

REGIOSPECIFIC PREPARATION OF SUBSTITUTED FURANS FROM SOME 5-SUBSTITUTED DERIVATIVES OF 1,1-DIETHOXYALK-3-YN-2-ONES

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Leiv K. Sydnes

Department of Chemistry, University of Bergen, Allégaten 41, 5007 Bergen, Norway

(e-mail: leiv.sydnes@uib.no)

Abstract. A number of 1,1-diethoxyalk-3-yn-2-ones with a OH, t-BuPh₂SiO and RCOO substituent attached to C-5 give furans in up to excellent yield when treated with nucleophiles capable of reacting in a Michael fashion. The final product depends on the nature of the nucleophile and the substituent at C-5, but for a given combination of nucleophile and substituent the reaction is regiospecific. The nucleophile always ends up in position 4 of the furan ring whereas a formyl group or a diethoxymethyl moiety is in either position 2 or 3. All the syntheses perform well at a small and a large scale.

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1. Introduction

Furans have constituted a very important class of compounds in organic chemistry for decades and continue indeed to do so.¹⁻⁵ This is reflected by the rich and constantly growing flow of literature about furan chemistry in a large number of original papers and review articles in journals, books and annual reports.⁶⁻¹¹ At least three trends are emerging from this: The number of natural products containing a furan moiety is increasing, the furan motif is applied much more frequently to develop products of potential commercial value, and furans are becoming more important as reactants in organic synthesis.

The first trend is illustrated by chemical formulae in Figure 1. These structures clearly illustrate how the furan ring can be embedded in fascinating chemical motifs exhibiting biological activity and filled with multifunctional chemical entities. The substitution pattern at the ring also varies, and these variables may certainly make it a challenge to prepare furans with the right substituents in the right positions in an efficient

manner.¹²⁻¹⁴ The need for a good selection of robust synthetic methods that can furnish furans with the right regiochemistry is therefore apparent.

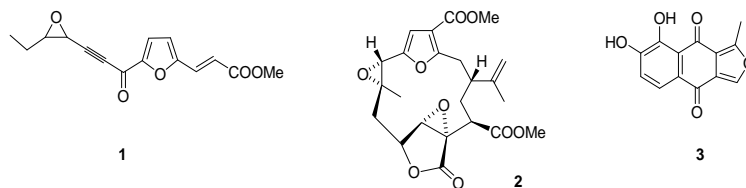


Figure 1. Some biologically active molecules found in nature; **1**: wyerone epoxide, isolated from infected broad beans (ref. 12); **2**: iopholide, isolated from the soft coral *S. polydactyla* (ref. 13); **3**: an isofuranonaphthoquinone, isolated from cultures of an *Actinoplanes* isolate (ref. 14).

The other trend is increased incorporation of the furan moiety in commercial products for various purposes. Synthesis of furan-containing compounds exhibiting biological activity of pharmaceutical interest is well known and has been ongoing since ranitidine (**4**), a histamine-2 blocker, was introduced in the 1970s.¹⁵ A more recent example is sulfonylfuran **5**, also an urea derivative, which has emerged as a potent inhibitor of endothelial lipase (Figure 2).¹⁶ A new development, however, is the use furan to make stimuli-responsive healable (self-healing) synthetic polymeric materials; their preparation is based on the ability of furans to undergo Diels-Alder reactions.^{17,18} Furans are also used in research aiming at developing optoelectronic devices where one of the key steps is modification of solid surfaces by deposition of furan-containing compounds and polymers.¹⁹⁻²¹

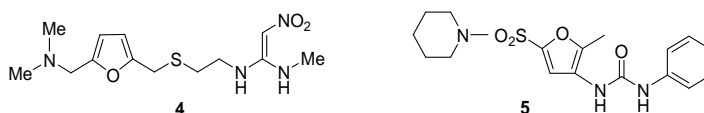


Figure 2. Furan-containing pharmaceuticals; **4**: ranitidine; **5**: a sulfonyl urea derivative.

As for the third feature, *viz.* the use of furans as reactants in synthesis, a lot of activity has been noted for a long time and furans continue to constitute a flexible and powerful group of reactants to apply to attach functionalized motifs to a range of compounds, often in a predictable fashion.²²⁻²⁸ Their synthetic role is mainly associated with four transformations. The most well-established reaction is hydrolysis, which utilizes the fact that furans, in addition to being aromatic, are bis(enol ethers) and undergo hydrolytic ring opening under acidic conditions to afford 1,4-dicarbonyl compounds (Figure 3, Eq. 1).^{29,30} Dicarbonyl compounds with a 1,4 relationship are much more difficult to synthesize by performing chain elongation than 1,3 and 1,5 analogues, and this has indeed made furans attractive precursors for the synthesis of 1,4-dials, 4-oxoaldehydes, and 1,4-diones. Another powerful reaction applied to furans is the Diels-Alder reaction.^{21,31-34} Furans were among the first dienes to be studied by Diels and Alder, and in recent years the 7-oxabicyclo[2.2.1]heptane derivatives thus obtained have appeared to be versatile intermediates for the preparation of a range of structural motifs, including tetrahydrofurans, cycloalkenes, tetrahydropyrans, and

benzene derivatives (Figure 3, eq. 2).³⁴ Furthermore, furans can also be oxidized and reduced by a number of reagents. By oxidation unsaturated dialdehydes, lactones and acetals are obtained (Figure 3, eq. 3),^{5,35-38} whereas hydrogenation, for instance under Birch reactions conditions, affords dihydrofurans in high yields, in general as isomeric mixtures if that is a possibility (Figure 3, eq. 4).²⁸

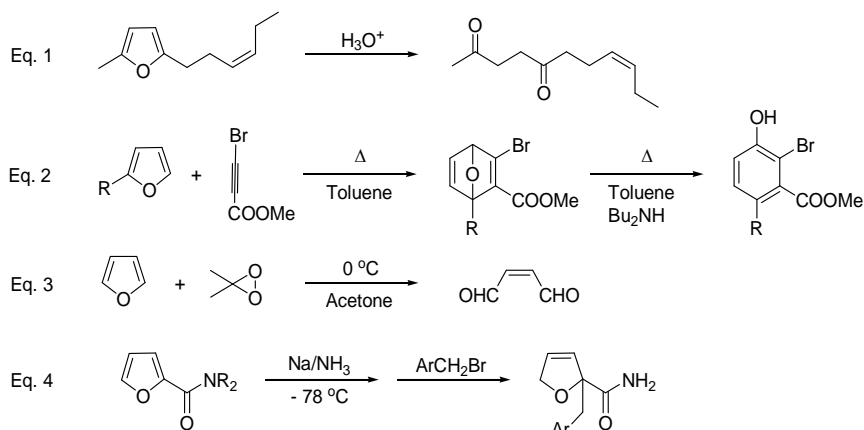


Figure 3. Some valuable furan transformations; eq. 1 from refs. 29 and 30; eq. 2 from ref. 34; eq. 3 from refs. 35 and 36; eq. 4 from ref. 28.

2. Syntheses of furans; a condensed overview

Furans have been synthesized since the advent of organic synthesis. Furfural, one of the first furans made, was prepared from vegetable residues as early as 1831. Over the years, this method was developed further, and acid-catalyzed dehydration of aldoses and ketoses emerged in due course as a transformation of commercial importance for the synthesis of a range of furan derivatives. The harsh reaction conditions and the complexity of the product mixtures, however, proved the need for milder and more versatile synthetic methodology for the preparation of furans with functionalized substituents, and over the years many such syntheses have been developed.

Most of the first methods developed were based on intramolecular cyclization of multi-carbonyl compounds. The most widely used method soon became the so-called Paal-Knorr reaction, which dates back to 1884 and is based on cyclization of 1,4-dicarbonyl compounds under acidic conditions.^{39,40} This method made a variety of substituted furans easily available, but the range increased considerably when it turned out that other stable substrates, *e.g.* epoxyketones,⁴¹ alk-2-yne-1,4-diols,^{42,43} and 2-buten-1,4-diones,⁴⁴ and intermediates generated *in situ*⁴⁵⁻⁴⁹ could be applied successfully instead. Three representative examples are shown in Figure 4.

Many syntheses based on 1,3-dicarbonyl compounds, *e.g.* 2,4-pentanedione and ethyl acetoacetate, have also been developed. Under basic conditions the corresponding enolates react with a variety of electrophiles including α -halogenated aldehydes, ketones and ethers (examples of the so-called Feist-Bénary reaction),⁵⁰⁻⁵⁵ alkyl sulfonium salts,⁵⁶ and propargyl halides,⁵⁷ and by multistep processes, combining

substitution, elimination, rearrangements and/or isomerization, furans are formed.⁵⁸⁻⁶⁰ Three illustrative examples are shown in Figure 5.

