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Synthesis of Tri- and Tetrasubstituted Furans Catalyzed by Trifluoroacetic Acid

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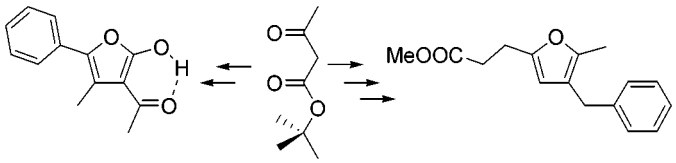
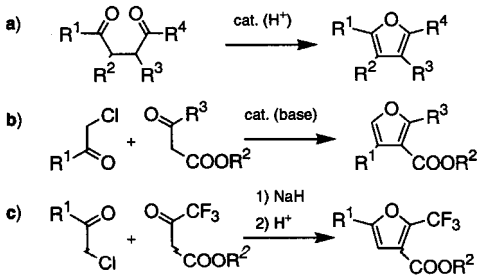
ABSTRACT



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 method[1] (Scheme 1a). The synthesis of furan from β-ketoesters and α-halogenoketones under basic condition is called the Feist−Benary[2] 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 treatment[3] (Scheme 1c).

Scheme 1



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-

(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.

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

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

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

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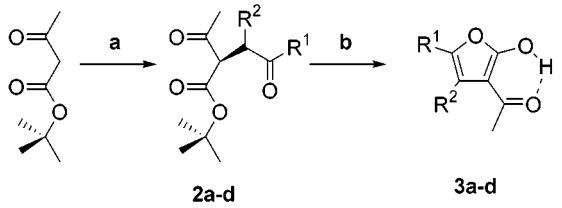
talysis is reported starting from *tert*-butyl acetoacetate and different α-haloketones (Scheme 2). A further alkylation with

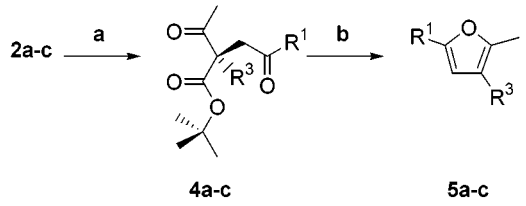
Scheme 2[a]



[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.

Scheme 3[a]



[a] (**a**) NaH (1.1 equiv) in THF, 1 h at 0 °C, then BrBn or $BrCH_2CO_2Me$ (1.1 equiv), 2 h at 0 °C and overnight at rt; (**b**) CH_2Cl_2/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).

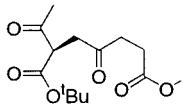
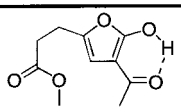
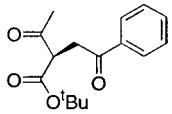
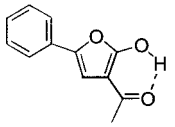
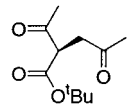
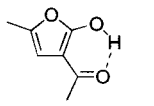
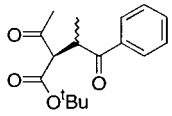
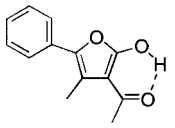
The racemic intermediate **2a** was further alkylated with benzyl bromide and the racemic intermediates **2b**,**c** were alkylated with methyl bromoacetate to give the intermediates **4a**−**c**. Overnight treatment of the intermediates **4a**−**c** by a TFA (10%) solution in CH_2Cl_2 gives access to 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 **4a**−**c** and the corresponding furans **5a**−**d** are listed in Table 2.

In the case of the racemic dialkylated *tert*-butyl acetoacetate **4a**−**c**, the acid treatment leads to a decarboxylation whereas in the case of the monosubstituted *tert*-butyl acetoacetate **2a**−**d**, the carboxylic acid function liberated by

Table 1. 3-Acetyl-2-hydroxyfuran Derivatives

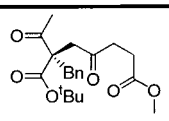
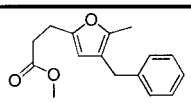
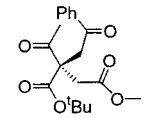
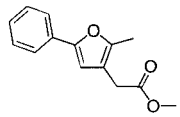
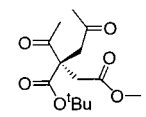
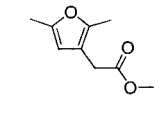
entry	**2**	yield	**3**	yield
a		92%		87%
b		95%		67%
c		60%[7]		77%
d		94%[8]		75%

the acid treatment is involved in the formation of the furan ring. In the case of compounds **4a**−**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 **2a**−**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 4,7-dioxodecandioate are not converted into furans by TFA

Table 2. Electron-Rich 2-Methylfuran Derivatives

entry	**4**	yield	**5**	yield
a		56%[9]		71%
b		89%		67%
c		88%		71%

(10%) in CH_2Cl_2 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.

Acknowledgment. We thank the Swiss National Science Foundation and Hoffmann-La Roche for financial support.

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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