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Specific conjugate addition to α,β-acetylenic ketones*

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Abstract: A variety of α,β-unsaturated acetylenic ketones, prepared in good yields from 3,3,4,4-tetraethoxybut-1-yne (TEB), have been reacted with selected mono- and bis-nucleophilic reagents. The mononucleophiles react in a Michael fashion and give in most cases the corresponding α,β-unsaturated alkenones in good yield. Many of the alkenes are formed as single stereoisomers, but the configuration depends on the nature of the nucleophile. If hydrogen bonds can be formed, the *Z* geometry is preferred, otherwise the *E* geometry is completely predominant. Experiments have also uncovered that α,β-unsaturated acetylenic ketones with a *gem*-diethoxy moiety in the α' position decompose when reacted with sodium hydroxide in aqueous tetrahydrofuran (THF); the carbonyl group is attacked and a carboxylic acid and a terminal alkyne are formed.

If the nucleophiles contain two nucleophilic centers or if the α,β-unsaturated acetylenic ketones contain an additional reactive group, such as a hydroxyl group or an acyloxy moiety, useful secondary reactions may occur. By taking advantage of such secondary transformations, two completely regioselective syntheses of furans have so far been developed.

Keywords: amine addition; conjugate addition; conjugated alkenones; dialkylcuprates; 1,3-dithiane; regiospecific transformations; tetrasubstituted furans; thiolate addition; trisubstituted furans.

INTRODUCTION

When a synthetic method was developed that made 3,3,4,4-tetraethoxybut-1-yne (TEB) easily available in large quantities [1,2], a program was launched to explore the chemical potential of this highly functionalized molecule. Among the studies in progress is an investigation of the ability of α,β-unsaturated acetylenic ketones to react with a range of nucleophiles. So far, the study has focused on three groups of ketones. The simplest one consists of one compound only, viz. 1,1-diethoxybut-3-yn-2-one (**1**), which is obtained in good yield by exposing TEB to slightly acidic conditions [3]. The second group consists of γ-hydroxylated α,β-unsaturated acetylenic ketones (**2**) (synthesized by TEB-acetylide coupling with a range of aldehydes followed by deketalization), whereas the third is comprised of a variety of 5-acyloxy-1,1-diethoxyalk-3-yn-2-ones (**3**) (prepared by TEB-acetylide coupling with a range of aldehydes, followed by esterification, and completed by deketalization) (Scheme 1) [4]. Regarding the nucleophiles the focus has so far been mostly on thiolates, alcohols, amines, and dialkyl cuprates, and the results presented here will therefore be limited to these nucleophilic species.

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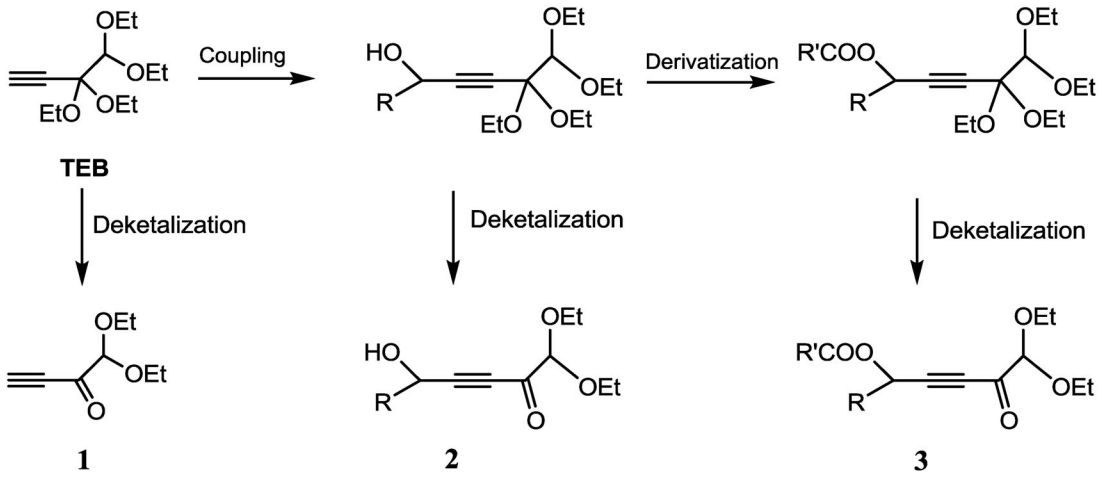
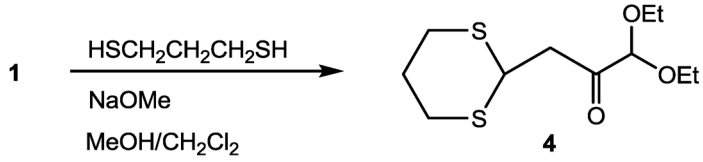