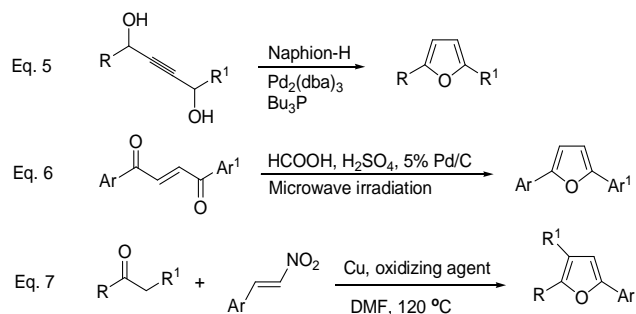


Figure 4. Some furan syntheses representing extensions of the Paal-Knorr reaction; eq. 5 from ref 42; eq. 6 from ref. 44; eq. 7 from ref. 49.

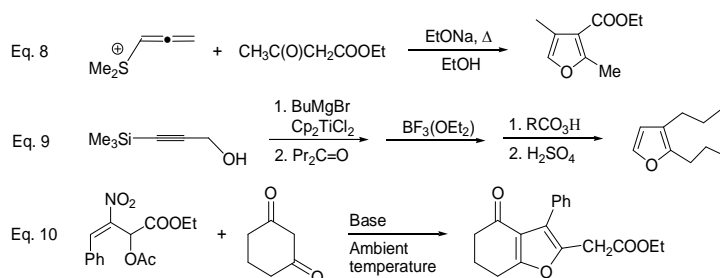


Figure 5. Three furan syntheses involving addition(s), elimination(s) and rearrangement(s); eq. 8 from ref. 56; eq. 9 from ref. 58; eq. 10 from ref. 55.

With ample access to a wide variety of substituted furans by application of the carbonyl-based methods mentioned further modifications, by taking advantage of the nucleophilic character of the ring itself⁶¹ or the carbanions obtained by treating furans and halofurans with a strong base such as butyllithium and sodium amide,⁶²⁻⁶⁵ have expanded the manifold of substituted furans enormously.²⁻⁵ In more recent years the scope has been extended much further by using transition metals as both counterions, *e.g.* Sn and Hg, and catalysts, for instance Zn, Pd and Ag.⁶⁶⁻⁷⁴ Some methods are illustrated in Figure 6.

The last couple of decades have also seen the development of a number of new methods for the synthesis of furans from acyclic functionalized molecules. Many of the methods are based on (mixed) transition-metal catalysis which induces several combinations of isomerizations, rearrangements and cyclizations and leads to reactions that are termed cycloisomerizations.⁷⁵⁻⁹⁰ An excellent overview of the substrates applied in such reactions, published recently by Gevorgyan and co-workers,¹¹ shows that attractive structural features include allenyl, ethynyl, and but-1-en-3-yl motifs appropriately substituted.^{91,92} Some illustrative examples of the latter are shown in Figure 7.

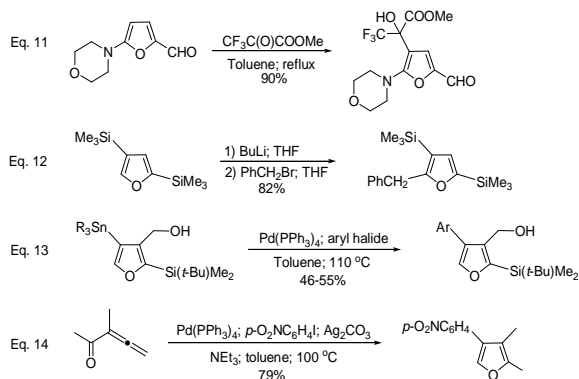


Figure 6. Some valuable furan transformations; eq. 11 from ref. 62; eq. 12 from ref. 65; eq. 13 from ref. 69; eq. 14 from ref. 70.

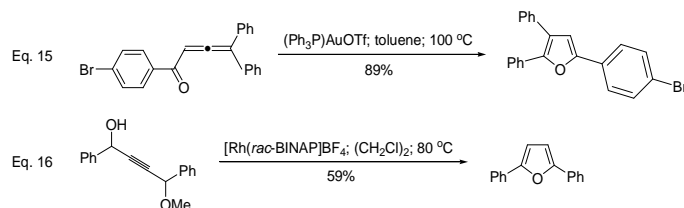


Figure 7. Two transition metal-mediated syntheses of furans; eq. 15 from ref. 91; eq. 16 from ref. 92.

3. Interlude

Our interest in furan synthesis was triggered by two independent developments. The first was a need for some functionalized furans which were so related structurally that we envisaged to prepare them in a few steps from a couple of furan substrates having a formyl group either directly attached to the heterocycle or incorporated in another substituent attached to the ring. Review of the literature revealed that although an enormous number of methods for making furans are available, formylated furans are not easy to synthesize in a regiospecific manner. The reason for this is probably related to the fact that many furan syntheses involve at least one carbonyl group in the ring-closing step, and if an aldehyde motif is present at this stage of the synthesis, either as a formyl group or an acetal moiety, the aldehyde group is in a vulnerable position and might in fact be preferentially attacked. This problem could be resolved if the formyl group was rendered essentially inactive by some sort of deactivation caused by neighboring groups, but what these groups should look like was not clear to us.

At about this point in time interesting results from studies of the chemical properties of 1,1,2-trihalocyclopropanes emerged and came to our assistance. First, it was discovered that such compounds undergo ring opening when exposed to 50% sodium hydroxide in the presence of triethylbenzylammonium chloride, dichloromethane and ethanol and give mixtures of acetylenic ketals and acetals;⁹³⁻⁹⁶ then it was revealed that the composition of the product mixture was sensitive to the nature of the other substituents attached to the ring;^{97,98} and finally it was shown that regiospecific ring opening resulted if certain polar groups were present.⁹⁸ Among the compounds prepared on the basis of these observations was 1,1,2,2-

tetraethoxybut-3-yne (**TEB**), whose acetal group turned out to be unreactive under most of the conditions applied to convert acetals into aldehydes.⁹⁹⁻¹⁰² The **TEB** ketal, however, was transformed to the **TEB** ketone under the same conditions, and it is therefore clear that the α,β -unsaturated acetylenic ketone stabilized the acetal motif immensely, and this encouraged us to try to make formyl-substituted furans by means of 1,1-diethoxyalk-3-yn-2-ones properly substituted in position 5.

4. Synthesis of 5-substituted 1,1-diethoxyalk-3-yn-2-ones

The key to the successful conversions of **TEB** to furans is the ease with which first 1,1,2-tetraethoxyalk-3-yn-5-ols (**6**) and then the corresponding 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones (**7**) can be obtained.¹⁰³⁻¹¹⁰ These ketones were expected to be only a Michael addition away from compounds known to form furans under appropriate conditions, but in addition they should easily be converted to other ketones that have a potential to furnish furans as well. So far we have focused on modification by silylation and esterification following the plan outlined in Figure 8, and the results of our studies so far are reported here.

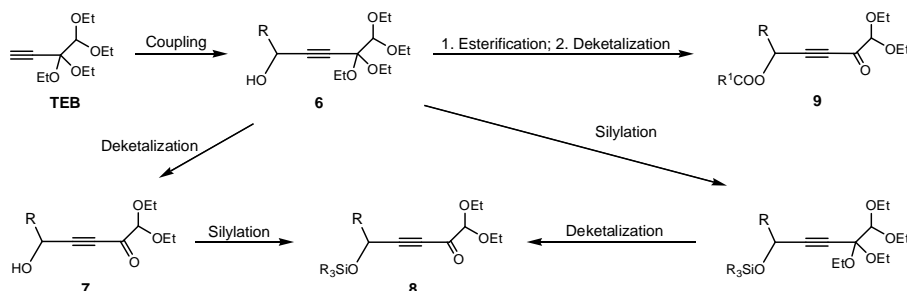
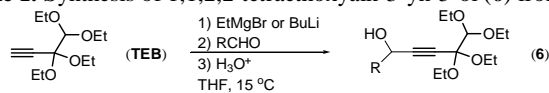


Figure 8. Outline of the syntheses of the α,β -unsaturated acetylenic ketones used to prepare the furans discussed in the chapter. The starting material is 3,3,4,4-tetraethoxybut-1-yne (**TEB**), easily available in high yield from ethyl vinyl ether in four steps.⁹⁹⁻¹⁰¹

The basis for successful furan syntheses would have to be easy access to propargylic alcohols **6** and this was indeed achieved by reacting **TEB** acetylide with aldehydes (Table 1).^{103,106,107} The yields, in many cases good to excellent, were slightly lower when the acetylide was made with butyllithium than ethylmagnesium bromide.⁹⁸

Table 1. Synthesis of 1,1,2-tetraethoxyalk-3-yn-5-ol (**6**) from **TEB**.



