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Synthesis of Dihydrophenanthridines and Oxoimidazolidines from Anilines and Ethylglyoxylate via Aza Diels–Alder Reaction of Arynes and KF-Induced Annulation

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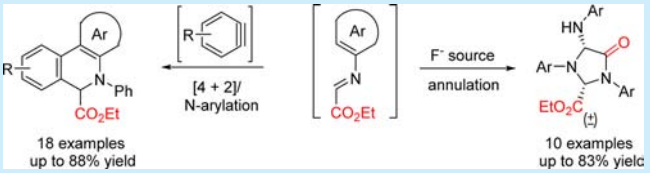
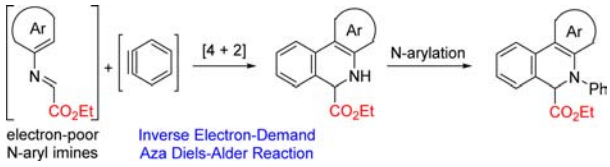
Supporting Information

ABSTRACT: The transition-metal-free multicomponent coupling of arynes, anilines, and ethylglyoxylate, proceeding via an inverse electron-demand aza Diels–Alder cycloaddition and N-arylation, has been demonstrated. This protocol allows rapid access to *N*-aryl dihydrophenanthridine derivatives in moderate to high yields at room temperature from readily available starting materials. In addition, an unprecedented fluoride induced annulation of ethyl(arylimino)acetates led to the formation of highly functionalized oxoimidazolidine derivatives in good yields under mild conditions.



The construction of nitrogen-containing heterocycles using arynes as building blocks[1] has become increasingly popular after the development of the new synthetic method to generate aryne by Kobayashi et al.[2] The electrophilic coupling,[3] [4 + 2] cycloaddition,[4] and 1,3-dipolar cycloaddition[5] of arynes, in particular, as opposed to transition-metal-catalyzed reactions, have produced a number of very useful biologically active heterocycles through multiple bond-forming transformations (MBFTs). However, the use of an aza Diels–Alder reaction (ADAR) of arynes has received only scant attention and remains largely unexplored,[6] presumably due to the aryne reactivity toward imines and 2-aza-dienes to provide the corresponding benzazetidines via [2 + 2] cycloaddition.[7] Recently, (i) Wang and co-workers reported a three-component ADAR for the preparation of phenanthridines from electron-enriched anilines, benzaldehyde derivatives, and benzenediazonium-2-carboxylate;[6b] (ii) Coquerel/Rodriguez co-workers reported the ADAR for the synthesis of functionalized isoquinolines and *N*-arylated 1,2-dihydroisoquinoline using electron-rich *N*-heteroaryl imines and arynes with an additional oxidant or excess of aryne.[6c,d] All these approaches mainly rely on the normal electron-demand ADAR of highly electron-rich 2-aza-dienes with variation on benzaldehyde derivatives (Supporting Information, Scheme 1). In view of its efficiency in the rapid construction of synthetically important structural motifs, further exploration of new procedures with alternative substrates would be particularly attractive. Moreover, an approach to access *N*-heterocycles via this highly efficient ADAR with electron-poor 2-aza-dienes and arynes in an inverse electron-demand (IED) manner has yet to be established. As part of our continuing efforts on the transition-metal-free synthesis of valuable bioactive scaffolds using arynes,[8] we sought to address this problem by employing ethyl(arylimino)acetates as an electron-poor dienes (Scheme 1).[9] The presence of a carboxylate group not only increases the reactivity of the aldimine (2-aza-diene) but also opens a new entry to the preparation of polycyclic heterocyclic compounds, such as 5,6-dihydrophenanthridine derivatives containing a carboxyl group in position 6. While the dihydrophenanthridine derivatives are present in the skeleton of a wide number of biologically active compounds,[10] only a few synthetic methods for this class of compounds have been reported in the literature. Furthermore, the reported methods generally suffer from low yields due to the limited functional group tolerance and the undesired *in situ* oxidation.[11]

Scheme 1. Inverse Electron-Demand Aza Diels–Alder Reaction of Arynes with Electron-Poor 2-Azadienes



Herein we report a mild and novel multicomponent cascade reaction initiated by an inverse electron-demand ADAR of arynes, ethylglyoxylate, and anilines for the construction of 5,6-dihydrophenanthridine derivatives with a broad substrate scope. In addition, an unexpected annulation of ethyl(arylimino)-acetates leading to the formation of highly functionalized oxoimidazolidine derivatives in good yields under mild conditions from simple and easily available starting materials is also reported.

