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Graphical Abstract

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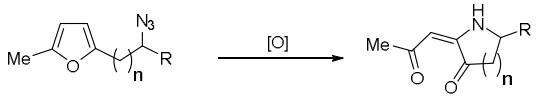

Oxidation of azidoalkyl furans

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Abstract

The oxidation reactions of various azidoalkyl furans were explored under different conditions to access structurally complex compounds from simple starting materials in an operationally simple, single step reaction. The strategically placed azide functional groups on the alkyl chain of the furan led to the discovery of a new and simple method for the synthesis of five-, six-, and seven-membered nitrogen heterocycles bearing prochiral centers and stereocenters.

Key words: *azidoalkyl furans, oxidation, pyrrolidine, piperidine, homopiperidine*

Introduction

Nitrogen containing heterocycles are important natural and unnatural products possessing a wide range of biological activities. A recent review by Njardarson and co-workers showed that 59% of the US FDA approved drugs contain at least one nitrogen heterocycle,[1] in which five- and six-membered nitrogen heterocycles are the most abundant. These structures are present in natural products and synthetic biologically active motifs,[2] and are considered to be privileged structures in medicinal chemistry.[3] Cyclic vicinal enamines possessing stereocenters and prochiral centers are also highly versatile intermediates in the syntheses of many structurally complex nitrogen hetereocycles.[4]

The furan ring has been harnessed as a building block in the syntheses of various natural products exhibiting significant pharmaceutical interest.[5] To unearth its hidden building block features, furans are oxidized either

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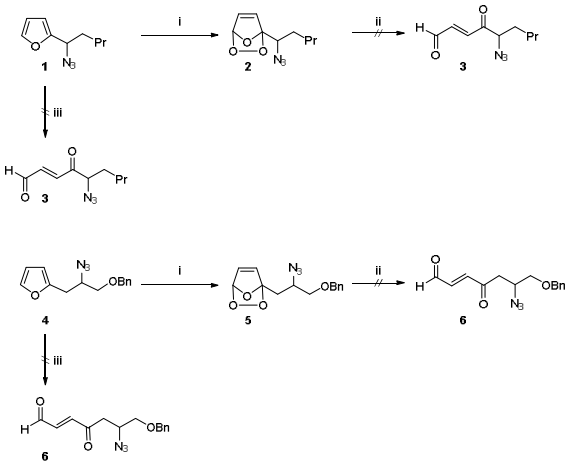
chemically[6] or photochemically[7] with the preference for particular oxidation conditions strictly dependent on the substrate and targeted product. The oxidation of alkyl furans possessing nucleophilic substituents such as hydroxyl[8] and amino groups,[9] has been extensively implemented in the synthesis of structurally complex and pharmaceutically important compounds. The azide group is also very common and usually functions as a precursor for both amines and triazoles. Despite the interesting properties of the azide group, the oxidation of azidoalkyl furan derivatives is surprisingly rare in the literature.[10] Prior to this work, there have only been two reported studies, one of which was conducted in our laboratory. In our previous study, we disclosed the TPP (*meso*-tetraphenylporphyrin) sensitized photooxygenation of azidoalkyl furans giving triazoles *via* an unusual cycloaddition reaction and a new endoperoxide rearrangement pathway.[10a]

Currently, our group is focused extensively on furan-based strategies for the development of new methods for obtaining nitrogen heterocycles.[9h,10a] Herein, we report the oxidation of azidoalkyl furans leading to a straightforward method for synthesizing 5-, 6- and 7-membered nitrogen heterocycles bearing prochiral centers.

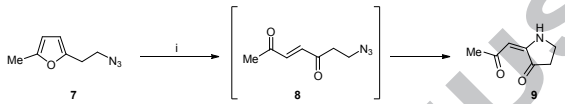
Results and discussion

The syntheses of azidosubstituted alkyl furans at different positions of the alkyl chain was achieved by bond formation and functional group transformations.[10a] Our investigation began with the model substrate 2-(1-azidopentyl)furan **1**. The RB (Rose Bengal) sensitized photooxygenation of **1** was carried out in MeOH at -78 °C using a 500 W halogen lamp while oxygen was bubbled through the solution. Upon reaction completion (TLC), the reaction mixture was treated with excess Me_2S and left to warm slowly to room temperature. After solvent removal, ^{1}H NMR spectroscopy revealed neither the starting material nor the expected α,β-unsaturated-1,4-dione **3**, the commonly encountered oxidation product in furan chemistry. Under the same conditions the photooxygenation of furan **4**, bearing an azide group at C-2, also did not yield α,β-unsaturated dione **6**. After these disappointing results using photooxygenation, we surveyed commonly used chemical oxidants such as *m*CPBA and NBS. The oxidation of compounds **1** and **4** did not provide any identifiable oxidation products or the returned starting material. In these oxidation attempts, the consumption of starting materials clearly indicated that the employed oxidation conditions were functioning but not in the desired manner. In this regard, the probable instability of the expected aldehydes **3**, **6** resulted in discouraging results.



