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Synthesis of dibenzo[*a*,*d*]cycloheptanoids *via* aryne insertion into 2-arylidene-1,3-indandiones†

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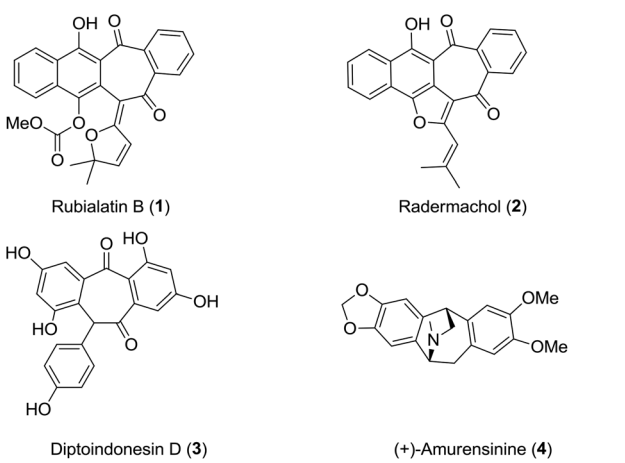
A novel and unexpected aryne insertion cascade reaction on 2-arylidene-1,3-indandiones *via* conjugate addition of fluoride followed by formal C–C insertion is developed to afford dibenzo[*a*,*d*]cycloheptanoid derivatives in good yields with a single isomer. This reaction represents a rare instance of cyclic enone C–C bond insertion (acyl-alkenylation) in aryne chemistry. Interestingly, 2-arylidene-1,3-indandiones bearing electron rich functional groups provided dibenz[*a*,*c*]anthracene-9,14-dione derivatives *via* [4 + 2] cycloaddition followed by ring expansion.

Mono- and dibenzannulated carbocyclic frameworks are privileged structural motifs, endowed with broad and important biological activities.[1] Among these, dibenzo[*a*,*d*]cycloheptanoid scaffolds have found extensive applications in drug discovery and attracted much attention, as they are the commonly occurring key structural units of biologically active natural products, such as rubialatin B (**1**) shows cytotoxicity and a synergistic effect with TNF-α for NF-κB activation,[2a] radermachol (**2**) is used in folk medicine,[2b] diptoindonesin D (**3**) has potent antifungal activity and is cytotoxic against P-388 murine leukemia cells,[2c] and amurensinine (**4**) exhibits CNS activity for the treatment of Parkinson's and Alzheimer's diseases[2d] (Scheme 1).

Several synthetic approaches for the preparation of benzannulated seven-membered frameworks have been reported. These involve Friedel–Crafts reactions,[3] ring-closing metathesis,[4] intermolecular cationic cyclization reactions,[5] ene reactions,[6] intramolecular cycloadditions,[7a–e] [2 + 2] cycloaddition of alkenes and alkynes,[7f–i] and transition metal-mediated hydroacylation.[8] However, only a few methods have been disclosed for the preparation of dibenzo[*a*,*d*]cycloheptanoids, which include the synthesis of iodo-substituted dibenzocyclohepten-5-ones from iodine monochloride reported by Chen *et al.*,[9a] aryne insertion into the C–C bond of cyclic β-ketoesters to access mono- and dibenzocycloheptanes[9c] recently reported by Stoltz *et al.*,[9b] aryne insertion into the C–C bond of α-arylated cyclic ketones reported by Zeng *et al.*,[9d] and similar aryne insertion into the C–C bond of cyclic 1,3-diketones to furnish mono- and dibenzocycloheptanes and cyclooctanes reported by Srihari *et al.*[9e] (Scheme 2). Due to their high importance, a flexible and rapid synthesis of dibenzocycloheptane libraries with further functionalization for high-throughput screening and further drug discovery research and a one-pot synthesis with multiple bond-forming transformations (MBFTs) and aryl group incorporation would be more practical and desirable.[10]

In continuation of our studies on the synthesis of valuable bioactive scaffolds using 2-arylidene-1,3-indandiones,[11] herein we report a fluoride-anion-induced ring expansion of 2-arylidene-1,3-indandiones by insertion of arynes into the C–C bond of cyclic enones for the first time (acyl-alkenylation of arynes).



