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Formal Synthesis of 7-Methoxymitosene and Synthesis of its Analog via a Key $PtCl_2$-Catalyzed Cycloisomerization

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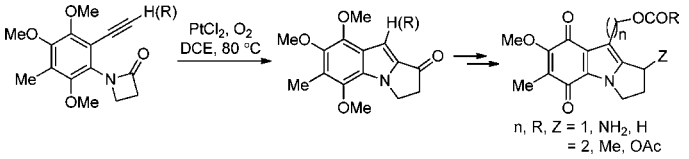
ABSTRACT



A formal synthesis of 7-methoxymitosene is achieved via a key platinum-catalyzed cycloisomerization. The precursor for the Pt catalysis, a fully functionalized benzene intermediate, was prepared via a regioselective electrophilic bromination followed by a chemoselective Sonogashira cross-coupling. It underwent the $PtCl_2$-catalyzed cycloisomerization smoothly despite its hindered and highly electron-rich nature. Analogs of 7-methoxymitosene can be accessed in an expedient manner by following a similar synthetic sequence.

Mitomycins were isolated originally from *Streptomyces caespitosus* in the 1950s[1] and later from *Streptomyces verticillatus*.[2] They are members of a few aziridine-ring-containing natural products[3] and possess potent antibiotic and antitumor activities (Figure 1). Mitomycin C is currently in clinical use and cross-links DNA upon in vivo activation. The more stable aziridinomitosenes, different from mitomycins by the formal loss of MeOH, possess activities against tumor cells similar to mitomycin C.[4] Among various analogs of these pharmacologically important mitosenes, 7-methoxymitosene, a compound lacking the aziridine ring of **1**, has shown to be effective against Gram positive bacteria.[5] Its total synthesis has been realized by various creative approaches targeting the tricyclic pyrrolo-[1,2-*a*]indole skeleton.[6] In this manuscript, we describe a new

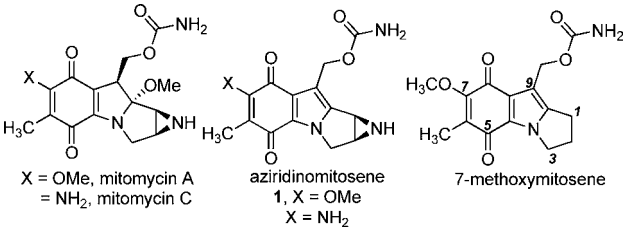


Figure 1. Mitomycins, aziridinomitosenes, and 7-metoxymitosene.

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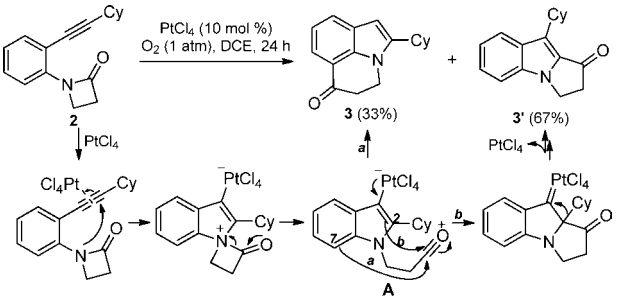
synthetic approach to this compound, where its tricyclic core is constructed via a key $PtCl_2$-catalyzed cycloisomerization reaction; in addition, a designed structural analog, which might possess interesting biological activities, is easily prepared by following a similar synthetic route.

A few years ago we reported a platinum-catalyzed formation of cyclic ketone-fused indoles from *N*-(2-alkynylphenyl)lactams.[7] For example, when the *β*-lactam **2** was the substrate, the dihydropyrrolo[1,2-*a*]indolone **3′** was formed as the major product (Scheme 1). Mechanistically, the reaction likely begins with an initial Pt-promoted cyclization of the *β*-lactam nitrogen onto the C−C triple bond and then undergoes heterolytic fragmentation of the amide bond; the acylium intermediate **A** thus formed then cyclizes to either the 7- or 2-position of the indole moiety. In the case of the former, it leads to the minor tricyclic product **3**; in the case of the latter, a Pt carbene is formed, which would promote a 1,2-alkyl migration, eventually yielding **3′**. This rapid access to the pyrrolo[1,2-*a*]indole skeleton provides us with an opportunity to study the synthesis of mitosenes and in particular 7-methoxymitosene, while testing the Pt catalysis under more demanding scenarios.

