Organic LETTERS

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Multiple Aryne Insertions into Oxindoles: Synthesis of Bioactive 3,3-Diarylated Oxindoles and Dibenzo[*b*,*e*]azepin-6-ones

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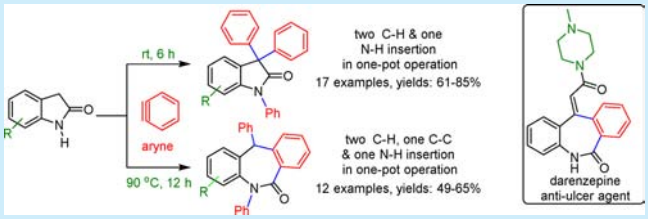
Supporting Information

ABSTRACT: An aryne insertion cascade reaction on oxindoles has been observed and constitutes a convenient "one pot" preparation of bioactive di- and triarylated oxindoles in good yields under mild conditions. A temperature controlled "reaction switch" enables ready access to dibenzo-[*b*,*e*]azepin-6-one derivatives employing the same reaction regime. This tactic has been extended to a short synthesis of potent antiulcer agent darenzepine.



Diversely substituted 3,3-diaryloxindole and dibenzo[*b*,*e*]-azepin-6-one scaffolds are potentially useful pharmacophoric constructs that display a broad range of interesting biological activities (Figure 1).[1,2] For example, 3,3-diarylated-2-oxindole derivatives are known to exhibit anticancer, antioxidant, Ca^{2+}-depleting translation initiation inhibitory, and mineralocorticoid receptor antagonist activities among others.[1] On the other hand, dibenzo[*b*,*e*]azepin-6-one derivatives possess antiulcer, central nervous system (CNS), and anticonvulsant activities.[2] These potentially useful bioactivity attributes harbored by 3,3-diaryloxindole and dibenzo[*b*,*e*]-azepin-6-one bearing structural motifs have drawn the attention of organic and drug discovery communities to develop practical synthetic methodologies for the construction of these scaffolds.

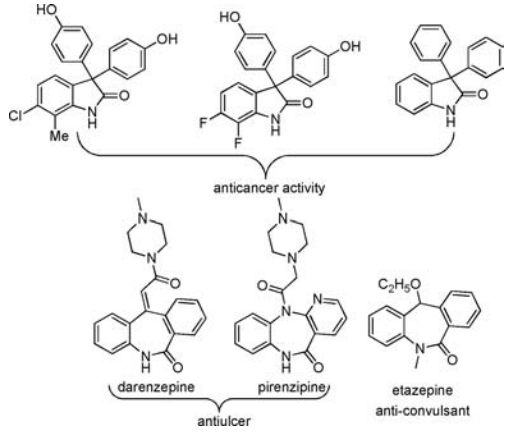


Figure 1. Bioactive 3,3-diarylated oxindoles and dibenzoazepinones.

Although many approaches to 3,3-disubstituted oxindoles have been reported in recent years,[3] those specifically targeted toward 3,3-diaryloxindoles **1** are relatively few, thus limiting access to structural diversity around this scaffold. In this context, the most commonly pursued approach to **1** and its derivatives are based on Friedel–Crafts type arylation using various protic and Lewis acids on the corresponding isatins **2** and 3-hydroxyoxindoles **3**.[4] Similarly, aryl-α-ketoamides **4** on exposure to superacid in the presence of another electron-rich aromatic moiety furnishes the 3,3-diarylated oxindole sytem.[5] Another approach to system **1** involves acid/thermal rearrangement of *O*-aryl ethers **5**[6] (Figure 2). Preformed 3-monoarylated oxindoles **6** too have been converted to 3,3-diaryloxindoles through a Pd and chiral phase transfer catalyst (PTC) mediated α-arylation reaction.[7] Recently, a nontransition metal mediated approach to **1** through montmorillonite K-10 driven cyclization of 2,2-*N*-triarylacetamides **7** has been reported (Figure 2).[8]

