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Photooxygenation of Azidoalkyl Furans: Catalyst-Free Triazole and New Endoperoxide Rearrangement

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ABSTRACT

Photooxygenation of azidoalkyl furans has revealed both a novel triazole formation method and a unique endoperoxide rearrangement. The key step of this method is a 3 + 2 cycloaddion of the azide to the endoperoxide intermediate. The reduction of the peroxide bond and two subsequent C−C bond cleavages provide a triazole having a newly formed carboxylic acid functionality. The reactions are clean and efficient with yields ranging from 60% to 90%.

Furan core units are widely distributed in natural products and biologically important compounds.[1] Furan subunits also appear as building blocks in the synthesis of natural products possessing biological activities.[2] Furan can be transformed either chemically[3] or by photooxygenation of singlet oxygen into α,β-unsaturated-1,4-dione moieties. Photochemical oxidation by singlet oxygen is mostly preferred since singlet oxygen has been known to be a nontoxic, higher yielding, and more functional group tolerant oxidant.[4] Due to their electron-rich nature, furans can function as dienes and undergo a 4 + 2 cycloaddition reaction with singlet oxygen to produce tricyclic compounds called endoperoxides. Endoperoxides are thermally unstable and rearrange to α,β-unsaturated-1,4-dicarbonyl compounds depending on the peroxide bond cleavage conditions[5] and the substituent on the furan.[6] The photooxidation of hydroxyalkylfuran derivatives has been studied frequently for two reasons: (1) to explore the effect of the hydroxyl group on the endoperoxide rearrangement mechanism, depending on its position on the alkyl chain and reaction conditions[5b,7] and (2) to synthesize stereoselectively natural and unnatural compounds having multistereocenters with the help of an already existing stereocenter where the hydroxyl group can be readily installed.[4b,8] The oxidation of 1-aminoalkyl furan has also been of great interest in the syntheses of highly diversified

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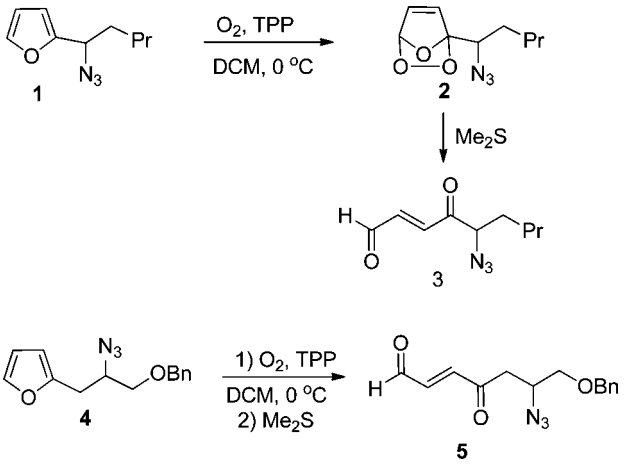
structures exhibiting a wide range of pharmaceutical activities.[9] In addition to the hydroxyl and amine functionality, the azide is also a very common functional group and serves as both an encoded amine[10] and triazole precursor. Triazoles have become targets in the fields of medicinal chemistry[11] and synthetic organic chemistry[12] after the revolutionary discovery of a new triazole synthesis.[13] The toxicity of the residual copper catalyst in biological studies makes the metal-free triazole protocols more attractive in drug discovery programs.[14] Despite all of these beneficial features of azides, the chemical or photooxidation of azides bearing alkyl furans is exceedingly rare.[15] The only account noted thus far was photooxidation of 2-(3-azidoalkyl) furan carried out in order to establish the substituted piperidine ring system.