Scheme 1 The conjugated acetylenic ketones investigated.

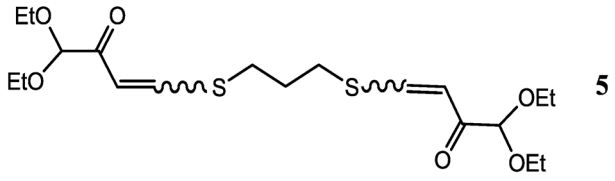
ADDITION OF VARIOUS NUCLEOPHILES TO BUTYNONE 1

Thiolates

Among the best and easiest-to-handle nucleophiles, we find the thiolates. We therefore decided to start the exploration of the reactivity of the first α,β-unsaturated alkynone we made, viz. ketone **1**, with such a reagent. Inspired by the work of Ley and co-workers [5], we opted to try propane-1,3-dithiol, which under basic conditions forms a thiolate that has been used to prepare 1,3-dithianes from several similar, but less functionalized α,β-unsaturated alkynones. Butynone **1** appeared to react in the same fashion as these ketones and furnished 3-(1,3-dithian-2-yl)-1,1-diethoxypropan-2-one (**4**) in good to excellent yields by a double Michael addition to the conjugated ketone system [6]. Under some reaction conditions the thiolates reacted to some extent with two different substrate molecules and furnished a bisadduct (**5**) as a by-product, but when sodium methoxide was used as base and a 4:1 mixture of methanol and dichloromethane as solvent, only double conjugate addition occurred and gave **4** in 91 % yield (Scheme 2).

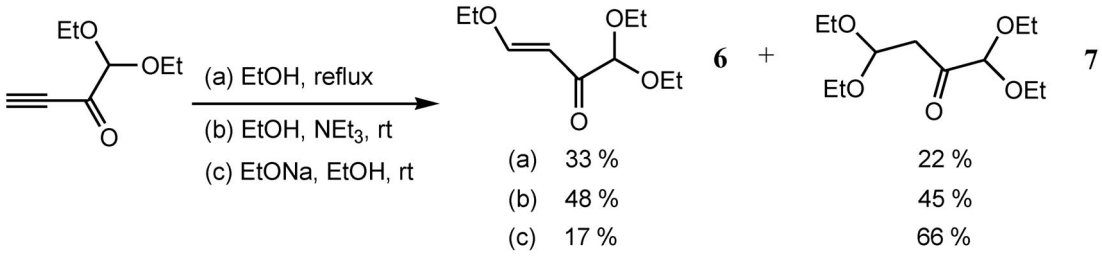


Scheme 2 Double Michael addition of propane-1,3-dithiol to butynone **1**.



