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MILD AND EFFICIENT SYNTHESIS OF BENZO-FUSED SEVEN- AND EIGHT-MEMBERED RING LACTAMS: A CONVENIENT APPROACH TO BIOLOGICALLY INTERESTING CHEMOTYPES

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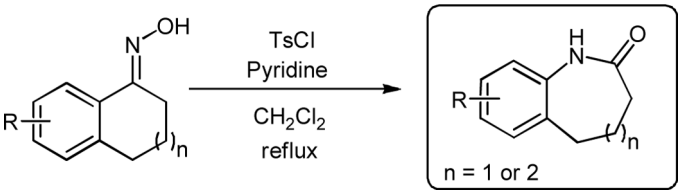
GRAPHICAL ABSTRACT



Abstract *A general and efficient method for the synthesis of benzo-fused 7- and 8-membered ring lactams via the Beckmann rearrangement of cyclic oximes is presented.*

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Keywords Lactam; medium ring; methodology

INTRODUCTION

The importance of medium-ring lactams (Seven- to 10-membered)[1] in organic chemistry is exemplified by their presence in a large number of biologically active and pharmaceutically relevant molecules.[2] One therapeutically important class of compounds incorporating this motif is the benzo-fused medium ring lactams. Numerous compounds based around a benzo-fused seven-membered lactam ring core (commonly referred to as a benzazepinone motif) have been found to demonstrate interesting biological properties (Fig. 1). For example, benzazepril **(1)** is an angiotensin converting enzyme inhibitor, L-692428 **(2)** is a growth hormone secretago,[3] and the structurally related compound alsterpaullone **(3)** is a cyclin-dependent kinase inhibitor.[4]

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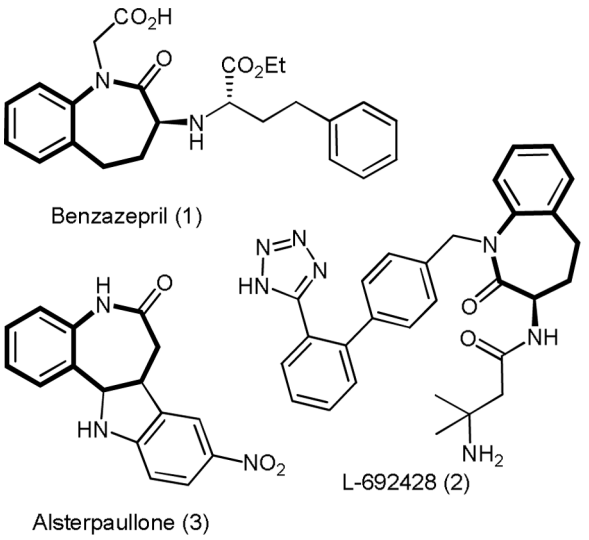


Figure 1. Some examples of biologically active compounds based around a benzo-fused seven-membered lactam ring core (highlighted in bold).

Despite the interesting biological properties associated with seven-membered benzo-fused lactams, compounds containing the equivalent eight-membered ring systems are relatively scarce. Consequently, benzo-fused eight-membered ring lactams (indeed, medium-ring lactams in general) are underrepresented in current small-molecule libraries.[1,5] This relative paucity of compounds can be attributed primarily to synthetic difficulties.[1,2] Thus, there is a need for the development of efficient methods of broad utility for the synthesis of benzo-fused eight-membered ring lactams so that the biological usefulness of this structural moiety can be investigated and exploited further. Herein we describe a general procedure for the synthesis of benzo-fused seven- and eight-membered ring lactams via the Beckmann rearrangement of oximes under mild conditions. Additionally, we describe subsequent synthetic manipulations of the products, which allow the generation of further compound diversity; this may be valuable for the exploration of biological activity space around the lactam core and the delineation of possible structure–activity relationships in any future biological studies.

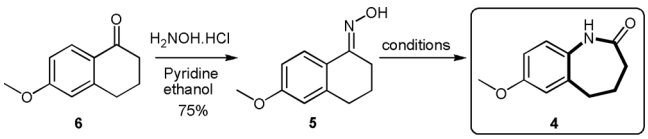
DISCUSSION

The direct lactamization of acyclic precursors is arguably the most conceptually straightforward approach to medium-ring lactams,[2] but it is both kinetically and thermodynamically challenging, typically requiring the use of dilute reaction conditions or carefully designed substrates.[1,2,6,7] Ring closure by other methods (e.g., C-C bond formation) generally necessitates elaborate synthetic precursors,[6] and the formation of unsaturated lactams by olefin metathesis can proceed with unpredictable levels of geometrical selectivity.[2] The use of cycloadditions is generally restricted to the synthesis of seven-membered lactam ring systems.[2] Ring

