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Reactions of HDDA Benzynes with *C,N*-Diarylimines (ArCH=NAr')

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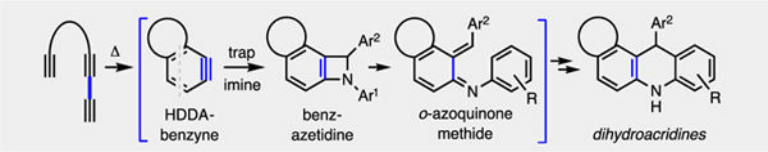
Abstract

o-Benzynes can be utilized to construct heterocyclic motifs using various nucleophilic and cycloaddition trapping reactions. Acridines have been synthesized by capture of *C,N*-diarylimines with benzynes generated by classical methods (i.e., from *ortho*-elimination of precursor arene compounds), although in poor yields. We report here that these imines can be trapped by benzynes generated by the hexadehydro-Diels–Alder (HDDA) reaction in an efficient manner to produce 1,4-dihydroacridine products. These dihydroacridines were subsequently aromatized using MnO_2 to provide structurally complex acridines.

Abstract

Benzynes generated by the hexadehydro-Diels–Alder (HDDA) reaction are shown to capture *C,N*-diarylimines to produce 1,4-dihydroacridine products. The reaction is thought to proceed via benzazetidine intermediates that then undergo electrocyclic ring-opening and -closing (and final rearomatization) to give the dihydroacridines. These were easily aromatized with MnO_2 to provide structurally complex acridines.

Graphical Abstract



Keywords

HDDA-benzynes; benzazetidines; azoquinone methides; dihydroacridines; acridines

Introduction

o-Benzynes and related arynes have been used as versatile intermediates for construction of various aromatic heterocycles.[1] In a few instances, six-membered nitrogen-containing heterocycles of the acridine family have been produced, at least to small extents, by trapping

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of a classically generated aryne (i.e., one formed by way of an *ortho*-elimination of a precursor aromatic compound) by an imine. The previously observed reaction pathways may be roughly placed into two categories: a) a net [2+2] process by way of an initial, transient zwitterion (Scheme 1a); b) initial [4+2] cycloaddition between the benzyne (acting as a dienophile) and the *N*-aryl imine moiety (acting as the diene) (Scheme 1b).

The first reports of reactivity between *o*-benzynes and *C,N*-diaryl imines came from the laboratories of M. Yoshida[2] (1975) and Storr[3] (1984), which independently reported the reaction of *N*-benzylideneaniline [**2**, $R^1 = R^2$ = Ph (= **2a**)] with *o*-benzyne (**1**) generated from benzenediazonium-2-carboxylate. In both studies the dihydrophenanthridine **7a** was isolated (8% or 6% yield) and in the latter the dihydroacridine **4b** (5%) was also obtained. These were rationalized as arising from competitive [2+2]- vs. [4+2]-cycloaddition of *o*-benzyne with **2a** via intermediates **3b** (through **3d**) or **6a** and **6b**, respectively. The major isolated product in both of these original studies (18% and 16%, respectively) was the diamine **4a**.

More recently, additional modes of reactivity between *o*-benzynes and imines have been studied. Some have focused on trapping of the presumed 1,3-zwitterion **3a**, which arises via imine nitrogen attack on the electrophilic benzyne. In 2006 H. Yoshida and coworkers[4] demonstrated the ability to access benzoxazinones **5b** via trapping of the 1,3-zwitterion by carbon dioxide using imines in which the carbon-bound group is an alkyl moiety. In 2015 Hwu et al.[5] showed the diastereoselective formation of imidazolidines **5a** and other *N*-heterocycles via trapping of the intermediate 1,3-dipole **3e**, formed via intramolecular proton transfer within **3a**. Finally, in 2017 researchers in the Tian laboratory[6] showed that **3a** may be trapped by protic carbon nucleophiles in a three-component fashion to form products of the type **5c**.