Our study was initiated with the optimization of reaction conditions for the multicomponent inverse electron-demand

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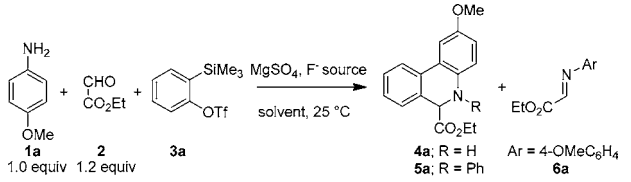
ADAR of arynes. In an initial experiment, treatment of anisidine (**1a**) and ethylglyoxylate (**2**) with aryne (1.2 equiv) generated *in situ* from the 2-(trimethylsilyl)aryl triflate (**3a**) using KF and MeCN as solvent resulted in the formation of *N*-arylated Diels–Alder adduct **5a** in 42% yield along with imine **6a** (38%). Surprisingly, the corresponding 5,6-dihydrophenanthridine **4a** and phenanthridines were not observed under this reaction condition. Notably, when the reaction was performed using Coquerel/Rodriguez aromatization reaction conditions (KF/18-crown-6, MnO_2 (10 equiv)) with aryne (1.2 equiv) at rt or 70 °C, it furnished only the *N*-aryl- dihydrophenanthridine **5a**. The aromatization product was not observed as expected for a "push–pull" system,[6d] which could be attributed to the fact that the carboxylate group at position 6 of 5,6-dihydrophenanthridine **4a** favors N-arylation over aromatization by increasing the nucleophilicity of nitrogen through hydrogen bonding. The effects of solvent, fluoride source, temperature, additive, and stoichiometry were systematically studied (Supporting Information, Table S1). Interestingly, when the reaction was performed using 3.0 equiv of **1a** and 5.0 equiv of KF/18-crown-6, *N*-aryl-dihydrophenanthridine **5a** was formed in an improved yield of 88% at rt in 3 h (entry 7, Table 1). Other fluoride sources

Table 1. Optimization of the ADAR Conditions[a]



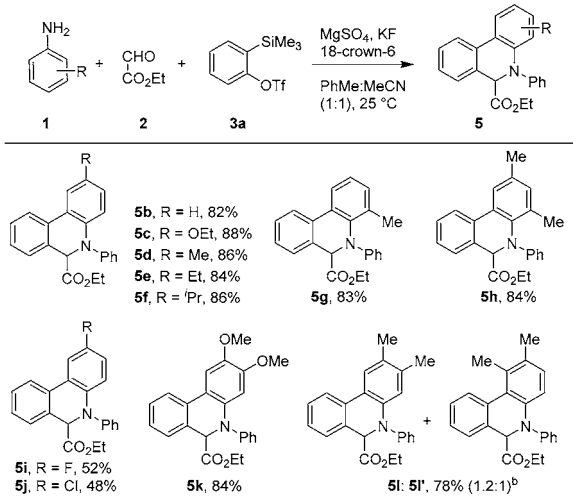
entry	3a [equiv]	F^- [equiv]	additive [equiv]	solvent	yield [%][b] 5a	6a
1	1.2	KF (2.5)	18-c-6 (2.5)	MeCN	42	38 (9)[c]
2	1.2	CsF (2.5)	–	MeCN	36	40 (9)[c]
3	1.2	KF (2.5)[d]	18-c-6 (2.5)	THF	38	40 (12)[c]
4	1.2	KF (2.5)[d,e]	18-c-6 (2.5)	MeCN	38	36 (9)[c]
5	1.2	KF (2.5)[f]	18-c-6 (2.5)	MeCN	40	41 (12)[c]
6	2.0	KF (4.0)[e]	18-c-6 (4.0)	THF	48	32 (12)[c]
7	3.0	KF (5.0)	18-c-6 (5.0)	MeCN/PhMe[g]	88	4 (4)[c]

