

A Short, Gram-Scale Synthesis of 2,5-Disubstituted Furans

Stanley Chang,^[a] Saheena Desai,^[a] Daniel B. Leznoff,^[a] Nabyl Merbouh,^{*[a]} and Robert Britton^{*[a]}

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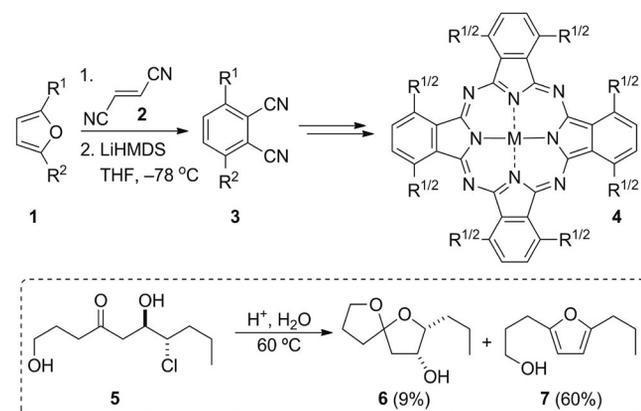
A modified Feist–Bénary furan synthesis has been developed that involves a lithium aldol reaction between a methyl ketone and an α -chloroaldehyde followed by a thermally induced tetrahydrofuran formation/dehydration sequence and affords 2,5-disubstituted furans in good overall yield. This

process is demonstrated on multigram scale and is amenable to the production of symmetric or asymmetric furans that incorporate a range of substituents (e.g., aryl, *tert*-butyl, ferrocenyl).

Introduction

Substituted furans are important structural components of many natural products,^[1,2] pharmaceuticals,^[1,2] and organic materials.^[3] As such, the development of new methods for furan synthesis has been the subject of a large body of research.^[1] Previous work by Cook^[4a] has also demonstrated that 2,5-disubstituted furans can serve as precursors to phthalocyanines (e.g., **4**; Scheme 1) through a sequence of reactions that involves a [4+2] cycloaddition followed by base-promoted dehydration to provide phthalonitriles (e.g., **3**), which are well-known precursors of phthalocyanines.^[4] On the basis of the use of phthalocyanines as ligands,^[5] we recently became interested in systematically investigating the relationship between peripheral substitution on the phthalocyanine core and the physical and chemical properties of their early transition-metal complexes.^[6] Bearing this in mind, we sought a straightforward synthetic approach to symmetrical and unsymmetrical 2,5-disubstituted furans that also permits the incorporation of aryl-, secondary alkyl-, or tertiary alkyl groups in the 2- and 5-positions on the furan ring. Although numerous strategies have been reported for the synthesis of 2,5-disubstituted furans,^[7,8] during our investigations of the β -keto-chlorohydrin to spirocyclic acetal transformation (e.g., **5** \rightarrow **6**; Scheme 1),^[9] we observed that heating the former substances in water effected their efficient conversion into 2,5-disubstituted furans (e.g., **7**).^[10] Considering that β -keto-chlorohydrins (e.g., **5**) are readily available through a high-yielding lithium aldol reaction between a methyl ketone and an α -chloroaldehyde,^[11]

this variant of the Feist–Bénary furan synthesis^[12] should permit the rapid production of a wide range of differentially functionalized furans. The development of this process as well as its use in the preparation of several 2,5-disubstituted furans on multigram scale is detailed below.



Scheme 1. Synthesis of phthalocyanines from furans and a modified Feist–Bénary furan synthesis.

Results and Discussion

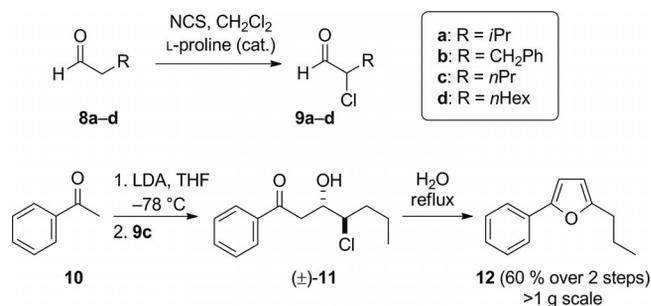
Building on our previous efforts in the synthesis of tetrahydrofurans^[13] and pyrrolidines^[14] from β -keto-chlorohydrins, we initiated these investigations with the organocatalytic preparation of several racemic α -chloroaldehydes **9a–d** following the procedure reported by Jørgensen.^[15] As it is often difficult to separate α -chloroaldehydes from small amounts of unreacted starting aldehyde and/or the corresponding dichloroaldehyde, only minimal purification (short-path distillation) of chloroaldehydes **9a–d** was performed. As depicted in Scheme 2, coupling of the lithium enolate derived from acetophenone (**10**) with a slight excess

[a] Department of Chemistry, Simon Fraser University, Burnaby, British Columbia, V5A 1S6, Canada
Fax: +1-778-782-3765
E-mail: nmerbouh@sfu.ca
rbritton@sfu.ca

Homepage: <http://chemistry.sfu.ca>

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amount (1.2 equiv.) of semipurified α -chloropentanal afforded β -keto-chlorohydrin **11** in excellent yield as the *anti* diastereomer (96%, *dr* > 20:1).^[13] With chlorohydrin **11** in hand, we were delighted to find that simply heating this material in water with a catalytic amount of acid (pyridinium *para*-toluenesulfonate, PPTS) resulted in smooth conversion into desired furan **12**. Notably, furan formation from crude β -keto-chlorohydrin **11** also proceeded readily in boiling water or methanol, whereas heating of **11** in polar aprotic solvents (e.g., EtOAc) failed to provide any furan **12**. As highlighted in Scheme 2, this three-step process could be carried out on gram scale without rigorous purification of intermediates **9c** and **11** to afford 2-phenyl-5-propylfuran (**12**) in good overall yield (60%).



