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Expeditious Pd-Catalyzed $\alpha$-Arylation Route to Dibenzoxepinones. Pivotal Manske’s Ketone for the Formal Synthesis of Cularine Alkaloids

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In Memoriam Richard H. F. Manske, an outstanding alkaloid chemist who also demanded excellence in scientific verse.

Abstract: The general synthesis of diversely substituted dibenzoxepinones by a combined Pd-catalyzed $\alpha$-arylation and $S_N$Ar strategy is reported and applied to the synthesis of Manske’s ketone, a key intermediate en route to the total synthesis of four cularine alkaloids. In the course of this work, an unanticipated ring contraction reaction to a xanthone was observed and serves as a caveat for the conditions of the widely used $\alpha$-arylation reaction.

In his systematic, lifelong study of benzyl isoquinoline alkaloids, Manske discovered the structurally unusual family of bioactive cularines[1-4] (Figure 1, A). Since its original isolation in 1938,[5] cularine (1) and its congeners have suffered a scarcity of isolated material[5,6] due to limitations of plant extraction strategies which, together with their bioactivity, served as inspiration to the synthetic community. In pioneering studies, Manske proposed 10,11-dihydro-2,3,4-trimethoxy-dibenz[b,f]oxepin-10-one (2, Figure1, A) as a key intermediate for the synthesis of cularine. However, his classical Friedel-Crafts approach, afforded low yield(1%) of 2 leaving "little hope for the synthesis of cularine by this method."[7] It was not until 1963 that Kametani and Fukumoto prepared sufficient quantities of Manske’s ketone (2) to allow the first total synthesis of cularine.[8] Given the harsh conditions required to forge the dibenzoxepine core, demands for an alternative strategy were met by Domínguez, who developed an effective but lengthy route to 2 using dithiane alkylation and Ullmann coupling as key steps.[9] Their subsequent elaboration of this key intermediate provided access to the full spectrum of cularine[10] as well as the non-natural $O$-methyllimousamine[10] and aristocularine.[11] In concurrent biomimetic approaches to the cularines,[12] intermediates in the synthesis of crassifoline were shown to undergo 7-membered ring formation either through oxidative coupling,[12a] Ullmann condensation,[12b] or nucleophilic substitution.[12c] Although elegant, such strategies necessitate early-stage installation of the N-heterocycle thereby limiting the range of accessible Cularines.

Aside from approaches developed during the synthesis of the cularine alkaloids, the classical Friedel-Crafts acylation, a reaction suffering from harsh reaction conditions (e.g up to 4 equiv AlCl$_3$ at rt or excess PPA at 100 °C), constitutes the dominant tactic for the construction of 10,11-dihydropyridin[b,f] oxepin-10-ones and biologically active dibenzoxepine containing compounds. A retrosynthetic analysis for dibenzoxepinones 3.

Figure 1. A) The cularine alkaloids and Manske’s ketone 2, the key synthetic intermediate. B) Previous synthetic strategies to 10,11-dihydropyridin[b,f] oxepin-10-ones and biologically active dibenzoxepine containing compounds. C) Retrosynthetic analysis for dibenzoxepinones 3.

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Table 1. Scope of 2'-fluoroacetophenones 7 in the Synthesis of Dibenoxepinones 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>SaAr Product</th>
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Yields of isolated products; for 10, yields in parenthesis obtained using PdCl\(\text{2}(\text{PPh\textsubscript{3}})\) (10 mol%), PPh\(\text{3}\) (30 mol%), Cs\(\text{2}CO\text{3}\) (3 equiv), PhMe, reflux, 16-20h.

Mindful of the limitations of the previous approaches to Manske's ketone (2) and inspired by the diversity of Cularine natural products accessible from this pivotal intermediate, we sought to develop a more efficient route to this ubiquitous heterocycle which is also prevalent in medicinal agents (Figure 1, B). We envisaged two key sequential disconnections to dibenzoxepinones 3 (Figure 1, C): intramolecular palladium-catalyzed α-arylation\(^{[16]}\) to effect oxepine ring closure and C−O bond formation to furnish intermediate diaryl ether 4 by an SaAr reaction between the readily available 2'-fluoroacetophenones (5) and 2-bromophenols (6). Herein we report a general synthesis of dibenzoxepinones and the application of this method to the construction of Manske's ketone (2), the pivotal late-stage intermediate for four Cularine alkaloids.\(^{[17]}\)

To initiate the study, the intramolecular α-arylation of diaryl ether 9a, prepared from SaAr reaction of 2-fluoroacetophenone (7a) with 2-bromophenol (8a), to the prototype dibenzoxepinone 10a was examined (Table 1, entry 1). The cyclization was initially carried out using a catalyst system comprising PdCl\(\text{2}(\text{PPh\textsubscript{3}})\) (5 mol%)/PPh\(\text{3}\) (30 mol%), which delivered the desired product in 61% yield. Considerable further optimization studies in catalyst loading, solvent, and temperature (see SI) demonstrated that a 1:1 ratio of Pd to XantPhos(5mol%), Cs\(\text{2}CO\text{3}\) as base, and toluene as solvent is optimal for the...
process, giving 10a in 72% yield. The reaction also proceeded to completion when run at 80 °C and the catalyst loading could be decreased to 0.625 mol% before starting material consumption was significantly affected. Control experiments performed in the absence of both Pd(dba)₃ and ligand led to complete recovery of starting material 9a.