Here, we report herein the discovery of both a new triazole formation method and endoperoxide rearrangement pathway with two concomitant C−C bond cleavages in the photooxydation of azidoalkyl furans. These transformations were discovered during our research program, which is primarily focused on the furan-based synthesis of diverse structural motifs. Syntheses of azidoalkyl furans were successively achieved by employing and tuning appropriate bond formation and functional group transformation methodologies. First, we studied the photooxygenation of 2-(1-azidopentyl)furan (**1**) at −78 °C (Scheme 1). A solution of **1** and a catalytic amount of TPP (*meso*-tetraphenylporphyrin) were dissolved in DCM, cooled to −78 °C, and then irradiated with a 500 W halogen lamp while oxygen was bubbled into the solution. Upon completion of the reaction (as monitored by TLC), excess Me_2S was added into the reaction mixture and then the resulting mixture was allowed to warm to rt to completely cleave the unstable peroxide bond. After the removal of solvent, ^{1}H NMR showed that the starting material (**1**) had been consumed and converted to the *E*/*Z* mixtures of aldehyde **3** which was found to be unstable at 0 °C. The crude product was sufficiently clean for structural assessment by ^{1}H and ^{13}C NMR. Interestingly, photooxygenation of the methylfuran analogue of **1** did not show any sign of the product or starting material. Next, the photooxygenation of **4**, with an azide at C-2 of the alkyl chain, was explored under the developed conditions (Scheme 1). The crude ^{1}H NMR showed only trace amounts of the oxidation product **5**. Unfortunately, we were unable to fully characterize **5** due to its instability at rt. The RB (Rose bengal)-sensitized oxygenations of **1** and **4** in MeOH were also performed. Sadly, these experiments did not provide **3** and **5** or any MeO group incorporated product which is generally observed under these conditions.[15] After these disappointing observations, we turned our attention to 3-azidoalkyl furan. First, **6** was exposed to the TPP-sensitized oxygenation (Scheme 2). ^{1}H and ^{13}C NMR from the isolated product showed new distinctive signals that appeared at 11.09 (br s), 7.72 (s), 7.65 (s) ppm and 174.5 ppm. Surprisingly, the characteristic aldehyde and α,β-unsaturated system signals of the expected oxidation product were not seen in ^{1}H and ^{13}C NMR. In addition, the expected total carbon signals were one carbon less than the number of carbons in the starting material. From these data, it was obvious that we had encountered a new structural motif in furan oxidation. After this intriguing

Scheme 1. Photooxygenation of 1-Azido- and 2-Azidoalkylfurans



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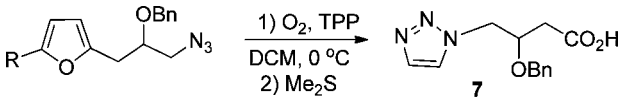
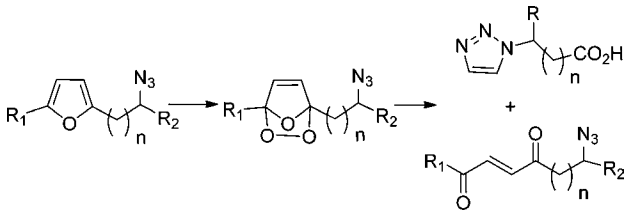
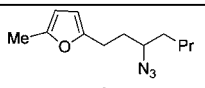
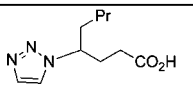
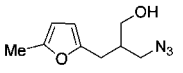
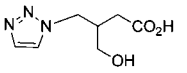
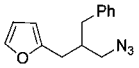
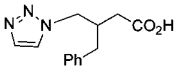
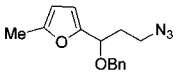
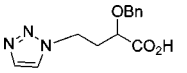
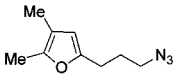
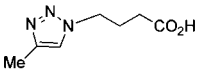
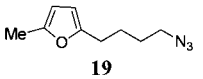
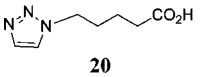
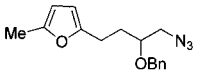
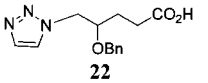
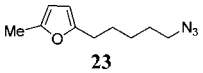
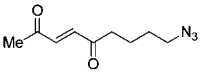
Scheme 2. Photooxygenation of 3-Azidoalkylfurans