Ethanol and ethoxide

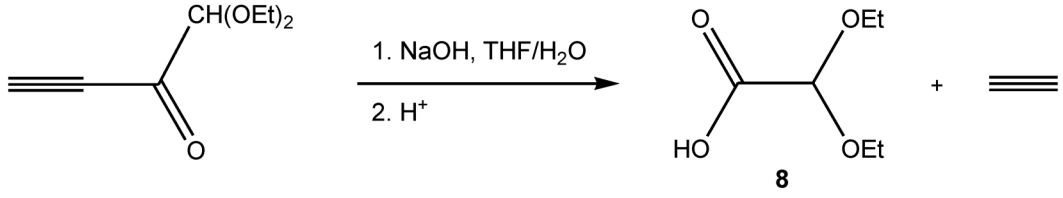
The outcome of reactions with alcohols and alkoxides is quite sensitive to the reaction conditions [7]. This is illustrated by addition of ethanol and ethoxide to **1**. When this α,β-unsaturated ketone is treated with pure ethanol at room temperature no reaction occurs, but when the same reaction is carried out at reflux temperature two products were obtained in moderate yield, viz. (*E*)-1,1,4-triethoxy-3-buten-2-one (**6**) and 1,1,4,4-tetraethoxybutan-2-one (**7**) (Scheme 3; conditions a). Interestingly, the former compound, which was formed as a single isomer with *E* configuration (proved by ^{1}H NMR), turned out to be the main product even when a fairly large excess of ethanol was used. Making the reaction conditions basic appeared to be beneficial; not only did the consumption of **1** increase considerably, the yield of double-protected ketodialdehyde **7** also improved. Thus, in the presence of triethylamine (conditions b), ethanol reacted at room temperature and gave **6** and **7** in a 1:1 ratio in 93 % total yield, and when the amine was replaced by sodium ethoxide (conditions c) the yield of **7** increased to 66 % isolated yield.



Scheme 3 Addition of ethanol to butynone **1** under various reaction conditions.

Hydroxide

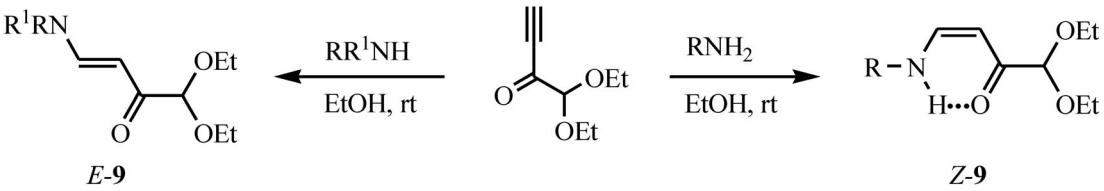
Changing the oxygen nucleophile from an alkoxide to the hydroxide ion dramatically changes the course of reaction [7]. When **1** was stirred in a 1:1 water/THF solution of sodium hydroxide, no Michael addition occurred at all; instead, ethyne formation took place by attack of the carbonyl group followed by cleavage of the bond to the ethynyl group. Experiments aimed at trapping the released acetylene were unsuccessful, but 2,2-diethoxyacetic acid (**8**) was isolated in 67 % (Scheme 4). This reaction is important to keep in mind in the sense that when reactions involving α,β-unsaturated acetylenic ketones, e.g., **1** and other 1,1-diethoxyalk-3-yn-2-ones, such as ketones **2** and **3**, are worked up under basic hydrous conditions, decomposition of unreacted starting material by similar cleavage of the C2–C3 bond might occur.



Scheme 4 Decomposition of butynone **1** by means of sodium hydroxide.

Amines

Ketone **1** has also been reacted with ammonia and a number of primary and secondary amines using ethanol as solvent, and without exception the only product in every case was the corresponding 4-aminated 1,1-diethoxybut-3-en-2-one (**9**) even when a large excess of amine was used [7]. The yield of **9** was generally excellent (>90 % isolated yield), but just as important is the observation that the reaction was absolutely stereospecific in almost all cases. All secondary amines afforded the Michael adduct with *E* configuration, whereas ammonia and all primary amines reacted except one gave adducts with *Z* stereochemistry (Scheme 5). The only exception so far among the amines we have studied has been aniline, which furnished 1,1-diethoxy-4-phenylaminobut-3-en-2-one (**9c**) in 98 % isolated yield as a 9:1 mixture of the *Z* and the *E* isomers, respectively (Table 1).



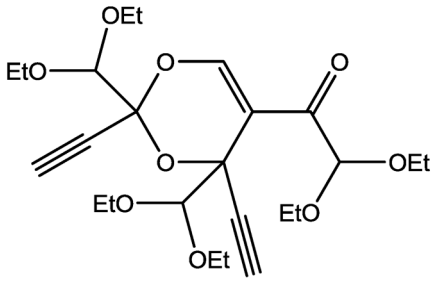
Scheme 5 Michael addition of amines to butynone **1**.