The scope of the new methodology with respect to substitution on the acetophenone ring was next explored. For this purpose, diaryl ethers 9b-i were prepared via S_{Ar} chemistry between variously substituted 2'-fluorocacetophenones 7b-l and 2-bromophenol 8a (Table 1, entries 2-9). When compounds 9b-l were subjected to the standard α-arylation conditions, the corresponding dibenzoxepinones 10b-h were obtained in good yields. Weakly electron donating groups (EDGs) and electron donating groups (EWGs) (entries 2 and 3) and strongly EWGs para to ortho to the ketone (entries 4 and 5) were well tolerated. However, the chloroacetophenone 9f afforded the corresponding dibenzoxepinone 10f in only 34% yield. The role of electronics on the reactivity of the acetophenone moiety is emphasized by the slightly lower yields observed when strong EDGs were para to meta to the ketone (entries 7 and 8). An incomplete conversion to 10g and 10h was observed after 15 h. However, increasing the reaction time to 40 h led to synthetically useful yields of 59% and 63% respectively. When the rates of the intramolecular α-arylation step for 9a, 9d, and 9g were compared, full conversion of para-trifluoromethyl-containing substrate 9d to 10d was observed after 8 h while conversion of the 7-methoxy-substituted dibenzoxepinone 10g required 40 h, considerably longer than that needed for the unsubstituted substrate 9a (15 h). Unfortunately, no conversion of the acyl pyridine 9i was detected under the reaction conditions.

We next turned our attention to variation of the phenol partner in the S_{Ar} and intramolecular α-arylation sequence and the reaction of differentially substituted 2'-bromophenol 8 with 2'-fluorocacetophenone 7a to give products 10j-r was established (Table 1, entries 10 to 18). Sterically encumbered phenol 9j (entry 10) as well as corresponding substrates bearing a weak EDG (entry 12), halogen (entries 13 and 14), or strongly EDG (entry 15) were well tolerated. An EWG para to the bromo substituent (entry 16) performed significantly better than an EDG (entry 15). 2-Naphthol derived substrate 9r also performed well to give the benzophenoxepinone 10r (entry 18). Much like the reactivity observed for 9i, the α-arylation of heterocycle-derived substrate 9s (entry 19) afforded 10s in low yield. Looking to expand the scope to other heterocyclic systems, diaryl thioether 9t was prepared and exposed to the optimized α-arylation conditions (Table 1, entry 20). Unfortunately, the reaction proved sluggish, with 10t being isolated in only 32% after 40 h reaction time and with increased catalyst loading (5 mol% Pd(dba)₃/10 mol% XantPhos). Substrate 9u, prepared via Ullmann condensation of 2-iodoacetophenone with 2-bromo-N-methylaniline, failed to deliver dibenzazepinone 10u (Table 1, entry 21).

The reaction scope was also successfully expanded to provide 11-substituted dibenzoxepinones 10v-x (Table 1, entries 22-24). Thus, diaryl ethers 9v-x, prepared via S_{Ar}, addition of the appropriate Grignard reagent to 2-(2-bromophenoxy)benzonitrile, or by alkylation of 9a (see SI), were subjected to the standard α-arylation conditions to afford products 10v-x in 39-85% yields.

Further manipulation of 10a/10l highlights the utility of the dibenzoxepinone products (Scheme 1). Thus, Suzuki-Miyaura coupling of 10l with 3-methoxyphenylboronic acid and C-N coupling with morpholine both proceeded smoothly to give biaryl 11a and tertiary amine 11b in 90% and 61% yields, respectively. Alkylation of 10a with ethyl chloroformate gave an excellent yield of β-keto ester 11c that provides an opportunity for further functional group transformation. Furthermore, ketone 10a was subjected to a sequence of trification and Suzuki-Miyaura coupling to afford 11d in 73% yield over two steps.

Scheme 1. Selective chemistry of dibenzoxepinones. (a) 10l (0.50 mmol), 3-methoxyphenylboronic acid (1.5 equiv), Pd(OAc)₂ (2.5 mol%), SPhos (10 mol%), K₂CO₃ (3.0 equiv), MeCN (0.4 M), 100 °C 4 h; (b) 10a (0.25 mmol), NaH (0.25 mmol), NaN₃ (0.092 mmol), CuI (0.13 mmol), 110 °C, 20 h; (c) 10a (0.48 mmol), NaH (2.0 equiv), HOAc (3.0 equiv), THF, rt, 18 h; (d) 10a (0.24 mmol), Ti(OiPr)₄ (2.0 equiv), DEPEA (3.5 equiv), CH₂Cl₂, rt, 24 h, 78%; 2. 3-methoxyphenylboronic acid (1.5 equiv), Pd(PPh₃)₄ (10 mol%), 2M eq. Na₂CO₃ (5.0 equiv), DME; 90 °C, 18 h, 94%.

