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Intramolecular Cyclization Reactions of 5-Halo- and 5-Nitro-Substituted Furans

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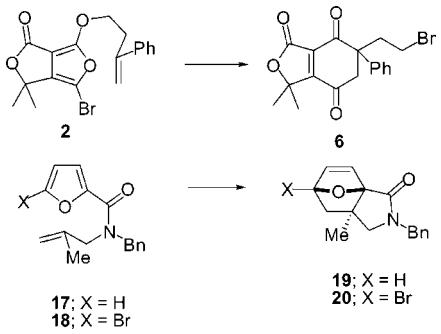
ABSTRACT



Intramolecular cyclization reactions of 5-halo- and 5-nitro-substituted furanylamides were examined. The 2-alkoxy-5-bromofuran derivative 2 produced the rearranged dihydroquinone 6 (36%), a product from the rearrangement of the intermediate oxabicycle 3. The 5-halo substituted furoyl amide 18 was converted to the polyfunctional oxabicycle 20 in 82% yield and at a much faster rate than the unsubstituted furanyl system 17. The 5-nitro-substituted furfuryl amide 33b underwent an unusual isomerization–cyclization reaction under microwave conditions to provide 1,4-dihydro-2*H*-benzo[4,5]furo[2,3-*c*]pyridin-3-one 34.

The intramolecular Diels−Alder reaction of furans (IMDAF) has proven to be a powerful tool for the rapid construction of polycyclic skeletons.[1] In earlier papers, we have exploited the cycloaddition−rearrangement cascade reaction of 2-amidofurans as a key disconnection for the construction of alkaloid frameworks.[2] As part of our broader interest in using furan-cycloaddition products for the synthesis of natural products, we examined the strategic incorporation of several functional groups into the furan moiety that could be leveraged for further transformations.[3] After our initial success using 2-alkylthio-5-amidofurans,[2c,4] we decided to use other substituents that would allow for the further manipulation of the resulting cycloadducts. Herein, we report some of the interesting results obtained from the thermolysis of various 5-halo- and 5-nitro-substituted furans.

One useful route for the preparation of substituted furans is through the Rh(II)-catalyzed cyclization of diazo 2-propynyl malonate esters.[5] For example, we discovered that heating a sample of diazo ester **1** with a catalytic amount of $Rh_2(OAc)_4$ at reflux in benzene gave 2-bromofuran **2** (Scheme 1). Interestingly, when a solution of **2** in xylene was heated to 145 °C (sealed tube) overnight, bromide **6** was isolated as the major product. Presumably, **6** arises from

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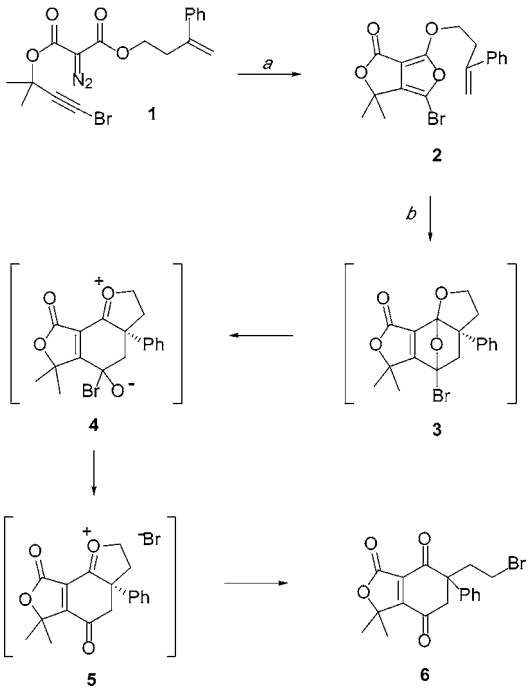
Scheme 1[a]

