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STUDIES ON THE SYNTHESIS OF FURANS BY ANIONIC CYCLIZATION OF 4-PENTYNONES

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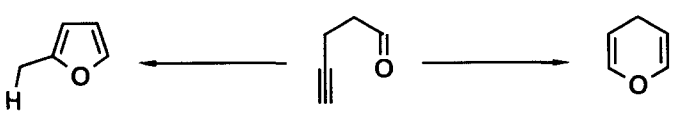
Summary. The synthesis of 5-substituted 2-carbomethoxymethyl-furans **4** is achieved by base promoted cyclization of the 4-pentynones **3a-e** which are easily accessible from the 4-pentynal **1**.

Among the heteroaromatic compounds the furan system owes its unique role to the combination of a variety of features, *i.e.* (i) the occurrence as main portion or substructure of innumerous natural products;[1] (ii) the presence in the structures of many important pharmaceuticals;[2] (iii) the use as variable building block in synthetic chemistry,[3,4] and (iv) the possible access from biomass which is applied for the large scale production of furfural.[5]

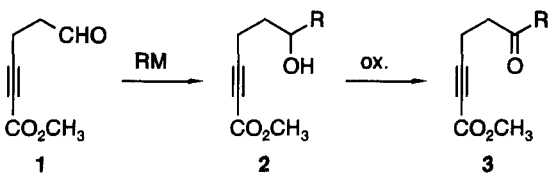
Besides modification of the substitution pattern of the furan moiety and ring transformation reactions, the ionic, radical or metal mediated ring closure of acyclic compounds represents a common and very flexible methodology for the synthesis of furan derivatives.[3] In quite a number of such cyclizations the bond formation takes place between an oxygen and an alkyne functionality of compounds with the appropriate oxidation state.[3,6] One possible application involves the ring closure of 4-pentynones as acyclic component, which, however, can take place according to a *5-exo-dig* or *6-endo-dig* mode leading to 4*H*-pyrans and 2-alkyl furans, respectively, as final products (see reaction type **A** → **B/C**).



B **A** **C**

Whereas some examples for the ring closure of enolizable pentynones are described using acid[7] or transition metal catalysis,[8] only very few results were obtained under basic conditions.[9] With special interest in the synthesis of furans which are substituted by an electron withdrawing group at a 2-alkyl group we investigated the base-catalyzed transformation of the 4-alkynones **3a-3e** which are activated by an ester function (to the best of our knowledge no example of this type of substitution has been described in any of the other cyclization methods).

The required precursors **3a-3e** were synthesized starting with the alkyne derivative **1**,[10] available in four steps from 4-pentynol (53%), by a Grignard reaction and subsequent Swern or MnO_2 oxidation of the secondary alcohols **2a-e** (for yields see Table 1).[11,13]



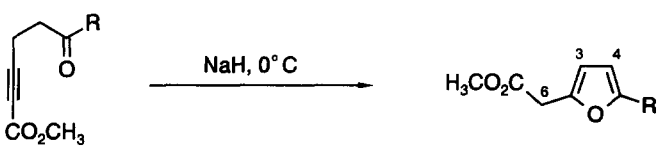
1 **2** **3**

Table 1. Synthesis of **2a-e** and **3a-e**

	RM	**2** [%] [a]	Oxidation	**3** [%] [a]
a	n C_4H_9-MgBr	90	Swern [b]	85
b	2-Furyl-MgBr	72	Swern [b]	95
c	C_6H_5-≡-MgBr	96	MnO_2 [c]	90
d	THP-O-$(CH_2)_3$-≡-MgBr	61	MnO_2 [c]	70
e	C_6H_5-MgBr	87	Swern [b]	71

[a] Isolated yield after chromatographic purification and/or recrystallization.-
[b] $C_2Cl_2O_2$, DMSO, CH_2Cl_2, -60°C, Et_3N.- [c] MnO_2, CH_2Cl_2, 25°C

The cyclization of the pentynones is performed at 0°C using sodium hydride as base and THF/DMPU or DMF as solvent. Under carefully controlled reaction conditions the expected furan derivatives **4a-e** are obtained in medium to good yields (see Table 2).[13,14] In order to obtain reproducible results it is particularly important not to exceed the reaction time of approximately 2-5 min (the procedure for **4b** is given below);[15] therefore it is advisable to control the progress of the reaction by thin layer chromatography, and to work up immediately after quantitative conversion.



3 **4**

Table 2. Cyclization of the 4-pentynones **3a-e**

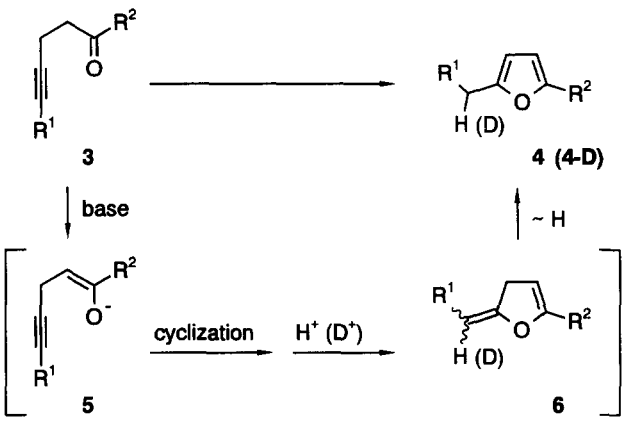
	R	Solvent	Time [min]	**4** [%] [a]
a	n C_4H_9	THF / DMPU (2:1) [b]	2	57-63
b	2-Furyl	DMF [c]	2	67
c	C_6H_5-≡-	DMF [c]	5	68
d	THP-O-$(CH_2)_3$-≡-	DMF [c]	3	67
e	C_6H_5	DMF [c]	2	91

[a] Isolated yield after chromatographic purification and/or recrystallization.-
[b] 0.03 molar solution; DMPU = dimethyl-1,3-propanediylurea.- [c] 0.05 molar solution

All attempts for effecting the ring closure of **3** (e.g. **3e**) under acid catalysis failed. On the other hand, base-catalyzed cylization experiments with 4-pentynones bearing a methyl or trimethylsilyl group at the terminal alkyne position remained unsuccessful as well. Obviously the described procedure for 4-pentynones with an electron withdrawing substituent complements the acid promoted cyclization of the corresponding electron rich systems.