In 2017 H. Yoshida and coworkers[7] showed that trapping of the aza-*ortho*-quinone methide intermediate **3c** to form 2:1 imine:benzyne adducts **4c** was possible when benzyne was used in molar excess. This mode of reactivity prevails when the aryl moieties are more highly substituted, presumably slowing the electrocyclization of **3c** to **3d**.

Finally, in addition to M. Yoshida and Storr's initial isolation of phenanthridine adducts, other groups have sought to exploit the [4+2] pathway to access this class of product more efficiently. In 2006 Wang et al.[8] showed that benzyne could be used in a 3-component process to access phenanthridines **7c** with high efficiency using an electron-poor benzaldehyde and an electron-rich aniline. Similarly, in 2016 researchers in the He group[9] were able to isolate **7b** in a three-component process using Kobayashi[10] arynes, an aldehyde ester, and an aniline. In 2015 Coquerel and coworkers[11] reported the formation of isoquinolines **7d** derived from an imine containing a nitrogen-bound pyrazole moiety, and, through a computational study, suggested that an electron-rich aromatic group bound to the imine nitrogen favors [4+2] cycloaddition over a [2+2] pathway.

To summarize, reported examples of benzynes reacting with imines to give acridine-like products have shown low selectivity and efficiency. Given the interest in acridine compounds more broadly as well as the fact that hexadehydro-Diels–Alder (HDDA)-derived benzynes[12]

often lead to outcomes complementary to those from classical benzynes, we have explored the reactions of several polyyne substrates with various imine trapping agents and report the results of those studies here.

Results and Discussion

We first examined (Scheme 2) the reaction between the HDDA benzyne **9**, generated by warming triyne **8**, with *N*-benzylidene-aniline (**2a**). This resulted in formation of the dihydroacridine **11** in a remarkably clean reaction, which contrasts significantly with the lower efficiencies of previous reactions giving rise to dihydroacridines (cf. Scheme 1a). Compound **11** was subsequently oxidized with MnO_2 to afford the acridine derivative **12a** in 68% yield.

To demonstrate generality of this reaction with different types of electronically modified aryl substituents in the imines, we explored the reactions between benzyne **9** and imines **2b-2g** (Table 1). For each entry, only the acridine product that results from subsequent MnO_2 oxidation of the intermediate dihydroacridine is shown (see Supporting Information for characterization of the dihydro-intermediates **SI-1**–**SI-6**). The reaction showed relatively broad tolerance of electronic perturbation of the aryl substituent on both the carbon and nitrogen atoms composing the imine. That is, imines **2b-g** all provided the corresponding dihydroacridines and, then, the acridines **12b-g** (Table 1). Only in the instance of the most electron-poor imine **2f**, was the yield of the initial dihydroacridine low. This is consistent with the view that the initial event in the engagement of benzyne with imine is nucleophilic attack by the nitrogen atom to generate the zwitterion **3a** (Scheme 1a).

As a final example, this with a different type of imine, the 1-naphthyl derivative **13** gave the more highly annulated benzoacridine derivative **14** (Scheme 3). This suggests that additional analogs with yet more extended conjugation can also be accessed.

Amidines are amino-substituted analogs of imines. *N,N*-Dimethyl-*N'*-phenylamidine (**15**) efficiently engaged the benzyne **9** (Scheme 4). It gave rise directly to the acridine derivative **17a**, which has no substituent at C9 of the acridine. However, this reaction was accompanied by the formation of a similar amount of the dimethylamine-trapped benzyne product **17b**. Presumably the dihydroacridine **16**, arising from a [2+2] pathway directly analogous to that depicted for **8** to **11** (Scheme 2), underwent an elimination event under the reaction conditions to produce **17a**. That process can be envisioned to proceed by a direct (and possibly unimolecular) loss of dimethylamine, which, once released, then competitively trapped benzyne **9** (red arrows). Alternatively, a second copy of **9** could engage the tertiary aliphatic amine in intermediate **16** to give the 1,3-zwitterion[13] **18** (shown in a truncated form for simplicity), which could then collapse directly to one molecule each of **17a** and **17b**. Although of limited preparative value, this trapping reaction with an amidine provides interesting mechanistic insights.