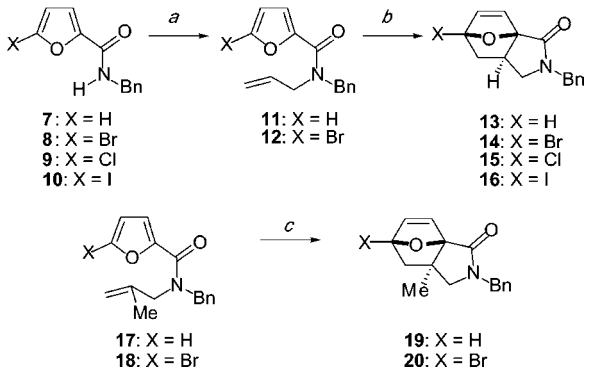


[a] Reagents: (a) $Rh_2(OAc)_4$, PhH, 2; (b) xylenes, 145 °C, 36%.

an initial intramolecular Diels−Alder reaction of furan **2** to give oxabicycle **3**. Fragmentation of the oxabridge results in a zwitterionic intermediate **4**, which can ketonize with the expulsion of a bromide ion, producing oxonium ion **5**. The ejected bromide ion then attacks the oxonium ion at the adjacent methylene position, leading to the observed product.

Intrigued by these initial results, we decided to examine related systems that could provide polyfunctional oxabicycles. Thus, 5-bromo-2-furoyl amide **12** was prepared by N-allylation of the secondary amide **8** under phase transfer conditions (Scheme 2). Heating a sample of furan **12** at 110 °C for 90 min provided the stable oxatricycle **14** as a single diastereomer, resulting from an exo cyclization with respect

Scheme 2[a]



[a] Reagents: (a) NaOH, K_2CO_3, *n*-Bu_4NHSO_4, allyl bromide, PhH, rt (**11** or **12**) or 2; (b) $PhCH_3$, 2, 1 week (**13**, 90%) or 90 min (**1**, 100%); (c) PhH, 2, 6 days (**19**, 60%) or 36 h (**20**, 82%).

to the tether.[6] In contrast to this finding, it was necessary to heat the unsubstituted amidofuran **11** for 1 week at 110 °C in order to complete the cycloaddition of **11** to **13**. Alternatively, furans **7** and **8** could directly be converted to cycloadducts **13** and **14** by conducting the N-allylation at reflux temperatures. After 48 h, the bromofuran **8** was completely transformed to cycloadduct **14**, whereas the unsubstituted variant **7** gave a mixture of **11** (40%) and cycloadduct **13** (48%).

The rate enhancement observed by incorporating a halogen at the 5-position appears to be general.[7] Accordingly, when the analogous 5-chloro- and 5-iodofurans **9** and **10** were subjected to the allylation conditions in benzene at reflux, cycloadducts **15** and **16** were isolated in 92 and 94% yields, respectively.

The presence of the bromo substituent also dramatically influenced the rate of the IMDAF cyclization of substituted alkene tethers. For example, while the cycloaddition of **17** was only 40% complete after 6 days of constant heating at 80 °C, bromofuran **18** was completely converted to **20** after only 36 h.[8]

The origin of the increased rate of cycloaddition for the halo-substituted furans when compared to unsubstituted examples is unclear.[7] While FMO theory predicts that electron-releasing groups should facilitate a normal-demand Diels−Alder reaction,[9] predicting the electronic effect of a halo group is complicated by their σ-withdrawing nature juxtaposed with their weak π-donating ability. Recent theoretical work, however, predicts the transition state-stabilizing effect of halogen substituents in the Diels−Alder reaction and suggests that this is a result of the high polarizability of these substituents.[10]

The remarkable enhancement in the rate of the cycloaddition involving bromofurans, combined with our recent success with cycloadditions across an indole C(2)−C(3) π-bond,[2a] prompted us to examine these reactions in the context of a (±)-morphine synthesis.[11] Ciganek had previously reported the intramolecular Diels−Alder reaction of **21** to provide the *ACDE* core **22**, albeit in only 10% yield (Scheme 3).[12] α-Pyrone derivative **23**, however, produced **24** in 53% yield. Inspired by this report, we envisioned an IMDAF reaction of furanyl amide **26** to furnish the cycloadduct **25**.