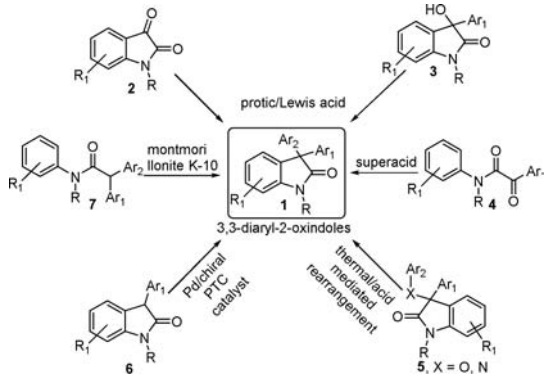


Figure 2. Previous approaches for 3,3-diaryl-2-oxindoles **1**.

Similarly, synthetic routes to the pharmacophoric dibenzo-[*b*,*e*]azepin-6-ones **8** are limited, and besides some classical approaches,[9] the recent ones of general applicability consist of

Received: October 27, 2016
Published: November 18, 2016

DOI: 10.1021/acs.orglett.6b03224
Org. Lett. 2016, 18, 6184–6187

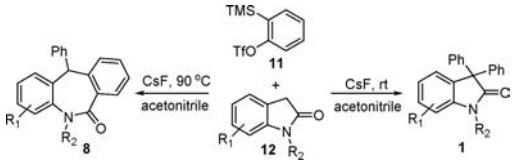
Pd-mediated intramolecular reductive Heck cyclization[10] of **9** and intramolecular Pd-mediated benzylation of primary benzamides[11] **10** (Figure 3).

Figure 3. Previous approaches for dibenzo[*b*,*e*]azepin-6-ones **8**.

The available methods for accessing the scaffolds **1** and **8**, though variously successful, are self-limiting because of severe reaction conditions, use of expensive transition metal catalysts, multistep substrate preparation, and lack of functional group tolerance in many cases. These limitations underscore the need for a mild, efficient, and general method.

During the past decade, aryne chemistry[12] has emerged as a powerful synthetic tool for obtaining diverse arylated/benzoannulated scaffolds in view of the ready availability of Kobayashi aryne precursor[13] **11** (2-(trimethylsilyl) phenyltrifluoromethanesulfonate). Thus, aryne insertion into variously activated C−H, C−C, and C−X (X = heteroatom) bonds and commonly available heterocyclic systems continues to be an area of intense scrutiny.[14] As part of our continuing interest[15] in accessing diverse scaffolds through new aryne insertion protocols, we report here an interesting variant of the aryne insertion chemistry involving multiple aryne insertions into oxindoles **12** to furnish either 3,3-diaryloxindoles or dibenzo[*b*,*e*]azepin-6-one, two seemingly diverse scaffolds, through a common strategy involving a one-pot reaction and employing reaction temperature as a product control switch (Scheme 1).

Scheme 1. Present Work: Temperature Controlled Aryne Insertions Leading to Either 1 or 8



Reaction of oxindole **12a** with an *in situ* generated aryne in the presence of CsF proceeded quite smoothly and after some optimization efforts (see entry 5 in Table 1 in the Supporting Information (SI)) furnished *N*-3,3-triphenylated compound **1a** in 85% yield at room temperature in the presence of 3.5 equiv of the aryne precursor **11**.

With the optimized reaction conditions, the scope of the aryne insertion reaction was further explored with substituted *N*-unprotected oxindoles (**12b**−**g**) to deliver the corresponding triphenylated oxindoles (**1b**−**g**) in 75−81% yields (entry 1, Figure 4). Formation of triphenylated oxindole products was unambiguously secured by X-ray crystal structure determination of **1d**.

