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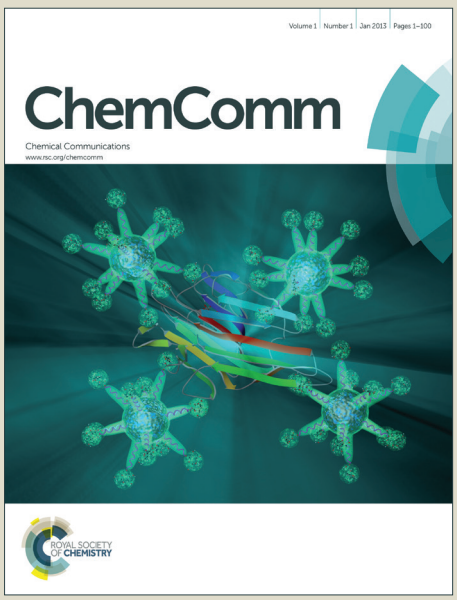

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ARTICLE TYPE

MeOTf-induced Carboannulation of Arylnitriles and Aromatic Alkynes: A New Metal-free Strategy to Construct Indenones

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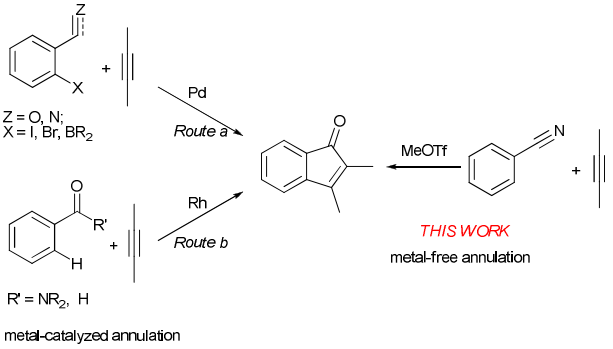
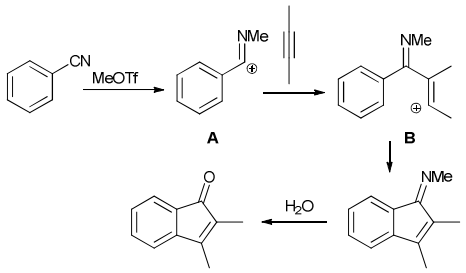
MeOTf-induced carboannulation of arylnitriles and aromatic alkynes for synthesis of indenones has been described under metal-free condition. When *ortho*-substituted benzonitriles were used, indeno[1,2-*c*]isoquinolines were formed.

Indenones are valuable frameworks in organic and bioorganic compounds.[1] In addition, they have also found applications in material 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 limited substrate scope.[3] Transition metal-catalyzed syntheses of indenones have been developed in recent years.[4-7] Among them, Pd-catalyzed annulation of alkyne with *ortho*-functionalized arylcarbonyl or arylnitrile compounds is a powerful strategy leading to indenones (Scheme 1, *route a*).[4,5] However, these approaches require prefunctionalized arenes and this both time and cost consuming in synthetic sequence. Recently, direct construction of indenones *via* Rh-catalyzed annulation of benzimide or benzaldehyde 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 simple reaction process under metal-free are still highly desirable, particular in the drug scanning process. Herein, we report the methyltriflate (MeOTf) induced annulation of arylnitriles and aromatic alkynes to afford indenones under metal-free condition.



Scheme 1 Synthetic strategy leading to indenone.

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



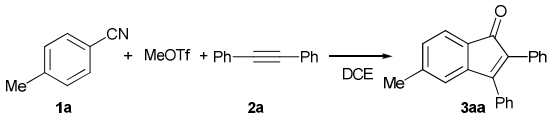
Scheme 2 Design of construction of indenones by MeOTf-induced carboannulation.

In the preliminary experiment, heating the mixture of *p*-tolunitrile **1a**, MeOTf, and diphenylacetylene **2a** (1:1:1) in dichloroethane at 150 °C for 12 h, the desired indenone **3aa** was formed in 30% yield after hydrolysis. The byproduct was pyrimidine which was produced by acid-catalyzed cyclotrimerization of alkyne and nitrile.[10] This side-reaction was inhibited when increasing the amount of MeOTf. Then we tried different ratio of substrates, and found it gave the best result when the ratio of *p*-tolunitrile, MeOTf, and diphenylacetylene is 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). When the reaction was treated in CCl_4, only trace amount of the product was observed (entry 9).

