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COMMUNICATION

Synthesis of ranitidine (Zantac) from cellulose-derived 5-(chloromethyl)furfural†

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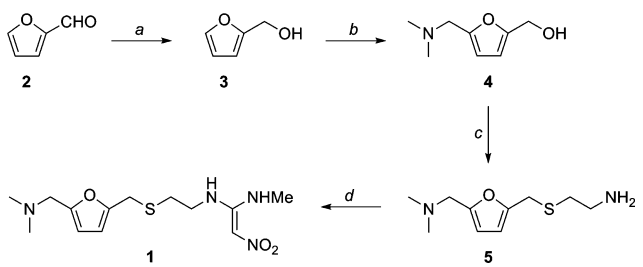
The biomass-derived platform chemical 5-(chloromethyl)furfural is converted into the blockbuster antiulcer drug ranitidine (Zantac) in four steps with an overall 68% isolated yield.

Ranitidine **1**, sold under the trade name Zantac, is a histamine H_2-receptor antagonist which is used in the management of gastroesophageal reflux disease (GERD) and the treatment of gastric and duodenal ulcers. It was introduced by Glaxo (now GlaxoSmithKline) in 1981 and by 1986 had total sales in excess of $1 billion, the first-ever drug to achieve this milestone.[1] Although Zantac has been largely surplanted as a prescription drug by modern proton pump inhibitors such as omeprazole (Prilosec) and esomeprazole (Nexium), it has recently been reformulated for over-the-counter sales as a general antacid preparation.

The synthesis of ranitidine **1** has been described for the most part in the patent literature, and has been the subject of multiple reviews.[2–5] Given the commercial interest in this molecule, all of the synthetically reasonable disconnections have been probed in one way or another, but perhaps the most straightforward approach up to now remains that which was described in the original patent (Scheme 1).[6] This route starts from furfuryl alcohol **3**, which can be sourced from the reduction of furfural **2**. The furan ring in **3** is aminomethylated to **4**, which reacts with cysteamine in concentrated aq. HCl to give **5**. The patent literature puts the yields of both of these steps at <50%,[7] although more recent studies report conversions of 82%[8] and 75%[9] for **4** and **5**, respectively. Condensation of **5** with 1-methylthio-1-methylamino-2-nitroethylene **7** then provides **1**, with yields of up to 90% having been reported for this reaction.[10]

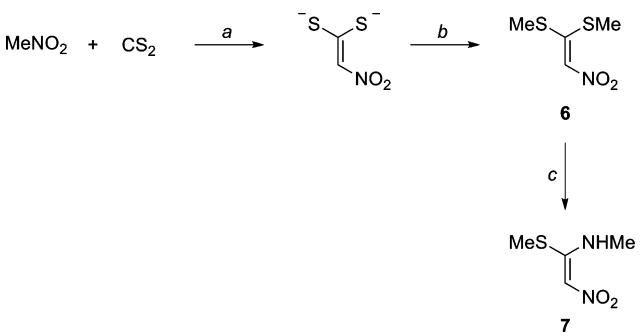


Scheme 1 Reagents *a*. H_2, cat.; *b*. CH_2O, Me_2NH, H^+ cat.; *c*. $HSCH_2CH_2NH_2$, aq. HCl; *d*. **7**.

In a reversal of roles in **4**, the dimethylamino group can be quaternized and serve as the leaving group for the introduction of cysteamine,[11] but this necessitates the re-introduction of the dimethylaminomethyl function from the hydroxymethyl group, which lengthens the synthesis.

Other approaches to **1** have been developed which avoid the use of cysteamine altogether, in which the OH group of either **3** or **4** is converted to SH and then aminoethylated using aziridine, 2-chloroethylamine, chloroacetonitrile, or *N*-(2-chloroethyl) phthalimide.[3]

A key intermediate in the synthesis of **1** is 1-methylthio-1-methylamino-2-nitroethylene **7**. This can be prepared by addition of the nitromethane anion to CS_2 and methylation to give 1,1-bis(methylthio)-2-nitroethylene **6**, followed by substitution of one of the MeS groups with methylamine (Scheme 2). The terminal aminonitroethylene fragment of **1** can also be introduced in two steps by direct condensation of **5** with **6**, or various analogues thereof, followed by treatment with methylamine. Yet another alternative is the reaction of **5** with either methyl isocyanate or methyl isothiocyanate and subsequent replacement of the chalcogen by nitromethane.[3,12]



Scheme 2 Reagents: *a*. KOH; *b*. MeI; *c*. $MeNH_2$.

