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A continuous-flow synthesis of annulated and polysubstituted furans from the reaction of ketones and α -haloketones

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ABSTRACT

A synthesis of di-, tri- and tetra-substituted furans from reaction of the corresponding ketones and α -haloketones with LiHMDS is reported. Reaction under continuous-flow conditions gave increased yields and removed the need for external cooling when compared to the unoptimised batch conditions. Crown Copyright © 2011 Published by Elsevier Ltd. All rights reserved.

The synthesis of substituted furans is an area of continuing interest in organic chemistry due to the presence of the furan nucleus in a wide variety of natural products, drugs and other materials of industrial and academic relevance.¹⁻³

The performance of chemical transformations under continuous-flow conditions (either on meso- or microscale) is an area of intense current research. This interest can be explained, at least in part, by a number of potential advantages that continuous-flow processes have over traditional batch chemistry including the ease of scaling, high reproducibility, rapid heat transfer and mixing and inherently higher safety due to small reactor volumes and the containment of hazardous intermediates.⁴

During the course of our research into the synthesis and application of photochromic dyes,⁵ we had reason to prepare a number of polysubstituted furan compounds. For this purpose we investigated the reaction between ketones **1** and α -haloketones **2** in the presence of lithium bis(trimethylsilyl)amide (LiHMDS) with the object of isolating not the perhaps expected 1,4-diketone compound **3**, or the corresponding furan **4**, but furan product **5** (Scheme 1). Such a route would give furans with complementary functionality to that seen using the standard 1,4-diketone method.

The formation of **5** can be thought of as occurring through an initial addition of the enolate **6** derived from ketone **1** with α -haloketone **2** to give alkoxy adduct **7**. This can then cyclise with the loss of lithium bromide to the corresponding epoxide **8** which is ring-opened by an intramolecular reaction with the carbonyl oxygen to furnish dihydrofuran **9**. This can then aromatise with

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the loss of water to give furan **5** (Scheme 2). A similar reaction sequence has been previously reported by Migita and co-workers,⁶ but this required the use of extended reaction times at elevated temperatures and preformed tributyltin enolates, necessitating the addition of a further reaction step and also the handling and potentially problematic removal of toxic tin compounds.⁷ An electrochemical method for the synthesis of 4-aryl-2-methyl furans,⁸ a zinc-mediated method allowing the preparation of 2,4 symmetrically substituted furan compounds,⁹ and a homo-coupling of phenacyl bromides in the presence of sodium telluride,¹⁰ have also been reported to proceed via a similar mechanism.

The results of the initial trial experiments on the reaction between phenacyl bromide and either α -tetralone or acetone can be seen in Table 1. When phenacyl bromide reacted with α -tetralone at -78 °C the corresponding furan was isolated in 65% yield. This was reduced to 46% when the cooling was removed (Table 1, entries 1 and 2). Similarly, the product derived from reaction with acetone could also be isolated, albeit in very low yields for both the cooled and room temperature reactions (Table 1, entries 3 and 4). No attempt to further optimise the batch reactions was made.

In an attempt to increase the yields seen with the batch reactions and avoid the need for external cooling, the process was attempted under continuous-flow conditions using a commercially available flow reactor (Vapourtec). In this way a 2 M solution of ketone in toluene (from a vessel containing a stock solution) and a commercially available 1 M solution of LiHMDS in THF were combined at ambient temperature and the resulting reagent stream passed through a 10 mL flow coil to enable complete formation







Scheme 1. Synthetic route to polysubstituted furan compounds.



Scheme 2. Proposed mechanism of formation for polysubstituted furan compounds.





^a A solution of ketone (0.81 g, 5.53 mmol) in toluene (15 mL) was treated dropwise with a solution of LiHMDS (1 M in THF, 5.53 mL, 5.53 mmol) and stirred for 15 min. Phenacyl bromide (1.00 g, 5.02 mmol) in THF (20 mL) was then added dropwise and stirring continued for 30 min. The mixture was quenched by the addition of H₂O (30 mL), the organic phase separated, dried (MgSO₄) and evaporated in vacuo, the residue being purified by column chromatography eluting with 0–5% v/v EtOAc/petroleum ether. ^b Reaction performed at -78 °C.

^c Reaction performed at 22 °C.