Scheme 2. Synthesis of α -chloroaldehydes and 2,5-disubstituted furan **12** (NCS = *N*-chlorosuccinimide, LDA = lithium diisopropylamide)

Having established a short and high-yielding synthesis of 2,5-disubstituted furan **12**, we investigated the scope of this three-step process. As summarized in Table 1, the chlorination/lithium aldol/cyclization–dehydration sequence afforded a variety of 2,5-disubstituted furans in good to excellent overall yield on gram scale. This concise furan synthesis is also amenable to bulky substituents on both the methyl ketone and the aldehyde coupling partners (Table 1, entries 1, 3–5). As a general exception, and as indicated in entries 6–9, the preparation of *n*-hexyl-substituted furans proceeded with slightly lower overall yield. These lower yields can be attributed to competing reaction of the α -chloroaldehydes with the thermodynamic lithium enolate produced competitively during the reaction of 2-octanone with LDA, which translates into the production of small amounts (approximately 10%) of the corresponding 3-methyl-2-pentyl-substituted furans (not shown) after cyclization/dehydration. For example, heating of the crude aldol adduct derived from 2-octanone and 2-chlorooctanal (**9d**) in water (Table 1, entry 9) afforded 2,5-dihexylfuran **24** in moderate yield (40%) along with 5-hexyl-3-methyl-2-pentylfuran (8%). Finally, this process was demonstrated in the multigram-scale preparation of ferrocenylfuran **25** from acetylferrocene (**15**) and chloroaldehyde **9c** (Table 1, entry 10). The good overall yields observed for this modified Feist–Bénary furan synthesis, combined with its scalability, independence from transition metals, and the ready access to both the methyl ketone and the aldehyde starting materials, should bode well for its adoption as a general process to prepare 2,5-disubstituted furans.

Table 1. Synthesis of 2,5-disubstituted furans.

Entry	Methyl ketone	Aldehyde	Furan	% Yield ^[a] (scale)
1	10	8a	16	55 (1 g)
2	10	8b	17	60 (0.5 g)
3	13	8c	18	55 (1 g)
4	13	8a	19	50 (1 g)
5	13	8b	20	55 (0.5 g)
6	14	8c	21	45 (1.8 g) ^[b]
7	14	8a	22	42 (1 g) ^[b]
8	14	8b	23	40 (0.5 g) ^[b]
9	14	8d	24	40 (2.6 g) ^[b]
10	15	8c	25	60 (3 g)

[a] Isolated yield of furan over two steps from methyl ketone. [b] Product accompanied by the formation of isomeric furan (see text).

Conclusions

In summary, we have developed a concise method for preparing a variety of 2,5-disubstituted furans in three steps from commercially available ketones and aldehydes on scales of up to 3 g. This process tolerates the incorporation of both bulky aliphatic (e.g., *tert*-butyl) and aryl (e.g., phenyl, ferrocenyl) substituents. Resulting 2,5-disubstituted furans **16–25** should prove useful for the preparation of a range of phthalocyanines, work that is currently ongoing in our laboratories.

Experimental Section

Synthesis of α -Chloroaldehydes 9a–d: In a round-bottomed flask (500 mL), a solution of the aldehyde [0.35 M] in CH_2Cl_2 (200 mL) was cooled to 0 °C by using an ice bath. NCS (1.05 equiv.) was then added with vigorous stirring, followed by L-proline (0.1 equiv.), and the reaction mixture was warmed gradually to room temperature. The progress of the reaction was monitored by ^1H NMR spectroscopy. After completion of the reaction (4–8 h), the crude mixture was cooled to –78 °C, pentane (200 mL) was added, and the resulting precipitate was removed by filtration. The filtrate was concentrated by using a rotary evaporator connected to a water aspirator. This precipitation/concentration operation was repeated, and the resulting oil was distilled under vacuum to yield the desired α -chloroaldehyde. The semipurified α -chloroaldehydes could be stored at –15 °C as solutions in THF for up to 2 weeks without noticeable degradation. The spectroscopic data derived from each α -chloroaldehyde was in accord with that reported previously.

Synthesis of β -Ketochlorohydrins: To a cold (0 °C), stirred solution of diisopropylamine (1.2 equiv.) in THF (0.5 M) was added *n*-butyllithium dropwise (2.5 M in hexanes, 1.1 equiv.), and the mixture was stirred for 15 min. The resulting mixture was cooled to –78 °C, and a solution of the ketone (1.0 equiv.) in THF (1.0 M) was added dropwise at a rate of 0.1 mL per minute. After stirring for 30 min, the α -chloroaldehyde (1.2 equiv.) was added as a solution (1.0 M) in THF at –78 °C, and the reaction mixture was stirred for an additional 30 min. The mixture was then treated with saturated aqueous NH_4Cl , diluted with ethyl acetate and water, and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 \times), and the combined organic phase was washed with brine (10 mL), dried with MgSO_4 , and concentrated to provide a crude oil, which was used without further purification.

Preparation of Furans: The crude β -ketochlorohydrin was suspended in water (50 mL) and heated at reflux for 12 h. The reaction mixture was then cooled to room temperature and extracted with CH_2Cl_2 (3 \times). The combined organic layer was washed with brine, dried (MgSO_4), and concentrated. The crude furan was purified by flash column chromatography (cyclohexane).

Supporting Information (see footnote on the first page of this article): General experimental details, characterization data, and copies of the ^1H NMR and ^{13}C NMR spectra for all final products.

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