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Synthesis of benzoxepins via rearrangement of dihydrofurans derived from carbonyl ylide [3+2] cycloaddition

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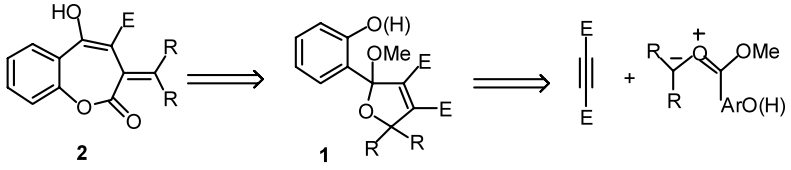
Abstract—Highly substituted benzoxepins can be prepared via BBr_3-induced rearrangement of functionalized dihydrofurans derived from carbonyl ylide [3+2] cycloaddition.

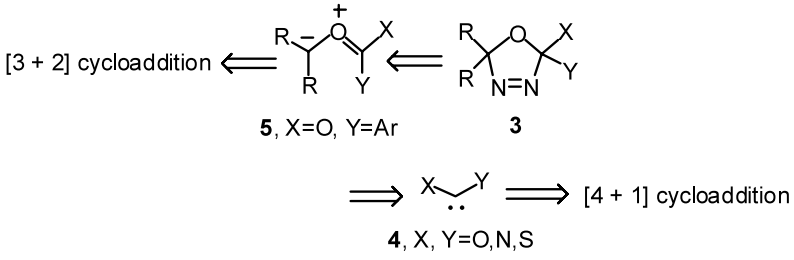
Efforts directed toward the development of new methods for the preparation of benzoxepins continues unabated. Interest in these heterocycles is driven both by the opportunity to test new reaction schemes and by the extensive pharmacology of compounds possessing this heterocyclic sub-structural core. 1-Benzoxepin-based compounds exhibit biological activities that include antifungal,[1a] antimicrobial,[1b,c] and potent cytotoxicity.[1d] A consequence of these important features has been the development of a multitude of approaches into the benzoxepin ring system.[2]

Scheme 1 depicts our approach into highly substituted 1-benzoxepins. It was envisioned that carbonyl ylide [3+2] cycloaddition would provide convenient access to a range of functionalized aryl substituted dihydrofuran derivatives (**1**) exhibiting an *ortho* oxygen substituent that could be transformed into the desired seven-membered heterocycles **2** via a properly defined acid-mediated bond reorganization process. The approach described herein represents a useful modification of some relevant chemistry previously reported in the literature.[3]

Δ^3-1,3,4-Oxadiazolines (**3**)[4] are known to be convenient precursors to so-called nucleophilic carbenes **4** when X and Y are π-donors capable of stabilizing the singlet form of the resultant carbene. These reactive intermedi-



Scheme 1.



Scheme 2.

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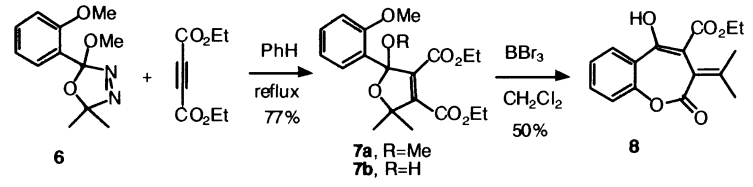
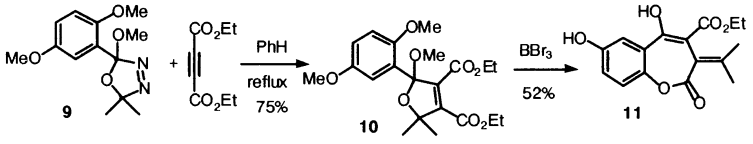
ates, produced through thermolytic decomposition of the corresponding oxadiazolines, have been shown to undergo a multitude of synthetically useful [4+1] cycloaddition processes with electrophiles such as isocyanates, ketenes, and so forth to deliver five-membered heterocyclic and carbocyclic products (Scheme 2).[5]

However, an appropriately positioned aryl substituent on the heterocyclic precursor often impedes carbene production and serves to divert the reaction pathway toward the corresponding carbonyl ylide **5**, which can be trapped by dipolarophiles.[6] Our plan was to prepare a range of aryl substituted dihydrofuran intermediates (**1**) by exploiting this alternate oxadiazoline decomposition pathway and then to transform them into highly functionalized benzoxepins.