expansion of cyclic ketones by nitrogen insertion eschews some of the difficulties associated with the direct closure of acyclic precursors and has attracted significant attention as a method for the synthesis of medium-ring lactams.[2] One commonly used nitrogen-insertion process is the Beckmann rearrangement of cyclic oximes.[2,8] There are numerous examples of medium-ring lactams of various sizes generated by this reaction, including benzo-fused systems (generally isolated examples of primarily seven-membered lactams of the benzazepinone family).[9] However, a wide range of different reaction conditions have been reported for these processes, with no one set showing a truly broad utility; optimization of reaction conditions (catalyst, temperature, concentration) is usually required on a case-by-case basis.[2] Often very harsh conditions (e.g., high reaction temperatures and very acidic and dehydrating reaction media) are needed, which limit substrate functional group tolerability and thus the structural diversity and synthetic manipulability of the resulting products.[2,10] In addition, the regioselectivity of Beckmann-type rearrangements of cyclic oximes can be somewhat variable.[2,11] In theory, the reaction is stereospecific if a geometrically defined oxime is used.[11] However, isomerization of the oxime starting material can occur under some rearrangement conditions, leading to a mixture of amide products.[2,11,12] Secondary cleavage reactions can also complicate the progress of the reaction.[11] We therefore sought the use of relatively mild reaction conditions for the Beckmann rearrangement process that could be exploited to generate of a range of benzo-fused seven- and eight-membered ring lactams, amenable to further modification, with predictably high levels of regioselectivity. Initial optimization studies focused upon the formation of the seven-membered benzo-fused lactam (a 1-benzazepin-2-one) **4** via the Beckmann rearrangement of oxime *E*-**5** (Table 1).

Treatment of commercially available ketone **6** with hydroxylamine hydrochloride and pyridine in ethanol furnished the desired *E*-isomer **5** (with no evidence for the formation of the corresponding *Z*-isomer). Lactam formation from geometrically-pure *E*-**5** was then attempted using three different sets of reaction conditions previously employed in Beckmann rearrangements (conditions A–C, Table 1). The first two sets of conditions (conditions A and B, Table 1) involved the use of catalytic cyanuric chloride.[13] Only under conditions A was there any evidence for the formation of

Table 1. Optimization of conditions for the synthesis of lactam **4**



Conditions	Observations
A, cyanuric chloride, $ZnCl_2$, MeCN, rt	UPLC[a] indicated a small amount of **4** had formed after 7 days of reaction time, but this could not be isolated.
B, cyanuric chloride, DMF, rt	UPLC[a] indicated essentially no consumption of starting material after 7 days of reaction time.
C, TsCl, pyridine, CH_2Cl_2, reflux, 4 h	93% isolated yield of **4**.

[a]UPLC, ultraperformance liquid chromatography; rt, room temperature; h, hour.

the desired product, but the quantity was negligible and it could not be isolated. The third set of reaction conditions examined (conditions C, Table 1) involved the use of tosyl chloride and pyridine. It is commonly believed that under such conditions the oxygen of the oxime is tosylated, creating a better leaving group and thereby accelerating the rate of the rearrangement process.[14] Pleasingly, an excellent isolated yield of **4** was obtained under reaction conditions C. In addition, there was no evidence for the formation of the lactam resulting from alkyl rather than aryl migration, which implies that there is no geometrical scrambling of the oxime functionality under these reaction conditions.

With optimized conditions in hand, the rearrangement of various other commercially available oximes was examined to explore the substrate scope of the methodology (Table 2). Pleasingly, several seven- and eight-membered benzo-fused lactams **(7–11)** could be accessed. Gratifyingly, in all cases only a single amide product was observed, suggesting that there is no scrambling of oxime geometry under the relatively mild reaction conditions. Both substituted and unsubstituted aromatic ring systems were tolerated, and it also was proved possible to carry out the rearrangement process on an oxime substituted at the α-position to generate the novel phenyl-substituted benzo-fused lactam derivative **10**.

