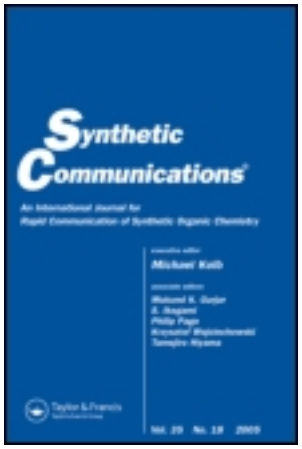

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REGIOSPECIFIC SYNTHESIS OF TETRA-SUBSTITUTED FURANS

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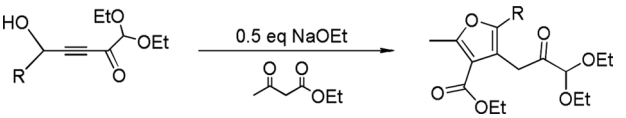
GRAPHICAL ABSTRACT



Abstract α,β-*Unsaturated acetylenic γ-hydroxyketones have been shown to react with ethyl acetoacetate in a Michael-addition fashion and subsequently undergo cyclization followed by dehydration to give substituted furans with a predictable regiospecificity. The yields were good to excellent. A mechanism for the transformation is proposed, and this mechanism explains why furan formation does not take place when the same unsaturated ketones are treated with α-methylated acetoacetate and diethyl malonate.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource: Full experimental and spectral details.]*

Keywords Conjugated acetylenic ketones; ketoesters; propargylic alcohols

INTRODUCTION

Furans constitute an important class of compounds in organic chemistry. This five-membered heterocycle is found in a number of natural products and in some pharmaceuticals,[1] and in recent years the furan moiety has been incorporated in materials with promising commercial potential.[2,3] In addition furans are applied as synthetic intermediates to prepare a number of interesting substructures including unsaturated esters, 1,4-dicarbonyl compounds, and modified carbohydrates.[4] All these applications have boosted interest in furan chemistry, and in recent years a number of new synthetic methods of furans have been published.[5]

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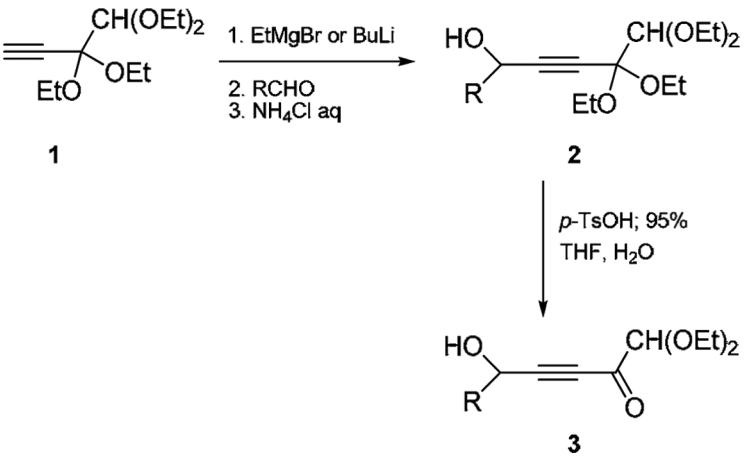


Scheme 1. Synthesis of acetylenic ketones **3**.

Some time ago we reported a simple synthesis of 3,3,4,4-tetraethoxybutyne (TEB) (**1**),[6] which has made the preparation of propargylic alcohols **2** and 5-substituted 1,1-diethoxy-5-hydroxypent-3-yn-2-ones (**3**) straightforward (Scheme 1).[7–9] Ketones **3** are highly functionalized, and by exploiting their reactive moieties in a selective fashion synthesis of a range of interesting compounds has been achieved.[8,10] Among the valuable transformations realized is conversion of esters of **2** to tetra-substituted furans in a regiospecific manner by treatment with various Gilman-type cuprates.[11] On this basis we envisaged that furans could also be made under mild conditions by treating **3** with Michael donors that were not basic enough to react with the hydroxyl group in the hydroxyketone. So far we have studied reactions with the monoenolate of ethyl acetoacetate, which appears to convert **3** to substituted furans in good yields in a predictable fashion.