To establish that the reaction is not limited to benzyne **9**, we have trapped the HDDA benzynes derived from the precursor tetraynes **19a** and **19b** with *N*-benzylideneaniline (**2a**) (Scheme 5). The symmetrical tetrayne, which previously has been shown to react with

various nucleophiles to give a pair of constitutional isomers with relatively little preference, produced only the single regioisomeric isoindoline derivative **20a** in 42% yield along with the oxidized acridine **21a** (19%), presumably from air oxidation. Reaction of **19b** and **2a** produced the expected indolinoquinoline **21b** in 51% yield over two steps. The formation of a single benzyne (i.e., **22b**; see dashed lines in **19b**) from this unsymmetrical tetrayne precursor was first observed[14] by Lee and coworkers (and on many subsequent occasions) and is consistent with a computational study[15] that addressed exactly that point. To summarize, the reactions of both **19a/b** with **2a** proceeded via the corresponding benzazetidine **23a/b** and azo-quinonemethide species **24a/b** en route to the 1,4-dihydroacridines **20a/b**.

Conclusions

In summary, these results establish that trapping of thermally generated, polycyclic benzyne derivatives with *C,N*-diaryl imines leads to dihydroacridine derivatives, which can be further and readily oxidized to their acridine analogs. These reactions proceed considerably more efficiently than those reported earlier for imine trapping of benzyne itself (from benzenediazonium-2-carboxylate thermolysis). In no case have we observed products arising from initial [4+2] cycloaddition, as has been seen in previous studies.[2,3,8,9,11] This work represents another instance in which the arynes generated through the HDDA-cycloisomerization reaction, which are performed in a purely thermal environment, has allowed for the formation of the trapping products in a much cleaner,[16] if not unique,[17] manner.

Experimental Section

General Experimental Protocols

^{13}C and ^{1}H NMR spectra were recorded on a Bruker HD-500, AV-500, AV-400, or AX-400 spectrometer. Proton chemical shifts are referenced to TMS (δ 0.00 ppm) in $CDCl_3$ solutions and to the residual CHD_5 (δ 7.16 ppm) in benzene-d_6 solutions. A non-first order multiplet, doublet, or doublet of doublets in a ^{1}H NMR spectrum is denoted as a ‘nfom’, ‘nfod’, or ‘nfodd’, respectively. For the latter two, the coupling constant is listed as an apparent value (J_{app}), because the spacing between the two major lines for the population of molecules having magnetically equivalent protons (ca. 50%) is actually the value of $J_o + J_p$). Resonances are reported in the following format: chemical shift (ppm) [multiplicity, coupling constant (s) (in Hz), integral value (to the nearest integer), and assignment of the substructural environment within the structure]. First-order coupling constants were analyzed using methods we have published elsewhere.[18,19] The ^{13}C NMR chemical shifts are taken from the “1D” spectrum where possible, although some were deduced from HMBC correlations. Carbon chemical shifts are referenced to δ 77.16 ppm in $CDCl_3$ solutions and to δ 128.06 for C_6D_6 solutions. Infrared spectra were recorded using a Bruker Alpha II Spectrometer. Samples were prepared as thin films on a diamond window in the attenuated total reflectance (ATR) mode. Absorption maxima are given in cm^{-1}. The high-resolution mass spectrometry (HRMS) measurements were made in the ESI mode using a Thermo Orbitrap Velos instrument (mass accuracy of ≤3 ppm). An external calibrant was

used (Pierce™ LTQ) and the samples were directly injected into the ion source. Medium pressure liquid chromatography (MPLC) was often used to purify newly synthesized materials. Hand-packed silica gel columns (normal-phase, 25–200 psi, 20–40 μm, 60 Å pore size, Teledyne RediSep Rf Gold®) were used. The apparatus consisted of a Waters HPLC pump (model 510), a Gilson (111 UV) detector, and a Waters (R401) differential refractive index detector. Preparative flash chromatography was performed on columns packed with Agela silica gel (230–400 mesh). Thin layer chromatography (TLC) was performed on silica-gel coated, plastic-backed plates that were visualized by UV light and/or by a solution of potassium permanganate and heating. The indicated reaction temperature refers to the temperature of the external cooling or heating bath. HDDA reactions, including those performed at temperatures higher than the boiling point of the reaction solvent, were done in a screw-top culture tube that was capped with an inert, Teflon®-lined closure. Poly-yne substrates **8**[20], **19a**[21], and **19b**[21] were synthesized according to reported methods. *N*-Benzylideneaniline (**2a**) was prepared according to a reported procedure.[22]

