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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.

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Isoxazolidines, which can be considered as pyrrolidine derivatives where the carbon attached to the nitrogen atom has been replaced by an oxygen atom, are valuable intermediates in synthetic organic chemistry[3] and are commonly used in drug discovery.[4] Recently *O*-alkylhydroxylamines have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 oxidation[7] 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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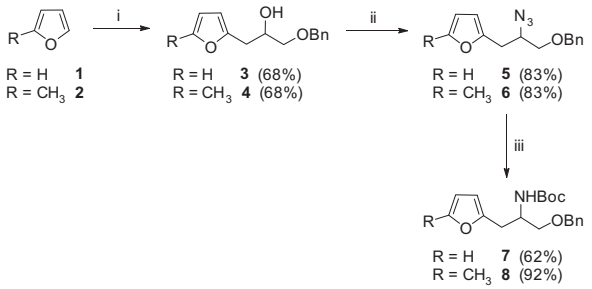
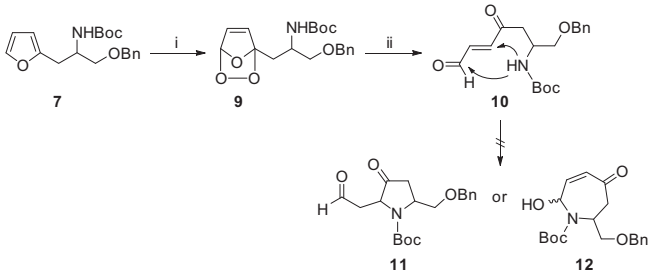
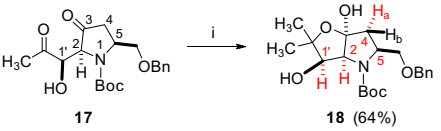


Scheme 1. Reagents and conditions: (i) (a) *n*-BuLi, THF, −78 °C to −5 °C, 2 h; (b) 2-((benzyloxy)methyl)oxirane in THF, −78 °C to rt, 1 d, 68% (**3** and **4**); (ii) (a) MsCl, Et_3N, 0 °C, 4 h; (b) NaN_3, DMF, 70 °C, 24 h, 83% over two steps (**5** and **6**); (iii) (a) H_2, 10% Pd/C, EtOH, rt, 10 h; (b) $(Boc)_2O$, Et_3N, THF, 0 °C to rt, 20 h, 62% over two steps (**7**), and 92% over two steps (**8**).

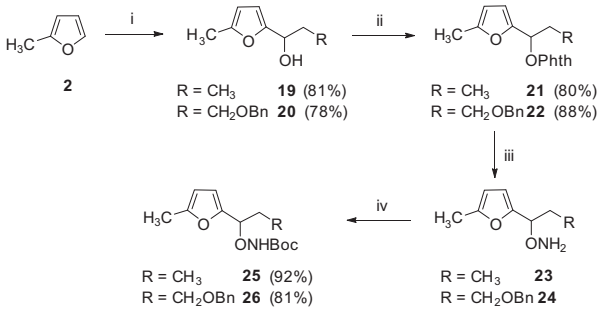


Scheme 2. Reagents and conditions: (i) O_2, (0.4 mol %) TPP, 500 W lamp, CH_2Cl_2, 0 °C, 4 h; (ii) Me_2S, CH_2Cl_2, rt, 7 d.

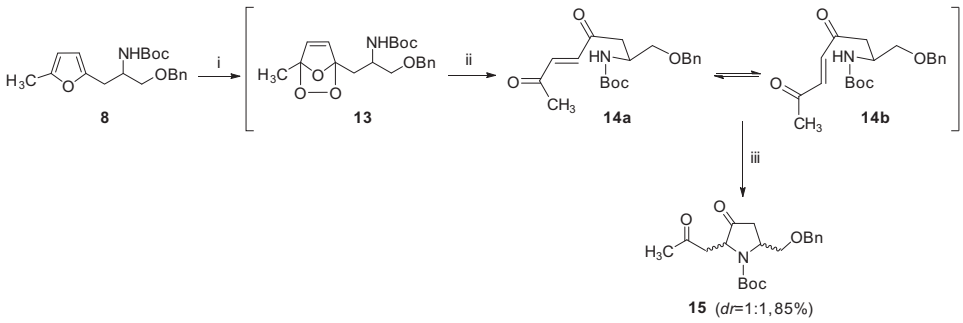
Next, aldehyde **10** was treated with either catalytic *p*-TSA, TFA or NaH to effect cyclization (Scheme 2). However, ^{1}H NMR spectroscopy revealed only decomposed material with no evidence of the desired cyclization products. Because aldehyde **10** was unstable and did not undergo conjugate addition 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