RESULTS AND DISCUSSION

The α,β-unsaturated acetylenic ketones used were synthesized from TEB as outlined in Scheme 1, with an overall yield ranging from 63 to 81% (Table 1). In the first step the bromomagnesium acetylide of **1** was applied when aliphatic aldehydes were reacted, but when benzaldehyde and *p*-tolylaldehyde were used it appeared more favorable to use the lithium acetylide instead because this change prevented significant by-product formation, mainly by the Cannizzaro reaction.[9] In the second step all the substrates behaved basically in the same way and gave **3** in 90% yield or better (Table 1).

Ketones **3** were reacted with 1 molar equivalent of the monoenolate of ethyl acetoacetate by dropping ethanol solutions of the ketones to an ethanol solution of a 1:1 mixture of the ester and its enolate. At room temperature the reaction was slow (as indicated by thin-layer chromatography [TLC] analysis), but when the reaction temperature was increased to 80 °C all the starting material was consumed at a reasonable rate and complete conversion was achieved after 3 h when

Table 1. Isolated yields of acetylenic alcohols **2** and ketones **3**

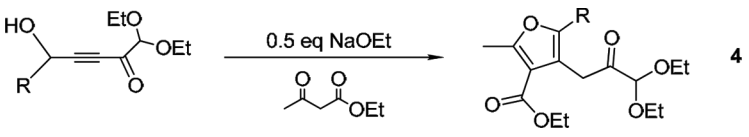
R	Step 1 product/yield (%)	Step 2 product/yield (%)
H	**2a**/90[a]	**3a**/93
Me	**2b**/85[a]	**3b**/91
n-C_6H_{13}	**2c**/80[a]	**3c**/95
n-C_7H_{15}	**2d**/82[a]	**3d**/95
i-Pr	**2e**/81[a]	**3e**/90
Ph	**2f**/70[b]	**3f**/92
p-MeC_6H_4	**2g**/75[b]	**3g**/92

[a]EtMgBr as base.
[b]*n*-BuLi as base.

R = H or alkyl and 5 h when R = aryl (Table 2). The longer time required for the aromatic aldehydes probably reflects steric interactions in the ring-closure steps. In all cases one product predominated, namely, the corresponding 5-substituted 2-methyl-3-ethoxycarbonyl-4-(3,3-diethoxy-2-oxopropyl)furan (**4**) (Table 2). The workup was straightforward and after purification by flash chromatography (hexanes/ethyl acetate) furans **4** were obtained in excellent yields (Table 2).

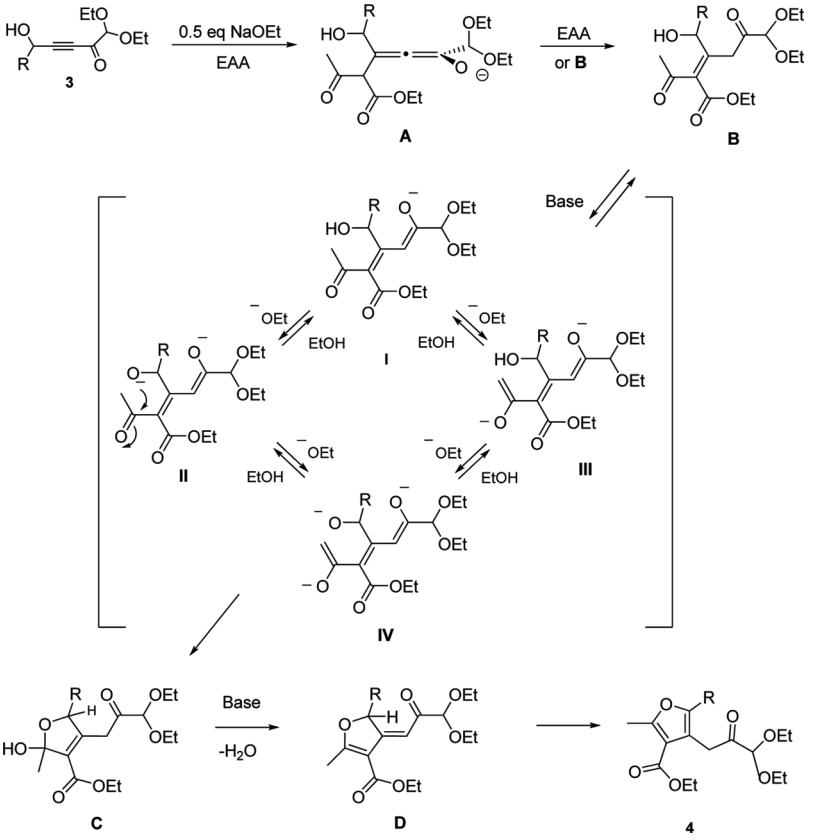
A conceivable reaction mechanism for the furan formation is outlined in Scheme 2. In the first step the acetylenic ketones react with the monoenolate of ethyl acetoacetate (EAA^-) in a Michael fashion[12,13] and give intermediate **A**. This intermediate is an enolate, which reacts either with ethyl acetoacetate furnishing its monoenolate and the more stable intermediate **B**, or with **B** already formed, affording another molecule of **B** and a carbanion from **B**. The latter species is stabilized by delocalization of the anion as indicated by some conceivable resonance forms (**I**–**IV**; not exhaustive) in Scheme 2. Intermediate **B** contains three carbonyl groups, two keto functions, and one ester moiety, which theoretically can react with a nucleophilic site elsewhere in the molecule and lead to cyclization. The only nucleophile present in **B** is the OH group (or the corresponding alkoxide), which apparently reacts in a regiospecific fashion, attacking only the acetyl group originally belonging