Entry	R	Product	Isolated yield (%)
1	H	6a	94
2	Methyl	6b	92
3	Isopropyl	6c	78
4	<i>tert</i> -Butyl	6d	55
5	Hexyl	6e	87
6	Heptyl	6f	82
7	Phenyl	6g	70
8	<i>para</i> -Methylphenyl	6h	75

A drop in yield was also observed when the steric crowding around the carbonyl group was increased (in Table 1, compare a yield of 94% with methanal (entry 1) with only 55% when 2,2-dimethylpropanal was employed (entry 4)).

With **6** at hand, several groups of 5-substituted α,β -unsaturated acetylenic ketones suitable for Michael addition were easily made. The simplest were the corresponding 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones (**7**), which were isolated in better than 90% yield when deketalization was carried out using moist acetone containing a small amount of an acidic resin (Dowex 50W) (Table 2).^{100,106} It is noteworthy that the acetal group remained untouched under these conditions, conceivably due to deactivating interactions between the triple bond and the acetal moiety via either the ketal motif or the carbonyl group.

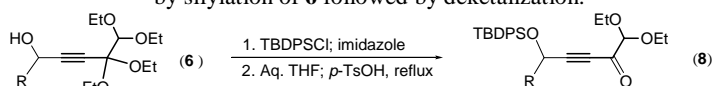
Table 2. Synthesis of 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones (**7**) by deketalization of **6**.

Starting material	R	Product	Isolated yield (%)
6a	H	7a	93
6b	Methyl	7b	91
6c	Isopropyl	7c	90
6e	Hexyl	7e	95
6f	Heptyl	7f	95
6g	Phenyl	7g	92
6h	<i>para</i> -Methylphenyl	7h	92

In order to facilitate Michael addition of strongly basic nucleophiles to ketones **7**, protection of the hydroxyl group was deemed necessary. Since it was desirable to keep the acetal moiety untouched during the subsequent deprotection, it was regarded as attractive to protect the alcohols as the corresponding silyl ethers (**8**). This should be straightforward to achieve in a two-step synthesis from hydroxyketal **6**, either by silylation of hydroxyketone **7**, or by silylation of **6** followed by deketalization of the resulting silyl ether. The best results were obtained when the latter approach was adopted and *tert*-butyldiphenylsilyl chloride (TBDPSCI) was used instead of trimethylsilyl chloride (TMSCl). One important reason for this is that TBDPS ethers are about 10^6 times more stable to hydrolysis under acidic conditions than the TMS analogues.¹¹⁰ The change from TMS to TBDPS protection was a success; not only were propargylic alcohols **6** converted to the corresponding TBDPS ethers in better than 80% yield in all cases but one, the deketalization proceeded also smoothly and furnished the 5-siloxyated conjugated alkynones **8**, in almost quantitative yield in the best cases (Table 3).¹¹¹

Ester derivatives **9** also turned out to be flexible substrates capable of affording furans when subjected to Michael reaction conditions with dialkylcuprates. They were easily obtained by esterification of **6** with carboxylic anhydrides, followed by deketalization employing *para*-toluenesulfonic acid at somewhat elevated temperature. These esters were isolated in up to 80% total yield from **TEB** whether the syntheses were carried out on a small or a large scale (Table 4).¹⁰⁶ Steric congestion influenced as expected the yield somewhat in both reactions, but the yield was less sensitive to this parameter in the synthesis of **9** than the preparation of **8** (compare the results in Table 4 with those in Table 3).¹⁰⁶

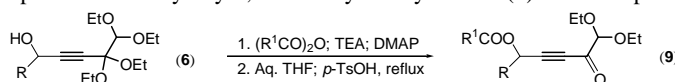
Table 3. Synthesis of 1,1-diethoxy-5-(*t*-butyldiphenylsiloxy)alk-3-yn-2-ones (**8**) by silylation of **6** followed by deketalization.



Substrate	R	Product	Isolated yield, silylation (%)	Isolated yield, deketalization (%)	Overall isolated yield from 6 (%)
6a	H	8a	94	56	50
6b	Methyl	8b	82	80	66
6c	Isopropyl	8c	82	97	80
6e	Hexyl	8e	84	94	79

^aTBDPSCl; Et₃N; DMAP; CHCl₃; room temperature. ^b*p*-TsOH; THF/H₂O; reflux.

Table 4. Preparation of 5-acyloxy-1,1-diethoxyalk-3-yn-2-one (**9**) in two steps from alcohol **6**.



R	R ¹	Isolated yield, esterification (%)	Isolated yield, deketalization (%)	Product	Overall isolated yield from TEB (%)
H	CH ₃	95	90	9a	80
H	<i>i</i> -Pr	87	95	9b	78
H	Ph	76	90	9c	64
CH ₃	CH ₃	96	91	9d	80
CH ₃	<i>i</i> -Pr	82	88	9e	66
CH ₃	Ph	85	91	9f	71
<i>i</i> -Pr	CH ₃	90	95	9g	67
<i>i</i> -Pr	<i>i</i> -Pr	84	92	9h	60
<i>i</i> -Pr	Ph	84	92	9i	60
<i>t</i> -Bu	CH ₃	90	89	9j	44
<i>t</i> -Bu	<i>i</i> -Pr	80	88	9k	39
<i>t</i> -Bu	Ph	82	85	9l	38
Ph	CH ₃	81	94	9m	53
Ph	<i>i</i> -Pr	80	98	9n	55
Ph	Ph	75	95	9o	50
C ₆ H ₁₃	CH ₃	90	92	9p	72
C ₆ H ₁₃	<i>i</i> -Pr	84	90	9q	66
C ₆ H ₁₃	Ph	85	91	9r	67

5. Furans from 1,1-diethoxy-5-hydroxyalk-yn-2-ones

5.1. With secondary amines

This furan synthesis was inspired by the discovery that when 1,1-diethoxybut-3-yn-2-one was treated with amines, diethylamine underwent Michael addition once in a stereospecific manner and afforded (3*E*)-1,1-diethoxy-4-diethylaminobut-3-en-2-one in excellent yield.¹¹² If 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones (**7**) would react in a similar way, the corresponding (3*E*)-1,1-diethoxy-4-diethylamino-5-hydroxyalk-3-en-2-ones, with the hydroxyl and carbonyl groups ideally line up for hemiketal generation followed by furan formation, should be obtained (Figure 9). That was indeed achieved when these substrates were reacted with several secondary amines.¹¹³ Most reactions were carried out with diethylamine which reacted quickly and

furnished one product only, *viz.* the corresponding 5-R-substituted 2-diethoxymethyl-4-(diethylamino)furan (**10**), in better than 70% yield (Table 5). No trace of any of the postulated intermediate Michael adducts was detected in any of the reactions, and this indicates that the carbonyl group is activated toward nucleophilic attack due to electronic impact from the diethoxymethyl group attached to it.¹¹³

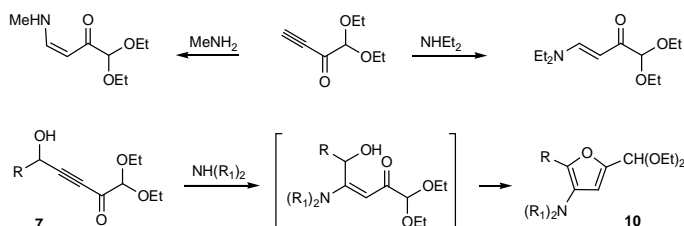


Figure 9. Michael addition of amines to α,β -unsaturated acetylenic ketones.

Table 5. Synthesis of 4-dialkylaminofurfural diethyl acetals (**10**) by reacting 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones (**7**) with secondary amines.