To impart further substituent variation in accessing 3,3-diphenyloxindoles, *N*-protected oxindoles (**12h**, *N*-Me and **12i**, *N*- Boc) were exposed to aryne **11** (2.5 equiv) under the optimized reaction conditions to eventuate **1h** and **1i**, respectively, in decent yields (Figure 4). In addition, it was of interest to explore whether 3-monosubstituted oxindoles could also be arylated through this aryl insertion protocol. Indeed, it

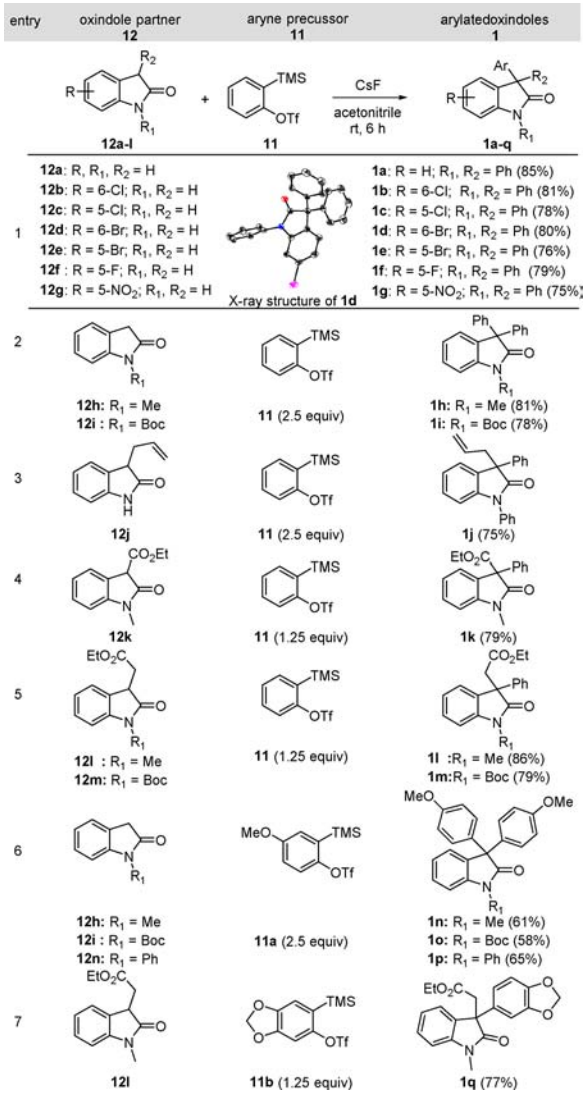


Figure 4. Reaction of diverse oxindoles with arynes.

was determined that 3-allyloxindole **12j**, 3-carboethoxyoxindole **12k**, and *N*-Me and *N*-Boc, 3-carboethoxymethyl-substituted oxindole **12l** and **12m** reacted smoothly with aryne precursor **11** to furnish the corresponding *N*- and 3*C*-arylated oxindoles **1j**−**1m**, respectively, in good yields (Figure 4). It was also considered useful to demonstrate that substituted arynes reacted likewise with oxindoles. Toward this end, substituted arynes generated from Kobayashi-type precursor **11a** was reacted with *N*-substituted oxindoles **12h**, **i**, **n** to furnish 3,3-diarylated oxindoles **1n**−**p** respectively. Similarly, reaction of *N*-Me-3-carboethoxymethyl oxindole **12l** with substituted aryne precursor **11b** led to the corresponding 3-arylated oxindole **1q** (Figure 4).

During our experiments to optimize the yield of 3,3-diarylated oxindole **1a** through aryne C−H insertions (Table 1 in the SI), it was observed that at elevated reaction temperature an additional new product was being formed. After some trials, it was found that when the aryne-oxindole reaction was carried out with **11** and **12a** at 90 °C, the yield of this new product enhanced to 59% and was determined to be dibenzo[*b*,*e*]azepin-6-one **8a** (Figure 5).