A. General Procedure for trapping of HDDA-generated arynes with imines— The polyyne precursor (1 equiv) and the imine (1–3 equiv) were combined in a screw-capped culture tube. 1,2-Dichloroethane was added (0.05 M) and the resulting solution was placed in an oil bath maintained at 90 °C and allowed to react overnight. Subsequently, the solvent was removed under reduced pressure, and the crude material was purified using MPLC with the elution solvent mixture indicated for each compound.

B. General Procedure for oxidation of 1,4-dihydroacridines to their respective acridines—A scintillation vial or a culture tube was charged with a stir bar and the respective 1,4-dihydroacridine (1 equiv). Chloroform or dichloromethane (0.005 M) was added, along with MnO_2 (ca. 10–20 equiv). The resulting slurry was allowed to stir at ambient temperature until the reaction was observed to be complete by TLC analysis. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo.

C. General Procedure for one-pot synthesis of acridines from HDDA-generated benzynes and imines—The HDDA polyyne precursor (1 equiv) and the imine (1–3 equiv) were added to a screw-cap culture tube. 1,2-Dichloroethane was added (0.05 M), and the resulting solution was placed in an oil bath maintained at 90 °C and allowed to react overnight. MnO_2 (ca. 10–20 equiv) and a stir bar were added. The slurry was then stirred at ambient temperature until the reaction was observed to be complete by TLC. The reaction mixture was filtered through Celite® and the filtrate was concentrated in vacuo.

10,11-Dimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-5,13-dihydro-8H-indeno[1,2-a]acridin-8-one (11)—Following general procedure A, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.024 g, 0.074 mmol, 1 equiv), (*E*)-*N*,1-diphenylmethanimine (**2a**, 0.015 g, 0.083 mmol, 1.1 equiv), and dichloroethane (2 mL) were used to prepare the 1,4-dihydroacridine **11**. Purification of the crude product by MPLC (2:1 hexanes:EtOAc) yielded **11** (0.038 g, 0.076 mmol, 98%) as an orange crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 7.8, 1.4 Hz, 1H, *H1*),

7.29 (nfod, J_{app} = 7.5 Hz, 2H, ArH_o), 7.22 (nfodd, J_{app} = 7.7, 7.7 Hz, 2H, PhH_m), 7.126 (ddd, J = 7.4, 7.4, 1.5 Hz, 1H, *H3*), 7.125 (tt, J = 7.4, 1.5 Hz, 1H, ArH_p), 7.10 (s, 1H, *H9*), 7.09 (s, 1H, *H12*), 6.95 (dd, J = 7.4, 7.4, 1.1 Hz, 1H, *H2*), 6.81 (dd, J = 7.9, 1.3 Hz, 1H, *H4*), 6.48 (s, 1H, N*H*), 5.77 (s, 1H, *H13*), 3.90 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.45 (s, 3H, ArCH_3), and 0.46 (s, 9H, Si(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): 193.6, 153.0, 149.0, 144.7, 143.1, 142.6, 141.2, 137.6, 137.5, 133.8, 129.1, 128.70, 128.67, 127.8, 127.1, 127.0, 125.3, 123.9, 122.3, 118.8, 115.2, 107.8, 106.7, 56.6, 56.2, 44.7, 18.2, and 3.2. HRMS (ESI-TOF): Calcd for $C_{32}H_{32}NO_3Si^+$ $[M+H^+]^+$ requires 506.2146; found 506.2150. IR (neat): 3440, 3390, 3059, 3001, 2924, 2853, 2359, 2342, 2069, 2034, 1976, 1961, 1944, 1694, 1605, 1577, 1546, 1489, 1465, 1432, 1416, 1375, 1343, 1324, 1299, 1283, 1259, 1245, 1215, 1173, 1158, 1091, 1045, 1027, 991, 936, 873, 854, 797, 771, 751, 727, 699, 676, 645, 630, 613, 599, 575, 519, 493, 449, and 408 cm^{-1}. mp: 249–250 °C.

