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The reaction of photochemically generated α-hydroxyalkyl radicals with alkynes: a synthetic route to γ-butenolides

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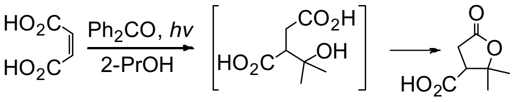
ABSTRACT

The photomediated generation of α-hydroxyalkyl radicals from simple acyclic and cyclic alcohols, and acyclic diols, and their subsequent carbon–carbon bond forming reaction with propiolate esters and acetylenedicarboxylates, gives a mixture of a β-(hydroxyalkyl)enoate, the result of a formal cis addition, and the unsaturated lactone (γ-butenolide) resulting from the spontaneous cyclization of the corresponding trans addition product. Treatment of the cis adduct with NBS converts it to the same lactone, and so the method overall constitutes a particularly direct route to this important structural unit. Cyclic alcohols give rise to spiro-γ-butenolides. The use of supported photomediators simplifies product isolation and allows for the recovery and reuse of the photomediator.

The synthetic potential of carbon–carbon bond forming reactions based on carbon radicals is well established.[1] In many cases these reactions exploit the nucleophilic properties of carbon radicals and involve them in reacting with electron-deficient unsaturated systems. The generation of carbon radicals for synthetic purposes generally involves the use of either peroxides or diazo and tin compounds, with neither approach being entirely satisfactory from the perspective of sustainability. The potential of photocatalysis in terms of carbon–carbon bond formation is considerable[2] and we, and others, have been interested in the possibility of developing a sustainable method of generating carbon radicals which is based on the ability of ketones in their n,π^* excited state to abstract hydrogen from C–H bonds.[3] Although this is a well-known process, its synthetic potential has remained substantially unexplored, largely due to the perception that conversion of the ketone to the corresponding pinacol should predominate. This is particularly true in relation to producing α-hydroxyalkyl radicals, as the reaction conditions required, for example, to produce 2-hydroxypropyl radicals from 2-propanol using benzophenone, are effectively those encountered in the classic introductory experiment in synthetic photochemistry which produces ‘a nearly quantitative yield of lovely white crystals of analytically pure benzpinacol’.[4] However, in the presence of an alkene (see below) or an alkyne, as shown here, with an electron withdrawing group (EWG), nucleophilic addition of α-hydroxyalkyl radicals produced in this way is competitive with pinacol formation.

There are relatively few non-photochemical methods available for the direct generation of α-hydroxyalkyl radicals from alcohols. They include the use of peroxides,[5] and more recently, a method involving an *N*-hydroxyphthalimide/oxygen/cobalt(II) system.[6] The use of a triplet ketone to abstract an α-hydrogen atom from an alcohol, generating an α-hydroxyalkyl radical which is subsequently trapped by an electron-deficient alkene, was first applied in the context of a synthesis of racemic terebic acid[7] (Scheme 1).

The face selectivity of the photomediated addition of 2-propanol to (*R*)-(−)-5-menthyloxy-2,5-dihydrofuranone was more recently the basis of an asymmetric synthesis of (−)-terebic acid.[8] Stereoselectivity is also a feature of the addition of α-hydroxyalkyl radicals to chiral 3-hydroxy-1-(methylthio)-1-(*p*-tosyl)-1-alkenes[9] and 1,3-dioxin-4-ones.[10] In general, the range of electron-deficient alkenes used has been extended to include carbohydrate-derived enones,[11] cyclopentenones,[12] butenolides[13] and pyrrolidin-2-ones.[14] Although only 0.15 equiv of the photomediator (relative to the alkene) is sufficient in some cases,[10,11] a common disadvantage of this methodology when applied to alkenes is the fact that 1 equiv of the photomediator is actually required.[9,13] On the other hand, we have shown that the lower value is consistently sufficient in reactions involving alkynes. This observation argues for the operation in these cases of an inefficient chain reaction and we have recently provided quantum yield data which support this suggestion.[15] The greater reactivity of alkynes may be due in part to the ability of the more reactive alkenyl radical formed from them to abstract a hydrogen atom from a molecule of substrate



Scheme 1.

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and so propagate a chain reaction. In comparison to the volume of results reported for the reaction of photochemically generated α-hydroxyalkyl radicals with alkenes, there has been little interest in their reaction with alkynes. The few reactions reported[16,17] involve a direct irradiation approach and do not make use of a photomediator such as benzophenone. Unsurprisingly, this approach results in very long reaction times and poor yields. We now wish to report that the photomediated reaction of alcohols, particularly secondary alcohols, with acetylenic esters provides synthetically significant yields of addition products and provides the basis for a very direct method for the synthesis of simple and spirocyclic γ-butenolides.