The generality of this new ring expansion reaction was demonstrated employing diverse oxindoles **12b**−**g** with aryne

DOI: 10.1021/acs.orglett.6b03224
Org. Lett. 2016, 18, 6184−6187

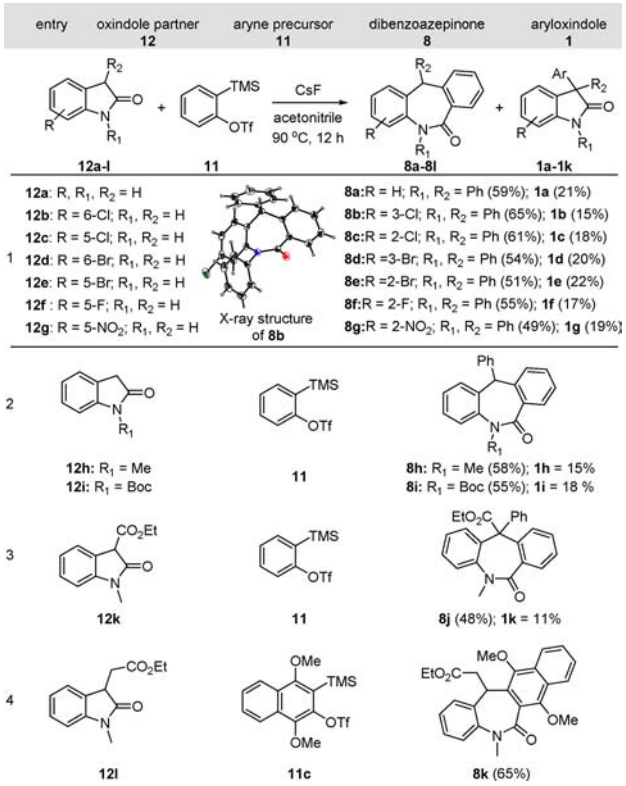


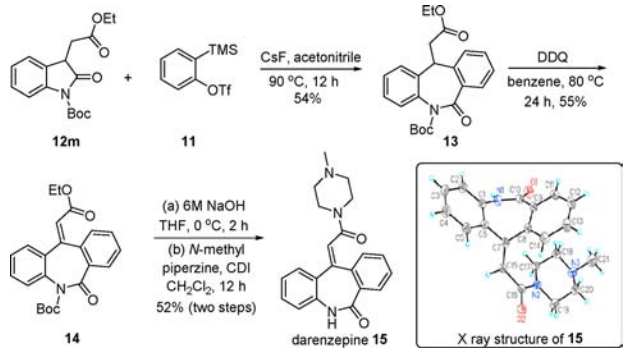
Figure 5. Accessing dibenzoazepinones from various oxindoles and arynes.

11 to furnish *N*-phenyl-dibenzo[*b*,*e*]azepin-6-one **8b−g** as the major products along with varying amounts of corresponding 3,3-diarylated oxindoles **1b−1g** as minor products (Figure 5). Structures of newly formed dibenzo[*b*,*e*]azepin-6-ones were secured through their characteristic spectral features and single crystal X-ray structure determination of one of them, **8b**. Further variations of this interesting reaction were demonstrated through aryne insertion to *N*-substituted oxindoles **12h**, **i**, **k** to deliver corresponding dibenzo[*b*,*e*]azepin-6-ones **8h**, **i**, **j**. Also, the reaction of *N*-Me-3-carboethoxymethyl oxindole **12l** with naphthyne derived from **11c** eventuated in the corresponding dibenzo[b,e]azepin-6-one **8k** (Figure 5).