Entry	Substrate	R	(R ¹) ₂	Product	Isolated yield (%)
1	7a	Hydrogen	Et ₂	10a	70
2	7b	Methyl	Et ₂	10b	81
3	7b	Methyl	(CH ₂) ₅	10c	69
4	7b	Methyl	(CH ₂) ₂ O(CH ₂) ₂	10e	66
5	7b	Methyl	(CH ₂) ₄	10f	60
6	7c	Isopropyl	Et ₂	10g	78
7	7d	Hexyl	Et ₂	10h	77
8	7e	Phenyl	Et ₂	10i	75

Other secondary amines turned out to react in the same way as diethylamine. Thus, piperidine, morpholine and pyrrolidine were almost as efficient as diethylamine and furnished the expected 4-amino-substituted furfural diethyl acetals in about 60% yields (Table 5, entries 3-5).¹¹³ However, when less nucleophilic secondary amines were employed, *e.g.* diphenylamine, no reaction occurred at all.

The stability of furfural acetals **10** appeared to be somewhat amine dependent in the sense that all the furans except pyrrolidine derivative **10f** were stable when kept dry at and below room temperature.¹¹³ Why the pyrrolidine derivative is so special is still not clear, but a key point is probably that the interaction between the nitrogen electron pair and the π system of the furan ring is different for this compound due to conformational constraints imposed by the butylene chain in the pyrrolidine ring.

An obvious consequence of the mechanism for furan formation is that if tertiary propargylic ketoalcohols are used, furan formation would not take place. And indeed, reacting 1,1-diethoxy-5-hydroxy-5-methylhex-3-yn-2-one (**7i**) with diethylamine gave no furan at all; instead, 4-ethoxy-2-diethoxymethyl-4-diethylamino-4,5-dihydro-5,5-dimethylfuran (**11**) was obtained in 86% yield.¹¹³ This compound turned out to be unstable unless it was dried thoroughly; even when exposed to ambient air at room temperature, **11** was converted to the corresponding ketone, 5-diethoxymethyl-2,2-dimethylfuran-3(2*H*)-one (**12**), conceivable as outlined in Figure 10.¹¹³

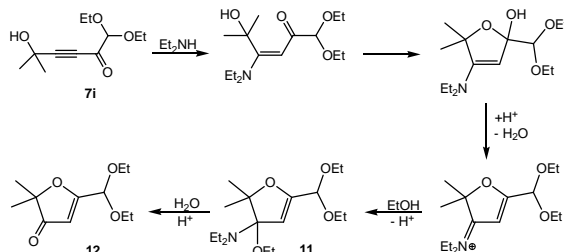
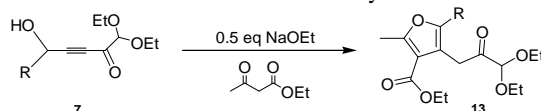


Figure 10. No furan formation takes place with tertiary propargylic ketoalcohol **7i**.

5.2. With the ethyl acetoacetate monoenolate

The reaction between ketones **7** and the monoenolate of ethyl acetoacetate (**EAA**) proceeded smoothly when **7** was treated with a 1:1 mixture of $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{COOEt}$ and its enolate.¹¹⁴ Although several reactions can be envisaged to occur after conjugate addition of the enolate has taken place, one main product was obtained as long as 1,1-diethoxy-5-hydroxypent-3-yn-2-one (**7a**) and corresponding secondary hydroxylated ketones were applied, *viz.* the corresponding 5-substituted 2-methyl-3-ethoxycarbonyl-4-(3,3-diethoxy-2-oxopropyl)furan (**13**). The reaction was slow at room temperature, but at 80 °C all the starting material was consumed fairly quickly and furnished **13** in excellent yields (Table 6).¹¹⁴

Table 6. Preparation of furans **13** from ketone **7** and ethyl acetoacetate under basic conditions.



Starting material	R	Reaction time (hr)	Product	Isolated yield (%)
7a	H	3	13a	80
7b	Methyl	3	13b	74
7c	Isopropyl	3	13c	90
7e	Hexyl	3	13e	84
7f	Heptyl	3	13f	70
7g	Phenyl	5	13g	85
7h	<i>para</i> -Methylphenyl	5	13h	88

A reaction mechanism for the conversion of hydroxyketone **7** to furan **13** is outlined in Figure 11.¹¹⁴ Attack by ethyl acetoacetate monoenolate (**EAA**⁻) affords intermediate **A** which subsequently reacts either with **EAA** and form **EAA**⁻ and intermediate **B**, or with **B** already formed and afford another molecule of **B** and **B**⁻. The latter carbanion is stabilized by carbanion delocalization, *e.g.* resonance forms **I-IV** in the brackets in Figure 11 (not exhaustive), and its three carbonyl groups may react intramolecularly with a nucleophile and undergo cyclization. Interestingly, the carbonyl group in the acetyl group originally belonging to **EAA** is specifically attacked by the only nucleophile present in **B**, *viz.* the OH group or the corresponding alkoxide, and the resulting intermediate (**C**) then suffers dehydration and furnishes intermediate **D** which ultimately gives furan **13** by isomerization.¹¹⁴

From the mechanism in Figure 11, it is clear that if furan formation is going to take place, intermediate **C** must be able to undergo dehydration. This transformation should be prevented if 2-substituted analogues

of ethyl acetoacetate are used, and this was indeed the case. When 1,1-diethoxy-5-hydroxy-3-pentyn-2-one (**7a**) was reacted with ethyl 2-methyl-3-oxobutanoate monoenoate, no furan was detected; instead two other heterocyclic compounds were formed, *viz.* 4,4-diethoxy-2-diethoxymethyl-2-hydroxytetrahydrofuran (**14**) and the *Z* isomer of 1,1-diethoxy-3-(2-(diethoxymethyl)-2-(3-hydroxyprop-1-ynyl)-1,3-dioxolan-4-ylidene)propan-2-one (**15**) (Figure 12), in 60% and 15% yield, respectively.¹¹⁴

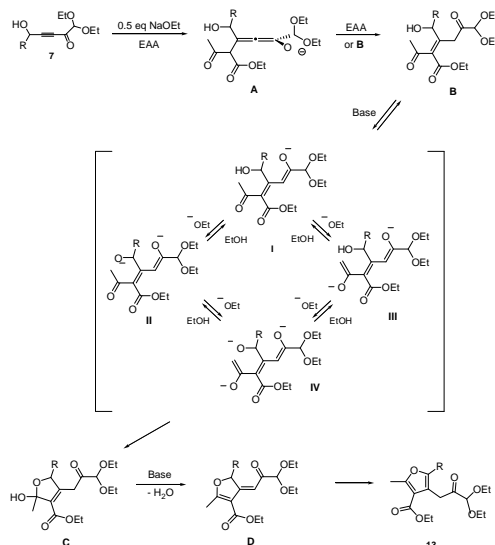


Figure 11. Reaction mechanism for the formation of furans **13** from ketones **7** and EEA.

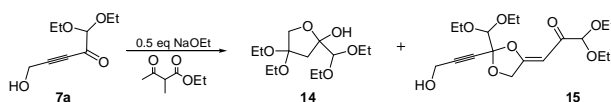


Figure 12. Reactions of **7a** with ethyl 2-methyl-3-oxobutanoate monoenoate.

5.3. With the diethyl malonate enolate

The clean formation of furans in the reactions between **7** and the monoenoate of ethyl acetoacetate is the consequence of a regioselective attack of the carbonyl moiety of the acetyl group over that of the ester motif in intermediate **B** (Figure 11). This selectivity may be due to a combination of several factors including the stereochemistry of the double bond between C-2 and C-3, the different electrophilicity of the carbonyl groups in the acetyl and ester motifs, and their different ability to form hydrogen bonds. In order to make attack of a keto function impossible and achieve attack of an ester group instead, ethyl acetoacetate was replaced with diethyl malonate but otherwise reacted under the same conditions. However, this idea did not materialize; as exemplified by the reaction between 1,1-diethoxy-5-hydroxypent-3-yn-2-one (**7a**) and diethyl malonate, the only product obtained was 1,3-dioxolane **15**, which is formed by dimerization of **7a** and was isolated in 50% yield (Figure 13).¹¹⁴

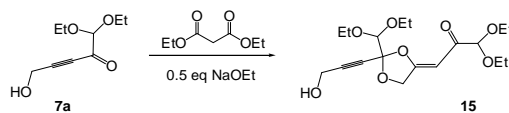


Figure 13. Reactions of **7a** with diethyl malonate

6. Furans from 1,1-diethoxy-5-(*t*-butyldiphenylsiloxy)alk-3-yn-2-one with dialkylcuprates

Furans have also been prepared from silyl ethers **8** following a two-step procedure. First, monoalkylation was carried out by conjugate addition of lithium dimethylcuprate, whereas the second step was desilylation applying tetrabutylammonium fluoride.¹¹¹ In the first reaction the corresponding 5-(*t*-butyldiphenylsiloxy)-1,1-diethoxy-4-methylalk-3-en-2-ones (**16**) were obtained in up to excellent yield (Table 7). With one exception the compounds were mixtures of the *E* and *Z* isomers and this is a problem because only the latter are capable of forming furans.¹¹¹ The exceptional case occurred when 5-(*t*-butyldiphenylsiloxy)-1,1-diethoxy-4-methyl-3-yn-2-one (**8a**) was reacted with dimethylcopper lithium and afforded (3*E*)-1,1-diethoxy-4-methyl-5-(*t*-butyldiphenylsiloxy)alk-3-en-2-one (*E*-**16a**) as the only acyclic conjugated ketone in 39% yield. Thus, the reaction seemed to be stereospecific, but that appeared in fact to be a deception. Instead, we envisage that some of the *Z*-**16a** isomer is formed, but this compound is unstable under the reaction conditions and reacts further to give 4-(*t*-butyldiphenylsiloxy)-5-ethoxy-3-methylcyclopent-2-enone (**17**) in low yield (< 5%) (Figure 14).¹¹¹

Table 7. Synthesis of 5-(*t*-butyldiphenylsiloxy)-1,1-diethoxy-4-methyl-3-alken-2-ones (**16**) by treatment of **8** with Me₂CuLi.