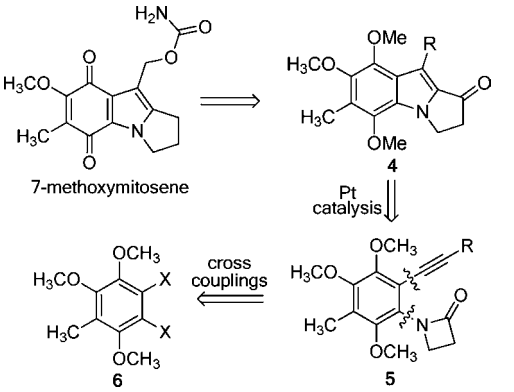
Scheme 1. Example of Pt-Catalyzed Formation of Pyrrolo[1,2-*a*]indolones



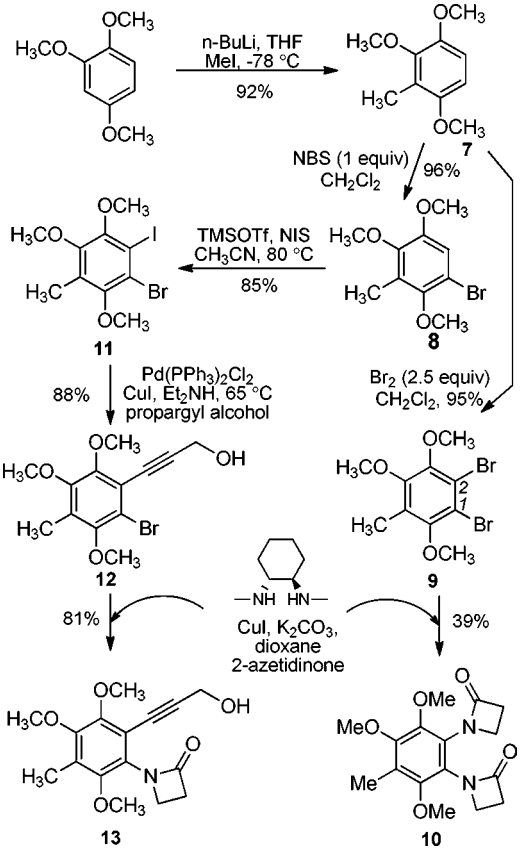
Scheme 2 shows the retrosynthetic analysis of 7-methoxymitosene. This mitosene could be accessed through oxidation and other manipulations of dihydropyrrolo[1,2-*a*]indolone **4**, the precursor of which would be the fully substituted benzene **5** based on our Pt chemistry. The side product of type **3** should be avoided due to substitution at the 7-position of the nascent indole ring. Elaboration of dihalogenated benzene **6** to the sterically congested **5** would rely on regio- or chemoselective sequential coupling reactions.

At the onset, 2,3,6-trimethoxytoluene (i.e., **7**) was prepared in an excellent yield from commercially available 1,2,4-trimethoxybenzene by following a known procedure (Scheme 3).[8] Treatment of **7** with excess Br_2 results in efficient double bromination, yielding dibromobenzene **9**. Attempts to achieve regioselective mono-cross-coupling of **9** with the parent *β*-lactam (i.e., 2-azetidinone) surprisingly

Scheme 2. Retrosynthetic Analysis of 7-Methoxymitosene



Scheme 3. Preparation of the Precursor for Pt Catalysis



led to the double coupling product **10**, and neither mono-coupling product was observed at all even with azetidinone as the limiting reagent, suggesting that the second coupling was much faster than the first one. Alternatively, a mono-Sonogashira reaction with **9** was not successful. To achieve regiocontrol in the desired double couplings, we decided to install two different halogens onto **7**. Fortuitously, the targeted *ortho*-bromoaryl iodide **11** could be prepared easily via sequential bromination and iodination. Of note, the initial