Scheme 1 Biologically active dibenzo[*a*,*d*]cycloheptanoid derivatives.

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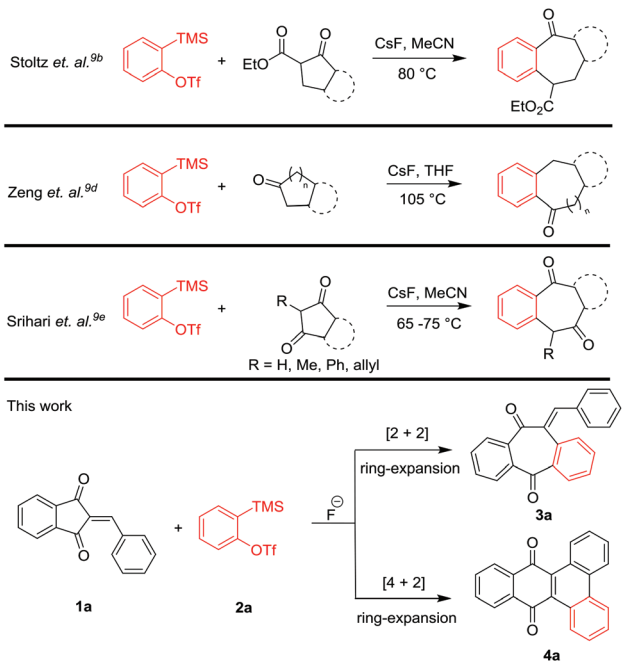


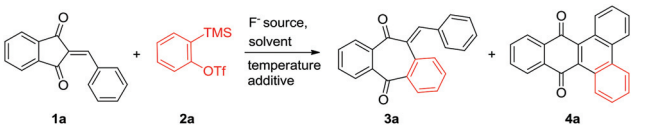
Scheme 2 Aryne insertion based approaches for benzannulated carbocyclic motifs.

It provides a straightforward, diastereoselective, and transition-metal-free protocol for the creation of dibenzo[*a*,*d*]cycloheptanoid frameworks in a simple manner with a broad substrate scope (Scheme 2).

As part of our research work on the development of transition metal free newer methodologies for the synthesis of bioactive scaffolds, we sought a new synthetic route to obtain a relatively rare and expensive polycyclic hydrocarbon, dibenz[*a*,*c*]anthracene-9,14-dione (**4a**) from an *in situ* generated aryne **1a** and 2-arylidene-1,3-indandiones through [4 + 2]-cycloaddition followed by ring expansion. Surprisingly, the fluoride-anion-induced reaction took a different course during our studies, where 2-arylidene-1,3-indandiones underwent aryne insertion into the C–C bond of cyclic enone (acyl-alkenylation) to provide (*E*)-11-benzylidene-5*H*-dibenzo[*a*,*d*][7]annulene-5,10(11*H*)-dione (**3a**) as a major product. This unexpected aryne insertion comprised conjugate addition by fluoride, ring expansion and elimination process, all occurring in a single step leading to the dibenzo[*a*,*d*]cycloheptanoid **3a** in good yield as a single isomer.

Our study was initiated with the optimization of reaction conditions for this unusual transformation of arynes. In an initial experiment, the treatment of 2-benzylidene-1,3-indandione (**1a**) with aryne **2a** (1.2 equiv.) generated *in situ* from 2-(trimethylsilyl)aryl triflate (**2a**) using CsF and MeCN as the solvent resulted in the formation of dibenz[*a*,*c*]anthracene-9,14-dione (**4a**) in 35% yield, along with dibenzo[*a*,*d*]cycloheptanoid **3a** (10%), while 24% of **1a** remained unreacted. We noted that increasing the reaction temperature didn't have any remarkable effect on the yield of **3a** or **4a** (Table 1, entry 2), while changing the solvent from acetonitrile to THF or a