Having 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 observed using 1,2-bis(2-ethylphenyl) acetylene, wherein the steric hindrance largely may inhibit the

reaction. It is noteworthy that when unsymmetrical 4-methoxyldiphenylacetylene was used, only one product **3ag** was formed. The yield was modest, which may due to the interaction of MeOTf and methoxyl group. When 1-phenylpropyne and 1-phenylbutyne were employed, indenones **3ah** and **3ai** were formed in 45% and 50% isolated yield, respectively. In these cases, the alkyl group located at 2-position of indenone ring and the phenyl group located at 3-position, which was totally different with transition-metal-catalyzed annulation of arenes with aryl alkyl acetylenes.[6] This regioselectivity may be due to more stabilized effect of phenyl group in intermediate **B**. When dialkylacetylene such as 5-decyne was used in the same reaction condition, the cyclized product didn't observe and vinylketone **3aj** was formed as final product, which indicates the **B** as intermediate in this reaction.

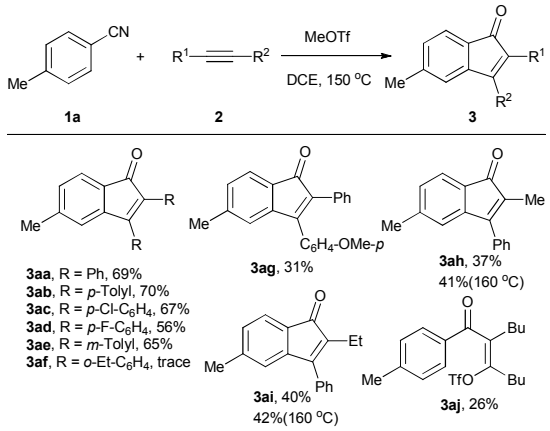
Table 1 Reaction optimization[a]



1a 2a 3aa

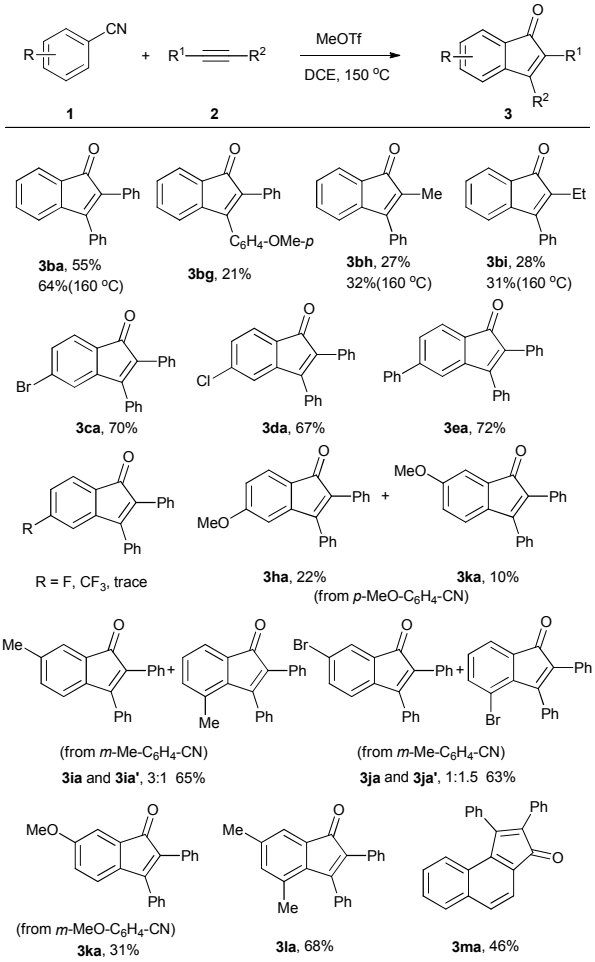
entry	ratio	temperature (°C)	yield(%)[b]
1	1:1:1	150	30
2	1.2:1.5:1	150	53
3	1.5:2.0:1	150	67
4	1.5:2.5:1	150	72
5	1.5:3:1	150	74(69)
6	1.5:3:1	140	58
7	1.5:3:1	160	73
8[c]	1.5:3:1	150	51
9[d]	1.5:3:1	150	trace

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



Scheme 3 Substrate scope of alkynes.