result, the oxidation of **8**, the 5-Me derivative of **6**, was carried out at 0 °C (Scheme 2). The ^{1}H NMR from the crude material was completely identical to the oxidation product of **6**. In addition, both IR spectra from the oxidation reaction of **6** and **8** did not show an azide signal at 2200 cm^{-1}. From further spectral studies, the structures of the products obtained from the oxidation of both **6** and **8** were elucidated as triazole **7**. The effect of temperature on the yield and product distribution was examined by repeating the reactions at −78 °C and rt. These studies showed that temperature has almost no effect on the reaction yields. Moreover, no workup and chromatography are needed after the reaction; the simple tritutation of crude materials provided clean triazole **7**. Photooxygenation of **6** was also repeated in the RB-sensitized oxygenation conditions. However we did not observe **7** or any meaningful product similar to a tetracyclic material containing triazoline unit along with MeO group based on the crude ^{1}H NMR as seen in a similar subsrate by Fall and co-workers.[15] After this study, we preferred the TPP-sensitized oxidation in DCM for the rest of our substrates. These remarkable discoveries motivated us to explore further examples by interchanging the azide functionality throughout the alkyl chain and introducing additional substituents either to the carbon where the azide resides or to the other carbons of the alkyl chain. In order to test the impact of the steric effect around azide, an *n*-butyl group was installed to the C-3 center (Table 1, entry 1). Photooxygenation of **9** was carried out under the optimized conditions, and triazole **10** was obtained as the sole product in 87% yield (Table 1, entry 1). Provoked by this observation, **11** was prepared by placing the hydroxymethyl group to C-2 by leaving the azide at C-3. To our delight **11** also provided triazole **12** (Table 1, entry 2). Contrary to common observations, the hydroxyl group did not interfere with the endoperoxide even though it was in close proximity. Substrate **13** carrying a benzyl group at C-2 furthermore furnished triazole **14** in 90% yield (Table 1, entry 3) without being affected by steric hindrance. Fascinatingly, the photooxygenation of **15** also provided only triazole **16** in 80% yield under the established reaction conditions (Table 1, entry 4). Upon enlightening results from the above examples, we turned our attention to study the photooxygenation of the trisubstituted furan. For this purpose, 5-(3-azidopropyl)-2,3-dimethylfuran (**17**) was prepared and then exposed to the photooxygenation (Table 1, entry 5). The crude ^{1}H NMR showed solely triazole **18** in 89% yield. The methyl group at the double bond of endoperoxide showed no restriction in the endoperoxide rearrangement en route to triazole **18**. To determine the

Table 1. Photooxygenation Result of Azidoalkylfurans[a]



entry	substrate	product	yield[b]
1	 **9**	 **10**	87%
2	 **11**	 **12**	76%
3	 **13**	 **14**	90%
4	 **15**	 **16**	80%
5	 **17**	 **18**	89%
6	 **19**	 **20**	73%
7	 **21**	 **22**	60%
8	 **23**	 **24**	78%[c]

[a] Reaction conditions: Cat. TPP, O_2, 500 W halogen lamp, 25 min to 2 h, 0 °C. [b] Isolated yields. [c] The reaction was carried out at −78 °C for 2 h and then stirred at −55 °C for 2 d; then Me_2S was added, and the reaction was stirred at −55 °C for 2 d.