10,11-Dimethoxy-6-methyl-13-phenyl-7-(trimethylsilyl)-8H-indeno[1,2-a]acridin-8-one (12a)—Following general procedure C, 1-(4,5-dimethoxy-2-(penta-1,3-diyn-1-yl)phenyl)-3-(trimethylsilyl)prop-2-yn-1-one (**8**, 0.010 g, 0.030 mmol, 1 equiv), (*E*)-*N*,1-diphenylmethanimine (**2a**, 0.007 g, 0.038 mmol, 1.3 equiv), MnO_2 (xs), and dichloroethane (2 mL) were used to prepare acridine **12a**. Purification of the crude product yielded acridine **12a** (0.011 g, 0.022 mmol, 71%) as a purple crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, J = 8.6 Hz, 1H, *H4*), 8.14 (d, J = 8.9 Hz, 1H, *H1*), 7.78 (nfod, J_{app} = 7.2 Hz, 2H, PhH_o), 7.77 (br dd, J = 8.8, 6.8 Hz, 1H, *H3*), 7.56 (nfodd, J_{app} = 7.5, 7.5 Hz, 2H, PhH_m), 7.53 (tt, J = 6.9, 1.7 Hz, 1H, PhH_p), 7.48 (br dd, J = 8.6, 6.6 Hz, 1H, *H2*), 7.04 (s, 1H, *H9*), 5.64 (s, 1H, *H12*), 3.83 (s, 3H, C10OCH_3), 3.51 (s, 3H, C11OCH_3), 3.06 (s, 1H, ArCH_3), and 0.51 (s, 9H, Si(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): 195.4, 153.0, 150.6, 149.0, 148.0, 146.9, 145.1, 143.0, 140.1, 138.6, 137.3, 136.1, 132.8, 130.9, 130.3, 129.5, 129.0, 126.7, 126.5, 125.2, 125.0, 120.8, 109.3, 106.5, 56.7, 56.1, 20.7, and 2.7. HRMS (ESI-TOF): Calcd for $C_{32}H_{30}NO_3Si^+$ $[M+H^+]^+$ requires 504.1989; found 504.1983. IR (neat): 3062, 2956, 2922, 2852, 2357, 2171, 2099, 2041, 2023, 1984, 1758, 1709, 1595, 1579, 1498, 1463, 1442, 1418, 1405, 1376, 1336, 1285, 1250, 1224, 1180, 1144, 1109, 1059, 1026, 1012, 972, 896, 842, 816, 799, 764, 734, 702, 671, 642, 619, 604, 568, 544, 519, 507, and 412 cm^{-1}. mp: 96–97 °C.

