzonitrile was used, indenone **3ka** was formed in 31% isolated yield. In this case, we did not observe the other isomer. 3,5-Dimethylbenzonitrile afforded **3la** in 68% isolated yield. 2-Naphthonitrile gave benzo[*e*]indenone **3ma** in 46% isolated yield as a single product.

When *o*-chlorobenzonitrile was employed under the same reaction conditions, the reaction did not afford an indenone product but indeno[1,2-*c*]isoquinoline **4a** was formed in 46% isolated yield. The structure of **4a** was further confirmed by its X-ray diffraction analysis.‡ The structure of **4a** contains two molecules of *o*-chlorobenzonitrile and one molecule of diphenylacetylene. Methylene and methyl groups were derived from methyl triflate. The reaction of benzonitriles with an *ortho*-bromo or iodo substituent was similar, and the corresponding indeno[1,2-*c*]isoquinolines **4b** and **4c** were isolated in 39% and 43% yields, respectively (Scheme 5). When *o*-tolunitrile was employed as the substrate, the reaction yielded a mixture of indenones and indeno[1,2-*c*]isoquinoline (see ESI†).

For the reaction of *ortho*-substituted benzonitrile, MeOTf, and diphenylacetylene, a plausible mechanism is proposed as follows (Scheme 6): first, methylation of nitrile by MeOTf affords nitrilium **5**. Then alkyne attacks the carbon atom of nitrilium to afford intermediate **6** which undergoes a Friedel–Crafts reaction to give indenone imine **7**. Then indenone imine **7** attacks another molecule of nitrilium to yield cation **8** or its resonance **8′**. The subsequent 1,3-H shift and double bond migration of cation **8′** affords intermediate **10** through **9**. Finally, the intramolecular Friedel–Crafts reaction of **10** affords product **4**.



Scheme 6 Plausible mechanism.

In conclusion, we have developed a MeOTf-induced annulation between arylnitriles and aromatic alkynes. A range of functionalized indenone products are obtained. Under the same reaction conditions, *ortho*-substituted benzonitriles afforded indeno[1,2-*c*]isoquinolines with the construction of one carbocycle and one heterocycle. Further investigations are still in progress in this area.

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‡ CCDC 965411.

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