Table 1 Formation of enamines **9** by addition of ammonia and amines to ketone **1**.

R, R^1	**9**	*E*	*Z*	Isolated yield (%)
R = R^1 = H	**9a**		100	92
R = CH_3, R^1 = H	**9b**		100	95
R = Ph, R^1 = H	**9c**	10	90	98
R= R^1 = Et	**9d**	100		88
R, R^1 = $(CH_2)_4$	**9e**	100		92
R, R^1 = $(CH_2)_5$	**9f**	100		90

As indicated in Scheme 5, we believe that the ability of the enamines obtained from ammonia and primary amines to form a hydrogen bond with the carbonyl group is the most important contributing factor to the selective formation of the *Z* isomer. If this explanation is correct, adducts from secondary amines should conceivably be formed as *E* isomers, because these enamines are unable to form intramolecular hydrogen bonds and the steric interactions between the olefin substituents, viz. the amino substituent and the diethoxymethylcarbonyl group, are larger due to the two alkyl substituents attached to nitrogen. And indeed, when **1** was treated with secondary amines, 4-dialkylamino-1,1-diethoxybut-3-en-2-ones were obtained in good yield as single isomers with *E* configuration (Table 1) [7].

When **1** was reacted with tertiary amines, a complex and interesting transformation occurred. The reaction with triethylamine is representative and illustrates the importance of the solvent used. When the reaction is carried out in hexane a fast reaction took place and a dark, tarry, intractable product mixture was obtained. In diethyl ether, however, a slower reaction occurred and one main product, ketone **10**, was obtained and isolated by flash chromatography in 57 % yield as a mixture of diastereomers. The same compound was furnished when **1** was treated with sodium hydride in THF, but the yield was somewhat lower (42 %). Although the mechanism for the formation of **10** has not yet been uncovered, inspection of the structure clearly indicates that the six-membered ring is formed by reactions involv-