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(7) For a study of substituent effects in related IMDAF reactions, see: Klepo, Z.; Jakop, K. *J. Heterocycl. Chem.* **1987**, *24*, 1787−1791.

(8) Slow conversion of furan **17** to oxabicyclo **19** (40%) over a 6 day period was followed every 24 h and was shown not to be the result of a retro Diels−Alder equilibrium.

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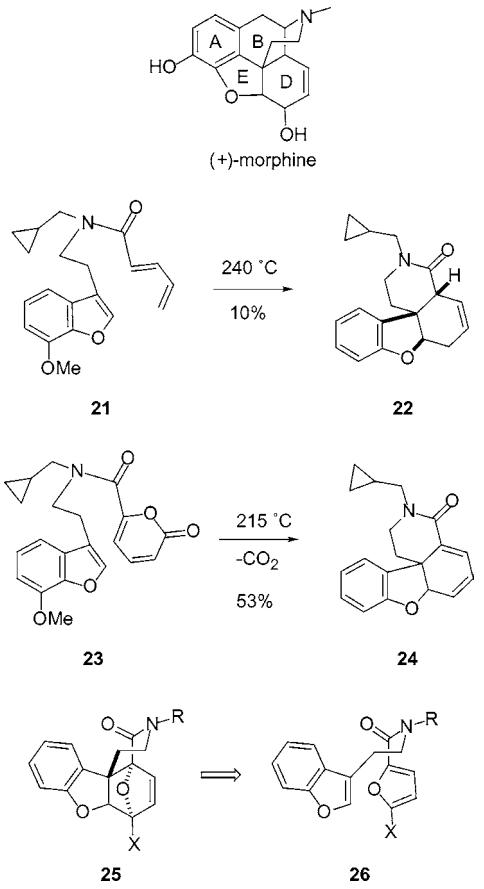
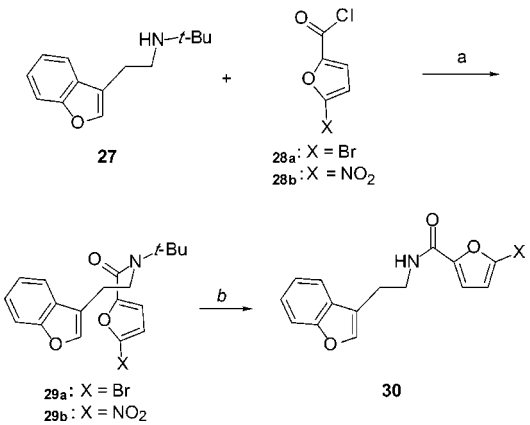
Scheme 3. Approach to Morphine's ACDE Core



Acylation of *tert*-butylamine **27** with acid chloride **28a**, derived from commercially available 5-bromo-2-furoic acid, gave the desired tertiary amide **29a** in good yield (Scheme 4). Unfortunately, all of our attempts to effect the cycloaddition of **29a** only resulted in the removal of the labile *tert*-butyl group to give **30**. Thermal conditions, microwave assistance, and the addition of several Lewis acids (i.e., $SnCl_4$, $TiCl_4$, $ZnCl_2 \cdot OEt_2$, $BF_3 \cdot OEt_2$, TMSOTf) all failed to promote the desired cycloaddition.

Scheme 4[a]

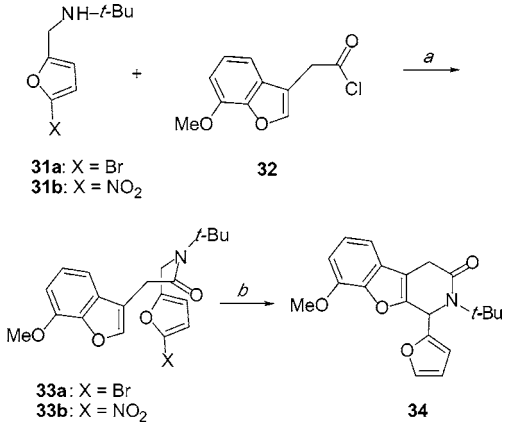


[a] Reagents: (a) Et_3N, CH_2Cl_2, 0 °C; (b) 2, μW or Lewis acid.