Table 1 Optimization of reaction conditions[a]



Entry	F⁻ source [equiv.]	18-c-6 [equiv.]	Solvent	Time (h)	Yield[b] (%) 3a	4a
1	CsF (2.5)	—	MeCN	16	10	35
2	CsF (2.5)	—	MeCN : PhMe	16	5	15
3	CsF (2.5)	—	THF	16	10	15
4	CsF (2.5)[c]	—	MeCN	8	5	42
5	KF (2.5)	2.5	MeCN : PhMe	16	35	5
6	KF (2.5)	2.5	MeCN	16	74	5
7	KF (2.5)[c]	2.5	MeCN	10	40	10
8	KF (5.0)[d]	5.0	MeCN	16	62	5
9	KF (2.5)	2.5	THF	16	20	5
10	TBAF (2.5)	—	THF	6	10	—
11	TBAT (2.5)	—	THF	6	15	5

[a] Standard conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), fluoride source, solvent (3.0 mL). [b] Isolated yields. [c] Reaction temperature 80 °C. [d] **2a** (0.40 mmol).

mixture of MeCN and PhMe decreased it (Table 1, entry 3). Surprisingly, when the reaction was performed using 1.2 eq. of **1a** and 2.5 equiv. of KF/18-crown-6, dibenzo[*a*,*d*]cycloheptanoid **3a** was formed in an improved yield of 74% and traces of dibenz[*a*,*c*]anthracene-9,14-dione (**4a**) at rt in 16 h with complete conversion of the starting material **1a** (entry 7, Table 1). To further optimize the yield and selectivity of the products, the effects of the fluoride source, temperature, additive, solvent, and stoichiometry were systematically studied (Table 1).

Encouraged by these results, the generality and scope of the domino reaction was examined by varying the electronic and steric properties of both 2-arylidene-1,3-indandione (**1**) and arynes (**2**) (Table 2), under the optimized conditions (2-arylidene-1,3-indandione (**1a**) (1.0 equiv.), aryne **2** (1.2 equiv.), KF (2.5 equiv.), 18-crown-6 (2.5 equiv.), CH_3CN, 25 °C, 16 h). As outlined in Table 2, electronic variations in the aryl substituent on the olefin β-position of 2-arylidene-1,3-indandiones (**1**) were well tolerated. Electronically neutral as well as rich substituents on the aryl group afforded products (**3a** & **3b**) in good to moderate yields. Interestingly, electron withdrawing substituents such as fluoro, chloro, bromo, iodo, and trifluoro methoxy groups were also tolerated and provided the desired products **3c–h** in good yields. Moreover, the presence of the trifluoro methoxy substituent on the aryl group at the *ortho* position had no steric effect on the reaction outcome and furnished the desired product (**3k**). It is noteworthy that the reaction of 3,4-dimethyl benzyne also provided the desired products **3l** & **3m** in good yields. The reaction of unsymmetrical 4-silyl benzyne failed to furnish the expected product **3o** under the optimized conditions. Most notably, unsymmetrical 4-fluoro benzyne resulted in the formation of a 4 : 1 inseparable regioisomeric mixture of products **3n** & **3n′** with a 72%