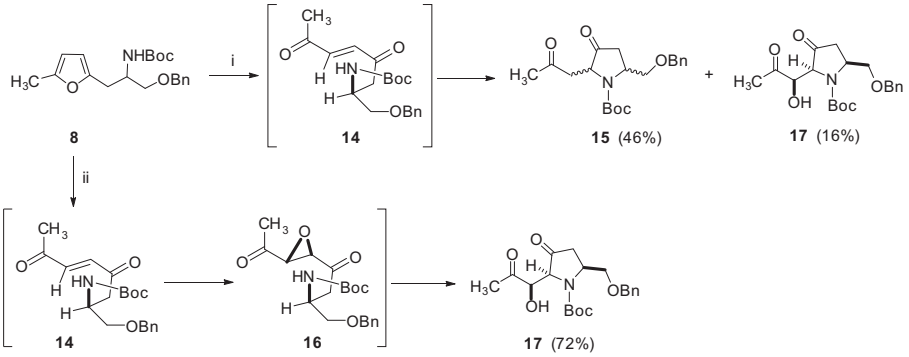
Scheme 5. Reagents and conditions: (i) MeMgBr, THF, −55 °C, 11 h, 64%.



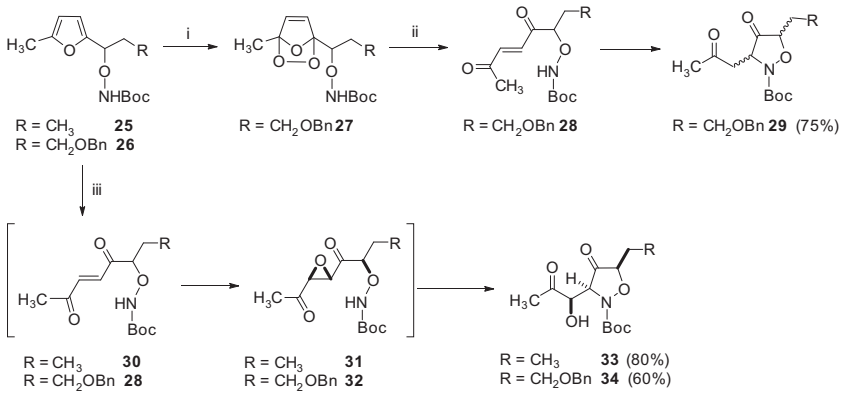
Scheme 6. Reagents and conditions: (i) (a) *n*-BuLi, THF, −78 °C to −5 °C, 2 h; (b) 3-(benzyloxy)propanal or propionaldehyde in THF, −78 °C to rt, 15 h, 81% (**19**) and 78% (**20**); (ii) DEAD, *N*-hydroxyphthalimide, THF, 0 °C, 19 h, 80% (**21**); 17 h, 88% (**22**); (iii) $NH_2NH_2.xH_2O$, CH_2Cl_2, 0 °C; (iv) $(Boc)_2O$, Et_3N, THF, 0 °C, 92% over two steps (**25**) and 28 h, 81% over two steps (**26**).



Scheme 3. Reagents and conditions: (i) O_2, (0.4 mol %) RB, 500 W lamp, MeOH, 0 °C; 2 h (ii) Me_2S, CH_2Cl_2, rt, 6 d; (iii) *p*-TSA, CH_2Cl_2, 2 d, 85% (*dr* = 1:1).



Scheme 4. Reagents and conditions: (i) *m*CPBA (1.2 equiv), CH_2Cl_2, 0 °C, 2 d, 46% (**15**) and 16% (**17**); (ii) *m*CPBA (2.5 equiv), CH_2Cl_2, 0 °C, 3 d, 72%.