Starting material	R	Product	<i>E</i> : <i>Z</i>	Isolated yield of 16 (%)
8a	H	16a	100 : 0	39
8b	Methyl	16b	59 : 41	83
8c	Isopropyl	16c	57 : 43	96
8e	Hexyl	16d	52 : 48	93

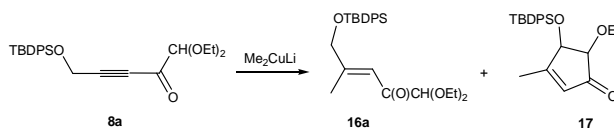


Figure 14. Treatment of **8a** with lithium dimethylcuprate; TBDPS = *tert*-butyldiphenylsilyl.

The reason for the deviating behavior of **8a** is still not clear, but conceivably it is the result of conformational effects caused by the presence of a methylene group at C-5 in this compound instead of the alkylated methylene group present at this position in its analogues. In the former case a methylene proton at C-5 becomes more available for abstraction for steric and statistical reasons, and this opens for the sequential steps illustrated in Figure 15. The first step is *cis* attack of lithium dimethylcuprate on the triple bond, which is assumed to give carbanion **I** (C-copper enolate).¹¹⁵⁻¹¹⁸ This intermediate equilibrates with its *trans* isomer (**II**) which can abstract a propargylic proton directly or *via* its O-copper enolate (**III**) and form carbanion **IV**.

The latter carbanion then gives *E*-**16a** upon hydrolysis, but it can also isomerize, due to its allylic nature, to its geometrical isomer **V**, which can undergo cyclization by substitution at C-1, in an S_N2 type reaction with ethoxide as the leaving group. This series of events will furnish **17** as a by-product instead of the *Z* isomer of **16a**. Since similar substitution reactions usually require boron trifluoride activation,^{119,120} it is invoked that the nucleophilicity of the carbanion in **V** is enhanced by the α -alkoxy group whereas the electrophilicity of C-1 is increased by the neighboring conjugated keto moiety.

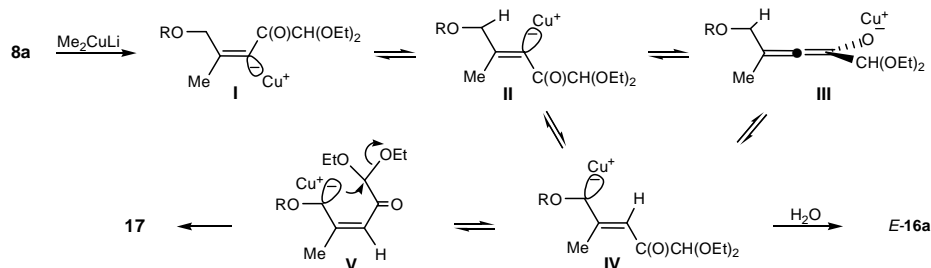


Figure 15. A sequence of equilibrations and transformations explaining the formation of *E*-**16a** and **17** in the reaction between **8a** and Me_2CuLi ; TBDPS = *tert*-butyldiphenylsilyl.

Deprotection of *Z*-**16** was then performed to generate the corresponding allyl alcohols which should attack the carbonyl group at C-2, furnish 2-hydroxydihydrofuran(s) as the primary product(s), and react further to form furans (Figure 16). Many methods are available for cleavage of TBDPS ethers,¹¹⁰ but we settled for the classical method developed by Hanessian and co-workers and used tetrabutylammonium fluoride (TBAF) in THF at room temperature.^{121,122} When (*Z*)-**16b**, (*Z*)-**16c** and (*Z*)-**16e** were reacted under these conditions, the predicted reaction took place and gave the expected furfurals, *viz.* 5-*R*-4-methylfuran-2-carboxaldehyde (**18**).¹²³ However, the isolated yields were disappointingly low due to formation of several by-products, which also made the isolation cumbersome.

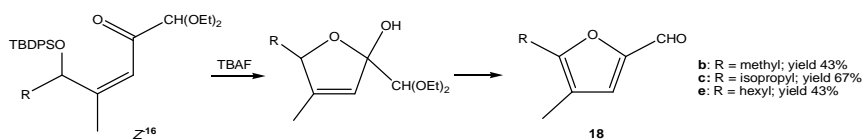


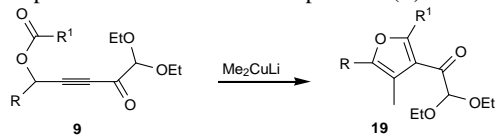
Figure 16. Conversion of (*Z*)-**16** to furfural **18**.

7. Furans from 1,1-diethoxy-5-acyloxyalk-3-yn-2-one with dialkylcuprates

Most syntheses of furans from ketoesters **9** have been carried out with the Gilman version of Me_2CuLi at temperatures ranging from room temperature to $-78\text{ }^\circ\text{C}$, and without exception the corresponding 3-(2,2-diethoxyacetyl)-4-methylfuran (**19**) was obtained in fair to good yield with a predictable substitution pattern (Table 8).¹⁰⁶ The yield increased significantly when the temperature was lowered from $0\text{ }^\circ\text{C}$ to the $-60\text{ }^\circ\text{C}$, but lowering the temperature even further gave no improvements; in fact in some cases the yield even dropped.¹⁰⁶

A mechanistic proposal for the reaction is outlined in Figure 17.¹⁰⁶ The initial step is attack of the carbon-carbon triple bond in a 1,4 fashion (conjugate addition). The steric congestion around C-5 varies considerably among the ketoesters so the outcome of the addition reaction was expected to show variation as well. That was indeed the case, but as the results in Table 8 show, *the furan yield generally increased as the steric crowding increased.*

Table 8. Isolated yields of furans **19** synthesized by treating ketoesters **9** with Me₂CuLi at temperatures between room temperature (rt) and -78 °C.



Entry	9	Furan	Isolated yield of 19 (%)			
			-78 °C	-60 °C	0 °C	rt
1	9a	19a		50	10	
2	9b	19b	45	45		
3	9c	19c		40	25	
4	9d	19d	46	48	20	
5	9e	19e	47	50	26	
6	9f	19f		53	40	
7	9g	19g	74	81 ^a	70	56
8	9h	19h		75	51	
9	9i	19i		47	45	
10	9j	19j	72	70	30	
11	9k	19k	68	68	25	
12	9l	19l		52		
13	9m	19m		52	24	
14	9n	19n		60	41	
15	9o	19o		53	35	
16	9p	19p	50	70	18	26
17	9q	19q	67	69	28	
18	9r	19r		50	32	

The temperature influence is for instance reflected in the outcome of the reactions with isobutyrate **9b**, **9e**, **9h**, and **9k**, which at -60 °C gave the corresponding furans in 45, 50, 75, and 68% yield, respectively, as R¹ changes from H via Me and *i*-Pr to *t*-Bu (see Table 8, entries 2, 5, 8, and 11, respectively).¹⁰⁶ This general trend is further underlined by reactions with ketoesters **9g** and **9h**; when they are treated with the butyl and *t*-butyl equivalents of the Gilman reagent (Me₂CuLi), the sterically quite congested furans **20** and **21**, respectively, are obtained in excellent and acceptable yield, respectively (Figure 18).¹⁰⁶