In the event, readily available oxadiazoline **6**[7] was heated in the presence of diethyl acetylenedicarboxylate to afford adduct **7a**[7] in 77% yield.[8] Compound **7** was in turn treated with BBr_3 (5 equiv.) for 48 h at room temperature to afford 1-benzoxepin **8**[7] in 50% yield (Eq. (1)).[9,10] Shorter reaction times gave only the hemiacetal **7b**.[7]

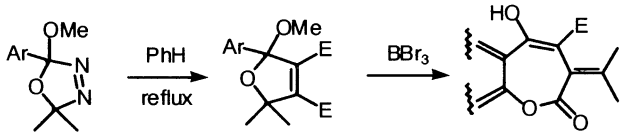


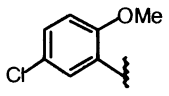
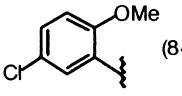
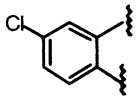
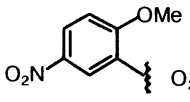
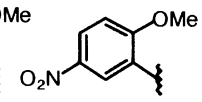
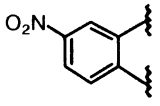
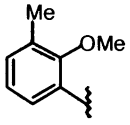
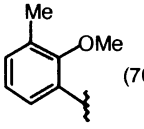
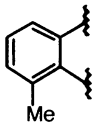
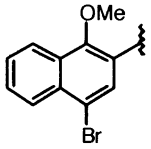
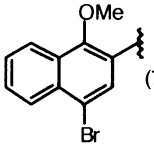
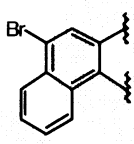
(1)



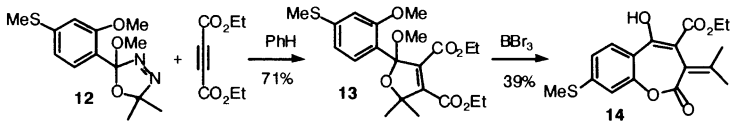
(2)

Table 1. Synthesis of dihydrofurans and benzoxepins



Entry	Oxadiazoline	Dihydrofuran (yield %)[a]	Benzoxepin (yield %)[a]
1		 (84)	 (52)
2		 (97)	 (34)
3		 (70)	 (62)
4		 (70)	 (29)[b]

[a] Reference 7 [b] This material exists as a mixture atropisomers as determined by x-ray analysis.



(3)

Equations (2) and (3) depict reactions in which the aryl ring moiety possesses either a methoxy or thiomethoxy substituent. Not surprisingly the methoxy methyl group is severed during the conversion of **10**[7] into **11**[7] whereas the thiomethyl group survives the corresponding transformation of **13**[7] into **14**.[7]

Several other examples of this novel ring forming process are collected in Table 1. It is noteworthy that a nitro substituent seems to survive the reaction conditions more or less intact, although the yield of the resultant benzoxepin is modest. It is possible that the powerful electron withdrawing character of this substituent has a deleterious influence on the course of the rearrangement process. Entry 4 reveals that this reaction sequence can be extended to a dihydrofuran exhibiting a naphthalene substituent.

Further work is currently underway in our laboratory to clarify certain aspects of the mechanistic pathway for the conversion of the dihydrofurans into benzoxepins.

Acknowledgements

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7. This compound exhibits spectral (^{1}H, ^{13}C NMR, IR) and analytical (HRMS and/or combustion analysis) data fully consistent with the assigned structure.
8. Typical cycloaddition procedure: A mixture of the oxadiazoline (1 equiv.) and DMAD (2 equiv.) was heated in benzene at reflux for 16–24 h. The products were purified by flash column chromatography.
9. Typical rearrangement procedure: To a solution of the dihydrofuran (1 equiv.) in CH_2Cl_2 at 0°C was added BBr_3 (4 equiv.). The resultant mixture was stirred at room temperature for 48 h at which time it was quenched with H_2O and extracted into CH_2Cl_2. The products were purified by flash column chromatography.
10. The identity of compound **8** was unambiguously established by single-crystal X-ray analysis.