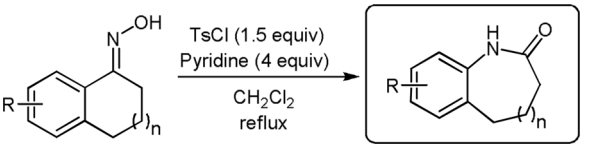
In addition, the structurally novel nitrogen-linked biaryl eight-membered ring lactam **12** could be generated (Fig. 2). Although the isolated product yield was very low, this nevertheless represents a significant result. The isolated yield of 12 was only 6% (1.4-mmol scale). Efforts are currently under way to improve the yield of this process and apply the methodology to the synthesis of other nitrogen-linked biaryl medium ring lactams. Though numerous compounds based around a seven-membered nitrogen-linked biaryl scaffold have been found to demonstrate interesting biological properties, there are relatively few example of the synthesis of the analogous eight-membered ring lactam scaffold.[15] Synthetic access to this very rare class of compound will allow the biological properties of this potentially valuable structural motif to be investigated further.

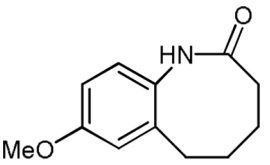
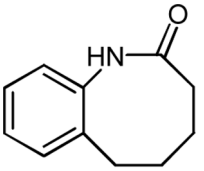
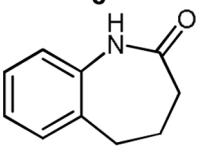
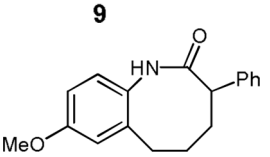
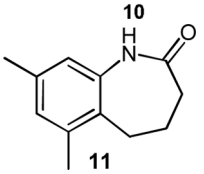
Having established a robust method for the synthesis of benzo-fused lactams, we were interested in creating additional compound diversity by scaffold decoration around the lactam core. To this end we investigated arylation reactions on the amide nitrogen. Under copper catalysis it proved possible to couple a range of aryl iodides onto both seven- and eight-membered benzo-fused lactams to generate several structurally novel derivatives (**15–18**, Scheme 1).

In summary, we have reported a convenient, efficient, and general method for the synthesis of benzo-fused seven- and eight-membered ring lactams by the Beckmann rearrangement of cyclic oximes. The process is technically simple, proceeds under relatively mild conditions with compete regioselectivity, and forms biologically interesting products that are generally difficult to synthesize by other methods. The biological activities of the compounds disclosed in this report are currently being evaluated. A full account of the results of our screening experiments will be reported in due course. In addition, several structurally novel *N*-arylated derivatives were prepared, demonstrating the capability to carry out structural elaboration around the lactam core.

Overall, the work herein reported represents a convenient approach to benzo-fused eight-membered ring lactams, a biologically interesting chemotype that

Table 2. Synthesis of benzo-fused medium ring lactams[a]



Entry	Time (h)	Product	Yield (%)
1	2	 **7**	95
2	2	 **8**	87
3	48	 **9**	27
4	12	 **10**	87
5	48	 **11**	21

[a]See Supporting Information for synthesis of oxime substrates; equiv, equivalents; h, hour.

is underrepresented in current small-molecule collections. The enrichment of screening libraries with compounds of this sort will allow the sampling of previously untapped regions of chemical space, which may thus facilitate the discovery of novel biologically active small-molecule agents. As such, we anticipate that this methodology will prove especially valuable in the diversity-oriented synthesis of structurally diverse small-molecule collections.[18]

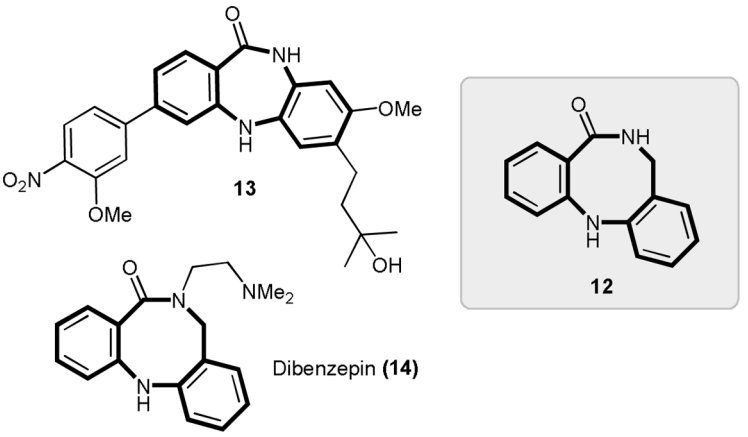
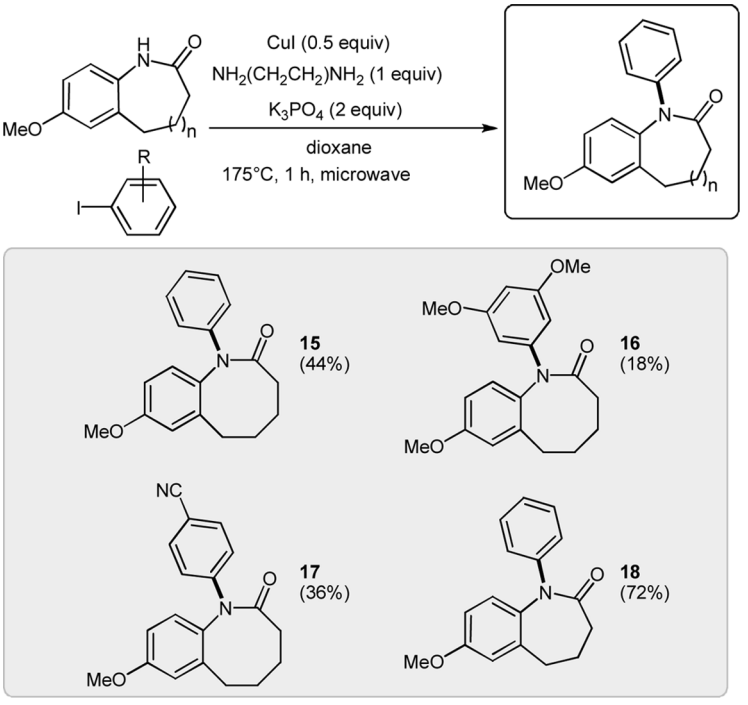