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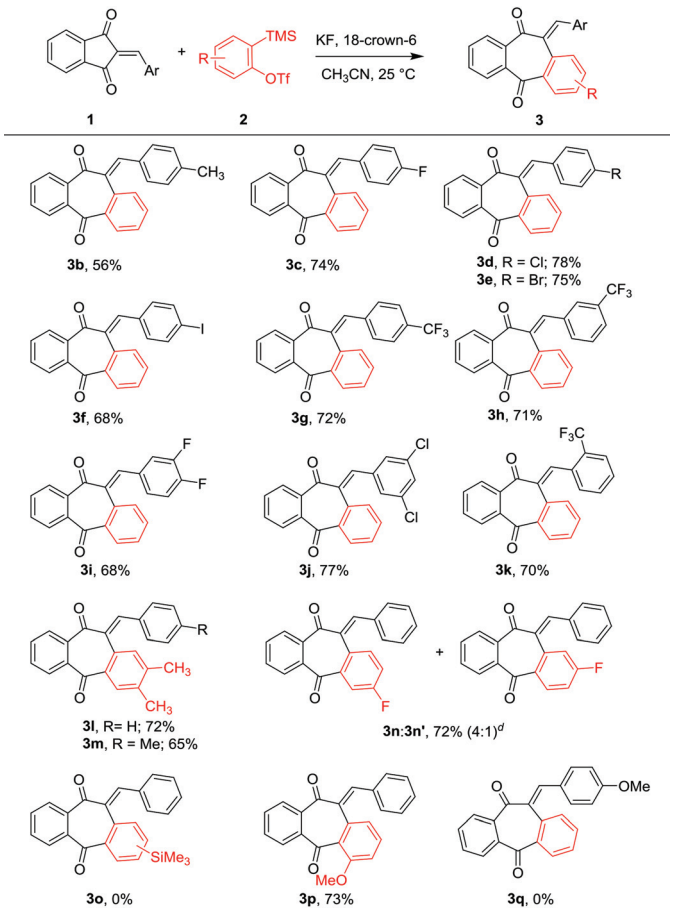
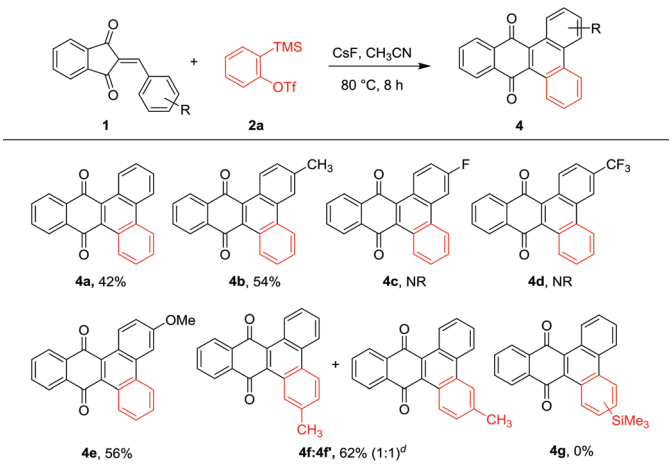
Table 2 Substrate scope of dibenzo[*a*,*d*]cycloheptanoids[a,b,c]



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.60 mmol), KF (1.00 mmol), 18-crown-6 (1.00 mmol), CH_3CN (3.0 mL), 25 °C, 6 h. [b] Yields of the isolated products with respect to **1**. [c] Only a negligible amount of [4 + 2] cycloaddition products observed. [d] Regioisomeric ratio determined by ^1H NMR analysis.

Table 3 Substrate scope of dibenz[*a*,*c*]anthracene-9,14-diones[a,b,c]



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.40 mmol), CsF (1.00 mmol), CH_3CN (3.0 mL), 80 °C and 6 h. [b] Yields of the isolated products with respect to **1**. [c] Only a negligible amount of [2 + 2] cycloaddition products observed. [d] Regioisomeric ratio determined by ^1H NMR analysis.

combined yield. The major regioisomeric structure of **3n** was further confirmed by NOE studies (ESI;† page-33). Furthermore, to gain insight into the reaction pathway and mode of addition of an enolate (nucleophilic addition) to arynes, we have performed the reaction using the unsymmetrical 3-methoxybenzyne under the optimized conditions and afforded the single regioisomer **3p** in 73% yield, which confirms that the nucleophilic enolate addition on 3-methoxybenzyne is more favoured at the *meta*-position than the *ortho*-position,[12] and the selective formation of **3p** is a clear indication that the present insertion reaction proceeds *via* conjugate addition by fluoride followed by enolate addition and ring expansion. The structure of **3p** was further confirmed by NOE studies (ESI;† page-37). Unfortunately, the reaction of an electron-rich 2-arylidene-1,3-indandione having a MeO substituent at the 4-position of the aryl group did not work under the standard reaction conditions to provide the desired product (**3q**). However, to demonstrate the practical utility of this methodology, this reaction was also performed on a gram scale (**1a**; 1.00 g) affording the product **3a** (1.13 g) in 74% yield. The structure of **3a** and its *E*-configuration was confirmed by NMR studies (see the ESI†).

