



Oxidation of aminoalkyl and hydroxylaminoalkyl furans



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ABSTRACT

The oxidation reactions of amino and hydroxylamino substituted alkylfurans were explored for the synthesis of structurally complex compounds from simple starting materials. A novel photooxygenation of the furan derivatives gave an α,β -unsaturated dicarbonyl moiety which underwent subsequent conjugate addition to yield diastereomeric mixtures of the corresponding pyrrolidine and isoxazoline heterocycles. Oxidation of the α,β -unsaturated dicarbonyl using *m*CPBA gave epoxide intermediates, which were opened by nucleophilic attack of the amino groups, furnishing pyrrolidine and isoxazolidine heterocycles.

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Introduction

Nitrogen containing saturated heterocycles are an important subclass of biologically active natural and synthetic products. Substituted pyrrolidines are found in many natural products and serve as building blocks for indolizidine and pyrrolizidine alkaloids.¹ Moreover, naturally occurring polyhydroxylated pyrrolidines and their synthetic derivatives have attracted much attention due to their biological activities.² Isoxazolidines, which can be considered as pyrrolidine derivatives where the carbon attached to the nitrogen atom has been replaced by an oxygen atom, are valuable intermediates in synthetic organic chemistry³ and are commonly used in drug discovery.⁴ Recently *O*-alkylhydroxylamines have been used in the straightforward stereoselective syntheses of various isoxazolidines.⁵

The oxidation of furan and its derivatives have been applied to the discovery of structurally diverse compounds and the syntheses of many biologically active compounds.⁶ Oxidation has been achieved by either standard chemical oxidation⁷ or photooxygenation using singlet oxygen.⁸ These two methods are selected according to the substrate utilized and the desired end product. 2-Alkyl furans containing hydroxyl or amine functional groups at different positions on the alkyl chain have been intensively explored to help understand the mechanism of oxidation and exploited in the synthesis of many natural and synthetic heterocycles.⁹

Although, the oxidation of aminoalkylfurans have been extensively reported in the literature,¹⁰ there is still unexplored

synthetic potential for forming complex multifunctional heterocyclic ring systems by manipulating the reaction conditions. In addition, despite the well known synthetic utility of *O*-alkylhydroxylamines, to the best of our knowledge, hydroxylamine substituted alkylfurans have not yet been evaluated in this reaction. Therefore, we have explored the oxidation of amine and hydroxylamine substituted alkyl furans leading to a straightforward method for the synthesis of pyrrolidine and isoxazolidine derivatives bearing consecutive stereocenters.

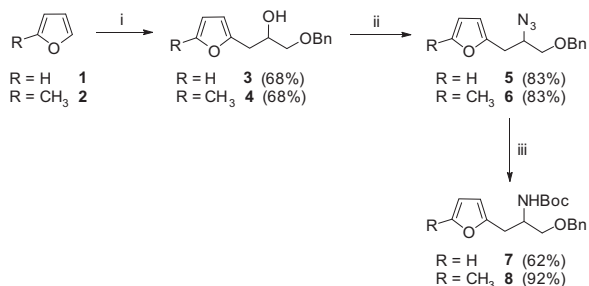
Results and discussion

The syntheses of starting materials (**3**, **4**) were achieved by epoxide ring opening of benzyl protected glycidol with furyllithiums (from **1**, **2**) at -78°C to give **3** and **4** in 68% yield. The alcohols (**3**, **4**) were converted to Boc protected amines (**7**, **8**) in good yields using a three step procedure including: azidation, reduction and protection (**Scheme 1**).

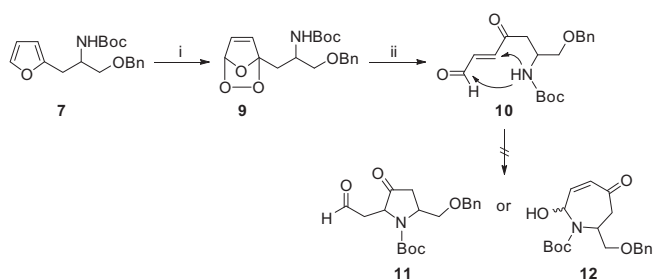
With compounds **7** and **8** in hand, we began by exploring oxidation conditions for the furan ring. Initially, a solution of **7** in CH_2Cl_2 was illuminated with a sun lamp in the presence of TPP (*meso*-tetraphenylporphyrin) at 0°C while passing O_2 gas through the solution. Upon consumption of **7** (TLC), the reaction was treated with excess Me_2S to furnish α,β -unsaturated-1,4-dicarbonyl **10** via cleavage of the peroxide bond of the ozonide-like intermediate **9**. Because the α,β -unsaturated unit of **10** could serve as a Michael acceptor for the intramolecular conjugate addition of the amine, the solution of **10** in CH_2Cl_2 was stirred at rt for one week. However, no cyclization took place, and only starting material was recovered (**Scheme 2**).

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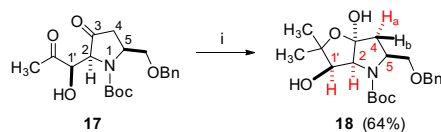


Scheme 1. Reagents and conditions: (i) (a) *n*-BuLi, THF, -78°C to -5°C , 2 h; (b) 2-((benzyloxy)methyl)oxirane in THF, -78°C to rt, 1 d, 68% (**3** and **4**); (ii) (a) MsCl, Et₃N, 0°C , 4 h; (b) NaN₃, DMF, 70°C , 24 h, 83% over two steps (**5** and **6**); (iii) (a) H₂, 10% Pd/C, EtOH, rt, 10 h; (b) (Boc)₂O, Et₃N, THF, 0°C to rt, 20 h, 62% over two steps (**7**), and 92% over two steps (**8**).

