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A C–N insertion of β-lactam to benzyne: unusual formation of acridone

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ABSTRACT

Intermolecular insertion of benzyne into the C–N bond of a β-lactam is described. This σ-insertion is followed by ring expansion that produces dihydroquinolinone, which rapidly reacts with an additional benzyne unit to afford an acridone through intramolecular C–C bond formation to the carbonyl group and rapid elimination of ethylene.

Recently, Larock and Greaney described σ-insertion of *N*-phenylamides **2** to arynes generated in situ from 2-(trimethylsilyl)phenyl triflate **1** in the presence of fluoride sources (Scheme 1).[1] Under the mild conditions described by both laboratories, aminobenzophenones (i.e., **3**) were obtained in overall good yields. Of particular note, an efficient synthesis of acridones (i.e., **5**) was achieved by employing *o*-halobenzamides **4** through tandem insertion and S_NAr reactions (Scheme 1). Non-enolizable *N*-aryl amides were required in the insertion reactions due to the low electrophilicity of the amide carbonyl group. Prompted by our interests in aryne insertion processes,[2] we became intrigued in the possibility of insertion of arynes into the strained C–N bond of β-lactams.[3] Over the years our group has been actively involved in developing novel applications of arynes toward the synthesis of nitrogen heterocycles.[4] For example, we recently reported methods that allow access to indolines and isoquinolines from *N*-acyl enamines through aryne annulation.[4,5] Herein, we disclose the first example of such an aryne insertion and an unexpected secondary process that leads directly to *N*-phenyl acridone (Scheme 2).

We initiated our C–N insertion studies by subjecting β-lactam **6** (1.0 equiv) and 2-(trimethylsilyl)phenyl triflate **1** (2.0 equiv) to a mixture of KF and 18-crown-6 in THF at 23 °C. We were surprised to find that the major component of the product mixture was acridone derivative **7**, obtained along with the anticipated dihydroquinolinone **8** in 3:2 ratio and 52% overall yield (Scheme 2).[1b,6] To the best of our knowledge, insertion of arynes into β-lactams to give acridones is unprecedented. The reaction also produced trace amount of *N*-phenyl lactam **9** (<5%). We believe that this mechanistically interesting transformation begins with the nucleophilic attack of the aryne triple bond by the β-lactam nitrogen to generate intermediate **11** (Scheme 3A). The possibility of fluoride anion deprotonating the β-lactam N–H prior to the nucleophilic attack cannot be ruled out. Addition of the aryl anion **11** to the lactam carbonyl moiety would furnish the highly strained azeidinium ion (**12**), which can rearrange to dihydroquinolinone **13**. Alternatively, the aryl anion in **11** may be quenched via H^+-abstraction to generate *N*-arylated β-lactam **9**. Dihydroquinolinone **13** can continue to react with another benzyne unit through its nucleophilic nitrogen to result in the zwitterionic intermediate **14** followed by intramolecular nucleophilic addition of the nascent aryl anion to the carbonyl group to generate intermediate **15** bearing a dibenzobicyclo[2.2.2]octane core. The release of ethylene gas from intermediate **15** through a formal retro Diels–Alder reaction can unravel acridone **16**, which once again can react with benzyne followed by H^+-abstraction to afford *N*-phenyl acridone **7**. It appears that H^+-abstraction in **14** is faster than intramolecular nucleophilic addition to the carbonyl group. The possibility of a formal [4+2] cycloaddition process between the *o*-azaxylylenyl tautomeric form of **13** (not shown) and benzyne cannot be ruled out at this point.

In order to better understand the mechanism of this transformation we examined *N*-phenyl and *N*-benzyl β-lactams (**17**) as substrates in reactions with benzyne under otherwise identical conditions (Scheme 3B). No ring expanded insertion adducts were observed in these reactions despite complex product mixtures. Additionally, *N*-phenyl dihydroquinolinone **8** also failed to react with benzyne under similar reaction conditions. These results