The online Supporting Information contains experimental procedures for all reactions, analytical characterization data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra as well as selected 2D NMR spectra.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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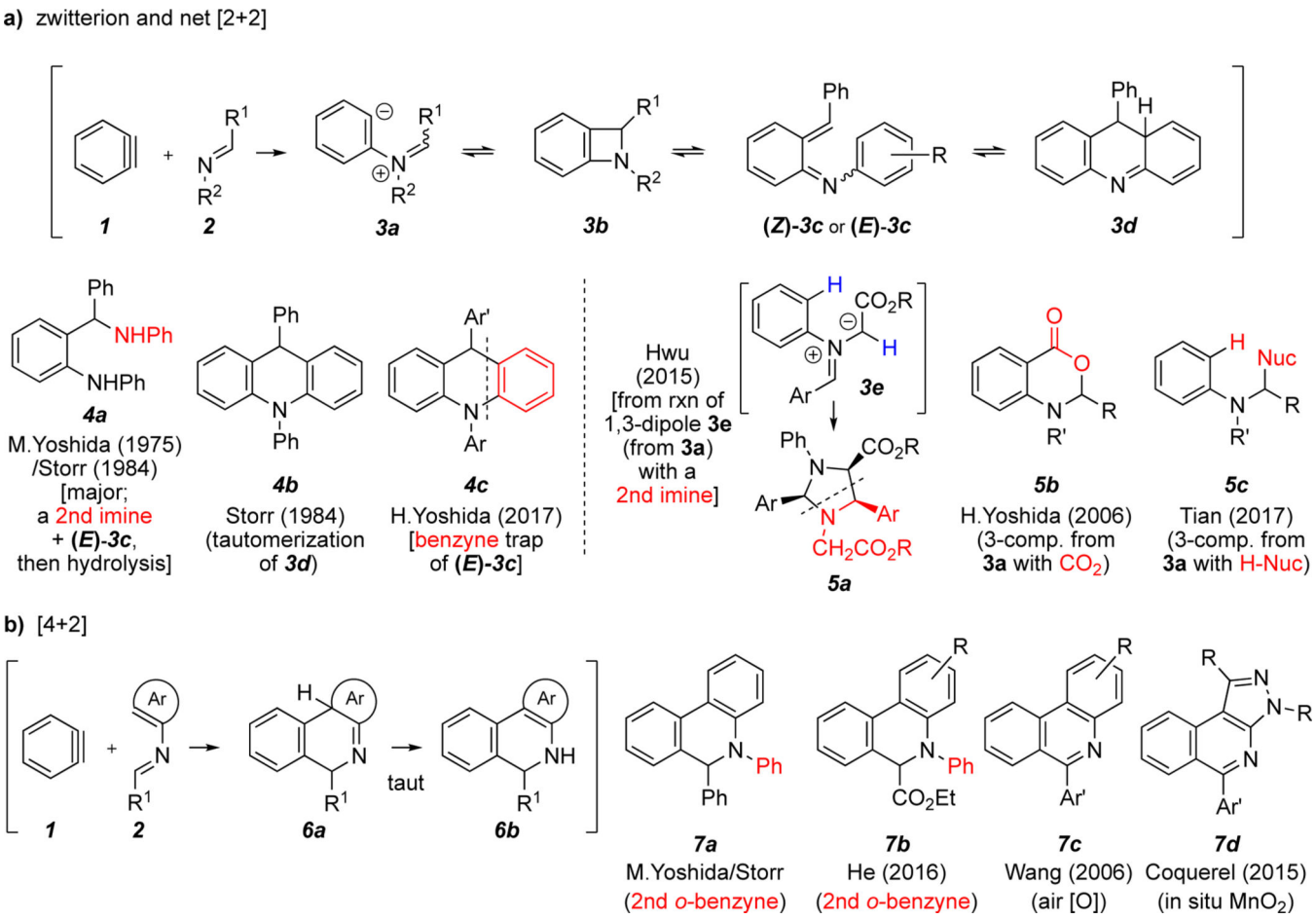
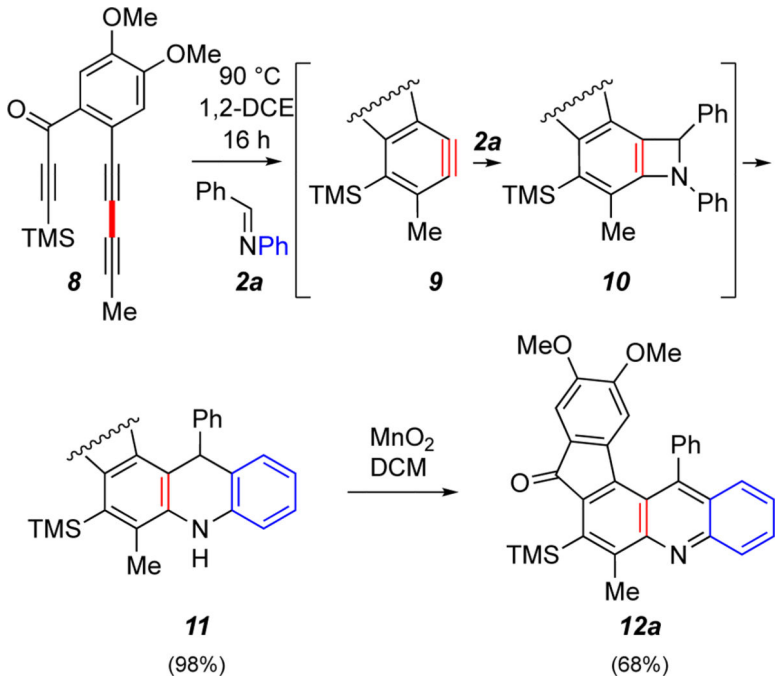