Scheme 1. Reagents and conditions: (i) O_2, RB (0.4 mol%), 500 W lamp, MeOH, 0 °C, 0.5 h; (ii) Me_2S, CH_2Cl_2, rt, overnight; (iii) *m*CPBA, CH_2Cl_2, rt, 5 h or NBS, acetone-H_2O (10:1), $NaHCO_3$, -40 °C, 10 min.

To avoid formation of the aldehyde functional group, we then explored 2-methyl furan derivatives which would supposedly yield 1,4-diketones after oxidation. Initially, we examined the RB-sensitized photooxygenation of 2-(2-azidopentyl)methyl furan **7** (Scheme 2). The ^{1}H NMR spectrum of the crude mixture showed no sign of the expected unsaturated-1,4-dione, but a new structure which after purification provided **9** in 77% yield (Table 1, entry 1). After this intriguing result using photooxygenation, additional chemical oxidants and reaction conditions were screened for this new pyrrolidine ring formation method. Unfortunately, the oxidation of **7** using either NBS in MeCN or *m*CPBA in DCM at both 0 °C and rt were ineffective (Scheme 2).



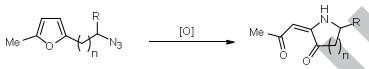
Scheme 2. Reagents and conditions: (i) (a) O_2, RB (0.4 mol%), 500 W lamp, MeOH, 0 °C, 2 h; (b) Me_2S, CH_2Cl_2, rt, 12 h, 77%.

The discovery of this novel method for obtaining the pyrrolidine ring system from simple azidoalkyl furan precursors motivated us to explore further substrates. Various reactions were performed by placing both the azide functional group as well as additional substituents at different positions of the alkyl chain. In order to test the role of steric effects around the azide during ring formation, the photooxygenation of furan **10** was carried out under the developed conditions to yield **11** as a single product in 66% yield (Entry 2). To improve the yield our focus turned to examining alternative oxidation conditions. Therefore, we first examined the efficiency of the *m*CPBA and NBS mediated oxidation of **10** using the same conditions as described above for **7**. Although the crude ^{1}H NMR spectrum from the NBS mediated oxidation did not show any product or starting material, pleasingly the *m*CPBA mediated oxidation gave **11** in 53% yield. The stereochemistry of the alkene geometry was confirmed by an NOE experiment. Irradiation of the olefinic proton at 5.60 ppm resulted in an enhancement of the NH signal at 9.69 ppm indicating that the geometry of the double bond was the (*E*)-configuration. In order to test the generality of this reaction and whether it could also be applied to form fused heterocycles, azidocyclopentyl furan **12** was oxidized using the established oxidation conditions. To our delight, compound **13** was obtained using RB (65%) and NBS (86%) while *m*CPBA gave no product (Entry 3).

We then turned our attention C-3 azidoalkyl furans. First, furan **14** was subjected to oxidation using either photooxygenation, *m*CPBA or NBS. Only the NBS conditions gave **15** in 60% yield while photooxygenation and *m*CPBA were unsuccessful (Entry 4). These findings clearly showed that the oxidants needed to be individually screened for each substrate. Having established a new method for the formation of a piperidine ring system with an unsubstituted alkyl chain, we further evaluated the reliability of this method with an additional substituent at C-3 or in its close proximity. For this purpose, compound **16** with an OBn group at C-2, was examined, giving product **17** in moderate yield using *m*CPBA (57%). Unfortunately, neither photooxidation nor NBS gave the desired piperidine

(Entry 5). However, oxidation of **18** was achieved with both *m*CPBA and NBS to give **19** in 52% yield. Unfortunately, the RB-sensitized photooxygenation did not form the desired piperidine derivative (Entry 6).

Following these results, an OBn group was installed at the C-1 position of compound **20**. This was envisioned to give an intermediate where the OBn group would be adjacent to the prochiral carbonyl group, paving the way to constructing contiguous stereocenters. Despite significant effort with chemical oxidants and screening reaction condition, neither of these led to formation of the piperidine ring system. On the other hand, both the RB-sensitized oxidation and TPP-sensitized photooxygenations of **20** furnished a triazole.[10b] Based on our proposed reaction mechanism, we then set out to eliminate triazole formation. Thiourea, as a peroxide cleavage reagent, was added at the beginning of the reaction in order to immediately cleave the peroxide bond upon formation. This tactic eliminated triazole formation, however, only trace amounts of the desired product **21** was observed in by ^{1}H NMR spectroscopy. Rapid separation of the crude material gave **21** in only 8% yield; we also found that this compound was unstable upon storage, even in a refrigerator.



