Synthesis of Tri- and Tetrasubstituted Furans Catalyzed by Trifluoroacetic Acid

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ABSTRACT



Substituted 2-hydroxy-3-acetylfurans are synthesized by alkylation of *tert*-butyl acetoacetate with an α -haloketone followed by treatment of the obtained intermediate with trifluoroacetic acid (TFA). A second alkylation of the intermediate followed by treatment with trifluoroacetic acid provides access to disubstituted 2-methylfurans.

The acid-catalyzed synthesis of furans from 1,4-diketones has been known for more than a century as the Paal–Knorr method¹ (Scheme 1a). The synthesis of furan from β -ke-



toesters and α -halogenoketones under basic condition is called the Feist–Benary² reaction (Scheme 1b). The first step of this reaction is an aldol reaction. The regioselectivity is

inverted when the alkylation of the β -ketoesters is executed first followed by acid treatment³ (Scheme 1c).

Usually the 2-hydroxyfuran tautomer is thermodynamicaly disfavored compared to the γ -crotonolactone form,⁴ but if an acetyl group is present in the 3 position of the furan ring the hydroxy function is stabilized by H-bonding. A few examples of such structures are known in the literature.⁵

The substituted furans are of general interest as natural products as well as synthetic building blocks. Regioselective methods to obtain substituted furans have been extensively reviewed.⁶ A versatile two-step synthesis of mono- and disubstituted 3-acetyl-2-hydroxyfurans based on TFA ca-

(7) The alkylation with the less reactive chloroacetone needed 2 days at rt.

(9) An additional 2 h reflux was necessary using BnBr.

⁽¹⁾ Friedrichsen, W. In *Furans and their Benzo Derivatives*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive heterocyclic chemistry II; Pergamon: Elsevier Science Ltd.: Oxford, 1996; Vol. 2, p 352.

⁽²⁾ Friedrichsen, W. In *Furans and their Benzo Derivatives*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive heterocyclic chemistry II; Pergamon: Elsevier Science Ltd.: Oxford, 1996; Vol. 2, p 359

⁽³⁾ Bambury, R. E.; Yaktin, H. K.; Wyckoff, K. K. J. Heterocycl. Chem. 1968, 5, 95–100.

⁽⁴⁾ Bodor, N.; Dewar, M. J. S.; Harget, A. J. J. Am. Chem. Soc. 1970, 92, 2929-2936.

⁽⁵⁾ For example, see: (a) Abdelrazek, F. M. J. Prakt. Chem. **1990**, 332, 479–483. (b) Blount, J. F. J. Org. Chem. **1978**, 43, 3821–3824. (c) Simkin, B. Y. et al. J. Org. Chem. USSR **1977**, 13, 1581–1593. (d) Hartke, K.; Matusch, R. Chem. Ber. **1972**, 105, 2584–2593.

⁽⁶⁾ Hou, X. L.; et al. *Tetrahedron* **1998**, *54*, 1955–2020.

⁽⁸⁾ Mixture of diastereoisomers (3:2).

talysis is reported starting from *tert*-butyl acetoacetate and different α -haloketones (Scheme 2). A further alkylation with



^{*a*} (**a**) NaH (1.1 equiv) in THF, 30 min at 0 °C, then **1** (1.1 equiv), 2 h at 0 °C and overnight at rt; (**b**) TFA, 1 h at rt or CH_2Cl_2/THF (10:1) overnight at rt.

different bromoalkanes previous to the acidic treatment gives access to disubstituted 2-methylfurans (Scheme 3). This is a straightforward synthesis for electron-rich trisubstituted furans.



^{*a*} (**a**) NaH (1.1 equiv) in THF, 1 h at 0 °C, then BrBn or BrCH₂CO₂Me (1.1 equiv), 2 h at 0 °C and overnight at rt; (**b**) CH₂Cl₂/THF (10:1) overnight at rt.

The alkylation of *tert*-butyl acetoacetate was achieved by deprotonation with sodium hydride in THF at 0 °C and treatment of the resulting anion with methyl 5-bromolevulinate (**1a**), phenacyl bromide (**1b**), chloroacetone (**1c**), and α -bromopropiophenone (**1d**) to yield the racemic intermediates **2a**-**d**. Treatment of the intermediates **2a**-**d** for 1 h at rt with TFA (97%) yields the 3-acetyl-2-hydroxyfuran derivatives **3a**-**d** in good yields (Scheme 2).

The racemic intermediate **2a** was further alkylated with benzyl bromide and the racemic intermediates **2b**,**c** were alkylated with methyl bromoacetate to give the intermediates **4a**-**c**. Overnight treatment of the intermediates **4a**-**c** by a TFA (10%) solution in CH₂Cl₂ gives access to 2-methylfuran derivatives **5a**-**c** (Scheme 3).

The synthesized intermediates 2a-d and the corresponding furans 3a-d are listed in Table 1.

The synthesized intermediates $4\mathbf{a}-\mathbf{c}$ and the corresponding furans $5\mathbf{a}-\mathbf{d}$ are listed in Table 2.

In the case of the racemic dialkylated *tert*-butyl acetoacetate $4\mathbf{a}-\mathbf{c}$, the acid treatment leads to a decarboxylation whereas in the case of the monosubstituted *tert*-butyl acetoacetate $2\mathbf{a}-\mathbf{d}$, the carboxylic acid function liberated by Table 1. 3-Acetyl-2-hydroxyfuran Derivatives



the acid treatment is involved in the formation of the furan ring. In the case of compounds $4\mathbf{a}-\mathbf{c}$, the attack of the keto function by the carboxylic acid leading to the formation of a cyclic intermediate can be assumed though no experimental identification of such species was achieved. The intermediates would be the alkylated analogues of the intermediates obtained with compounds $2\mathbf{a}-\mathbf{c}$. However, the β -ketoester moiety of the alkylated intermediates lacks the ability to tautomerize, consequently they would revert to their open form to lose carbon dioxide.

As one can expect, deprotection of the *tert*-butyl group and cyclization are both catalyzed by TFA. Cyclization could not be observed either starting from the *tert*-butyl 2-methoxycarbonyl-4-oxo-4-phenylbutyrate or from the methyl 3-*tert*-butyloxycarbonyl-4-oxopentanoate by standard TFA treatment. The carbonyl of the keto function should be electrophilic enough to allow attack of the carboxylic acid. The enolizability of the β -ketoester moiety is also an important factor stabilizing the cyclic intermediate formed by the attack of the carboxylic acid on the keto function.

Simple 1,4-diketones as 2,5-hexanedione or methyl 4,7dioxodecandioate are not converted into furans by TFA



(10%) in CH₂Cl₂ at rt overnight. However, under those conditions furan **5c** was observed when starting from 3-methyl-2,5-hexanedione. This last result allows an alternative pathway not induced by the direct trapping of the enol formed by decarboxylation.

The 3-acetyl-2-hydroxyfuran derivatives are methylated on the hydroxy function when treated with sodium hydride, DMPU, and iodomethane in THF. When furan **3a** is methylated, the keto function of the acetyl stays untouched when treated with 20 equiv of sodium borohydride in MeOH but the methylester function may be selectively reduced to the alcohol.

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Supporting Information Available: General experimental procedures as well as spectroscopic characterizations of compounds 2-5. This material is available free of charge via the Internet at http://pubs.acs.org.

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