Table 2. Preparation of furans **4**



4

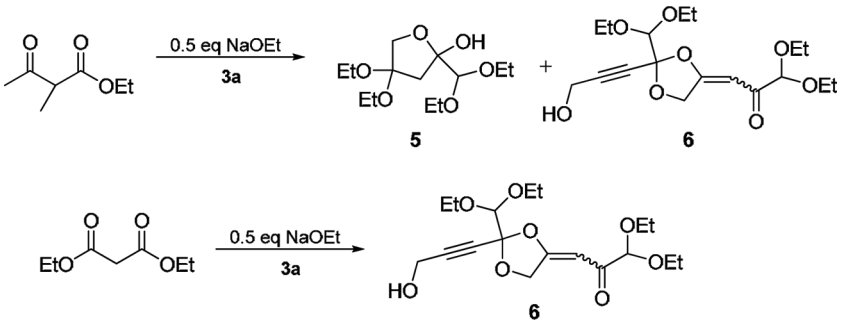
R	Furan	Reaction time (h)	Isolated yield (%)
H	**4a**	3	80
Me	**4b**	3	74
i-Pr	**4c**	3	90
n-C_6H_{13}	**4d**	3	84
n-C_7H_{15}	**4e**	3	70
Ph	**4f**	5	85
p-MeC_6H_4	**4g**	5	88



Scheme 2. Proposed mechanism for formation of furans **4**.

to ethyl acetoacetate, and gives intermediate **C** and finally tetra-substituted furan **4**, perhaps via intermediate **D**.

On the basis of the mechanism outlined previously a prerequisite for furan formation is dehydration. Consequently, if ethyl acetoacetate is replaced by a 2-substituted analog it is predicted that furan formation should not take place, and sure enough, when 1,1-diethoxy-5-hydroxy-3-butyn-2-one (**3a**) was reacted with ethyl 2-methyl-3-oxobutanoate following the procedure for reactions with ethyl acetoacetate no furan was formed. In fact the course of reaction changed completely and afforded two other heterocyclic compounds, 4,4-diethoxy-2-diethoxymethyl-2-hydroxytetrahydrofuran (**5**) and 1,1-diethoxy-3-(2-(diethoxy-methyl)-2-(3-hydroxyprop-1-ynyl)-1,3-dioxolan-4-ylidene)propan-2-one (**6**) (Scheme 3), in 60% and 15% yield, respectively. Chromatographic analyses of the latter compound indicate that it is formed as a single isomer, and on the basis of the proton NMR spectrum it is concluded that the compound has a *Z* configuration. Thus, both hydrogen atoms in the allylic group exhibit a 1.6–1.8 Hz coupling to the olefinic proton, and such a strong coupling is only compatible with a *cis* allylic coupling.[14]



Scheme 3. Reactions of 1,1-diethoxy-5-hydroxypent-3-yn-2-one (**3a**) with ethyl 2-methyl-3-oxobutanoate and diethyl malonate.

The formation of compound **5** is easy to understand on the basis of a double Michael addition of ethoxide/ethanol to **3a**[10] followed by intramolecular alkoxide attack of the keto moiety to give **5**. How **6** is formed in detail is less evident, but conceivably an *intermolecular* alkoxide attack of the carbonyl group in **3a** (alkoxide from **3a**) occurs first and the resulting alkoxide then reacts by *intramolecular* attack of the triple bond in a Michael fashion.