The reaction of 2-propanol with dimethyl acetylenedicarboxylate (DMAD)[18] is typical of these photomediated processes. It is complete in 45 min and after chromatography gives the substituted maleate **3a** and the butenolide **5a** in isolated yields of 37% and 31%, respectively. The conversion of the initially formed *E*-alkene **4a** to the lactone **5a** occurs very rapidly under the reaction conditions as in only one case, the reaction of methyl propiolate with 2-propanol, is there evidence (GC) for the formation of an *E*-alkene. ^{1}H NMR analysis of the product mixture indicates that little or no conversion of benzophenone to benzpinacol occurs in this case and, in general, photoreduction of the photomediator only becomes competitive when the addition of the α-hydroxyalkyl radical to the alkyne is slow, as is the case, for example, with propiolate esters.

The synthetic scope of the reaction was explored using a variety of alcohols and alkynes (Scheme 2) (Table 1). The reactivity profile that emerges is in accord with expectations: secondary alcohols (acyclic or cyclic), for example, are more reactive than primary alcohols as evidenced by the behaviour of 1- and 2-propanol, and of 1,2-propanediol and 1,2-butanediol which react regiospecifically at the secondary position. The reaction of larger alcohols (acyclic: >C$_4$; cyclic: >C$_6$) results in the formation of complex mixtures, which on the basis of a strong IR absorption in the 1730–1720 cm^{-1} region appear to consist substantially of unsaturated esters. This suggests that hydrogen abstraction in these cases is occurring from a number of sites in the molecule as the reactivity advantage enjoyed by the α-hydrogen is offset by the statistical effect of larger alkyl groups. Although somewhat less reactive, the behaviour of alkynes with only one EWG generally parallels that of the acetylenedicarboxylates. The failure of methyl propiolate to react with ethylene glycol in the presence of benzophenone is a unique exception to this pattern for which there is no obvious explanation.

Table 1
Photomediated addition of alcohols to alkynes

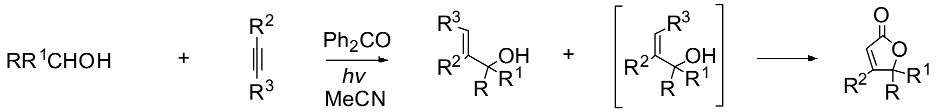
Entry	Alcohol	Alkyne	Time[a] (min)	Products (isolated yield, %)
Secondary alcohols				
1	**1a**	**2a**	45	**3a** (37), **5a** (31)
2	**1a**	**2b**	35	**3b** (54)[b]
3	**1a**	**2c**	35	**3c** (35), **5c** (29)
4	**1a**	**2d**	135	**3d/4d** (62)[c]
5	**1b**	**2a**	70	**3e** (40)
6	**1b**	**2c**	105	**3f** (24), **5f** (21)[b]
7	**1c**	**2c**	65	Complex mixture
Cyclic alcohols				
8	**1d**	**2a**	12	**3g** (32)[b], **5g** (29)[b]
9	**1e**	**2a**	15	**3h** (28), **5h** (31)
10	**1e**	**2c**	45	**3i** (42)[b], **5i** (14)
11	**1f**	**2c**	83	**3j** (32), **5j** (20)
12	**1g**	**2a**	420	Complex mixture
Primary alcohols				
13	**1h**	**2a**	195	**3k** (34)[b]
14	**1i**	**2a**	110	**3l** (40)[b]
Diols				
15	**1j**	**2a**	35	**3m** (71)[b]
16	**1j**	**2b**	35	**3n** (67)[b]
17	**1j**	**2c**	5	No reaction
18	**1k**	**2a**	35	**3o** (61)[b], **5o** (18)[b]
19	**1l**	**2a**	50	**3p** (60)[b]

[a] Complete reaction of alkyne.

[b] Previously unsynthesized compounds whose structures were assigned spectroscopically and for which appropriate analytical data were obtained (elemental analysis or HRMS(CI)).[20]

[c] Obtained as an inseparable mixture.