A consequence of the reaction mechanism outlined in Figure 17 is that if the propargylic motif in ketoesters **9** comes from a tertiary alcohol, no furan formation can occur because dehydration becomes impossible. In order to check out if this reasoning is correct, **6i** was made and converted to the corresponding ester 5,5-diethoxy-1,1-dimethyl-4-oxopent-2-ynyl acetate (**22**), which was treated with Me_2CuLi under the same conditions that led to furan formation. Only one product was detected, *viz.* 2,2-diethoxy-1-(2,5-dihydro-2-hydroxy-2,4,5,5-tetramethylfuran-3-yl)ethanone (**23**) (Figure 19), which indeed is the compound expected to be formed when the last step in the reaction sequence in Figure 17 is made impossible.¹⁰⁶

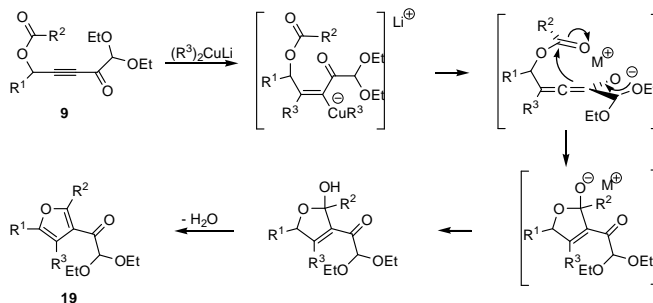


Figure 17. Suggested reaction mechanism for furan formation by cuprate addition to **9**; M^+ denotes an unknown cationic species, formed from Li^+ , CuR^3 , and one or several cuprate species.

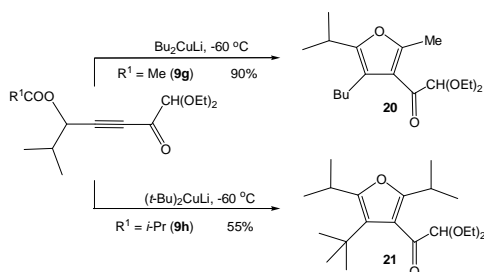


Figure 18. Synthesis of congested furans from ketoesters **9g** and **9h**.

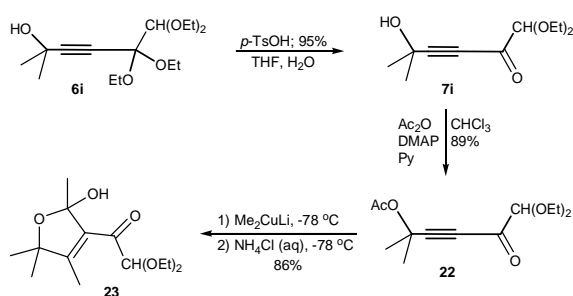


Figure 19. Conjugate addition of the Gilman reagent to **22**.

8. Furans from 5,5-disubstituted 1,1-diethoxy-5-hydroxypent-3-yn-2-ones generated *in situ*

In the furan synthesis described so far, the ketal moiety in **6** has been converted to the corresponding ketone before the substrate has been exposed to the reagent and reaction conditions initiating the cyclization leading to furan formation. However, such an approach is not necessarily a requirement, and this was taken advantage of in the TEB-mediated synthesis of a few furano[2,3-*b*]quinoxaline derivatives from a selection of 3-arylquinoxalin-2(1*H*)-ones (**24**).¹²⁴

The simple synthetic scheme followed for the synthesis of the substrates is included in Figure 20.¹²⁴ The best outcome was obtained by treating **24** with sodium hydride *before* TEB acetylide was added and the corresponding 3-(4,4,5,5-tetraethoxy-1-hydroxy-1-arylpent-2-ynyl)quinoxaline-2(1*H*)-ones (**25**) were formed. When refluxed in aqueous THF in the presence of *para*-toluenesulfonic acid (*p*-TsOH), **25** underwent cyclization and furnished furans.¹²⁴ Irrespective of the reaction conditions chosen for the cyclization two products were consistently formed, *viz.* the corresponding (*E*)-1,1-diethoxy-3-(3-hydroxy-3-arylfuro[2,3-*b*]quinoxalin-2(3*H*)-ylidene)propan-2-one (**26**) and 1,1-diethoxy-3-hydroxy-3-(3-arylfuro[2,3-*b*]quinoxalin-2-yl)propan-2-one (**27**) (Figure 20).¹²⁴ The substituent attached to the phenyl ring did not influence the outcome significantly; whether the aryl group contained hydrogen only, an electron-donating group (Me), or an electron-withdrawing group (Cl, NO₂), the result was essentially the same: the α,β -unsaturated ketone **26** and furan **27** were formed in a good total yield in an approximate ratio of 2:1 (Table 9). In all cases the products could be easily separated by flash chromatography, giving **26** in better than 50% yield and **27** in better than 20% yield.¹²⁴

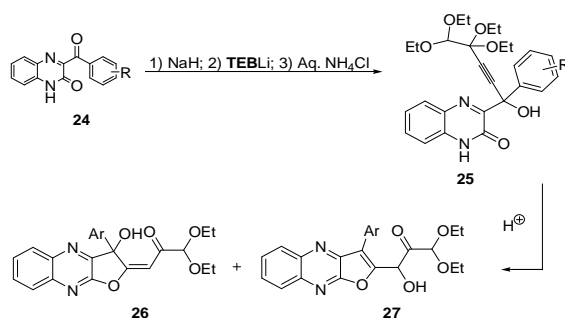


Figure 20. Synthesis of furan derivatives **26** and **27** from 3-arylquinoxalin-2(1*H*)-ones (**24**) and TEB acetylide.

Table 9. Synthesis of furan **27** from 3-arylquinoxalin-2(1*H*)-ones (**24**) as outlined in Figure 20.

24 - 27	Aryl	Isolated yield (%)			Overall isolated yield of 27 (%)
		25	26	27	
a	Ph	76	58	27	21
b	3-Me-Ph	91	63	28	25
c	4-Me-Ph	81	61	26	21
d	3-Cl-Ph	75	57	31	23
e	4-Cl-Ph	80	67	25	20
f	3-NO ₂ -Ph	92	51	21	19

A reaction mechanism for the formation of **26** and **27** has been proposed (Figure 21).¹²⁴ The first step is acid-catalyzed deketalization of **25**, which affords the corresponding α,β -unsaturated ketone **A**. This ketone is ideally set for Michael addition in a 5-*exo-dig* fashion, a reaction which is quite favorable according to the so-called Baldwin's rules,¹²⁵ and has solid literature precedence.¹²⁶⁻¹²⁹ This leads to ring closure and formation of enol **B**, and subsequent tautomerization gives ketone **26** in a stereospecific fashion. The presence of the tertiary OH group in **26**, which is both allylic and benzylic, destabilizes the compound under acidic conditions, and proton-catalyzed rearrangements take place by elimination and addition of water and formation of intermediates **C**, **D** and **E**, and ultimately furan **27**.

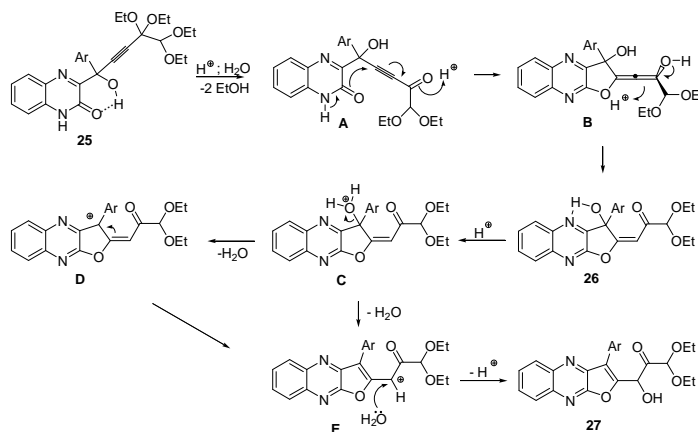


Figure 21. Proposed mechanism for the formation of furan derivatives **26** and **27**.

9. Concluding remarks

As stated in section 3, the purpose with this investigation has been and still is to prepare formyl-containing furans that are stable enough to function as starting materials for the synthesis of even more functionalized furans. This aim has indeed been achieved in the sense that Michael addition of various nucleophiles to a range of 5-substituted 1,1-diethoxyalk-3-yn-2-ones has given, in up to excellent yield, a large number of stable furans containing in most cases a diethyl acetal motif. In order to succeed completely, however, it remains to be proved that deprotection of the acetal indeed is an effective reaction and occurs in a predictable fashion and that the aldehyde group thus released can be utilized, preferably in a specific manner, in the presence of other functional groups.