 $\begin{bmatrix} 0 \\ R^{1} \downarrow R^{2} \\ 2 \text{ M in toluene} \\ 0.76 \text{ mL min}^{-1} \\ \end{bmatrix} \underbrace{ \begin{array}{c} \text{LiHMDS} \\ 1 \text{ M in THF} \\ 1.54 \text{ mL min}^{-1} \\ \end{bmatrix} \underbrace{ \begin{array}{c} 10 \text{ mL} \\ 22 \text{ °C} \\ R^{3} \\ 1.4 \text{ M in THF} \\ 1 \text{ mL min}^{-1} \\ \end{bmatrix} \underbrace{ \begin{array}{c} 0 \\ 10 \text{ mL} \\ 22 \text{ °C} \\ R^{3} \\ 1.4 \text{ M in THF} \\ 1 \text{ mL min}^{-1} \\ \end{bmatrix} \underbrace{ \begin{array}{c} 0 \\ 10 \text{ mL} \\ 22 \text{ °C} \\ R^{3} \\ 1.4 \text{ M in THF} \\ 1 \text{ mL min}^{-1} \\ \end{array} }$

Scheme 3. Experimental set-up for the flow synthesis of furans.

of the desired enolate. The material exiting this coil was then combined with a further reagent stream consisting of a 1.4 M solution of α -haloketone in THF (from a vessel containing a stock solution, injection time delayed so as to coincide with the enolate stream) and the mixture passed through a further two 10 mL flow coils before quenching and purification of the products (Scheme 3).¹¹ The total residence time for the reagents was approximately nine minutes, reaction at this rate equating to an α -haloketone throughput of 1.4 mmol per minute. The results of the continuous-flow synthesis of a number of polysubstituted furans can be seen in Table 2. Even when performed at ambient temperature the flow reactions gave considerable improvements in yield when compared to the unoptimised batch reactions which required cooling at -78 °C (Table 2, entries 1 and 2 vs Table 1, entries 2 and 4). The majority of products were isolated in fair to good yields with purification by column chromatography simplified by the fact that in all cases the product furan was the least polar, highest running component of the mixture.

Table 2	2
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continuous non synthesis or porysubstituted ruran compound	Continuous-flow	synthesis	of po	lysubstituted	furan	compounds
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Entry	α-Haloketone	Ketone	Product	Yield (%)
1	Br			75
2	Br	0		25
3	Br			47
4	Br			43
5	Br	°		52
6	Br	0		0
7	Br			22 ^a (9:1)
8	CI VIC		600	15
9	Br			51
10	CI Br		CI CI	23
11	Br	0	5	32
12	Br			80

^a Reaction produced a 9:1 mixture of regioisomers. Major isomer shown.

Examination of the reaction mixtures by ¹H NMR and TLC prior to chromatographic purification showed the presence of unreacted starting materials and decomposed baseline material in addition to the expected products. Although α -chloroketones could be used in the reaction they gave significantly lower yields than the corresponding α -bromoketone (Table 2, entry 1 vs entry 8). An attempt to replace the ketone reaction partner with an aldehyde did not give any isolable amounts of the corresponding furan (Table 2, entry 6). Annulated furans are often used as building blocks in natural product synthesis,² and such compounds can be readily made with

this methodology by the use of either cyclic ketones (Table 2, entries 1, 5, 9 and 12) or cyclic α -haloketones (Table 2, entry 4). An aromatic halogen substituent was tolerated in the reaction giving the desired furan, albeit in low yield (Table 2, entry 10).

In summary a synthesis of polysubstituted furan compounds from the reaction of a ketone and α -haloketone in the presence of LiHMDS has been developed. The performance of the reactions under continuous-flow gave increased yields of the desired products compared to reactions performed in batch-mode and removed the need for external cooling (although optimisation of the batch reactions was not attempted). The reaction gives ready access to a large number of furan products from the wide range of commercially available ketone and α -haloketone building blocks.

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Supplementary data

Supplementary data (experimental procedures and data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.083.

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- 11. Experimental Procedure. A solution of acetone (2 M in toluene, 4.62 mL of a 25 mL stock solution, 9.24 mmol) pumped at a rate of 0.76 mL min⁻¹ was mixed at ambient temperature with a solution of LiHMDS (1 M in THF, 9.24 mL, 9.24 mmol) pumped at a rate of 1.54 mL min⁻¹ via a T-piece and passed through a 10 mL reactor coil (PFA tubing, 1 mm i.d.). The eluent stream was then mixed with a solution of phenacyl bromide (1.4 M in THF, 6.00 mL of a 50 mL stock solution, 8.4 mmol) pumped at a rate of 1 mL min⁻¹ via a T-piece (injection time delayed so as to coincide with the enolate stream) and passed through two 10 mL reactor coils (PFA tubing, 1 mm i.d.). The flow solvent was toluene. The eluent stream was collected in a flask containing H₂O (20 mL), shaken and the organic phase separated, washed with H₂O (20 mL), dried (MgSO₄) and evaporated in vacuo, The residue was then purified by column chromatography eluting with 0–5% v/v EtOAc/petroleum ether to give 2-methyl-4-phenylfuran as a white solid (0.33 g, 25%). The product gave a good spectral comparison with the data previously reported.¹²
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