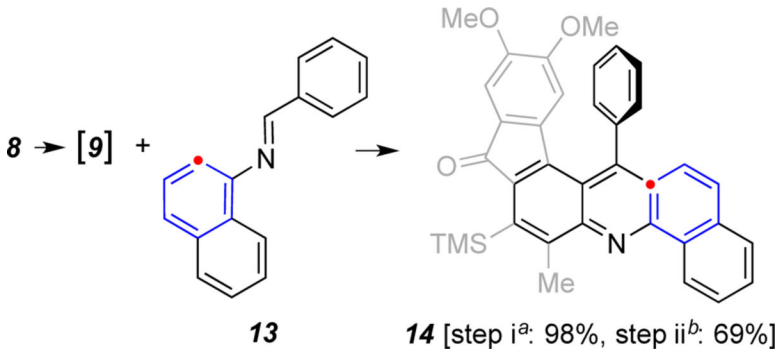
Scheme 1.

Previous studies of reactions of benzynes with imines in either (a) a net [2+2] pathway or (b) a [4+2] pathway



Scheme 2.

Reaction of the HDDA-generated benzyne **9** proceeds nearly exclusively to the 1,4-dihydroacridine **11**, presumably via the [2+2]-benzazetidine **10**. Compound **11** was subsequently oxidized to acridine **12a**.

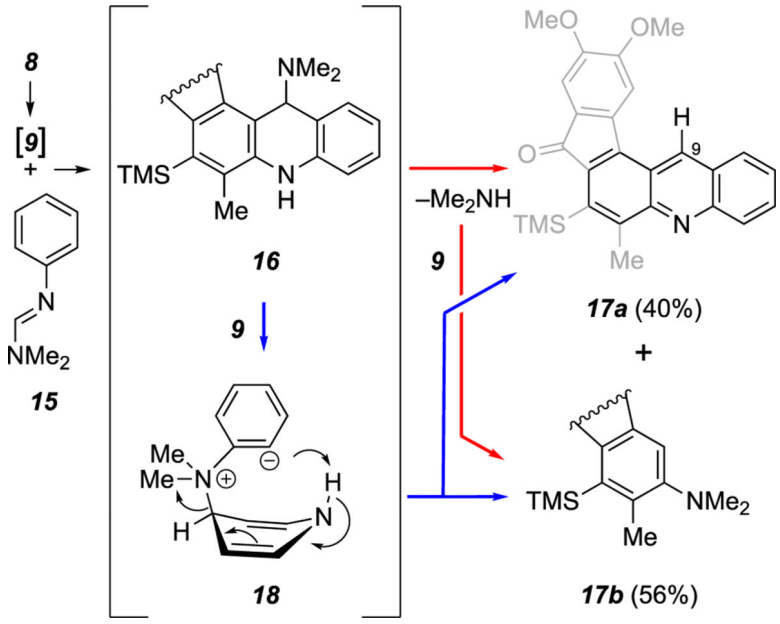


Scheme 3.

Reaction of triyne **8** with imine **13**.