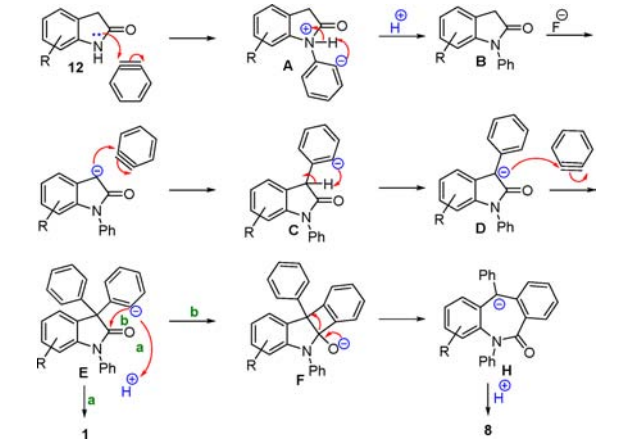
As a practical application of our new dibenzo[*b*,*e*]azepin-6-one synthesis, a four-step synthesis of potent antiulcer muscarinic antagonist darenzepine[16,2] **15** embodying this framework is outlined here. Accordingly, *N*-Boc protected 3-carboethoxymethyl oxindole partner **12m** was reacted with aryne precursor **11** at elevated temperature (90 °C) to furnish *N*-Boc-dibenzoazepinenone **13** and was further subjected to dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to stereoselectively deliver the *E*-isomer of *α*,*β*-unsaturated ester **14** (Scheme 2). The ester functionality in **14** was hydrolyzed with base, and the resulting acid was directly subjected to amidation with *N*-methylpiperzine which also resulted in concomitant *N*-Boc deprotection to furnish darenzepine **15**. Since full characterization data for **15** were not available in the patent and other literature, we confirmed its structure by single crystal X-ray structure determination (Scheme 2).

A possible mechanism for the formation of triarylated oxindole **1** and dibenzoazepinone **8** from oxindole **12** via a convergent aryne insertion pathway is depicted in Scheme 3. Initial nucleophilic attack of amide nitrogen of oxindole **1** on

Scheme 2. Synthesis of Darenzepine



Scheme 3. Possible Mechanism for the Formation of 3,3-Diaryl-2-oxindoles and Dibenzoazepinones



aryne results in the formation of an intermediate aryl anion **A**, which after intramolecular protonation leads to *N*-arylated oxindole **B**. The carbanion of **B** adds further to another aryne to form intermediate anion **C**, which through an intramolecular1,3-hydride shift generates carbon anion **D**. Anion **D** reacts with one more equivalent of aryne and forms aryl anion **E** that on protonation (path 'a') delivers triarylated oxindole **1**. Alternately, at higher temperature **E** can attack the amide carbonyl group (path 'b') to give cyclobutanoid intermediate **F** which fragments to deliver a ring expanded dibenzoazepinone **8** through an overall C−C insertion. The reaction temperature based dichotomous behavior of intermediate anion **D**, though intriguing, has precedence[17] in aryne chemistry.

In conclusion, an efficient "one-pot" multiple aryne insertion approach of general applicability to furnish either 3,3-diarylated or *N*-3,3-triarylated oxindoles from readily available precursors is disclosed. We have also found that 'reaction temperature control' can be deployed to divert this arylation reaction on oxindoles to deliver dibenzo[*b*,*e*]azepin-6-ones. A short synthesis of darenzepine, an antiulcer agent from substituted oxindole, is reported using this aryne insertion strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03224.

DOI: 10.1021/acs.orglett.6b03224
Org. Lett. 2016, 18, 6184−6187

Detailed experimental procedures and spectral data for all new compounds (PDF)
Crystallographic data for compound **15** (CIF)
Crystallographic data for compound **8b** (CIF)
Crystallographic data for compound **1d** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was conducted under the auspices of Indo-French "Joint Laboratory for Sustainable Chemistry at Interfaces". R.S., C.R.B., and P.S. thank CSIR-New Delhi for funding from the XII Five Year Plan project ORIGIN (under budget head CSC-0108). G.M. wishes to thank Dr. Reddy's Laboratory (DRL) for the award of Dr. Kallam Anji Reddy Chair Professorship. The authors thank Dr. N. Jagadeesh Babu (CSIR-IICT) and Mr. Showkat Rashid (University of Hyderabad) for their help with X-ray analysis.

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DOI: 10.1021/acs.orglett.6b03224
Org. Lett. 2016, 18, 6184–6187