Such investigations are currently in progress, and results obtained with furfural acetal **10** are quite encouraging as the representative example summarized in Figure 22 shows. Smooth deprotection was experienced with acid-catalysed hydrolysis (*para*-toluenesulfonic acid) in moist THF, and when a Wittig reaction subsequently was performed, the corresponding 2-ethenyl furans were obtained in up to excellent yield as well.¹³⁰ The work will continue and results will be published in due course.

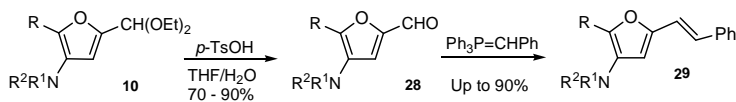


Figure 22. A representative preparation of a 2-ethenylfuran derivative (**29**) by performing deprotection of acetal **10** followed by a Wittig olefination of the resulting aldehyde (**28**).

Acknowledgments

I want to express my sincere thanks to the many research students in my group that have contributed to the results presented here. Through hard work, they became skilful practioners of organic synthesis and developed the creativity needed to uncover many interesting transformations made available to us due to the development of the TEB synthesis. The research in my group has been made possible by funding from the Research Council of Norway (through the KOSK Programme), Norsk Hydro, and the University of Bergen, for which I am grateful. But even more appreciation is extended to the MUNIN Foundation for unflinching support through years when funding from other sources dried up.

References

1. Stevens, T. S. in *Chemistry of Carbon Compounds*; Rodd, E. H., Ed.; Elsevier Publishing Company: Amsterdam, NL, 1957; vol. IVA, chap. III, pp. 138-202.
2. Donnelly, D. M. X.; Meegan, M. J. in *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 4, pp 657- 712.
3. Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*, 3rd ed.; Chapman & Hall, London, UK, 1995; chap. 15, pp. 278-300.
4. Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry. Five-Membered Heterocycles*; Springer, Berlin, DE, 1999; vol. II, chap. 3, pp. 82-121.
5. Gilchrist, T. L. *Heterocyclic Chemistry*, third edition; Longman, London, UK, 1997; chap. 6.3, pp. 209-221.
6. Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. J. *Tetrahedron* **1998**, *54*, 1955-2020.
7. Hou, X. L.; Yang, Z.; Wong, H. N. C. in *Progress in Heterocyclic Chemistry*; Gribble, G. M., Joule, J. A., Eds.; Pergamon Press: Oxford, UK, 2003; vol. 15, pp. 167-205.
8. Katritzky, A. R.; Hur, D.; Kirichenko, K.; Ji, Y.; Steel, P. J. *ARKIVOC* **2004**, 109-121.
9. Yeung, K.-S.; Yang, Z.; Peng, X.-S.; Hou, X.-L. in *Progress in Heterocyclic Chemistry*; Gribble, G. M., Joule, J. A., Eds.; Elsevier: Amsterdam, NL, 2011; vol. 22, pp. 181-216.
10. Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395-3442.
11. Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084-3213.
12. Delmarche, I.; Mosset, P. *Tetrahedron Lett.* **1993**, *34*, 2465-2468.
13. Bowden, B. F.; Coll, J. C.; Wright, A. D. *Aust. J. Chem.* **1989**, *42*, 757-763.
14. Zhang, Q.; Peoples, A. J.; Rothfeder, M. T.; Millett, W. P.; Pescatore, B. C.; Ling, L. L.; Moore, C. M. *J. Nat. Prod.* **2009**, *72*, 1213-1215.
15. Bradshaw, J.; Brittain, R. T.; Clitherow, J. W.; Daly, M. J.; Jack, D.; Price, B. J.; Stables, R. *Br. J. Pharmacol.* **1979**, *66*, 464P.
16. Goodman, K. B. et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 27-30.
17. Wu, D. Y.; Meure, S.; Solomon, D. *Prog. Polym. Sci.* **2008**, *33*, 479-522.
18. Murphy, E. B.; Wudl, F. *Prog. Polym. Sci.* **2010**, *35*, 223-251.

19. Tarducci, C.; Badyal, J. P. S.; Brewer, S. A.; Willis, C. *Chem. Commun.* **2005**, 406-408.
20. Helmy, S.; Oh, S.; Leibfarth, F. A.; Hawker, C. J.; de Alaniz, J. R. *J. Org. Chem.* **2014**, *79*, 11316-11329.
21. Chaudhry, A. R.; Ahmed, R.; Irfan, A.; Shaari, A.; Isa, A. R. M.; Muhammad, S.; Al-Sehemi, A. G. *J. Mol. Model.* **2015**, *21*, 1-28.
22. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795-819.
23. Magnus, P. D.; Kitchell, B. S. *A Short Synthetic Route to Taxol and Taxol Derivatives*, PTC, WO 95/32195, 1995.
24. Wong, H. N. C.; Yu, P.; Yick, C.-Y. *Pure Appl. Chem.* **1999**, *71*, 1041-1044.
25. Lee, H.-K.; Chan, K.-F.; Hui, C.-W.; Yim, H.-K.; Wu, X.-W.; Wong, H. N. C. *Pure Appl. Chem.* **2005**, *77*, 139-143.
26. Brown, R. C. D. *Angew. Chem. Int. Ed.* **2005**, *44*, 850-852.
27. Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076-2080.
28. Donohoe, T. J.; Pullin, R. D. C. *Chem. Commun.* **2012**, *48*, 11924-11938.
29. Büchi, G.; Wüest, H. *J. Org. Chem.* **1966**, *31*, 977-978.
30. Crombie, L.; Hemesley, P.; Pattenden, G. *J. Chem. Soc. (C)* **1969**, 1024-1027.
31. Kotsuki, H.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 496-499.
32. Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179-14233.
33. Sawama, Y.; Kawajiri, T.; Asai, S.; Yasukawa, N.; Shishido, Y.; Monguchi, Y.; Sajiki, H. *J. Org. Chem.* **2015**, *80*, 5556-5565.
34. Shinohara, H.; Sonoda, M.; Hayagane, N.; Kita, S.; Okushima, S.; Tanimori, S.; Ogawa, A. *Tetrahedron Lett.* **2015**, *56*, 2500-2503.
35. Adger, B. J.; Brennan, B. J.; McKervey, M. A.; Murray, R. W. *J. Chem. Soc., Chem. Commun.* **1991**, 1553-1554.
36. Adger, B. J.; Barrett, C.; Brennan, J.; McGuigan, P.; McKervey, M. A.; Tarbit, B. *J. Chem. Soc., Chem. Commun.* **1993**, 1220-1222.
37. Caddick, S.; Cheung, S.; Frost, L. M.; Khan, S.; Pairedeau, G. *Tetrahedron Lett.* **2000**, *41*, 6879-6882.
38. Kalaitzakis, D.; Triantafyllakis, M.; Alexopoulou, I.; Sofiadis, M.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 13201-13205.
39. Paal, C. *Ber. Deutsch. Chem. Ges.* **1884**, *17*, 2756.
40. Knorr, L. *Ber. Deutsch. Chem. Ges.* **1884**, *17*, 2863.
41. Cormier, R. A.; Francis, M. D. *Synth. Commun.* **1981**, *11*, 365-369.
42. Ji, J.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 764-765.
43. Mothe, S. R.; Lauw, S. J. L.; Kothandaraman, P.; Chan, P. W. H. *J. Org. Chem.* **2012**, *77*, 6937-6947.
44. Rao, H. S. P.; Jothilingam, S. *J. Org. Chem.* **2003**, *68*, 5392-5394.
45. Kornfeld, E. C.; Jones, R. G. *J. Org. Chem.* **1954**, *19*, 1671-1680.
46. Botteghi, C.; Lardicci, L.; Menicagli, R. *J. Org. Chem.* **1973**, *38*, 2361-2365.
47. Jacobson, R. M.; Rath, R. A.; McDonald III, J. H. *J. Org. Chem.* **1977**, *42*, 2545-2549.
48. Jacobson, R. M.; Abbaspour, A.; Lahm, G. P. *J. Org. Chem.* **1978**, *43*, 4650-4652.
49. Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 5364-5368.
50. Feist, F. *Chem. Ber.* **1902**, *35*, 1537-1544.
51. Feist, F. *Chem. Ber.* **1902**, *35*, 1545-1556.
52. Bénary, E. *Chem. Ber.* **1911**, *44*, 489-493.
53. Bénary, E. *Chem. Ber.* **1911**, *44*, 493-496.
54. Dann, O.; Distler, H.; Merkel, H. *Chem. Ber.* **1952**, *85*, 457-461.