Scheme 7. Reagents and conditions: (i) O_2, (0.4 mol %) RB, 500 W lamp, MeOH, 0 °C, 1 h; (ii) Me_2S, CH_2Cl_2, rt, 6 d, 75% (*dr* = 4:1); (iii) *m*CPBA (2.5 equiv), CH_2Cl_2, −40 °C, 8 h, then rt, 8 h, 80% (**33**) and −40 °C, 12 h then rt, 12 h, 60% (**34**).

successful using column or preparative thin layer chromatography (Scheme 3).

We envisioned that *m*CPBA mediated oxidation of furan **8** would only give the *E*-isomer of the intermediate alkene. The initially formed but less stable *Z*-alkene was assumed to isomerize in situ to give the *E*-isomer under our mildly acidic *m*CPBA oxidation conditions which would be followed by diastereoselective cyclization. A solution of **8** in CH_2Cl_2 was treated with *m*CPBA (1.2 equiv) at 0 °C for 2 d to give **15** in 46% yield as a diastereomeric mixture along with a new compound **17** in 16% yield. Structural elucidation of **17** was achieved using APT, HMBC and HMQC and NOE experiments. In Scheme 4, we show that **17** could also be obtained by epoxidation of unsaturated olefin **14**. Excited by this preliminary result, the reaction was optimized in order to increase the yield of **17** by altering the amount of *m*CPBA. Gratifyingly, 2.5 equiv of *m*CPBA at 0 °C in CH_2Cl_2 furnished pyrrolidine derivative **17** as a single diastereomer in 72% yield (Scheme 4). We presume that the diastereoselective epoxidation of **14** was caused by the directing ability of the amino group via hydrogen bonding with *m*CPBA.

The relative configuration of **17** could not be determined by 2D NMR spectroscopy techniques due to the fact that all the tertiary hydrogens (H-1′, H-2 and H-5) resonated in the same region (4.30–4.20 ppm). Therefore, compound **17** was transformed to a rigid compound that could be used to assign the relative configuration of the stereocenters. Treatment of **17** with 1 equiv of MeMgBr furnished hemiketal **18** as a single diastereomer (Scheme 5). NOE measurements of H-4a showed an enhancement of the peaks in compound **18**, which clearly supported the *syn* relation of H-4a with H-2.

After developing a successful method for the diastereoselective synthesis of polysubstituted pyrrolidine **17** via the oxidation of aminoalkylfuran **8**, we next explored the oxidation of furans bearing a hydroxylamine group on the alkyl chain. Starting materials (**19**, **20**) were prepared in excellent yields by the addition of 2-methylfuryl lithium to the corresponding aldehyde, followed by a Mitsunobu reaction using PPh_3, DEAD and *N*-hydroxyphthalimide. Subsequent treatments of the corresponding intermediates with hydrazine monohydrate provided *O*-alkylhydroxylamines (**23**, **24**) which were subjected to Boc protection (Scheme 6).

With **25** and **26** in hand, we began by exploring whether photooxygenation or *m*CPBA were the most suitable experimental conditions. Photooxygenation of **25** using either RB or TPP for 30 min at 0 °C, and subsequent treatment with excess Me_2S gave α,β-unsaturated-1,4-dicarbonyl **28**. The crude mixture was then stirred in CH_2Cl_2 for 6 d to afford **29** as an inseparable 4:1 mixture of diastereomers (Scheme 4). We then turned our attention to the oxidation of **25** and **26** using *m*CPBA. Pleasingly, after tuning the reaction conditions, the oxidation of **25** and **26** with *m*CPBA (2.5 equiv) in CH_2Cl_2 at −40 °C furnished isoxazolidines **33** in 80% and **34** in 60% yield as single diastereomers (Scheme 7).

Conclusions

The photooxygenation of amino and hydroxylamino substituted alkylfurans yielded diastereomeric mixtures of pyrrolidines and isoxazolidines, respectively. As opposed to the generally employed oxidation of furans with *m*CPBA leading to α,β-unsaturated-1,4-diones, we harnessed the further reaction with *m*CPBA to provide an epoxide intermediate which underwent nucleophilic opening with amino groups to diastereoselectively give polyfunctionalized pyrrolidine and isoxazolidine heterocycles. This work represents the first example in which furan based hydroxylamine derivatives have been used for the synthesis of structurally complex heterocycles. We believe that these discoveries will find application in the syntheses of polysubstituted pyrrolidine and isoxazolidine motifs. Further work on the oxidation of furan derivatives to provide access to other interesting structures will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.105.

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