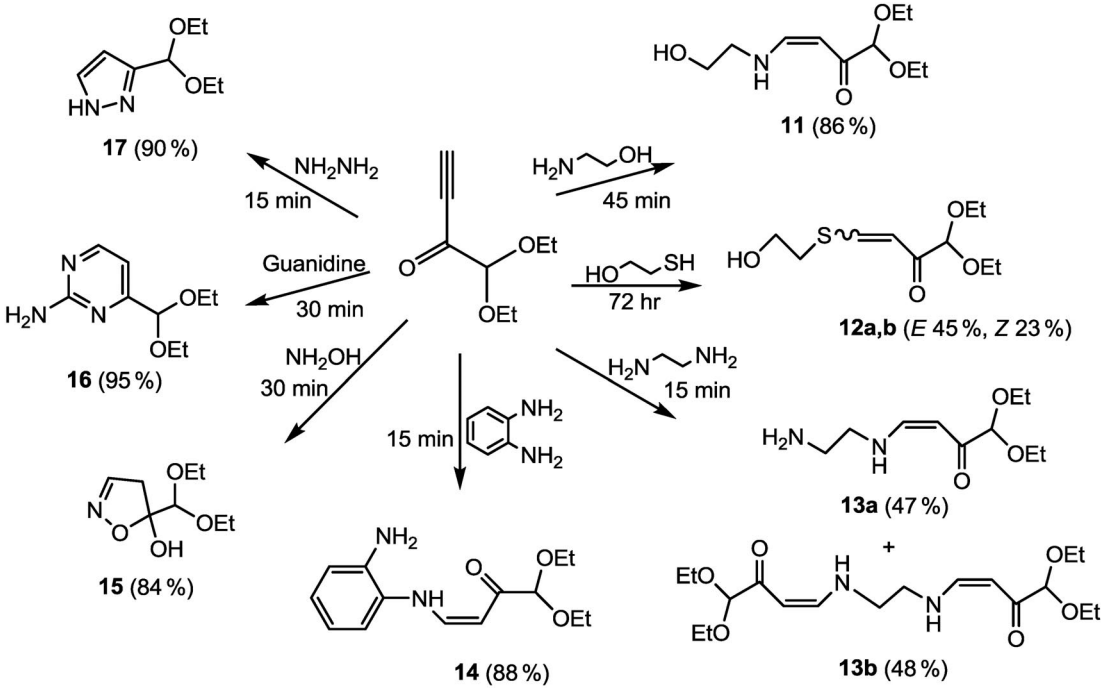


10

ing the carbonyl group from two molecules of the starting material and the triple bond in a third. Studies of the mechanism for the reaction are under way.

Bisnucleophilic reagents

Ketone **1** was also treated with a number of reactants containing more than one nucleophilic center [7]. Some representative results from reactions carried out in ethanol at room temperature are presented in Scheme 6, and they seem to reflect two general trends: When the two nucleophilic centers are different the more reactive nucleophile reacts first, and the primary attack always takes place at the triple-bond carbon atom β to the carbonyl group. The yields were generally very good, and when the product was a 4-substituted 1,1-diethoxybut-3-en-2-one the addition was completely stereospecific, with *Z* configuration, when a primary amine reacted and gave enamines, viz. **11**, **13**, and **14**, and stereoselective, with *E* predominance, when a thiol reacted first and gave vinylsulfide **12** (Scheme 6).



Scheme 6 Some representative reactions of **1** with some bisnucleophilic reagents. The yields given are isolated yields.

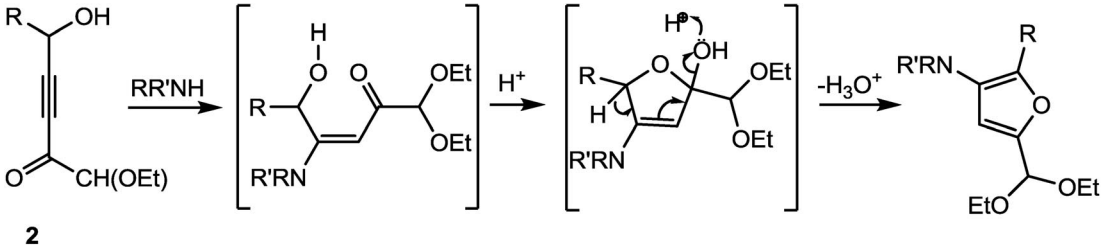
When the relative position of the two nucleophilic centers is favorable, a secondary reaction appeared to take place. Among the reagents behaving like this are hydroxylamine, guanidine, and hydrazine. These reagents conceivably attack the triple bond as an amine and form the corresponding *Z*-enamines first; the carbonyl group is then attacked by the second nucleophilic moiety and heterocycles **15**, **16**, and **17**, respectively, are formed in very good yields with a protected aldehyde group in a predictable position.

ADDITION OF SECONDARY AMINES TO γ-HYDROXYKETONES 2

The formation of heterocycles **15**–**17** (see Scheme 6) clearly proves that when the primary Micheal addition to the α,β-unsaturated ketone has occurred, cyclization may subsequently take place provided the primary product contains a nucleophile in a proper position. In the cases of the three heterocycles mentioned, this nucleophile was part of the nucleophilic reagent added to **1**, but it is also possible to envisage that a nucleophilic cite is present in the substrate at an appropriate position before the reagent is added. In order to explore this option we have started to make such compounds by introducing properly functionalized substituents at C4 in **1**. We are currently studying a range of such reactions, and a number of interesting results have so far been obtained with propargylic alcohols **2** as well as their corresponding esters **3**. Some results from reactions of the former with some secondary amines are reported in this section, whereas reactions of esters **3** with cuprate reagents are reported in the next section.