Further experimentation and detailed analysis of the optimized reaction conditions (Table 1, entry 4) indicated that this protocol can generate dibenz[*a*,*c*]anthracene-9,14-dione (**4a**). The structure of **4a** was confirmed by spectroscopic analysis and by comparison of the NMR data with structurally similar compounds reported in the literature.[13] After finding the optimal conditions for dibenz[*a*,*c*]anthracene-9,14-dione, we examined the substrate scope (Table 3). Aryne precursor **2a** reacted smoothly with both 2-arylidene-1,3-indandiones **1a** and **1b** to furnish the corresponding quinone products **4a** and **4b** in moderate yields. We didn't observe products **4c** and **4d** from the corresponding 2-arylidene-1,3-indandiones **1c** and **1d**. However, *para* methoxy substituted 2-benzylidene-1,3-indandione **1e** afforded the corresponding dibenz[*a*,*c*]anthracene-9,14-dione **4e** in moderate yield. The reaction of unsubstituted 4-methyl benzyne with 2-benzylidene-1,3-indandione **1a** afforded substituted quinones **4f** & **4f′** with a 1 : 1 inseparable regioisomeric mixture. To our dismay, the reaction of 4-silyl benzyne with 2-arylidene-1,3-indandiones **1a** also failed to furnish the expected product **4g** under the optimized conditions.

To clarify the reaction mechanism, the following control experiments were carried out (Scheme 3): (i) the one-pot reaction of 1,3-indandione (**5**), benzaldehyde (**6**) and benzyne provided **1a** and **7** and traces of **3a**; the treatment of **7** with benzaldehyde (**6**) under optimized conditions failed to provide the desired product (**3a**), this indicates that the reaction is not proceeding through either a one pot or from dibenzocyclooctanone **7**; (ii) further treatment of 2-benzyl-1,3-indandione (**8**)[14] with benzyne (**2a**) led to the benzyl substituted indenone

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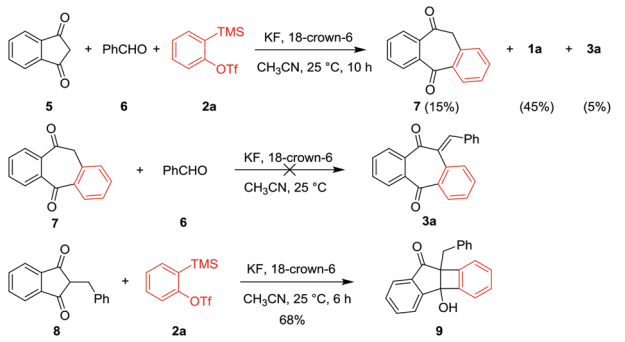
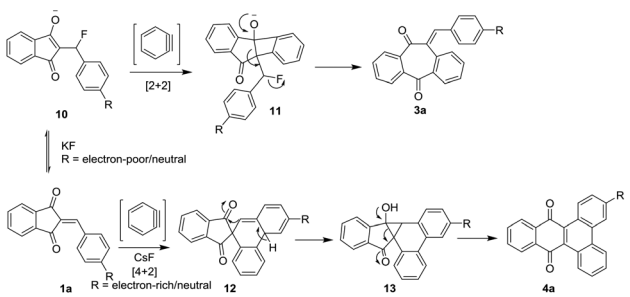


Scheme 3 Control experiments.

derivative **9** without opening of the 4-membered ring. These results support that these unconventional reactions with benzyne are taking place in a single step through different mechanisms.