[a]Standard conditions: **1a** (0.20 mmol), **2** (0.24 mmol), $MgSO_4$ (3.0 equiv), solvent (2.0 mL), 1 h then fluoride source, **3a**, rt, 2 h. [b]Isolated yields. [c]$(4\text{-}OMeC_6H_4)PhNH$. [d]MnO_2 (10.0 equiv). [e]Reaction temperature 70 °C. [f]O_2 (balloon). [g]MeCN/PhMe (1:1).

including CsF, TBAT, and TBAF did not improve the yield. A brief screening of the reaction media proved that MeCN/PhMe (1:1) was the best choice with respect to yields. It is noteworthy to mention that isolated ethyl (arylimino) acetate **6a** also reacted well with aryne **3a** under the same ADAR conditions to furnish the desired product without a significant difference in yield or reaction time.

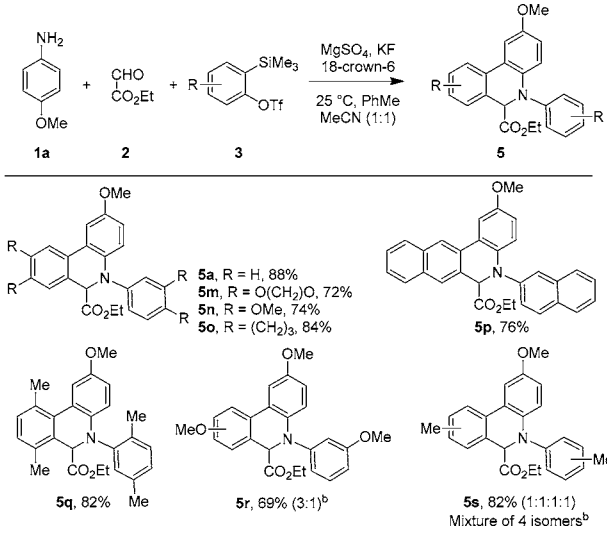
The generality of this reaction was subsequently explored by varying the electronic and steric properties of both anilines **1** and arynes **3** under the optimized condition (Schemes 2 and 3). As shown in Scheme 2 the multicomponent ADAR of benzyne **3a**, substituted anilines **1**, and ethylglyoxylate (**2**) proceeded effectively at rt furnishing dihydrophenanthridine carboxylates derivatives **5** with moderate to excellent yields. The substituted anilines containing electron-neutral and -donating groups such as

Scheme 2. Substrate Scope of the Inverse Electron-Demand ADAR: Variation of Anilines[a]



[a]Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), $MgSO_4$ (3.0 equiv), MeCN:PhMe (1:1) (2.0 mL), 1 h then KF (1.0 mmol), 18-crown-6 (1.0 mmol), **3a** (0.6 mmol), 25 °C, 2 h. Yields of the isolated products with respect to **1**. [b]Regioisomeric ratio determined by ^1H NMR analysis.

Scheme 3. Substrate Scope of the Inverse Electron-Demand ADAR: Variation of Aryne Precursors[a]



[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), $MgSO_4$ (3.0 equiv), MeCN/PhMe (1:1) (2.0 mL), 1 h then KF (1.0 mmol), 18-crown-6 (1.0 mmol), **3** (0.6 mmol), 25 °C, 2 h. Yields of the isolated products with respect to **1a**. [b]Regioisomeric ratio determined by ^1H NMR analysis.