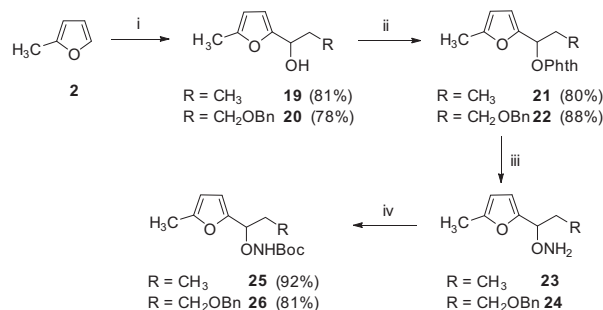


Scheme 2. Reagents and conditions: (i) O₂, (0.4 mol %) TPP, 500 W lamp, CH₂Cl₂, 0°C , 4 h; (ii) Me₂S, CH₂Cl₂, rt, 7 d.

Next, aldehyde **10** was treated with either catalytic *p*-TSA, TFA or NaH to effect cyclization (Scheme 2). However, ¹H NMR spectroscopy revealed only decomposed material with no evidence of

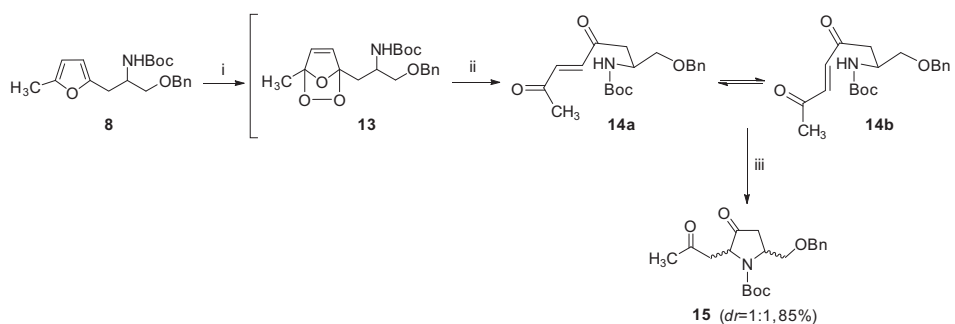


Scheme 5. Reagents and conditions: (i) MeMgBr, THF, -55°C , 11 h, 64%.

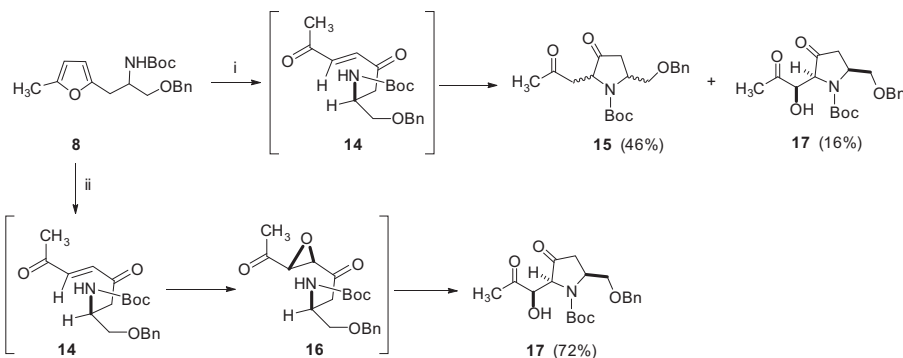


Scheme 6. Reagents and conditions: (i) (a) *n*-BuLi, THF, -78°C to -5°C , 2 h; (b) 3-(benzyloxy)propanal or propionaldehyde in THF, -78°C to rt, 15 h, 81% (**19**) and 78% (**20**); (ii) DEAD, *N*-hydroxyphthalimide, THF, 0°C , 19 h, 80% (**21**); 17 h, 88% (**22**); (iii) NH₂NH₂·xH₂O, CH₂Cl₂, 0°C ; (iv) (Boc)₂O, Et₃N, THF, 0°C , 92% over two steps (**25**) and 28 h, 81% over two steps (**26**).

the desired cyclization products. Because aldehyde **10** was unstable and did not undergo conjugate addition under the examined conditions, we turned our attention to furan **8** which upon oxidation would provide α,β -unsaturated ketone **14**, and was expected to be a better Michael acceptor. Pleasingly, the photooxygenation of **8** under RB (Rose Bengal)-sensitized conditions furnished **15** in 85% yield as a 1:1 diastereomeric mixture after treatment with *p*-TSA. Disappointingly, separation of the diastereomers was not



Scheme 3. Reagents and conditions: (i) O₂, (0.4 mol %) RB, 500 W lamp, MeOH, 0°C ; 2 h (ii) Me₂S, CH₂Cl₂, rt, 6 d; (iii) *p*-TSA, CH₂Cl₂, 2 d, 85% (*dr* = 1:1).



Scheme 4. Reagents and conditions: (i) *m*CPBA (1.2 equiv), CH₂Cl₂, 0°C , 2 d, 46% (**15**) and 16% (**17**); (ii) *m*CPBA (2.5 equiv), CH₂Cl₂, 0°C , 3 d, 72%.

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