Finally, to try to force the hydroxyl group/alkoxide in intermediate **B** to attack the ester group and form a lactone, **3a** was also reacted with diethyl malonate, but that hope was not met at all. The starting material was indeed consumed and one product only was isolated, 1,3-dioxolane **6**, but why this complete change in the course of reaction takes place remains to be investigated.

In summary, we have developed an easy and regiospecific method for construction of tri- and tetra-substituted furans, which involves addition of ethyl acetoacetate to γ-hydroxylated α,β-unsaturated alkynones followed by intramolecular cyclization. The ease with which the transformation occurs makes the method an attractive alternative to other syntheses available for the preparation of such furans.[15]

EXPERIMENTAL

Synthesis of Propargylic Alcohols 2: General Procedure

By bromomagnesium acetylide. A THF solution of ethylmagnesium bromide (7.3 mL, 3.0 M, 22 mmol) was added dropwise to TEB (**1**) (5.00 g, 22.0 mmol) in anhydrous THF (150 mL) under nitrogen over 10 min at rt. The mixture was refluxed for 2 h and cooled to 0 °C before aldehyde (22.0 mmol) in anhydrous THF (25 mL) was added dropwise. Stirring was continued at 20 °C until all the starting material was consumed (monitored by TLC).

By lithium acetylide. TEB (**1**) (5.00 g, 22.0 mmol) was dissolved in anhydrous THF (100 mL) under nitrogen and cooled to −78 °C before a 1.6 M hexane solution of *n*-butyllithium (15 mL, 22.0 mmol) was added dropwise. The mixture was stirred at −78 °C for 30 min and then slowly heated to 0 °C before aldehyde

(22.0 mmol) in THF was added dropwise. The mixture was stirred at rt until all the starting material was consumed (monitored by TLC).

Work-up for both procedures. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (100 mL). The phases were separated and the aqueous phase was extracted (Et_2O; 3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. From the residue **2** was obtained pure by flash chromatography (hexanes and ethyl acetate, 80:20).

Compounds **2a**–**2c**, **2e**, and **2f** are described in the literature[9,11] whereas 1,1,2,2-tetraethoxydodec-3-yn-5-ol (**2d**) and 4,4,5,5-tetraethoxy-1-(*p*-methylphenyl)pent-2-yn-1-ol (**2g**), isolated as yellowish liquids by flash chromatography, are new compounds.

Synthesis of 3 by Deketalization of 2: General Procedure

Propargylic alcohol **2** (15–5.5 mmol) was dissolved in 100 mL of a 7:3 mixture of THF and H_2O. *p*-Toluenesulfonic acid monohydrate (0.57 g, 3.0 mmol) was added, and the mixture was refluxed for 2 h until all the starting material was consumed (followed by TLC). Most of the THF was evaporated, and the residue was mixed with a saturated aqueous solution of NaCl (50 mL) and CH_2Cl_2 (50 mL). After thorough stirring, the phases were separated, the aqueous phase was extracted (CH_2Cl_2; 3 × 20 mL), and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and dried ($MgSO_4$). Filtration and evaporation gave the corresponding ketone essentially pure (^{1}H NMR).

Compounds **3a**–**3c**, **3e**, and **3f** are described in the literature[9,11] whereas 1,1-diethoxy-5-hydroxydodec-3-yn-2-one (**3d**) and 1,1-diethoxy-5-hydroxy-5-(4-methylphenyl)pent-3-yn-2-one (**3g**), isolated as yellow liquids by flash chromatography, are new compounds.

Furan Synthesis Sample Procedure: Reaction of Ethyl Acetoacetate with Conjugated γ-Hydroxyalkynones (3) and Ethyl 4-(3,3-Diethoxy-2-oxopropyl)-2-methylfuran-3-carboxylate (4a)