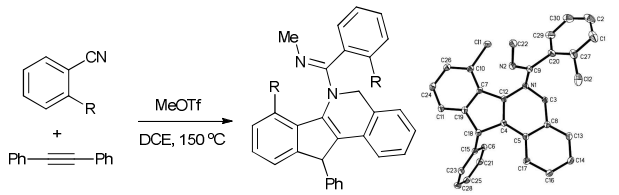
Next we investigated the scope of the arylnitriles (Scheme 4). Simple benzonitrile **1b** afforded indenones **3ba-3bi** in lower yields compared with *p*-tolunitrile. When benzonitriles with *para*-substituents such as bromo, chloro, and phenyl group were employed, the corresponding indenones **3ca-3da** 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 rearrangement isomer **3ka** in 10% yield (for possible formation of this isomers, see ESI). Again, the low yield may be attributed to the interaction of MeOTf and methoxyl group. Benzonitriles with strong electron withdrawing group such as fluoro and trifluoromethyl group in the *para*-position afforded the corresponding indenones in trace amount and the alkyne remained. Benzonitriles with *meta*-substituented 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 didn't observe 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.



Scheme 4 Substrate scope of arylnitriles.

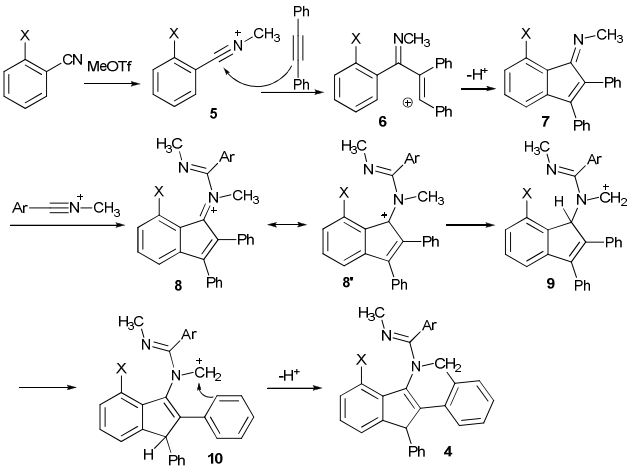
When *o*-chlorobenzonitrile was employed under the same reaction condition, the reaction didn't afford indenone product but indeno[1,2-*c*]isoquinoline **4a** formed in 46% isolated yield. The structure of **4a** was further confirmed by its X-ray diffraction analysis.‡ The structure of **4a** contains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

(see ESI).



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

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 Friedel–Crafts reaction to give indenone imine **7**. Then indenone imine **7** attacks another molecular of nitrilium to yield cation **8** or its resonance **8′**. Subsequent 1,3-H shift and double bond migration of cation **8′** affords intermediate **10** through 9. Finally, 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 condition, *ortho*-substituted benzonitriles afforded indeno[1,2-*c*]isoquinolines with construction of one carbocycle and one heterocycle. Further investigations are still in progress in this area.

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Notes and references

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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**. See DOI: 10.1039/b000000x/

‡ CCDC 965411.

1 (a) W. M. Clark, A. M. Tickner-Eldridge, G. K. Huang, L. N. Pridgen, M. A. Olsen, R. J. Mills, I. Lantos and N. H. Baine, *J. Am. Chem. Soc.,* 1998, **120**, 4550; (b) J. L. Jeffrey and R. Sarpong, *Org. Lett.,* 2009, **11**, 5450; (c) Q. Xi, W. Zhang and X. Zhang, *Synlett,* 2006, 945; (d) W. Liu, M. Buck, N. Chen, M. Shang, N. J. Taylor, J. Asoud, X. Wu, B. B. Hasinoff and G. I. Dmitrienko, *Org. Lett.*, 2007, **9**, 2915 (e) A. C. Glass, B. B. Morris, L. N. Zakharov and S.-Y. Liu, *Org. Lett.*, 2008, **10**, 4855.