Scheme 2. Synthesis of Manske’s ketone 2 via precursor 13. 84% yield of isolated 18 when aqueous work-up was avoided.
Having successfully established the scope of the new methodology for the construction of dibenz[b,f]oxepin-10-ones, attention turned to the original goal – Manske’s ketone (2), the key intermediate for the synthesis of the cularine alkaloids. In contrast to the general S-Ar protocol established above, the reaction of 2-fluoro-3-methoxyacetophenone (7h) with 2-bromo-4,5-dimethoxyphenol failed to deliver the requisite intermediate 13 (Scheme 2). The problem was circumvented by devising two effective synthetic routes. Thus, S-Ar of acetonaphthone 7h with 3,4-dimethoxyphenol followed by bromination afforded diaryl ether 14 with 2-bromo-4,5-dimethoxyphenol furnished diaryl ether 15 which, upon sequential bromination and MeMgBr treatment, delivered 13 (65% overall yield).

Exposure of diaryl ether 13 to our initial conditions used in the intramolecular α-arylation reaction (PdCl₂(PPh₃)₃/PPh₃) did not yield the anticipated Manske’s ketone 2 but, unexpectedly, afforded the xanthone 17 as the sole product in low yield (Scheme 2).[19] However, exposure of diaryl ether 13 to our general intramolecular α-arylation conditions furnished, gratifyingly, Manske’s ketone 2 in 69% yield. Our synthesis of Manske’s ketone in overall yields of 48% (3 steps from 7h) and 45% (4 steps from 14) may be favourably compared to those of Manske[7] (2 steps, 1% yield) and Domínguez[8] (6 steps, 18% yield) and its pivotal position in the synthesis of several Cularine alkaloids (e.g. cularine, cularimine, oxocularine, and dioxcularine) is well documented.[16]

In order to shed light on the mechanism of the ring contraction reaction to xanthone derivative 17, similar to an observed intermolecular reaction,[20] we noted the reported oxygen- and light-promoted oxidative cleavage of exocyclic xanthene to xanthone[21] and undertook reaction monitoring under the PdCl₂(PPh₃)₃/PPh₃/K₂PO₃ conditions by ¹H NMR analysis of the reaction mass at regular time intervals (see SI). Upon complete consumption of 13, the reaction mixture was subjected to column purification (avoiding the aqueous work-up) to afford the xanthene 18 and xanthone 17 in 46% and 3% yields, respectively. Furthermore, we found for ¹H NMR study, see SI) that the isolated xanthene 18 was readily converted to xanthone 17 and that the rate of conversion was accelerated by exposure to oxygen (Scheme 2), in accordance with previous studies of similarly substituted xanthenes.[22] This observation clarifies the source of the xanthone 17 product.

In conclusion, we have demonstrated a new combined S-Ar/α-arylation sequence for the synthesis of dibenz[b,f]oxepinones. Following a diversion which led unexpectedly led to the xanthene 17, the main goal of the devised two-step strategy, the synthesis of Manske’s ketone (2), was achieved, constituting the most efficient synthesis to date of this pivotal intermediate for the assemblage of the Cularine alkaloids. The present work constitutes the formal synthesis of four alkaloids (Cularine, Cularimine, Oxocularine, and Dioxcularine). Our efficient and abbreviated route to the dibenzoxepinones, which also represent a structural feature of a number of bioactive molecules (Figure 1, B), may elicit further application of our synthetic strategy.

Acknowledgements

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Keywords: dibenz[b,f]oxepin-10-ones • alkaloids • Palladium • α-arylation • Manske’s ketone

References:

[17] a) In the course of our studies, we became aware of a patent literature concerning the synthesis of derivatives of 10 by a similar route, see CN105111182A (Chinese language). However, the scope and generality were not defined and stoichiometric PdCl₂ was used in the key cyclization reaction as opposed to our catalytic PdCl₂(PPh₃)₃/PPh₃/Pd(OAc)₂/XantPhos method; b) for general synthesis of Benzoxepins, see: S. von Angerer, In Science of Synthesis, Weinreb, S. M. Eds.; Theme: Stuttgart, (2004); Vol. 17, 653–705.
[18] See Supporting Information for time-course study monitoring the conversion to α-arylated products.


We report on the intramolecular Pd catalysed α-arylation→cyclization sequence for the synthesis of dibenz[b,f]oxepin-10-ones 10 from diarylethers 9. Extensive substrate scope was investigated varying substitution pattern on both the rings of 9. The present work demonstrates the shortest route to Manske’s ketone 2, a pivotal intermediate for the synthesis of four of the Cularine alkaloids.

Key Topic: Pd-catalysis, Alkaloid Synthesis