A New Synthesis of 8-Oxabicyclo[3.2.1]octan-2-one and Its Use for the Preparation of Cycloheptane Annulated Furans

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In memoriam Professor Dr. Hans-Dieter Martin

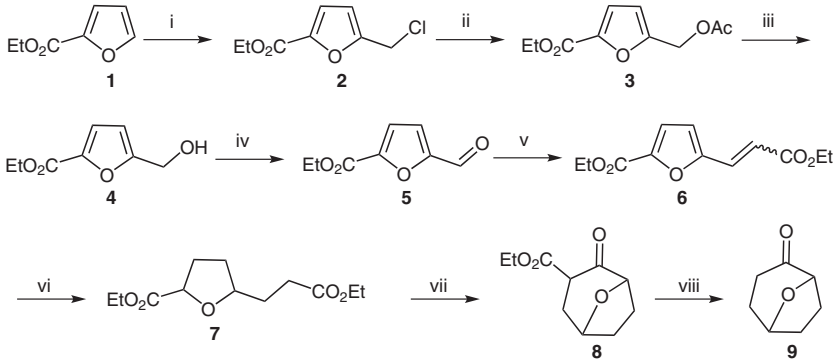
Abstract: Two novel syntheses of 8-oxabicyclo[3.2.1]octan-2-one are described, making this key intermediate readily available in preparative amounts. On chain elongation with various oxophosphonates this compound is converted to α,β-unsaturated ketones, which, on treatment with $BF_3{\cdot}OEt_2$, cyclize to furanocycloheptanols with a substitution pattern not reported previously.

Key words: bicyclic ketones, Wittig–Horner reactions, heterocycles, furan synthesis, annulated furan derivatives

In spite of the ease of preparation and its functionally enriched, strained structure, 8-oxabicyclo[3.2.1]octan-2-one (**9**, Scheme 1) has received only scant attention in organic synthesis. The only report on its chemistry was by Davies et al., who utilized it for the synthesis of tropanone.[1] The presence of the carbonyl function near to the oxygen bridge suggests that the molecule could be useful for annulation reactions through suitable derivatization. Herein we report the results of our investigations in this direction. The Horner–Wadsworth–Emmons (HWE) adducts of **9** with 2-oxoalkyl phosphonates were found to undergo a novel acid-catalyzed rearrangement leading to an efficient synthesis of cycloheptane-annulated furans.

To prepare **9** we first used a synthesis which resembles Davies' approach[1] in the initial and final steps, but differs in its central section. This protocol is summarized in Scheme 1. Since a direct Vilsmeier formylation of ethyl furoate **1** provided the desired aldehyde **5** in 20% yield only (reaction conditions: 100 °C, 8 h), an indirect route was employed. This involves chloromethylation to **2**,[2,3] conversion to the acetoxy derivative **3**,[4] selective cleavage of the acetoxy group,[5] and oxidation of the resulting alcohol **4**. For the oxidation of **4** PCC was used initially which gave 80% yield after a difficult workup and chromatographic purification. On the other hand, IBX was found to be a highly efficient oxidant in this case, providing a near quantitative yield of **5** after a simple filtration.[6] The Wittig olefination to **6** (mixture of diastereomers) and reduction to **7** also proceeded with excellent yields. The Dieckmann cyclization was carried out by treatment with NaH in refluxing THF. The decarboxylation of the resulting keto ester **8** yielded the oxabicycle **9** in 90% yield.

To make the preparation of **9** still more facile, a second route to this ketone was developed; this is presented in Scheme 2. The Wittig product **11**, available easily from furfural **10** could be readily formylated under Vilsmeier conditions. Alkaline iodine oxidation was utilized for the direct conversion of the thus prepared aldehyde **12** to the methyl ester **13**.[7] Reduction to **14** followed by cyclization to **15** and finally decarboxylation to **9** proceeded smoothly as in the previous case (63% over six steps, compared to 47% over eight steps for the first route, Scheme 1).



Scheme 1 Synthetic route to **9**. *Reagents and conditions*: i. $(CH_2O)_n$, $ZnCl_2$, dry HCl, $CHCl_3$, r.t., 83%; ii. NaOAc, AcOH, Ac_2O, 120 °C, 90%; iii. (a) NaOEt (cat.), EtOH, r.t., 24 h, (b) H^+ (ion-exchange resin), 85%; iv. IBX, EtOAc, reflux, 3 h, 99%; v. $Ph_3P{=}CHCO_2Et$, THF, r.t., 2 h, 98%; vi. Pd/C, H_2, EtOAc, 99%; vii. NaH, THF, reflux, 6 h, 85%; viii. HOAc–H_2O–H_2SO_4 (8:8:1), reflux, 2.5 h, 90%.