Ethyl acetoacetate (0.13 g, 1.0 mmol) was added to sodium ethoxide (0.034 g, 0.5 mmol) in ethanol (10 mL). The reaction mixture was stirred at rt for 30 min. Then 1,1-diethoxy-5-hydroxypent-3-yn-2-one (**3a**) (0.18 g, 1.0 mmol) in ethanol (5 mL) was added dropwise and the mixture was stirred at 80 °C for an additional 3 h before the mixture was allowed to cool down to rt. Water (30 mL) and CH_2Cl_2 (30 mL) were added and the phases separated. The aqueous phase was extracted (CH_2Cl_2; 3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated. Flash chromatography (hexane/ethyl acetate; 90:10) gave **4a** (0.24 g, 80%; colorless liquid). IR (film): 2978 (s), 2932 (s), 2900 (s), 1738 (s), 1709 (s), 1611 (w), 1567 (m), 1429 (m), 1388 (m), 1366 (w), 1297 (s), 1273 (s), 1218 (m), 1205 (m), 1153 (m), 1093 (s), 1057 (s), 939 (w), 836 (w), 780 (m), 609 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (s, 1H), 4.76 (s, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 3.92 (s, 2H), 3.76–3.60 (m, 4H), 2.55 (s, 3H), 1.32–1.25 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.2, 164.7, 160.6, 140.0, 118.5, 113.6, 102.9, 63.8, 60.5, 34.0, 15.8, 15.0, 14.8. HRMS calcd. for $C_{15}H_{23}O_6^+$ $[M + H]^+$ 299.14946; found 299.14861.

Reaction with 2-Methylacetoacetate: Formation of 4,4-Diethoxy-2-diethoxymethyl-2-hydroxytetrahydrofuran (5) and 1,1-Diethoxy-3-(2-(diethoxymethyl)-2-(3-hydroxyprop-1-ynyl)-1,3-dioxolan-4-ylid-ene) prop-an-2-one (6)

1,1-Diethoxy-5-hydroxy-6-methylhept-3-yn-2-one (**3a**) (0.50 g, 2.7 mmol) reacted with ethyl 2-methylacetoacetate (0.39 g, 2.7 mmol) for 3 h at 80 °C. Flash chromatography (hexanes/ethyl acetate; 80:20) provided **5** (0.45 g, 60%; yellowish) and **6** (0.15 g, 15%; yellow) as liquids.

Data for 5. IR (film): 3469 (m), 2975 (s), 2931 (w), 2883 (m), 1727 (m), 1608 (m), 1481 (m), 1444 (w), 1390 (m), 1368 (w), 1322 (m), 1285 (m), 1238 (m), 1158 (m), 1106 (m), 1052 (s), 976 (m), 908 (m), 870 (m), 820 (m), 790 (m), 765 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.39 (s, 1H), 4.07 (d, $J = 9.1$ Hz, 1H), 3.81–3.47 (m, 9H), 2.39 (d, $J = 13.2$ Hz, 1H), 2.16 (d, $J = 13.4$ Hz, 1H), 1.27–1.19 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.8, 106.3, 104.1, 72.7, 65.5, 65.2, 59.0, 58.6, 42.5, 16.0. HRMS calcd. for $C_{11}H_{19}0_4^+$ $[M–OEt–H_2O]^+$ 215.12833; found 215.12734.

Data for 6. IR (film): 3450 (s), 2977 (s), 2932 (s), 2882 (m), 2252 (m), 1736 (s), 1689 (s), 1605 (s), 1480 (m), 1444 (w), 1372 (s), 1322 (m), 1270 (m), 1237 (s), 1158 (m), 1097 (s), 1069 (s), 1039 (s), 969 (m), 900 (s), 864 (s), 831 (w), 759 (w), 763 (m), 633 (w), 606 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.26 (m, 1H, X part of ABX system), 5.18 (dd, 1H, $J = 16.1$ and 1.66 Hz, A part of ABX system), 5.06 (dd, 1H, $J = 16.1$ and 1.74 Hz, B part of ABX system), 4.65 (s, 1H), 4.51 (s, 1H), 4.34 (s, 2H), 3.85–3.55 (m, 8H), 1.98 (bs, 1H), 1 28–1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 171.0, 106.4, 103.7, 102.7, 94.5, 86.8, 79.2, 72.3, 66.3, 63.5, 61.1, 51.5, 15.8, 14.8. HRMS calcd. for $C_{18}H_{29}0_8^+$ $[M + H]^+$ 373.18624; found 373.18581.

Reaction with Diethyl Malonate

Diethoxy-5-hydroxy-6-methylhept-3-yn-2-one (**3a**) (0.50 g, 2.7 mmol) reacted with diethyl malonate (0.43 g, 2.7 mmol) for 3 h at 80 °C. Flash chromatography (hexanes / ethyl acetate; 80:20) provided **6** (0.50 g, 50%; yellowish liquid).

SUPPORTING INFORMATION

Full experimental detail and ^1H and ^{13}C NMR spectra can be found via the Supplementary Content section of this article's Web page.

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