

An Expedient Route to 3-Methoxy-2-furaldehyde

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Abstract: An expedient route to 3-methoxy-2-furaldehyde is presented.

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Furans are commonly used as substrates in Diels–Alder chemistry.¹ Despite the high reactivity of 3-alkoxyfurans as dienes in Diels–Alder reactions, they have appeared relatively infrequently in the literature, presumably due to the cumbersome synthetic routes used to prepare them. One advantage of using 3-alkoxyfurans in Diels–Alder reactions is that the vinyl alkyl ethers products can be further transformed into a number of different functionalities.

We have been exploiting an innovative synthetic platform that provides access to a broad range of previously inaccessible tetracycline analogues where 3-methoxy-2-furaldehyde is a component of a convergent synthesis of one of the key intermediates.² Many substituted furans are commercially available or easy to synthesize, but in this particular case a multistep route to 3-methoxy-2-furaldehyde had to be used due to lack of expedient routes. Previously published procedures for the manufacturing of the title compound are impractical and not amendable to the synthesis of the multi-kilogram quantities required.

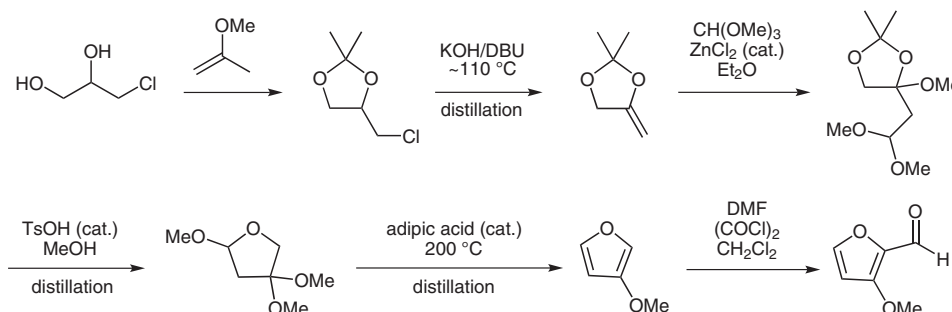
The initial attempts to develop a production route were based on chemistry previously reported (Scheme 1). 3-Methoxyfuran was prepared from commercially available cheap starting materials and reagents.³ Vilsmeier–Haack formylation of 3-methoxyfuran was reported by Myers et al. in their disclosure of a rapid synthesis of a key interme-

diate for tetracycline synthesis.^{2c} Unfortunately, several of the reported steps did not lend themselves to a robust scale up. Several distillations to dryness resulted in poor mixing, heat buildup and charred vessels. A sudden and strong exotherm occurred in step 2 when the neat mixture was heated under caustic condition to temperatures necessary to induce the reaction. Finally the instability of 3-methoxyfuran, presumably due to polymerization, as well as the low yield in the final Vilsmeier–Haack formylation prompted us to eventually abandon this route.

We believed that a significantly shorter and robust manufacturing route could be developed for manufacturing of multi hundred gram amounts of the title compound with the possibility of later targeting multi-kilogram manufacturing.

We investigated the use of 3-bromo-2-furaldehyde as substrate for the displacement of bromide with methoxide (Scheme 2). This substrate could either be manufactured using a lithiation–formylation approach from commercially available 3-bromofuran or be purchased as a commercial compound. We believed that the electron-withdrawing carbonyl functionality would facilitate the nucleophilic displacement of the bromide.

Regioselective lithiation of 3-halofurans has previously been described along with trapping of the resulting carbanion with various electrophiles.⁴ Using 3-bromofuran as substrate, we screened suitable bases for deprotonation of the 2-position and found that a strong base such as lithium diisopropylamide (LDA) was needed to get complete deprotonation with high regioselectivity. We next investigated the effect of solvents for the deprotonation–trapping sequence. While THF and 2-methyltetrahydrofuran (2-MeTHF) gave comparable results in terms of purity and



Scheme 1 Published route to 3-methoxy-2-furaldehyde

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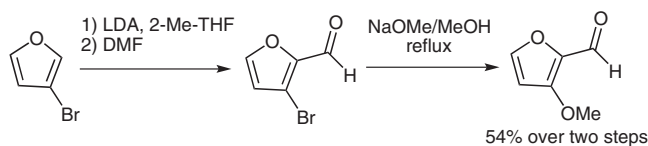
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yields, the use of methyl *tert*-butyl ether (MTBE) resulted in the formation of significant amounts of impurities as well as lower yields. As the 2-substituted furaldehyde was our final target compound, we used *N,N*-dimethylformamide (DMF) for the trapping of the anion but other electrophiles such as chlorocarbonates and CO₂ were also used successfully to form the corresponding furan derivatives.