2 (a) G. M. Anstead, R. J. Altenbach, S. R. Wilson and J. A. Katzenellenbogen, *J. Med. Chem.* 1988, **31**, 1316; (b) G. M. Anstead, S. R. Wilson and J. A. Katzenellenbogen, *J. Med. Chem.* 1989, **32**, 2163; (c) J. H. Ahn, M. S. Shin, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhee, W. H. Jung, S. D. Yang, S. J. Kim, J. R. Woo, J. H. Lee, H. G. Cheon and S. S. Kim, *J. Med. Chem.* 2006, **49**, 4781. (d) K. Morinaka, T. Ubukata and Y. Yokoyama, *Org. Lett.,* 2009, **11**, 3890; (e) M. Kose, E. Orhan, K. Suzuki, A. Tutar, C. S. Ünlü and Y. Yokoyama, *J. Photoch. Photobio. A*, 2013, **257**, 50.

3 (a) R. L. Frank, H. Eklund, J. W. Richter, C. R. Vanneman and A. N. Wennerberg, *J. Am. Chem. Soc.,* 1944, **66**, 1; (b) H. O. House, V. Paragamian, R. S. Ro and D. J. Wluka, *J. Am. Chem. Soc.,* 1960, **82**, 1452; (c) M. B. Floyd and G. R. Allen, Jr., *J. Org. Chem.,* 1970, **35**, 2647.

4 (a) R. C. Larock, Q. Tian and A. A. Pletnev, *J. Am. Chem. Soc.,* 1999, **121**, 3238; (b) A. A. Pletnev, Q. Tian and R. C. Larock, *J. Org. Chem.,* 2002, **67**, 9276; (c) T. Miura and M. Murakami, *Org. Lett.,* 2005, **7**, 3339; (d) H. Tsukamoto and Y. Kondo, *Org. Lett.,* 2007, **9**, 4227; (e) D. A. Alonso, C. Nájera and M. C. Pacheco, *Adv. Synth. Catal.,* 2002, **344**, 172; (f) R. C. Larock, M. J. Doty and S. Cacchi, *J. Org. Chem.,* 1993, **58**, 4579.

5 (a) L. S. Liebeskind and M. S. South, *J. Org. Chem.* 1980, **45**, 5426; (b) Y. Harada, J. Nakanishi, H. Fujihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.* 2007, **129**, 5766; (c) C. Liu, R. P. Korivi and C. Cheng, *Chem. -Eur. J.* 2008, **14**, 9503; (d) T. Morimoto, K. Yamasaki, A. Hirano, K. Tsutsumi, N. Kagawa, K. Kakiuchi, Y. Harada, Y. Fukumoto, N. Chatani and T. Nishioka, *Org. Lett.* 2009, 11, 1777.

6 (a) K. Kokubo, K. Matsumasa, M. Miura and M. Nomura, *J. Org. Chem.* 1996, **61**, 6941; (b) B. Li, H. Wang, Q. Zhu and Z. Shi, *Angew. Chem. Int. Ed.* 2012, **51**, 3948; (c) S. Chen, J. Yu, Y. Jiang, F. Chen and J. Cheng, *Org. Lett.* 2013, **15**, 4754; (c) Z. Qi, M. Wang and X. Li, *Org. Lett.*, 2013, **15**, 5440.

7 (a) Y. Kuninobu, T. Matsuki and K. Takai, *Org. Lett.* 2010, **12**, 2948; (b) K. Gao and N. Yoshikai, *Chem. Commun.* 2012, **48**, 4305; (c) X. Chen, Q. He, Y. Xie and C. Yang, *Org. Biomol. Chem.* 2013, **11**, 2582; (d) N. Wu, A. Messinis, A. S. Batsanov, Z. Yang, A. Whiting and T. B. Marder, *Chem. Commun.* 2012, **48**, 9986; (e) Y. Harada, J. Nakanishi, H. Fujihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2007, **129**, 5766.

8 (a) Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem. Int. Ed.* 2013, **52**, 5323; (b) X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou and M. Li, *Chem. Commun.*, 2013, **49**, 6752; (c) Y. Wang, C. Chen, S. Zhang, Z. Lou, X. Su, L. Wen and M. Li, *Org. Lett.*, 2013, **15**, 4794.

9 B. L. Booth, K. O. Jibodu and M. F. Proença, *J. Chem. Soc., Chem. Commun.* 1980, 1151.

10 (a) A. A. Pourzal, *Synthesis* 1983, 717; (b) M. A. García, F. A. Herrera, A. R. Martinez, L. M. C. Silva, V. D. Molero, L. R. Subramanian and M. Hanack, *Synthesis* 1990, 881.