Figure 2. Structurally novel nitrogen-linked biaryl eight-membered ring lactam **12** was generated. The isolated yield of 12 was only 6% (1.4-mmol scale). Efforts are currently under way to improve the yield of this process and apply the methodology to the synthesis of other nitrogen-linked biaryl medium ring lactams. Some examples of biologically active compounds based around a nitrogen-linked biaryl lactam scaffold (highlighted in bold) are also shown: **13** is a potent Chk1 inhibitor,[16] and Dibenzepin **(14)** is an antidepressant that has been shown to also have activity as a defibrillatory agent.[17]



Scheme 1. Synthesis of arylated lactam derivatives. In the case of compound **18**, 4 equivalents of aryl iodide were used, with a total reaction time of 2 h; equiv, equivalents; h, hour.

EXPERIMENTAL

General Procedure for Oxime Synthesis

The protocol was adapted from the method of Learmonth et al.[19] with the following modifications: Pyridine (1.75 equiv) was added to a stirring solution of ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) in EtOH. The reaction mixture was heated at reflux overnight before removing the solvent under reduced pressure. The crude product was purified using flash chromatography.

General Procedure for the Beckmann Rearrangement

Pyridine (4 equiv) was added to a stirring solution of oxime (1 equiv) and TsCl (1.5 equiv) in CH_2Cl_2, and the reaction mixture was heated at reflux until complete consumption of starting material (as indicated by thin-layer chromatography, TLC). The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous copper(II) sulfate solution ($\times 3$). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure to give the product. The crude product was purified using flash chromatography.

General Procedure for Amide Arylation

A microwave tube was charged with amide (1 equiv), aryl halide (2 equiv), potassium *tert*-butoxide (2 equiv), ethane-1,2-diamine (1 equiv), CuI (0.5 equiv), and dioxane and was irradiated for 1 h at 175 °C. EtOAc was added to the reaction mixture and washed with water ($\times 2$). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified using flash chromatography.

Analytical Data for Compound 8

Mp 157.1–158.6 °C (EtOAc-petroleum ether, 1:1); $R_f = 0.35$ (SiO_2; EtOAc-petroleum ether, 1:1); IR: 3177 (N-H), 3047, 2943, 2931, 2853, 1651s (C=O), 1602, 1578, 1493, 1450, 1439, 1431, 1394, 1349, 1338, 1312, 1253, 1196, 1159, 1140, 1102 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO, 373 K) 9.09 (1H, s, br, NH), 7.31–7.27 (1H, m, aryl H), 7.24–7.17 (2H, m, aryl H), 7.07–7.03 (1H, m, H5), 2.64–2.54 (2H, m, H11), 2.01–1.93 (2H, m, H8), 1.80–1.67 (4H, m, H9 and H10); ^{13}C NMR (125 MHz, d_6-DMSO, 373 K) 175.03 (C7), 139.45 (C6), 137.61 (C1), 130.97 (CH), 127.16 (CH), 127.03 (CH), 125.48 (CH), 33.05 (CH_2), 31.18 (CH_2), 29.90 (CH_2), 24.79 (CH_2); HRMS (ESI+) m/z $[M+H]^+$ calcd. for $C_{11}H_{14}NO^+$: 176.1075; found 176.1084.

ACKNOWLEDGMENTS

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