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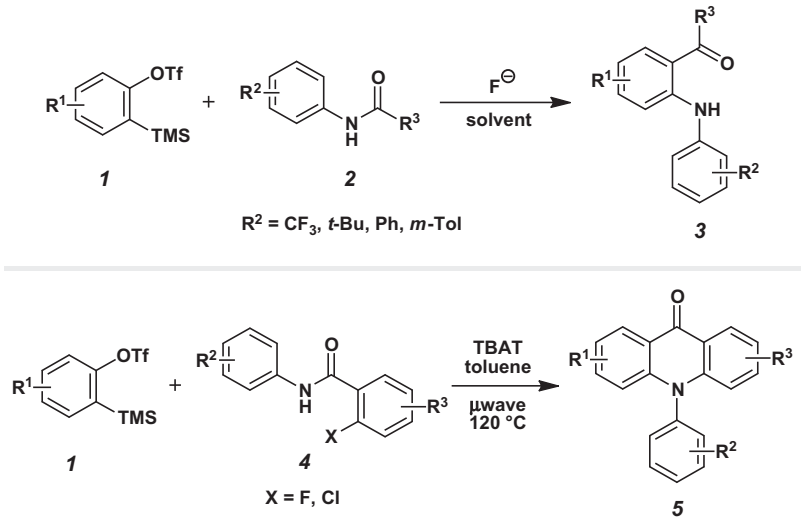
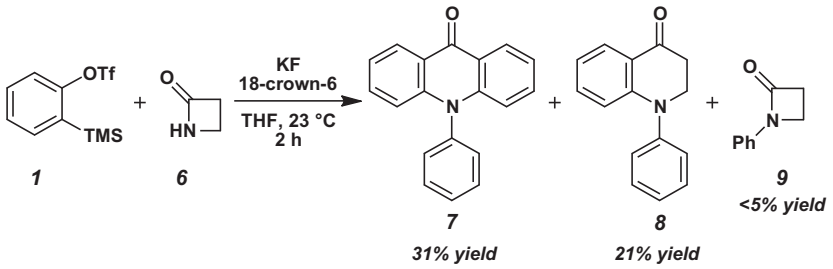
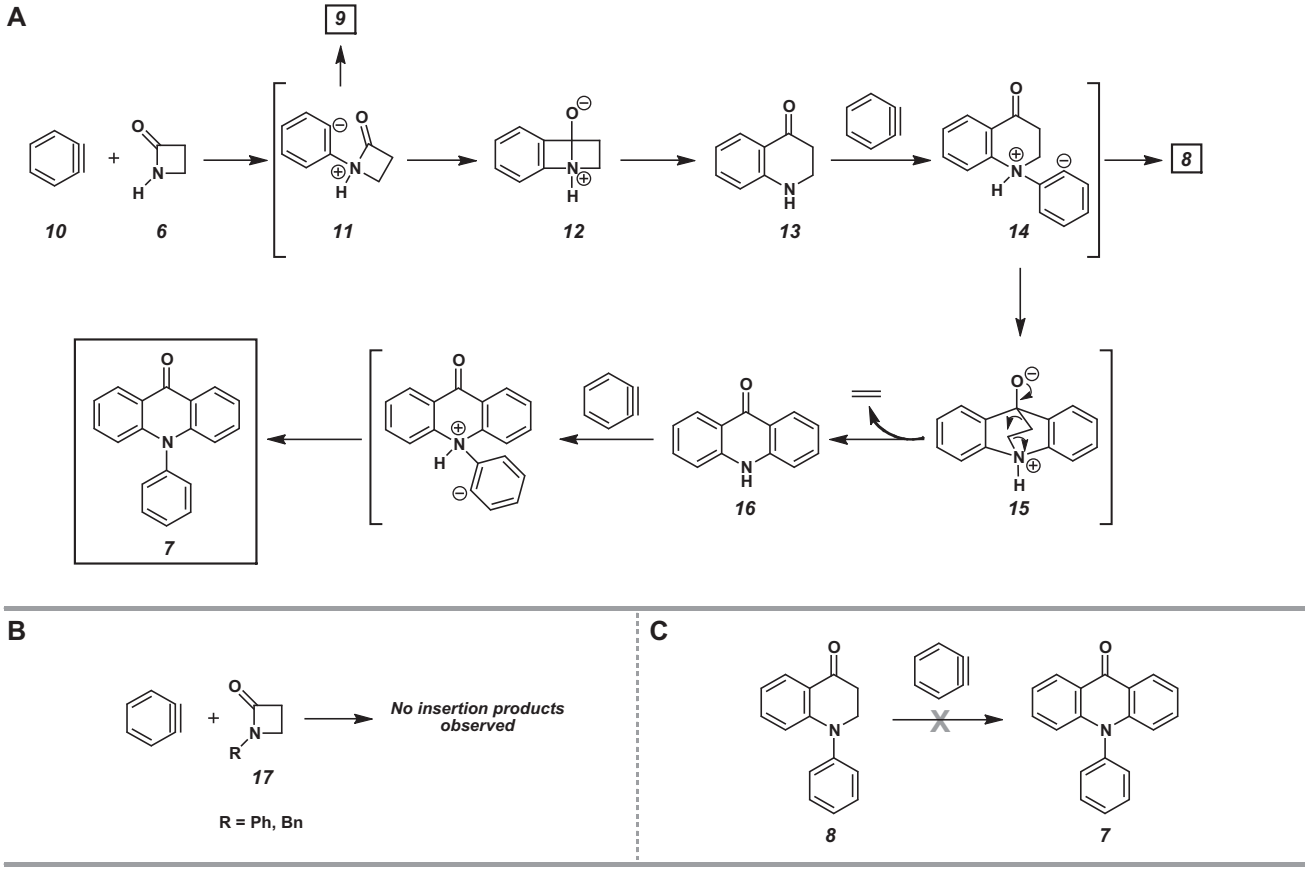