ethoxy, methyl, ethyl, and isopropyl at the *para* position afforded the desired products (**5b–f**) in high yields. Interestingly, the presence of the 2-methyl and 2,4-dimethyl substituent in the *N*-aryl group had no steric effect on the reaction outcome and provided the desired products **5g–h**. Moreover, electron-withdrawing substituent fluoro and chloro groups at the *para* position were also tolerated and provided desired products **5i–j** in moderate yields. We reasoned that the formation of imine and its stability lowered the overall yield in the case of aniline containing electron-withdrawing substituents compared to

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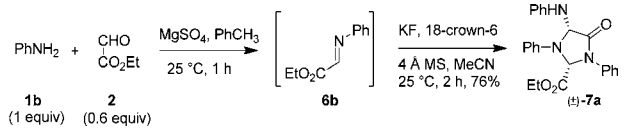
electron-releasing substituents.[9a] It is noteworthy that the 3,4-dimethoxy substituent in the N-aryl group reacted regioselectively and gave only one isomer of the desired product (**5k**). The regioselectivity could be explained in terms of the electronic and steric factors that favor the ADAR from the less hindered position. However, the 3,4-dimethyl substituent in the N-aryl group resulted in the formation of an inseparable mixture of regioisomers **5l**/**5l′** in a 1.2:1 ratio with a 78% combined yield.

To further understand the scope of this novel multicomponent ADAR, a wide range of β-trimethylsilyl triflates **3** were then examined with **1a** as the amine source and the results are summarized in Scheme 3. Interestingly, various electronically different symmetrical arynes generated from the corresponding precursors readily underwent multicomponent ADAR with anisidine (**1a**) and ethylglyoxylate (**2**) to form the *N*-aryl dihydrophenanthridine carboxylates (**5a**, **m**−**o**) smoothly in good yields. Moreover, the extended π conjugate naphthalene and the sterically hindered 2,5-dimethyl derived benzynes also afforded the desired compounds (**5p**−**q**). Most notably, unsymmetrical 3-methoxybenzyne resulted in the formation of a 3:1 regioisomeric mixture of products **5r**. Furthermore, 4-methylbenzyne furnished almost equal amounts of all four possible regioisomeric products (**5s**) in 82% yield, suggesting that the steric effect of aryne in this reaction is negligible.

During our studies on the multicomponent ADAR of the electron-withdrawing substituents, we unexpectedly observed the formation of oxoimidazolidine derivatives **7** in moderate yields under identical conditions (KF/18-crown-6, MeCN, rt) in the absence of benzyne.

Inspired by this result, to identify the optimal conditions for the formation of the desired product **7a**, we investigated the effect of aniline and ethylglyoxylate stoichiometry, fluoride salts, bases, solvents, reaction temperature, and time on the reaction yield (Supporting Information, Table S2). Based on these results, we found that the sequential reactions with 1.0 equiv of aniline and 0.6 equiv of ethylglyoxylate for the *in situ* imine formation, followed by treatment with KF (1.5 equiv)/18-crown-6 (1.5 equiv) in MeCN, provided the functionalized oxoimidazolidine **7a** in 76% yield (Scheme 4).[12] Imidazolidin-4-one derivatives are

Scheme 4. Fluoride Induced Synthesis of Functionalized Oxoimidazolidines 7a



found to have a large spectrum of biological activities such as antibacterial,[13a] cell inhibitor,[13b] antimalarial agents,[13c] antiproliferative,[13d] and anticancer.[13e] Despite a large and diverse set of synthetic methods reported for imidazole ring structures, methods for the synthesis of functionalized oxoimidazolidine analogs are yet surprisingly limited. In 2008, Shi and co-workers reported phosphine-catalyzed annulation of ethyl(arylimino)-acetates to polysubstituted oxoimidazolidine derivatives using methyl vinyl ketone (MVK).[12] However, rapid synthesis of a functionalized oxoimidazolidine framework under milder reaction conditions are still desirable. In this context, we further explored this fluoride induced rapid synthesis of functionalized oxoimidazolidines from anilines **1** and ethylglyoxylate (**2**) under mild conditions.