Amines

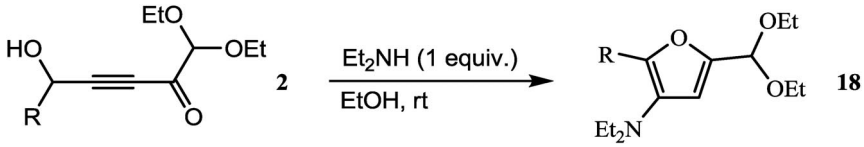
As previously discussed, secondary amines add stereospecifically to ketone **1** and give (*E*)-4-dialkylamino-1,1-ditheoxybut-3-en-2-ones as a single isomer in good yields. If the same amines are reacted with ketone **2**, which also contains a propargylic-alcohol motif, it can be envisaged that the short distance between the carbonyl group and the hydroxyl group will make furan formation possible as outlined in Scheme 7.



Scheme 7 Conversion of γ-hydroxyketones to substituted furans.

In order to test this hypothesis, 1,1-diethoxy-5-hydroxyhex-3-yn-2-one (**2a**) was treated with diethylamine. A smooth and clean reaction appeared to take place, and in less than 1 h all the starting material had been consumed and one product only, 3-diethylamino-5-diethoxymethyl-2-methylfuran (**18a**), had been formed and was subsequently isolated in 81 % yield [8]. If the reaction time was extended well beyond 1 h, by-product formation started and led gradually to formation of the corresponding furfural. On the basis of these observations, a number of 5-substituted 1,1-diethoxy-5-hydroxyalk-3-yn-2-ones were reacted with diethylamine, and without exception the corresponding 2-substituted 3-diethylamino-5-diethoxymethylfurans were obtained in good yields. Some representative results are compiled in Table 2.

Table 2 Formation of 3-diethylaminofurans (**18**) by addition of diethylamine to **1**.



Substrate	R	Reaction time (h)	Aminofuran	Isolated yield (%)
2a	Me	0.5	**18a**	81
2b	*i*-Pr	1.0	**18b**	78
2c	*n*-C_6H_{13}	1.0	**18c**	77
2d	Ph	1.0	**18d**	75
2e	H	1.0	**18e**	70

The scope of the transformation has been further investigated by reacting **2a** with several other secondary amines [8]. Interestingly, piperidine, morpholine, and pyrrolidine all reacted similar to diethylamine and furnished the expected analogues to **18a**, but the yield of the furan was in every case considerably lower (in the range of 60–69 % as compared to 81 % for **18a**). And when dephenylamine was applied, furan formation was not observed at all, probably because the nucleophilicity of the nitrogen atom is lowered due to influence from the two phenyl groups.

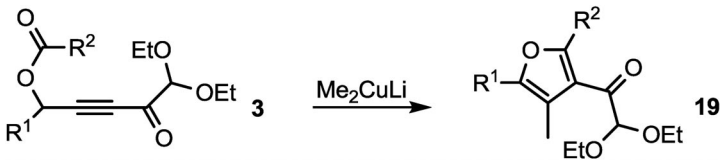
Because the furan-ring formation involves abstraction of a proton attached to C5 in ketone **2** (see Scheme 7), formation of aminofurans is only possible if the propargylic-alcohol moiety in the starting material is either primary or secondary. Based on this consideration, treatment of a compound like 1,1-diethoxy-5-hydroxy-5-methylhex-3-yn-2-one with diethylamine should not give any furan, and that was indeed observed; instead, a mixture of dihydrofurans was obtained and these are currently under investigation.

ADDITION OF CUPRATES TO KETOESTERS 3

The acidity of the hydroxyl group in **2** limits the number of reagents that can be reacted with this ketone, and to rectify this situation we have started to make derivatives of **2** by protecting the OH group by esterification [3,4]. A number of these ketoesters (**3**) have been reacted with dialkylcuprates and appeared to undergo a clean reaction under the optimum conditions. At about room temperature the conversion gave two products, a 2-alkenone and a substituted furan, but when the temperature was lowered furan formation became gradually more important and at about –50 °C, predominant.

The scope of the reaction was studied by treating selected ketoesters with one molar equivalent of Me_2CuLi at temperatures ranging from room temperature to –78 °C. As some representative examples in Table 3 show, a 3-(2,2-diethoxyacetyl)-4-methyl-5-R^1-2-R^2-furan (**19**) was obtained in fair to good yield with a predictable substitution pattern. The yield is sensitive to the reaction temperature; when the temperature decreased the yield increased (e.g., entry 8, Table 3), but, running the reactions below –60 °C was generally not beneficial [4].