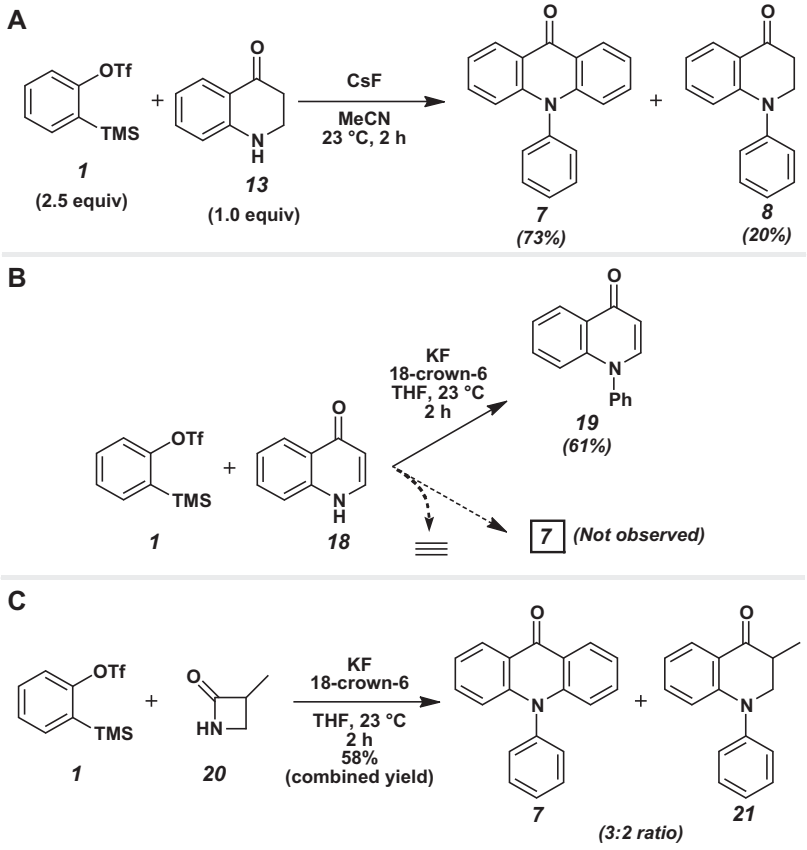
Scheme 1. Amide insertion into arynes.



Scheme 2. Insertion of benzyne into C–N bond of β-lactam.



Scheme 3. A plausible reaction pathway.



Scheme 4. Control experiments for mechanistic elucidation.

provide support to our mechanistic hypothesis wherein the N–H bond and the nitrogen geometry play a critical role in the transformation.

Gratifyingly, subjecting dihydroquinolinone **13**[7] to the reaction conditions resulted in the formation of *N*-phenyl acridone (**7**) and *N*-phenyl dihydroquinolinone (**8**) in 3.7:1 ratio, respectively in 93% combined yield (Scheme 4A).[8] Next, we subjected quinolinone **18** to the aryne insertion conditions, which could be expected to evolve acetylene based on the ethylene extrusion proposed in the previous example. However, we observed only *N*-arylated adduct **19** without the rearrangement product, presumably due to the reduced electrophilicity of the carbonyl group in the unsaturated case (Scheme 4B). Finally, 3-methylazetidione **20**[9] gave products **7** and **21** in 58% yield in a 3:2 ratio, providing further evidence in support of our proposed mechanism (Scheme 4C).[10]

In conclusion we have uncovered the unusual reactive combination of β-lactams and arynes through a mild and one-pot process to generate useful heterocyclic building blocks. Future efforts will be focused on detailed mechanistic studies and on the application of this methodology in the synthesis of complex heterocyclic molecules.

Acknowledgments

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