The probable mechanism of the cyclization process is sketched in the Scheme. After deprotonation of **3** to the enolates **5** *5-exo-dig* cyclization takes place affording the dihydrofurfurylidenes **6** which undergo rapid tautomerization to the furans **4**; the last step is supported by the formation of the labeled furan **4-D** after quenching with deuterium oxide. However, in contrast to results with 5-alkyl- or 5-aryl-4-alkynones (**3**, R^1= alkyl, aryl)[9b] no evidence for a competitive *6-endo-dig* cyclization was obtained.

Scheme



In conclusion, it has been shown that 4-pentynones bearing a terminal ester function and a phenyl, furyl, alkyl or alkynyl substituent at the carbonyl group undergo efficient transformation into 5-subsituted 2-carbomethoxymethyl-furans. The starting materials are easily accessible and the reaction takes place in satisfying yields representing a promising alternative to other cyclization methods. Investigations directed to the synthesis of higher substituted systems as well as quenching experiments with different electrophiles are underway.

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11. Due to the low chemoselectivity of alkyl and aryl lithium reagents to such bifunctional carbonyl compounds[12] the use of Grignard reagents is preferred in this reaction.
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13. All new compounds are characterized by spectroscopic data as well as by elemental analysis and/or mass spectra.
14. ^{1}H NMR data (250 MHz, $CDCl_3$, * = signals exchangeable) of **4a**: δ = 6.09 (d, 1H, *J* = 3.0 Hz, 3-H*), 5.91 (d, 1H, *J* = 3.0 Hz, 4-H*), 3.72 (s, 3H, CH_3O), 3.64 (s, 2H, 6-H), 2.59 (t, 2H, *J* = 7.6 Hz, 1'-H), 1.67-1.54 (m, 2H, 2'-H), 1.44-1.28 (m, 2-H, 3'-H), 0.93 (t, 3H, *J* =7.3 Hz, 4'-H); **4b**: δ = 7.39 (dd, 1H, *J* = 1.8 Hz, *J* = 0.8 Hz, 5'-H), 6.51 (dd, 1H, *J* = 3.2 Hz, *J* = 0.8 Hz, 3'-H), 6.49 (d, 1H, *J* = 3.3 Hz, 4-H), 6.43 (dd, 1H, *J* = 3.2 Hz, *J* = 1.8 Hz, 4'-H), 6.29 (dt, 1H, *J* = 3.3 Hz, *J* = 0.8 Hz, 3-H), 3.72 (m_c, 5H, 6-H, OCH_3); **4c**: d = 7.55-7.47 (m, 2H, Ph-2-H), 7.38-7.31 (m, 3H, Ph-3-H, Ph-4-H), 6.61 (d, 1H, *J* = 3.4 Hz, 4-H), 6.28 (dt, 1H, *J* = 3.4 Hz, *J* = 0.8 Hz, 3-H), 3.74 (s, 3H, OCH_3), 3.72 (s, 2H, 6-H); **4d**: δ = 6.41 (d, 1H, *J* = 3.4 Hz, 4-H), 6.20 (dt, 1H, *J* = 3.4 Hz, *J* =0.8 Hz, 3-H), 4.61 (m_c, 1H, THP-2-H), 3.94-3.80 (m, 2H, 5'-H*), 3.72 (s, 3H, OCH_3), 3.67 (m_c, 2H, 6-H), 3.57-3.45 (m, 2H, THP-6-H*), 2.56 (t, 2H, *J* = 6.8 Hz, 3'-H) 1.94-1.44 (m, 8H, 4-H, THP-3-H, THP-4-H, THP-5-H); **4e**: δ = 7.66-7.62 (m, 2H, Ph-2-H), 7.39-7.32 (m, 2H, Ph-3-H), 7.25-7.21 (m, 1H, Ph-4-H), 6.59 (d, 1H, *J* = 3.2 Hz, 4-H), 6.31 (d, 1H, *J* = 3.2 Hz, 3-H), 3.75 (s, 2H, 6-H), 3.73 (s, 3H, OCH_3).
15. Synthesis of **4b** (typical procedure): To a stirred solution of 22 mg of a 60% mineral oil dispersion of NaH (0.54 mmol) in 8 ml of dry DMF at 0°C (prepared under N_2 in a flame-dried round-bottom flask) a solution of **3b** (100 mg, 0.49 mmol) in 2 ml of dry DMF was rapidly added. After the reaction was complete (2 min, reaction control by TLC) 1 ml of saturated aqueous NH_4Cl, 20 ml of water and 50 ml of diethyl ether were added to the dark mixture. The organic phase was separated and the aqueous solution was extracted with diethyl ether (3 x 40 ml). The combined organic layers were washed with water (10 ml) and saturated aqueous NaCl (5 ml), and dried over $MgSO_4$. After careful concentration *in vacuo* purification was accomplished by flash chromatography (SiO_2; cyclohexane / ethyl acetate 20:1) affording 67 mg (67%) of **4b**.

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