55. Huang, W.-Y.; Chen, Y.-C.; Chen, K. *Chem. Asian J.* **2012**, *7*, 688-691.
56. Batty, J. W.; Howes, P. D.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 65-68.
57. Couffignal, R. *Synthesis* **1978**, 581-583.
58. Sato, F.; Kanbara, H.; Tanaka, Y. *Tetrahedron Lett.* **1984**, *25*, 5063-5066.
59. Schickmous, B.; Chritoffers, J. *Eur. J. Chem.* **2014**, 4410-4416.
60. Ohta, K.; Kobayashi, T.; Tanabe, G.; Muraoka, O.; Yoshimatsu, M. *Chem. Pharm. Bull.* **2010**, *58*, 1180-1186.
61. Liotta, D.; Saindane, M.; Ott, W. *Tetrahedron Lett.* **1983**, *24*, 2473-2476.
62. Medimagh, R.; Marque, S.; Prim, D.; Chatti, S. *Org. Biomol. Chem.* **2011**, *9*, 6055-6065.
63. Lukevits, E.; Pudova, O. A. *Chem. Het. Comp.* **1995**, *31*, 377-411.
64. Lukevits, E.; Pudova, O. A. *Chem. Het. Comp.* **1995**, *31*, 412-431.
65. Wong, M. K.; Leung, C. Y.; Wong, H. N. C. *Tetrahedron* **1997**, *53*, 3497-3512.
66. Larock, R. C.; Liu, C.-L. *J. Org. Chem.* **1983**, *48*, 2151-2158.
67. Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3602-3603.
68. Yu, P.; Yang, Y.; Zhang, Z. Y.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 6359-6366.
69. Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209-215.
70. Ma, S.; Zhang, J.; Lu, L. *Chem. Eur. J.* **2003**, *9*, 2447-2456.
71. Sniady, A.; Durham, A.; Morreale, M. S.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2007**, *9*, 1175-1178.
72. Arimitsu, S.; Jacobsen, J. M.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2886-2889.
73. Saito, A.; Enomoto, Y.; Hanzawa, Y. *Tetrahedron Lett.* **2011**, *52*, 4299-4302.
74. Ghosh, M.; Mishra, S.; Monir, K.; Hajra, A. *Org. Biomol. Chem.* **2015**, *13*, 309-314.
75. Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966-5968.
76. Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 2681-2684.
77. Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925-3927.
78. Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 727-730.
79. Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559-8561.
80. Wang, W.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 1640-1643.
81. Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 4360-4363.
82. Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5242-5348.
83. Gabriele, B.; Veltri, L.; Mancuso, R.; Plastina, P.; Salerno, G.; Costa, M. *Tetrahedron Lett.* **2010**, *51*, 1663-1665.
84. Chen, Z.; Huang, G.; Jiang, H.; Huang, H.; Pan, X. *J. Org. Chem.* **2011**, *76*, 1134-1139.
85. Müller, T. J. L. *Synthesis* **2012**, *44*, 159-174.
86. Jiang, Y.; Zhong, Z. Y.; Lourdasamy, E.; Park, C.-M. *Chem. Commun.* **2012**, *48*, 3133-3135.
87. Li, E.; Yao, W.; Wang, C.; Shao, Y.; Li, Y. *Org. Biomol. Chem.* **2012**, *10*, 2960-2965.
88. Ge, G.-C.; Mo, D.-L.; Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Tetrahedron Lett.* **2012**, *14*, 5756-5759.
89. Ye, J.; Ma, S. *Acc. Chem. Res.* **2014**, *47*, 989-1000.
90. Khafizova, L. O.; Shaibakova, M. G.; Chobanov, N. M.; Gubaidullin, R. R.; Thymkina, T. V.; Dzhemilev, U. M. *Rus. J. Org. Chem.* **2015**, *51*, 1277-1281.
91. Dudnik, A. S.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 5195-5197.
92. Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 2687-2699.
93. Sydnes, L. S.; Bakstad, E. *Acta Chem. Scand.* **1996**, *50*, 446-453.
94. Bakstad, E.; Sydnes, L. K. *Acta Chem. Scand.* **1998**, *52*, 1029-1033.

95. Bakstad, E.; Olsen, A. S.; Sandberg, M.; Sydnes, L. K. *Acta Chem. Scand.* **1999**, *53*, 465-472.
96. Sydnes, L. K. *Eur. J. Org. Chem.* **2000**, 3511-3518.
97. Sydnes, L. K.; Alnes, K. F. S.; Erdogan, N. *Monatshfte Chem.* **2005**, *136*, 1737-1749.
98. Holmelid, B.; Kvernenes, O. H.; Hodne, M.; Sydnes, L. K. *ARKIVOC* **2008**, (vi), 26-41.
99. Kvernenes, O. H.; Sydnes, L. K. *Org. Synth.* **2005**, *83*, 184-192.
100. Sydnes, L. K.; Holmelid, B.; Kvernenes, O. H.; Sandberg, M.; Hodne, M.; Bakstad, E. *Tetrahedron* **2007**, *63*, 4144-4148.
101. Shang, W.; Terranova, M.; Sydnes, L. K.; Bjørsvik, H.-R. *Org. Process Res. Dev.* **2014**, *18*, 891-896.
102. Sydnes, L. K.; Kvernenes, O. H.; Valdersnes, S. *Pure Appl. Chem.* **2005**, *77*, 119-130.
103. Sydnes, L. K.; Valdersnes, S. *Pure Appl. Chem.* **2007**, *79*, 2137-2142.
104. Sydnes, L. K.; Holmelid, B.; Valdersnes, S.; Sengee, M.; Boman, K. *Jordanian J. Chem.* **2007**, *2*, 105-116.
105. Sydnes, L. K.; Holmelid, B.; Kvernenes, O. H.; Valdersnes, S.; Hodne, M.; Boman, K. *ARKIVOC* **2008** (xiv), 242-268.
106. Sydnes, L. K.; Holmelid, B.; Sengee, M.; Hanstein, M. *J. Org. Chem.* **2009**, *74*, 3430-3443.
107. Valdersnes, S.; Sydnes, L. K. *Eur. J. Org. Chem.* **2009**, 5816-5831.
108. Sengee, M.; Sydnes, L. K. *Pure Appl. Chem.* **2011**, *83*, 587-596.
109. Valdersnes, S.; Apeland, I.; Flemmen, G.; Sydnes, L. K. *Helv. Chim. Acta* **2012**, *95*, 2099-2122.
110. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed; John Wiley & Sons, New York, USA, 1991; pp. 77-83.
111. Shang, W.; Fairhurst, M. E.; Sydnes, L. K. *Synthetic Commun.* **2016**, *46*, 775-792.
112. Sengee, M.; Sydnes, L. K. *Synthesis* **2011**, 3899-3907.
113. Erdenebileg, U.; Høstmark, I.; Polden, K.; Sydnes, L. K. *J. Org. Chem.* **2014**, *79*, 1213-1221.
114. Sydnes, L. K.; Isanov, R.; Sengee, M.; Livi, F. *Synth. Commun.* **2013**, *43*, 2898-2905.
115. Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851-1852.
116. Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 1853-1854.
117. Klein, J.; Turkel, R. M. *J. Am. Chem. Soc.* **1969**, *91*, 6186-6187.
118. Posner, G. H. *J. Am. Chem. Soc.* **1972**, *19*, 1-114.
119. Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3083-3086.
120. Normant, J. F.; Alexakis, A.; Ghribi, A.; Mangeney, P. *Tetrahedron* **1989**, *45*, 507-516.
121. Hanessian, S.; Lavalley, P. *Can. J. Chem.* **1975**, *53*, 2975-2977
122. Hanessian, S.; Lavalley, P. *Can. J. Chem.* **1977**, *55*, 562-565.
123. Shang, W.; Sydnes, L. K. *To be published*.
124. Isanov, R.; Holmelid, B.; Törnroos, K. W.; Sydnes, L. K. *J. Heterocyclic Chem.* **2015**, *52*, 711-718.
125. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.
126. Bacchi, A.; Chiusoli, G. P.; Costa, M.; Sani, C.; Gabriele, B.; Salerno, G. *J. Organomet. Chem.* **1998**, *562*, 35-43.
127. Gabriele, B.; Salerno, G.; Faziob, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251-6259.
128. Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936-5942.
129. Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863-6867.
130. Erdenebileg, U.; Høstmark, I.; Polden, K.; Sydnes, L. K. *J. Org. Chem.* **2014**, *79*, 1213-1221.