The scope and limitation of this unexpected annulation were explored by subjecting various substituted anilines (**1**) to the optimized reaction conditions. Compared with the result obtained for the reaction between aniline and ethylglyoxylate (Table 2, entry 1), reactions of anilines with *para* substituted

Table 2. Substrate Scope of Fluoride Induced Annulation of Ethyl(arylimino)acetates 6[a]

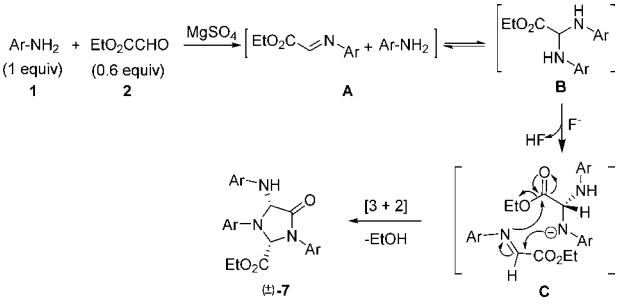
entry	Ar	product	yield [%][b]
1	C_6H_5	**7a**	76
2	*p*-FC_6H_4	**7b**	78
3	*p*-BrC_6H_4	**7c**	76
4	*p*-ClC_6H_4	**7d**	78
5	*p*-$CF_3C_6H_4$	**7e**	78
6	*p*-$CO_2EtC_6H_4$	**7f**	75
7	*p*-MeC_6H_4	**7g**	49[c]
8	*p*-$MeOC_6H_4$	**7h**	0
9	*m*-FC_6H_4	**7i**	83
10	*m*-BrC_6H_4	**7j**	80
11	*m*-$CF_3C_6H_4$	**7k**	81

[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.12 mmol), $MgSO_4$ (5.0 equiv), PhMe (2.0 mL), 1 h then filtered and filtrate was evaporated, followed by 4 Å MS (300 mg/mmol of **1**), KF (0.3 mmol), 18-crown-6 (0.3 mmol), MeCN (2 mL), 25 °C, 2 h. [b]Yields of the isolated products with respect to **1**. [c]5 h.

electron-deficient groups such as F, Br, Cl, CF_3, and CO_2Et showed similar results with respect to yield (Table 2, entries 2−6). Notably, electron-rich *p*-toluidine gave the desired product in moderate yield with 22% of recovered imine (Table 2, entry 7). Unfortunately, more electron-rich *p*-anisidine did not react under the optimized conditions (Table 2, entry 8). Gratifyingly, anilines bearing *meta* substituted electron-deficient groups such as F, Br, and CF_3 resulted in the formation of desired products with a significant increase in the yields (Table 2, entries 9−11).

Based on the literature precedence and our optimization results, a probable mechanism for the fluoride induced annulation reaction is outlined in Scheme 5. Reaction between ethylglyoxylate (**2**) and an excess of aniline (**1**) generates diamine adduct **B** which exists in equilibrium with imine and aniline (**A**).[9a] The presence of an electron-withdrawing group on the aryl nucleus of adduct **B** facilitates[14a] a proton abstraction by fluoride salt[14b] to afford a nitrogen anion, which subsequently undergoes intermolecular formal [3 + 2] annulation (**C**) with

Scheme 5. Proposed Mechanism of the Cascade Annulation



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another equivalent of imine through a cascade sequence: the nucleophilic nitrogen first adds across the C−N double bond of imine, followed by a subsequent intramolecular nucleophilic attack onto the ester carbonyl group to produce the desired product **7**.[15]

In conclusion, we have developed a multicomponent coupling of arynes, anilines, and ethylglyoxylate, allowing the rapid synthesis of *N*-aryl dihydrophenanthridine derivatives at rt. The reaction between easily accessible electron-poor 2-aza-dienes and arynes proceeds via an inverse electron-demand aza Diels−Alder cycloaddition reaction and subsequent N-arylation in a single step with two C−C and two C−N bond formations. In addition, we have also developed a fluoride induced novel method for the synthesis of polysubstituted oxoimidazolidine derivatives from simple and easily available starting materials. Further studies in related inverse electron-demand reactions of arynes are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02186.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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