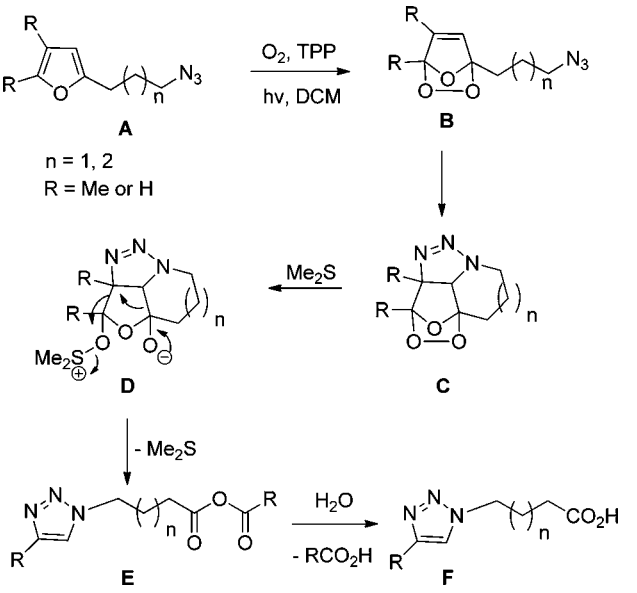
scope of this new reaction, the azide was first moved to C-4. Oxidation of **19** gave triazole **20** (Table 1, entry 6). Next, the steric crowding around the azide at C-4 was also increased by the introduction of a benzyl ether to C-3. Gratifyingly, the oxidation of **21** also furnished triazole **22** in a moderate yield (Table 1, entry 7). However, **23**, with a C-5-azido, did not furnish trace triazole when exposed to the oxidation, and **24** was the sole product (Table 1, entry 8). This could be attributed to the short lifespan of endoperoxides at 0 °C at which the peroxide bond can be cleaved thermally and rearranged to 1,4-diketone **24**. To overcome this obstacle, the new experiment was performed at −78 °C.

Upon consumption of the starting material as judged by TLC, the reaction was kept at −55 °C for 2 days to allow more time for the azide to convene with the endoperoxide. Disappointingly, not even a small amount of triazole was observed, and only the α,β-unsaturated-1,4-diketone **24** was again obtained. This experiment demonstrated that C-4 is the maximum chain length for the azide. After all of these instructive results, we proposed a plausible reaction mechanism for the triazole formation, using **A** as an example, which is illustrated in Scheme 3. The photooxidation of azidoalkyl furans first furnishes endoperoxide **B**. This is followed up by azide interacting with the double bond of endoperoxide **B** to undergo a 3 + 2 cycloaddition. Upon treatment with Me_2S, the O−O bond of **C** is reduced, and **D** rearranges into triazole **F** by two individual and consecutive C−C bond cleavages of the furan. Obtainment of the usual oxidation products, α,β-unsaturated-1,4-dione (**3, 5, 24**), rather than the corresponding triazoles, could be attributed to the difficulty of tetracyclic intermediate formation (**C**).

To summarize, we have discovered a new metal catalyst-free triazole synthesis and a unique endoperoxide rearrangement pathway with two unusual C−C bond cleavages from C-3 and C-4 azidoalkyl furans. Two new units, triazole and carboxylic acid, were formed simply in one single operation from azidoalkylfurans. However, C-1, C-2, and C-5 azido derivatives only gave unsaturated-1,4-diones probably due to geometric restriction in the tetracyclic ring formation. Triazole yields are moderate to high, and the crude reaction does not need tedious workup or chromatographic separations. The simple trituration is sufficient to obtain the pure product. Notably, enantiomerically pure triazole derivatives (e.g., entries 2 and 3) can also be achievable from the readily available epoxides (e.g., (*R*)-, and (*S*)-glycidols) by taking into account that the stereocenter is not affected. We believe that this methodology could find application in the syntheses of a new class of triazole derivatives containing multiple functional groups such as carboxylic acid, hydroxyl, and alkyl groups.

The new endoperoxide rearrangement pathway could also lead to the discovery of structurally diverse motifs from the furan based methodology. Further studies in the photooxidation of azide-containing alkyl furans to discover highly diverse product profiles are currently in progress, and the results will be reported in due course.

Scheme 3. Plausible Reaction Mechanism of Triazole Formation



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Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.