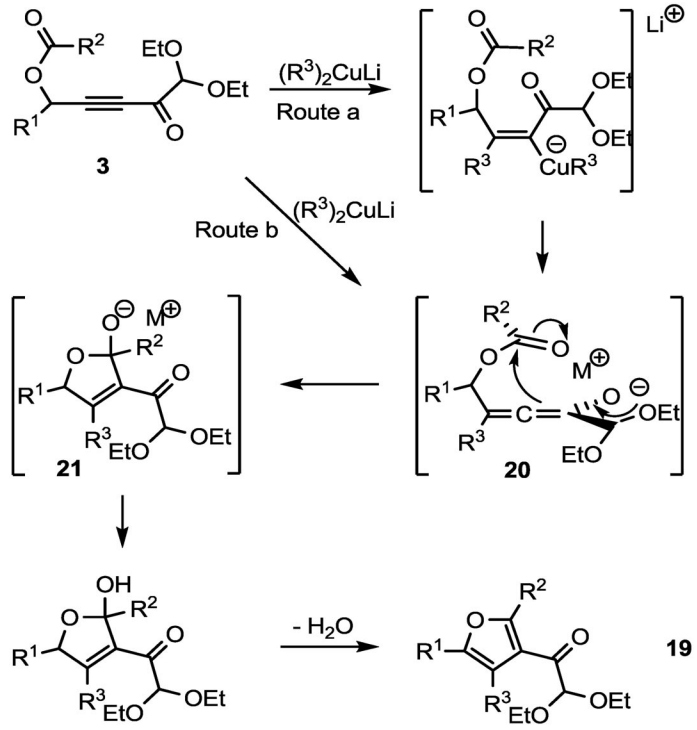
Table 3 Formation of furans **19** by treating **3** with Me_2CuLi between rt and -78 °C



Entry	R^1	R^2	Isolated yield (%)			
			–78 °C	–60 °C	0 °C	rt
1	H	Me		50	10	
2	H	*i*-Pr	45	45		
3	Me	*i*-Pr	47	50	26	
4	*i*-Pr	Me	74	81	70	56
5	*i*-Pr	*i*-Pr		75	51	
6	*t*-Bu	Me	72	70	30	
7	*t*-Bu	*i*-Pr	68	68	25	
8	C_6H_{11}[a]	Me	50	70	18	26

[a]Cyclohexyl

A reaction mechanism for the furan formation has been published and is presented in Scheme 8. The electron-deficient carbon–carbon triple bond is first attacked, either in a 1,2 fashion (route a) and/or a 1,4 fashion (route b), which both have solid literature precedence [9]. Allenolate **20** thus formed



Scheme 8 Suggested reaction mechanism for cuprate addition to **3**; M^+ denotes an unknown cationic species, formed from Li^+, CuR^3, and one or several cuprate species [4].

undergoes cyclization by a Dieckmann type to afford another unstable intermediate (**21**), and subsequent protonation followed by dehydration leads eventually to furan formation.

The ability of intermediate **20** to attain conformations that favor attack of the carbonyl group in the ester function is crucial for furan formation. It is therefore likely that the bulkyness of R^1 and R^2 is important for the outcome of the reaction. This appeared definitely to be the case and was particularly visible for the isobutyrates reacted at –60 °C; the corresponding furans were obtained in 45, 50, 75, and 68 % yield, respectively, as R^1 changes from H via Me and *i*-Pr to *t*-Bu (see Table 3, entries 2, 3, 5, and 7, respectively).

CONCLUSION

The studies reported here have revealed that TEB is a good starting material for the preparation of a range of chemical structures. Deprotection of the ketal moiety in TEB and TEB derivatives give α,β-unsaturated acetylenic ketones, which have been shown to react readily in a Michael fashion with a variety of nucleophiles. We believe that the results presented here warrant a range of further studies in the years to come.

ACKNOWLEDGMENTS

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