The amount of LDA used in the lithiation step was important. Use of small excesses of LDA resulted in a side product tentatively assigned as a bis-formylated product. The lithiation–trapping sequence could be performed at temperatures as high as –20 °C without significantly affecting the yield. However, as darker colored impurities appeared at higher temperatures, we chose to perform this reaction at –40 °C to –50 °C. We also opted to use 2-MeTHF for this reaction as it led to faster phase separations during workup, less color in the isolated product and a higher isolated yield. After these improvements, we were able to routinely produce multi hundred gram batches of 3-bromo-2-furaldehyde in 85–95% yield.



Scheme 2 Improved route to 3-methoxy-2-furaldehyde

Having developed the first step and with sufficient material in our hands, we turned our attention to the displacement of the bromide using methoxide. Using NaOMe in MeOH resulted in the conversion of the starting material into the corresponding hemiacetal (indicated by HPLC–MS) and potentially also the acetal followed by progressive formation of the product. The displacement step occurred cleanly up to approximately 30% conversion at which point a number of unidentified side products began to form resulting in a modest 50% isolated yield of the desired product. Modifications of this protocol such as slow addition of the substrate, higher reaction temperature in sealed tube (105 °C) with a shorter reaction time, the use of various co-solvents (DMF, DMSO or DME) and water did not provide any improvement in conversion and/or yield. We next investigated the use of other methoxide sources [KOMe, LiOMe, NaOMe and Mg(OMe)₂] as well as the effect of additives such as CuI (0, 0.5, 1 and 2 equiv). We concluded that KOMe with 0.5 equivalent of CuI or LiOMe (with or without CuI) gave the best conversion to the desired product. As the addition of CuI complicated the workup we decided to further investigate the use of LiOMe without the addition of CuI. The reactions were cleaner when using a less concentrated solution of LiOMe (10, 20 or 40 volumes were investigated) while the use of drying agents such as Na₂SO₄ or molecular sieves did not appear to improve the reaction profile.

To minimize the side-reactions,⁵ we investigated slow addition of the substrate to a refluxing solution of LiOMe in MeOH. This resulted in a significant improvement with less than 15–20% impurities/starting material (LC–MS) using a five hour addition time. Despite these improvements, the isolated yield remained low (30–50%) prompting investigations into how the workup and isolation was performed.

During the aqueous workup of our methoxy-substitution, insoluble dark material complicated the phase separation between the two layers as well as purification via chromatography or reslurry/crystallization. This insoluble material, presumably from polymerization, was believed to partly form during the workup and/or isolation stage. The most convenient workup resulting in the best yields was found to be a direct filtration of the crude reaction mixture through silica gel followed by elution of the silica using isopropyl acetate. Concentration of the filtrate resulted in a residue that was submitted to a second filtration through silica gel to remove more polar polymeric materials. After concentration to dryness, the resultant mixture was reslurried using MTBE and hexane to afford the desired product in reasonable yield.

After this successful development we went back to investigate the use of readily available and affordable NaOMe instead of LiOMe. We found that the improvements described above did indeed allow for use of NaOMe instead of LiOMe without significantly changing the reaction profile. We also found that closely monitoring the reaction progress using HPLC was critical. If the reaction was allowed to continue after completion, an increase of impurities resulting in lower purity and yield was observed. As mentioned before, a more dilute reaction led to a cleaner reaction and in order to further improve the yield, we investigated the possibility of simultaneously adding both the starting material and NaOMe into a refluxing solution of MeOH. This did suppress the dimerization side reactions described above resulting in higher purity and improved yield. In order to avoid the first direct silica gel filtration, we developed a workup that employed an aqueous acetic acid neutralization of the basic reaction mixture followed by evaporation of most of the MeOH. Extraction of the resulting aqueous layer using dichloromethane resulted in good mass recovery after concentration. Attempts to reslurry this crude material directly were not successful due to the presence of insoluble polymeric materials, therefore a filtration through silica gel was used to remove these more polar materials.

In conclusion, a convenient two-step process to 3-methoxy-2-furaldehyde has been developed⁶ using commercially available 3-bromofuran as starting material resulting in an overall yield of 50–60%.