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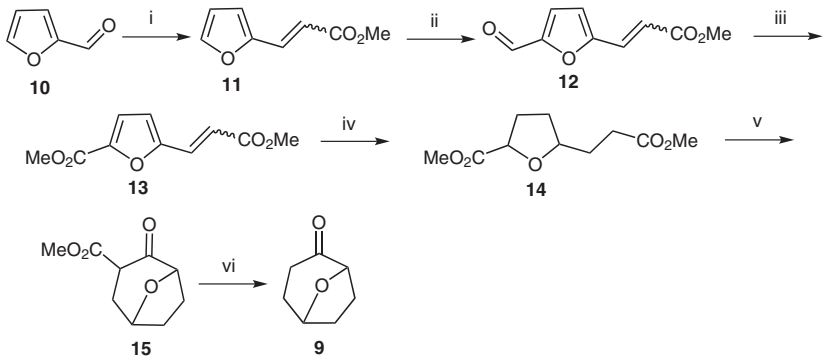
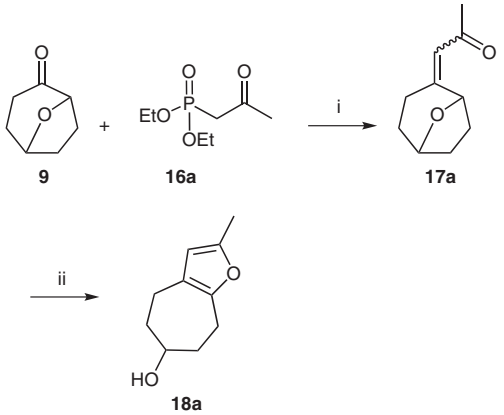


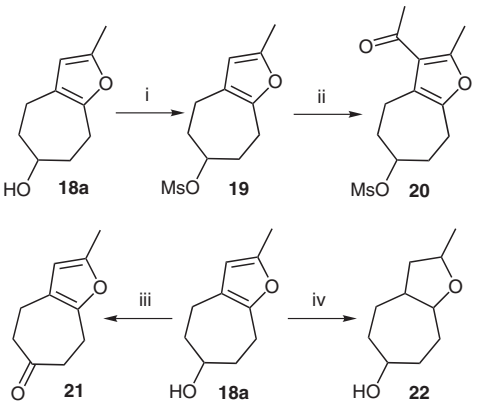
Scheme 2 Alternate synthesis of **9**. *Reagents and conditions*: i. $Ph_3P{=}CHCO_2Me$, THF, r.t., 2 h, 98%; ii. DMF, $POCl_3$, 0 °C to r.t. (12 h), then 60 °C (2 h), 90%; iii. I_2, KOH, MeOH, 0 °C to r.t., 1 h, 95%; iv. Pd/C, H_2, EtOAc, 99%; v. NaH, THF, reflux, 6 h, 85%; vi. AcOH–H_2O–H_2SO_4 (8:8:1), reflux, 2.5 h, 90%.

The oxoalkyl phosphonates required for the HWE reaction with **9** were synthesized following a reported procedure.[8] In an initial experiment diethyl (2-oxopropyl)phosphonate was added dropwise to an ice-cold suspension of NaH in dry THF under nitrogen. After complete addition the solution was stirred for one hour at room temperature. To this a solution of the ketone **9** in THF was added and allowed to stir at room temperature for 24 hours. After workup and chromatographic purification the HWE adduct was obtained as a mixture of the *cis*- and *trans*-isomers in 92% yield. The rearrangement of the HWE adduct was initially carried out with excess PTSA in refluxing benzene. After 30 minutes of reaction time followed by workup and chromatographic purification, the furan **18a**[9] was isolated in 80% yield (Scheme 3). The structure of **18a** was assigned on the basis of the spectroscopic data. In the IR spectrum of **18a**, the hydroxyl group exhibited a broad peak at 3333 cm^{-1}. In the ^1H NMR spectrum the furyl proton was visible as a singlet at $\delta = 5.73$ ppm. The methyl group resonated as a singlet at $\delta = 2.19$ and the hydroxyl bound CH was visible as a triplet of triplet at $\delta = 3.87$ ppm. Matching resonances in the ^{13}C NMR spectrum were also observed.



Scheme 3 HWE reaction followed by rearrangement to the furan. *Reagents and conditions*: i. NaH, THF, 0 °C to r.t., 24 h, 92%; ii. PTSA, benzene, reflux, 30 min, 80%.