At this point in time, we decided to attempt an inverse electron-demand Diels−Alder reaction using an electron-withdrawing nitro group, rather than a bromo substituent. Accordingly, we prepared the 5-nitro-furan variant **29b** through the acylation protocol using **28b** as an acylating agent. Again, all of our attempts to effect IMDAF cyclization of **29b** failed.

Undeterred by these initial results, we also examined the thermolysis of furfuryl amides **33a**,**b**, where the amide carbonyl group is transposed onto the opposite side of the nitrogen atom (Scheme 5). These substrates were prepared

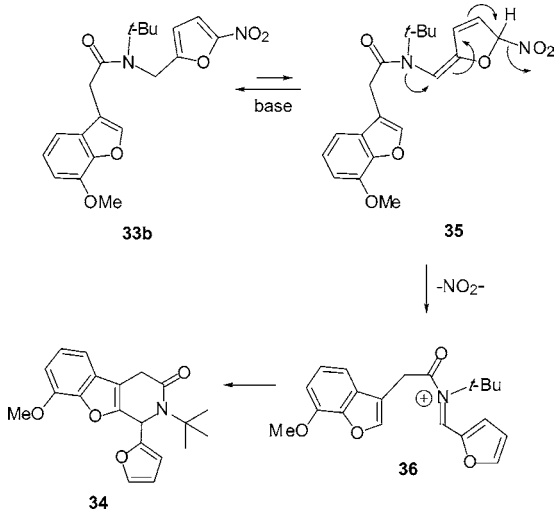
Scheme 5[a]



[a] Reagents: (a) pyridine, CH_2Cl_2, 0 °C, 39% (**31a**) or 41% (**31b**); (b) NMP, μW (300W), 15 min, 36%.

in modest yields (ca. 40%) by the acylation of secondary *tert*-butylamines **31a**,**b**, derived from the reductive amination[13] of *tert*-butylamine and the corresponding 2-furfurals, with acid chloride **32**.[11] Attempts to effect the cycloaddition of **33a**,**b** under thermal conditions once again resulted in the removal of the *tert*-butyl group. Most interestingly, when

Scheme 6



nitrofuran **33b** was exposed to microwave irradiation for 15 min in *N*-methyl-2-pyrrolidinone (NMP), furan **34** was isolated as the major product.

Compound **34** was unequivocally assigned by a single-crystal X-ray analysis.[14] Catalytic amounts of 2,6-lutidine enhanced the formation of **34**, suggesting a mechanism involving base-catalyzed tautomerization of the furfuryl moiety via intermediates **35** and **36** as shown in Scheme 6.

In conclusion, our studies have uncovered some interesting thermal transformations that arise from 5-halo- or 5-nitro-substituted furans. In particular, the presence of a 5-halo substituent on the furan greatly enhances the rate of the intramolecular [4 + 2]-cycloaddition reaction of 2-furoic acid amides. Investigation into the rearrangements of the resultant 7-oxabicyclo[2.2.1]heptene cycloadducts, as well as the application of this approach to the synthesis of alkaloid natural products, is currently under investigation and will be fully disclosed in due course.

Acknowledgment. We gratefully acknowledge the National Institutes of Health (GM59384) for generous support of this work. We also thank Dr. Kenneth Hardcastle for his assistance with the X-ray crystal structure of compound **34**.

Supporting Information Available: Experimental procedures and characterization data for new compounds, together with an ORTEP drawing for compound **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The authors have deposited coordinates for structure **34** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.