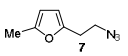
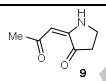
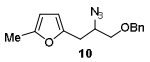
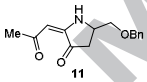
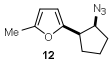
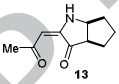
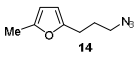
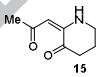
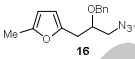
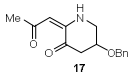
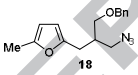
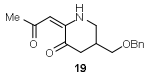
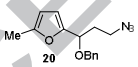
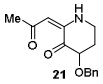
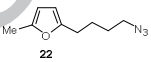
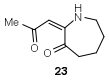
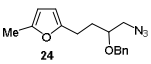
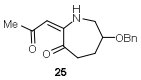
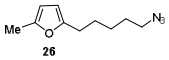
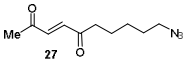
Entry	Substrate	Product	O_2, RB, hν[a]	*m*CPBA[b]	NBS[c]
1	 **7**	 **9**	77%	-	-
2	 **10**	 **11**	66%	53%	-
3	 **12**	 **13**	65%	-	86%
4	 **14**	 **15**	-	-	60%
5	 **16**	 **17**	-	57%	-
6	 **18**	 **19**	-	52%	52%
7	 **20**	 **21**	8%	-	-
8	 **22**	 **23**	60%	-	-
9	 **24**	 **25**	42%	50%	-
10	 **26**	 **27**	62%	-	-

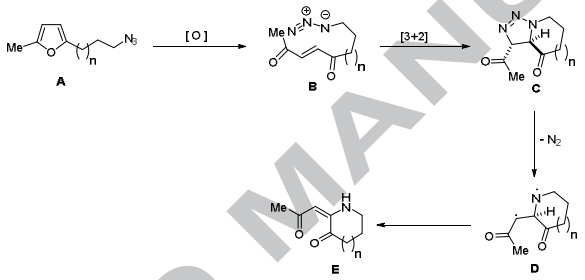
Table 1. Reagents and conditions: (a) O_2, RB (0.4 mol%), 500W lamp, MeOH, 0 °C; (ii) Me_2S, CH_2Cl_2, rt; (b) *m*CPBA, CH_2Cl_2, 0 °C; (c) NBS, acetone-H_2O (10:1), $NaHCO_3$, -40 °C.

Encouraged by the oxidation of C-2 and C-3 azidoalkyl furans, enabling access to the pyrrolidine and piperidine ring systems, respectively, we proceeded to examine whether this method could be applied to the

construction of homopiperidines. The RB-sensitized photooxygenation of **22** with an azide group at the C-4 position gave homopiperidine **23** in 60% yield. However, oxidation with either *m*CPBA or NBS did not yield the desired product (Entry 8). Furthermore, furan **24** bearing a functional group at C-3 was also screened to gain access to the multifunctionalised homopiperidine **25** (Entry 9).

To determine the scope of this new furan based heterocycle formation, the azide functional group was installed at the C-5 position in order to access eight membered heterocycles. Disappointingly, the oxidation of **26** did not yield the cyclized product and instead **27** was obtained as the oxidation product (Entry 10). To accomplish the cyclization, the crude material was treated with *p*-TSA, BF_3•OEt_2 and $Bi(NO_3)_3$ in DCM at rt. Unfortunately, not even trace amounts of the cyclization product were observed by crude ^{1}H NMR spectroscopy. This result clearly showed that C-4 is the last position where the azide can be placed for heterocycle formation.

Based on these results, a plausible reaction mechanism for ring formation was proposed (Scheme 3). The oxidation of furan first provides the unsaturated-1,4-dione **B** which undergoes 3+2 cycloaddition to yield the bicyclic intermediate **C.** Release of nitrogen from the five membered heterocyclic unit, results in intermediate **D** which rearranges to **E.**



Scheme 3. Plausible reaction mechanism for the formation of five-, six- and seven-membered heterocycles

Conclusion

In conclusion, the oxidation of azidoalkyl furans employing different oxidants and reaction conditions was explored to obtain structurally diverse compounds. Oxidation of azidoalkyl furans under either chemical or photochemical conditions did not provide valuable material for further elaboration or use as intermediates in the syntheses of more complex structures and was probably due to the instability of the aldehyde moiety in the oxidation product. Pleasingly, oxidation of the azidoalkyl 5-methyl furan derivatives proceeded efficiently, affording five-, six-, and seven-membered nitrogen containing heterocycles bearing prochiral centers and stereocenters in an operationally simple, single step reaction. Although the C-5 azidoalkyl 5-methyl furan derivative did provide the unsaturated-1,4-dione, it did not lead to the formation of an eight-membered ring.

Acknowledgements

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at htpp://

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Highlights

- The oxidation of azidoalkyl furans was achieved with singlet oxygen, *m*CPBA and NBS.
- Nitrogen heterocycles bearing a stereocenter and prochiral centers were obtained.
- The reaction proceeded *via* furan oxidation, cycloaddition, and nitrogen release.