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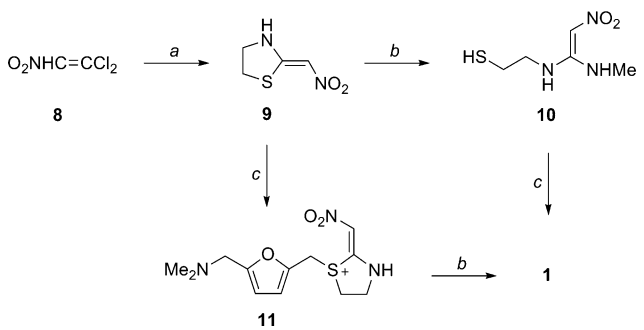
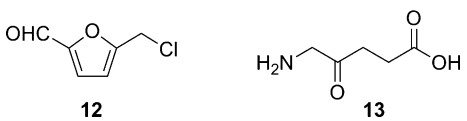
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra and experimental details for the preparation of compounds **14, 15, 5**, and **1**. See DOI: 10.1039/c1gc15537g

Finally, the right hand side of the molecule can be built up first and linked to **4** or a derivative thereof in which the OH has been converted into a leaving group (halide, sulfonate ester) as shown in Scheme 3.



Scheme 3 Reagents: *a*. $HSCH_2CH_2NH_2$; *b*. $MeNH_2$; *c*. **4** or derivative.

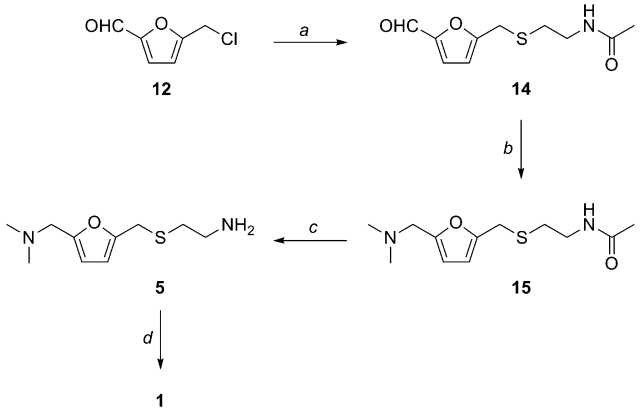
We have recently shown that 5-(chloromethyl)furfural (CMF) **12** can be derived in a single step from either sugars, cellulose, or raw cellulosic biomass in isolated yields between 80–90%,[13] and are now in the course of developing new applications and markets for this renewable platform chemical. For example, the natural pesticide δ-aminolevulinic acid **13** has been derived from **12** in three steps with an overall yield of 68%.[14]



Looking at the structures of CMF **12** and ranitidine **1**, a functional correspondence can clearly be seen, wherein the (dimethylamino)methyl group could be envisaged to be introduced by reductive amination of the C=O group, and the sulfide bond formed by taking advantage of the reactive chloromethyl functionality.

Our approach to **1** is presented in Scheme 4. Here, the key thioethylamino fragment is introduced in excellent yield by reaction of **12** with commercial *N*-acetylcysteamine. Early attempts to substitute **12** with cysteamine itself or directly with fragment **10** were found to proceed in low yields. Treatment of **14** with Me_2NH and $NaBH_4$ then gives amine **15**,[15] and hydrolysis of the acetyl group provides **5**. Our synthesis then merges with the literature at the reaction of **5** with reagent **7**,[10] which in our hands proceeded to give **1** in 90% yield.[16]

The strength of the approach described in Scheme 4, apart from the use of a renewable starting material, is that all the reaction yields are high (average 91%), culminating in an overall 68% yield of **1**. If this result is superimposed on previously reported yields of **12** from biomass sources,[13] the outcome would be 61, 57, and 54% isolated chemical yields of ranitidine **1** from sucrose, cellulose, and corn stover, respectively. From a green chemistry perspective, it is also noteworthy that no chromatography is required at any step in the synthesis. In terms of formal green metrics, we calculate an atom economy,[17] including all stoichiometric reagents (organic and inorganic), of 56.3% (see ESI†), which is good for a multistep process. We suggest that this efficient, renewable approach to the synthesis of ranitidine **1** will not only provide facile, economic access to this familiar drug, but also stimulate further development



Scheme 4 Reagents: *a*. $HSCH_2CH_2NHAc$, NaH, THF, 91%; *b*. Me_2NH, $NaBH_4$, MeOH, 90%; *c*. 2 M KOH, reflux, 94%; *d*. **7**, H_2O, 55 °C, 88%.

of CMF **12** as a biomass-derived platform chemical for the green synthesis of pharmaceuticals and other value-added products.

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