Based on the aforementioned results and literature precedent,[10] a probable mechanism for the synthesis of dibenzo[*a*,*d*]cycloheptanoid **3a** and dibenz[*a*,*c*]anthracene-9,14-dione (**4a**) is outlined in Scheme 4. Initially, 2-benzylidene-1,3-indandione (**1a**) (electron-poor/neutral substrates) transformed into the corresponding intermediate **10** through conjugate addition by fluoride, which subsequently created an enolate and attacked onto benzyne generated from **2a**, thus affording an aryl anion, which can undergo intramolecular nucleophilic attack on the carbonyl group with the formation of cyclobutene intermediate **11**. Our attempts to trap compound **10** with electrophiles failed confirming the fluoride addition. The eventual elimination of fluoride gives rise to the desired product with a preferred double bond geometry. However, in the case of 2-arylidene-1,3-indandione (**1**) having an electron-rich/neutral group in the presence of CsF, the 2-arylidene-1,3-indandione (**1**) could undergo [4 + 2]-cycloaddition to provide intermediate **12**. Furthermore, intermediate **12** can undergo intramolecular nucleophilic attack on the carbonyl group with the formation of a strained tricyclic alcohol intermediate **13**, which upon retro-aldol reaction (ring expansion) and air oxidation affords the dibenz[*a*,*c*]anthracene-9,14-dione (**4**). Overall the fluoride addition is prompted by the electron withdrawing groups on the arylidine group. When R of the arylidine is an electron donating group, there is extended conjugation by way



Scheme 4 Proposed mechanism.

of some push–pull electronics in the whole system that retards fluoride addition and permits another reaction pathway (4 + 2 cycloaddition & ring expansion).

In conclusion, we have demonstrated, for the first time, the synthesis of diastereoselectively substituted dibenzo[*a*,*d*]cycloheptanoid **3a** and dibenz[*a*,*c*]anthracene-9,14-diones (**4**) *via* conjugate addition by fluoride followed by ring expansion and [4 + 2]-cycloaddition/ring expansion of *in situ* generated arynes **2a** with 2-arylidene-1,3-indandione (**1**) in moderate to good yields. This protocol will find wide synthetic applications in natural product synthesis and SAR (structure–activity-relationship) studies. Easily accessible starting materials, milder reaction conditions, good yields, and excellent diastereoselectivities are the salient features of the methodology. Further studies on the mechanism, extension of the reaction scope and medicinal chemistry are in progress in our laboratory and shall be reported in due course.

General experimental procedures

Dibenzo[*a*,*d*]cycloheptanoid derivatives 3a–o

To a stirred solution of 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (0.200 g, 8.57 mmol) in dry MeCN (10 mL) were added 18-crown-6-ether (0.564 g, 2.13 mmol) and potassium fluoride (0.247 g, 4258.0 mmol) under an argon atmosphere and to this stirring solution was added appropriate aryl silyl triflate at room temperature. Then the reaction mixture was stirred at rt until the completion of the reaction (monitored by TLC (5% EtOAc/pet ether)). The reaction mixture was diluted with EtOAc (20 mL) and water (20 mL), the organic layer was separated and then the aq. layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography using hexanes/ethyl acetate (9 : 1 v/v) as the eluent affording compounds **3a–o**.

Dibenz[*a*,*c*]anthracene-9,14-dione derivatives (4a–g)

To a stirred solution of 2-benzylidene-1*H*-indene-1,3(2*H*)-dione (0.200 g, 8.57 mmol) in dry ACN (10 mL) was added cesium fluoride (0.389 g, 25.640 mmol), then added appropriate aryl silyl triflate and the reaction mixture was stirred at the same temperature for 6 h; TLC analysis (5% EtoAc/pet ether) showed the completion of the reaction. The reaction mixture was diluted with EtOAc (20 mL) and water (20 mL), the organic layer was separated and then the aq. layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography using hexanes/ethyl acetate (9 : 1 v/v) as the eluent affording compounds **4a–f**.

Conflicts of interest

There are no conflicts to declare.

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