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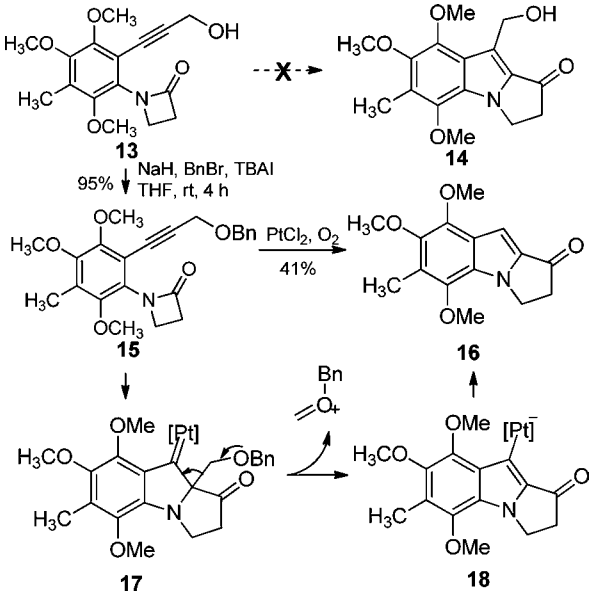
bromination was highly regioselective and efficient, yielding the monobromide **8** in 96% yield. A subsequent chemoselective Sonogashira reaction of **11** followed by a Cu-catalyzed C−N bond formation[9] was delightfully uneventful, providing the propargyl alocohol **13**, the precursor for the key platinum catalysis, in a combined 71% yield.

Treatment of the propargyl alcohol **13**, however, led to a messy reaction, and no desired product was detected (Scheme 4). We speculated that the free HO group might be the culprit; consequently, it was capped by a benzyl group. Treatment of the resulting benzyl ether **15** with $PtCl_2$ (5 mol %) under an oxygen atmosphere still did not afford the desired product; however, to our delight, the anticipated pyrrolo[1,2-*a*]indole skeleton was formed, as the tricyclic ketone **16** was isolated in a 41% yield. Notably, **16** has no substitution at its indole 3-position. The apparent loss of the benzyloxymethyl group during the reaction is rationalized in the same scheme. Apparently, the platinum carbene **17** undergoes C−C bond fragmentation preferentially over the desired Wagner−Meerwein-type rearrangement.

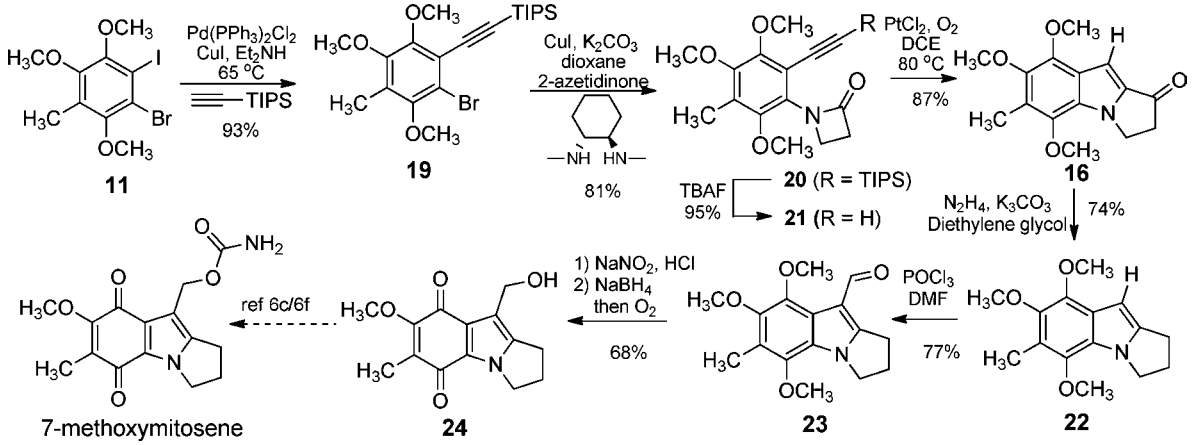
Scheme 4. Initial Studies with $PtCl_2$-Catalyzed Cycloisomerization: Access to the Pyrroloindole Skeleton