In order to confirm the proposed structure, further derivatizations were carried out. Thus **18a** underwent mesylation followed by acylation at the furan 3-position as expected. Furthermore, oxidation as well as catalytic hydrogenation proceeded smoothly (Scheme 4).



Scheme 4 Further functionalization of **18a**. *Reagents and conditions*: i. MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 1 h, 95%; ii. Ac_2O, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t., 2 h, 70%; iii. IBX, EtOAc, reflux, 3 h, 80%; iv. Pd/C, H_2, EtOAc, 4 h, 95% (mixture of diastereomers).

A limited study of different acidic reagents proved that $BF_3{\cdot}OEt_2$ is the most efficient catalyst for the cyclization. The reaction could be easily extended to various phosphonates leading to a general synthesis of furanocycloheptanols. The results are presented in Table 1. Interestingly, the cinnamyl and the furyl substituents were not tolerated under the acidic conditions.

In conclusion, the present method offers a novel and efficient route for the synthesis of furanocycloheptanols. It is to be noted that furanocycloheptanols with the particular substitution pattern were not reported previously.

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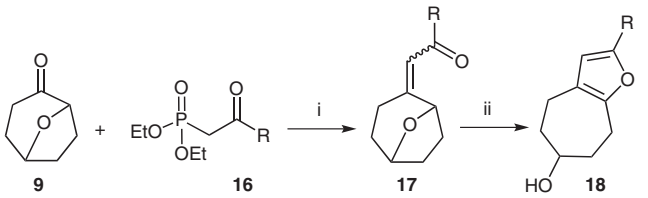
Table 1 Generality of the Reaction[a]



Entry	R	Yield (%)	
		HWE adduct[b]	Furan
1	Me	**17a** (92)	**18a** (82)
2	Et	**17b** (91)	**18b** (80)
3	Pr	**17c** (97)	**18c** (86)
4	Ph	**17d** (90)	**18d** (80)
5	4-MeC_6H_4	**17e** (96)	**18e** (77)
6	4-MeOC_6H_4	**17f** (90)	**18f** (77)
7	4-$O_2NC_6H_4$	**17g** (62)	**18g** (60)
8	cinnamyl	**17i** (64)	0
9	2-furyl	**17j** (72)	0

[a] Reaction conditions: i. NaH, THF, 0 °C to r.t., 24 h. ii. $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux, 6–10 h.
[b] Mixture of *E*- and *Z*-isomers, in roughly equal amounts.

References and Notes

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(9) **Representative Procedure**
To a suspension of NaH (67 mg, 60% suspension in oil, 1.67 mmol, 1.05 equiv) in dry THF (10 mL), cooled to 0 °C, was added a solution of diethyl (2-oxopropyl)phosphonate (339 mg, 1.75 mmol, 1.1 equiv) in dry THF (10 mL) dropwise under nitrogen. After complete addition the reaction mixture was allowed to stir for 1 h at r.t. To this solution the ketone **9** (200 mg, 1.59 mmol, 1 equiv) was added, and the mixture was allowed to stir for 24 h at r.t. The reaction was quenched by the addition of H_2O (50 mL) and worked up with Et_2O (4 × 50 mL). The combined extracts were dried over anhyd Na_2SO_4 and concentrated. The residue was purified by column chromatography (Et_2O–pentane, 1:1) to afford the HWE adduct **17a** (242 mg, 92%). To the HWE adduct (100 mg, 0.6 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL), was added $BF_3{\cdot}OEt_2$ (128 mg, 0.9 mmol, 1.5 equiv), and the solution was allowed to reflux for 6 h. The reaction was quenched by the addition of sat. $NaHCO_3$ solution and worked up by CH_2Cl_2 extraction. The combined extracts were dried over anhyd Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (Et_2O–pentane, 1:1) to afford the furan **18a** (82 mg, 82%) as a white amorphous solid.
Compound **18a**: white amorphous solid; mp 55–57 °C. IR (diamond ATR): ν_{max} = 3333, 2941, 2920, 2981, 2581, 1578, 1493, 1442, 1251, 1022, 957, 904, 802 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.53–1.76 (m, 2 H), 1.86 (br s, 1 H), 1.95–2.10 (m, 2 H), 2.19 (s, 3 H), 2.25–2.40 (m, 2 H), 2.47–2.65 (m, 2 H), 2.77–2.90 (m, 1 H), 3.87 (tt, 1 H, J_1 = 2.8 Hz, J_2 = 9.1 Hz), 5.73 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.2, 21.0, 23.1, 34.9, 37.0, 73.4, 108.7, 120.4, 147.9, 150.0. HRMS (EI): *m/z* calcd for $C_{10}H_{14}O_2$: 166.09938; found: 166.09902.