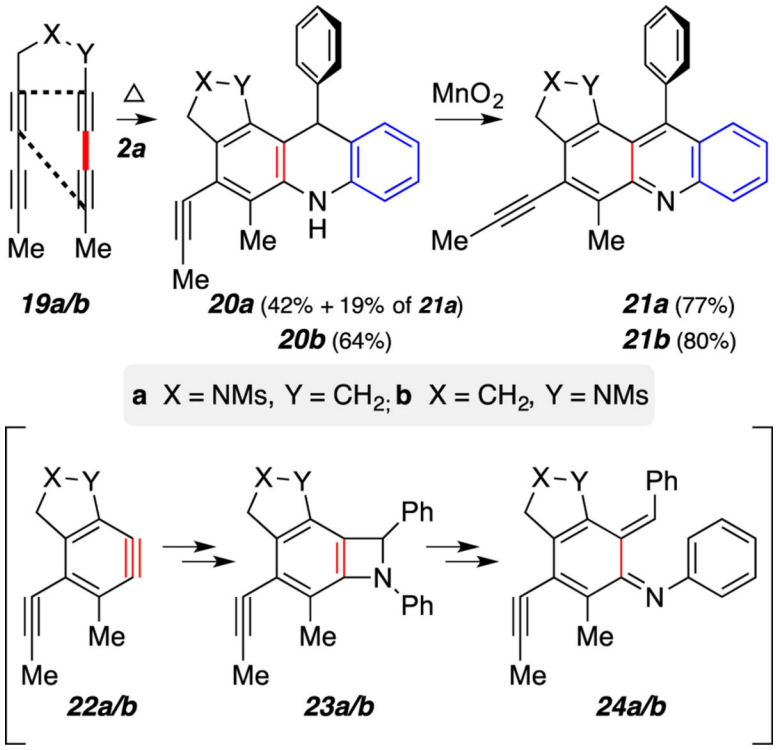
[a]yield of the 1,4-dihydroacridine from the HDDA reaction

[b]yield of the acridine adduct following MnO_2 treatment



Scheme 4.

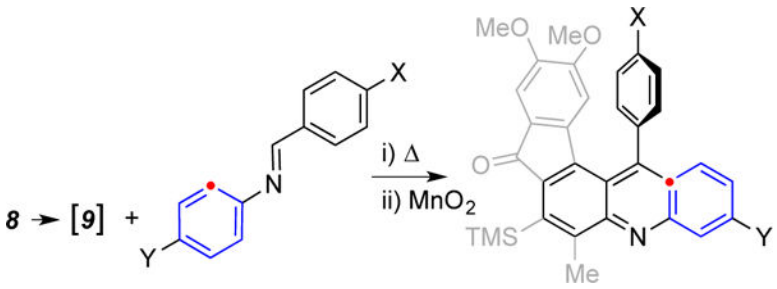
Reaction of amidine **15** with aryne **9** generated from triyne **8**.



Scheme 5.
Reactions of tetraynes **19a/b** with imine **2a** to give acridines **21a/b**.

Table 1.

Reactions of triyne **8** with several *C,N*-diaryl imines.



entry	*imine*	*product* [step i[a]: yield%, step ii[b]: yield%]
1	***2a***, X = H, Y = H	***12a*** [step i[a]: 98%, step ii[b]: 68%]
2	***2b***, X = NO_2, Y = H	***12b*** [step i[a]: 68%, step ii[b]: 90%]
3	***2c***, X = OMe, Y = H	***12c*** [step i[a]: 78%, step ii[b]: 86%]
4	***2d***, X = H, Y = NO_2	***12d*** [step i[a]: 62%, step ii[b]: 82%]
5	***2e***, X = H, Y = OMe	***12e*** [step i[a]: 100%, step ii[b]: 97%]
6	***2f***, X = NO_2, Y = NO_2	***12f*** [step i[a]: 19%, step ii[b]: 56%]
7	***2g***, X = OMe, Y = OMe	***12g*** [step i[a]: 88%, step ii[b]: 89%]

[a] yield of the 1,4-dihydroacridine from the HDDA reaction

[b] yield of the acridine adduct following MnO_2 treatment