Acknowledgment

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- (5) Two of the major impurities were tentatively assigned using HPLC-MS and ¹H NMR as a dimer and trimer likely resulting from side reaction of the starting material with the product.
- (6) **General Experimental:** All reactions were performed under a nitrogen atmosphere. ¹H NMR spectra were recorded using an Oxford ASR400 spectrometer operating at 400 MHz at a probe temperature of 25 °C. Assays by HPLC-MS analyses were performed on an Agilent 1200 using a Zorbax C18 column and H₂O-MeCN mobile phases that included 0.1% formic acid. 3-Bromofuran was obtained from Penn Specialty Chemicals and was separated from aqueous materials included for stabilization before use. All commercially available starting materials, reagents and solvents were used as received.
Preparation of 3-Bromo-2-furaldehyde: To a 5-L, 4-neck round-bottomed flask was charged 2-methyltetrahydrofuran (1000 mL) followed by *i*-Pr₂NH (173 mL, 1.3 equiv). The mixture was cooled to T_i = -10 °C and *n*-BuLi (410 mL, 2.5 M in hexanes, 1.0 equiv) was charged into a 1-L addition funnel. The *n*-BuLi was added dropwise to the reactor over 15 min while keeping the batch temperature below -10 °C. The resulting pale yellow solution was cooled to -45 °C and kept for 10 min at that temperature. 3-Bromofuran (neat, liquid, 150 g) was charged while maintaining batch temperature below -40 °C. The dark brown suspension was stirred at -45 °C for 30 min and DMF (108 mL, 1.4 equiv) was added dropwise over 10 min via addition funnel while observing an exotherm. Temperature was maintained below -40 °C during addition. The reaction was completed after 10 min at -40 °C and the batch was quenched by the addition of 25%

citric acid solution (1500 mL, w/v). The layers were separated and the aqueous layer was extracted once with EtOAc (1000 mL). The combined organics were subsequently washed with H₂O (500 mL) and then with sat. aq NaCl (500 mL). The organic layer was concentrated under reduced pressure at 30 °C to give a dark brown oil (178 g) along with some visible solids. The residue was diluted with MTBE (100 mL) and filtered through a medium fritted funnel. An additional portion of MTBE (100 mL) was used to wash the filter. The filtrate was concentrated to give 3-bromo-2-furaldehyde (164 g, 92%) as a dark brown oil. Analytical data were in accordance with those of a commercial sample.

Preparation of 3-Methoxy-2-furaldehyde: To a 50-L reactor equipped with an overhead stirrer, nitrogen inlet and reflux condenser was added anhyd MeOH (20 L) followed by NaOMe (25 mL, 25 w/w% solution in MeOH) to assure a basic media at start of addition. The solution was heated to T_i = 64 °C. 3-Bromo-2-furaldehyde (1034 g) was charged to a 1-L addition funnel and NaOMe (5 L, 25 w/w% in MeOH, 3.7 equiv) was charged into a second funnel. The NaOMe and 3-bromofurfural in the respective addition funnels were simultaneously added dropwise over 5 h, and the mixture was subsequently stirred at 64 °C for 13 h. After the reaction was complete, the mixture was cooled to 20 °C and stirred at that temperature for 3 h. The temperature was lowered further to -30 °C and 12% aq AcOH (10 L) was added resulting in a rise of the temperature to about 5 °C. Most of the MeOH (about 23 L) was removed at reduced pressure at 35 °C and the remaining mixture (about 12 L) was extracted with CH₂Cl₂ (2 × 10 L). The combined organics were washed with half-saturated aq NaHCO₃ (10 L). The organics were concentrated at reduced pressure at 25 °C to give a black crystalline material. Reslurry in MTBE (4 L) and hexane (4 L) gave about 250 g of product as filterable solids. Additional material (260 g of black amorphous material which was stuck to the flask) along with 120 g from evaporation of the mother liquors was combined, dissolved in CH₂Cl₂ (1.5 L) and passed through silica gel (500 mL) which was further eluted with 1.5 L CH₂Cl₂. The CH₂Cl₂ was evaporated and the resulting solids were combined with the first solids (250 g) followed by suspending the solids in MTBE (3 L). Hexanes (3 L) were then added over 5 h at r.t. After stirring for an additional 17 h the slurry was cooled to 0 °C. The solids were collected by filtration and provided after drying 3-MeO-2-furaldehyde (440 g, 59%) as a brown solid. Analytical data were in accordance with those described in the literature.^{2c}

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