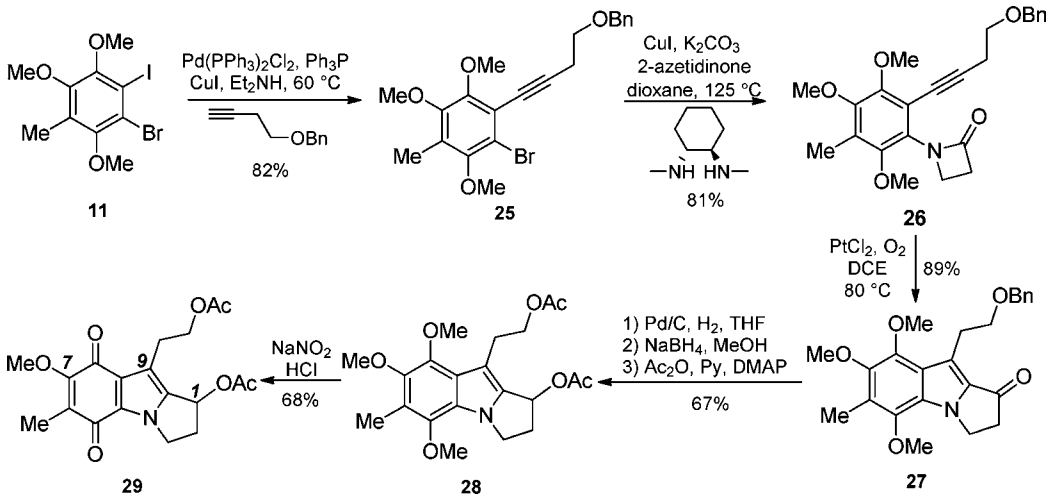
Knowing that the platinum catalysis could work with hindered substrates like **15**, we chose to avoid the problematic alkyl migration process and install the substituent at the indole 3-position at a later stage. The successful execution of this approach is detailed in Scheme 5. Starting from dihalide **11**, the desired arylacetylene **21** was prepared via similar sequential regiocontrolled cross-couplings and then a routine desilylation. The platinum catalysis, to our delight, occurred smoothly, converting **21** into the dihydropyrrolo[1,2-*a*]-indolone **16** in 87% yield. With the core structure set, the penultimate structure, hydroxyquinone **24** was accessed via the following sequence: first, a Wolff−Kishner reductive deoxygenation, then a Vilsmeier−Haack reaction to install the formyl group, which was followed by an oxidation of the *p*-dimethoxybenzene into a *p*-benzoquinone by nitrous acid, and finally a reduction of the aldehyde and reoxidation of the hydroquinone back to the desired quinone structure. Since the conversion of **24** to 7-methoxymitosene has been achieved previously,[6c,f] the synthesis of **24** constitutes a formal synthesis of the mitosene.

Although the hydroxymethyl group in **24** could not be secured directly via the Pt catalysis, other R groups might be possible. This approach (i.e., from **5** to **4**, R ≠ H, Scheme 2) would offer a succinct preparative route to various mitosene analogs with potential biological activities. To demonstrate feasibility, we targeted the bisacetate **29** (Scheme 6). Its 1-acetoxy group can act as a leaving group en route to generate a reactive alkylating moiety in a manner similar to the case of the aziridine ring in aziridinomitosene,[10] and its 9-acetoxyethyl group, though suspect in mimicking[11] the carbamoyloxymethyl moiety in aziridinomitosenes/mitomycins in the formation of the second alkylating site,[12] can demonstrate the feasibility of direct installation of functional groups at the 9-position via the Pt catalysis. As shown in Scheme 6, the synthesis of this designed structure commenced with the

Scheme 5. Synthesis of 7-Methoxymitosene



Scheme 6. Succinct Synthesis of an 1-Acetoxy-7-methoxymitosene Analog



same sequential chemoselective cross-coupling reactions as those in Scheme 5, but but-3-yn-1-yl benzyl ether was used as the alkyne. Much to our delight, the platinum catalysis proceeded with excellent efficiency, delivering the dihydropyrrolo[1,2-*a*]indolone **27** with a 2-benzyloxyethyl substituted at its 9-position in 89% yield. Sequential one-pot hydrogenative debenzylation, ketone reduction, and double acetylation readily converted **27** into bisacetate **28** in 67% overall yield, which in turn was oxidized to the targeted molecule in 68% yield. This short sequence constitutes a five-pot, seven-step synthesis of the mitosene analog from the dihalide **11** in 27% overall yield. Its biological activities will soon be studied.

In conclusion, we have successfully applied the platinum-catalyzed cycloisomerization, previously developed in our laboratory, as a key step in a formal synthesis of 7-methoxymitosene. The reaction precursor, a fully functionalized benzene intermediate, is prepared in a succinct manner featuring two highly selective events: a regioselective electrophilic bromination and a chemoselective Sonogashira cross-coupling. The Pt catalysis proceeds smoothly despite the hindered and highly electron-rich nature of the substrate. An analog of 7-methoxymitosene is prepared in an expedient manner by following a similar synthetic sequence.

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Supporting Information Available. Experimental procedures, NMR spectra, and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.