The stereochemical outcome of the reaction depends on the combination of alcohol and alkyne involved. As *E*/*Z* isomerization of the products does not occur under the reaction conditions used, the stereochemistry of the reaction is determined by the behaviour of the intermediate alkenyl radicals **A** and **B** (Scheme 3) which



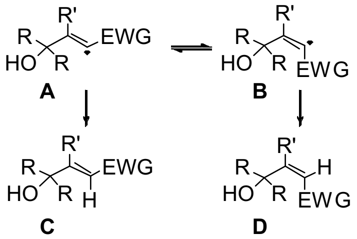
1 **2** **3** **4** **5**

a R = R^1 = Me
b R = Me; R^1 = Et
c R = Me; R^1 = Pr^i
d R, R^1 = -(CH$_2$)$_3$-
e R, R^1 = -(CH$_2$)$_4$-
f R, R^1 = -(CH$_2$)$_5$-
g R, R^1 = -(CH$_2$)$_6$-
h R = H; R^1 = Et
i R = H; R^1 = Pr^i
j R = H; R^1 = CH$_2$OH
k R = Me; R^1 = CH$_2$OH
l R = Et; R^1 = CH$_2$OH

a R^2 = R^3 = CO$_2$Me
b R^2 = R^3 = CO$_2$Bu^t
c R^2 = H; R^3 = CO$_2$Me
d R^2 = H; R^3 = CN

a R = R^1 = Me; R^2 = R^3 = CO$_2$Me
b R = R^1 = Me; R^2 = R^3 = CO$_2$Bu^t
c R = R^1 = Me; R^2 = H; R^3 = CO$_2$Me
d R = R^1 = Me; R^2 = H; R^3 = CN
e R = Me; R^1 = Et; R^2 = R^3 = CO$_2$Me
f R = Me; R^1 = Et; R^2 = H; R^3 = CO$_2$Me
g R, R^1 = -(CH$_2$)$_3$-; R^2 = R^3 = CO$_2$Me
h R, R^1 = -(CH$_2$)$_4$-; R^2 = R^3 = CO$_2$Me
i R, R^1 = -(CH$_2$)$_4$-; R^2 = H; R^3 = CO$_2$Me
j R, R^1 = -(CH$_2$)$_5$-; R^2 = H; R^3 = CO$_2$Me
k R = H; R^1 = Et; R^2 = CO$_2$Me; R^3 = CO$_2$Me
l R = H; R^1 = Pr^i; R^2 = CO$_2$Me; R^3 = CO$_2$Me
m R = H; R^1 = CH$_2$OH; R^2 = CO$_2$Me; R^3 = CO$_2$Me
n R = H; R^1 = CH$_2$OH; R^2 = CO$_2$Bu^t; R^3 = CO$_2$Bu^t
o R = Me; R^1 = CH$_2$OH; R^2 = CO$_2$Me; R^3 = CO$_2$Me
p R = Et; R^1 = CH$_2$OH; R^2 = CO$_2$Me; R^3 = CO$_2$Me

Scheme 2.



Scheme 3.

interconvert more rapidly than they undergo hydrogen abstraction.[19] Hydrogen abstraction by **A** leads to the formation of **C**, which is the result of a formal cis addition of the alcohol to the alkyne. In the same way, the formation of **D**, via **B**, is a formal trans addition. If the EWG on the alkyne is an ester, **D** spontaneously cyclizes to form a lactone. The effective lack of stereoselectivity which is generally apparent in the reactions of 2-propanol (Table 1, entries 1, 3 and 4), the cycloalkanols **1d**, **1e** and **1f** (Table 1, entries 8–11) and 1,2-propanediol (Table 1, entry 18) reflects the involvement of both **A** and **B** in the final hydrogen abstraction process. Steric hindrance in alkenyl radical **B** is responsible for the stereoselective cis addition of 2-propanol to di-*tert*-butyl acetylenedicarboxylate (Table 1, entry 2). The behaviour of 2-butanol depends on the alkyne with which it is paired. Stereoselective cis addition occurs with DMAD (Table 1, entry 5), again as a result of the steric destabilization of **B**. Its reaction with methyl propiolate (Table 1, entry 6) results in the formation of products of both cis and trans addition. The formation of a trans addition product is, however, not surprising as hydrogen abstraction by radical **B** should be particularly efficient in this case (R′ = H). The stereoselectivity of the reactions involving primary alcohols (Table 1, entries 13 and 14) suggests that alkenyl radical **B** is particularly disfavoured, possibly due to a combination of steric and electrostatic interactions.

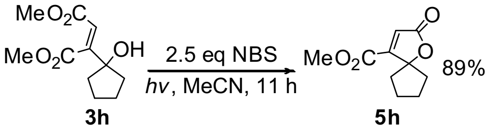
The photomediated reactions of diols with alkynes do not fit into an easily rationalized pattern. Thus, although unfavourable electrostatic interactions in **B** may again be responsible for the fact that ethylene glycol and 1,2-butanediol react selectively via **A** (Table 1, entries 15, 16 and 19), the lack of selectivity exhibited by 1,3-propanediol (Table 1, entry 18) is difficult to explain. Even more surprising is the failure of ethylene glycol to react with methyl propiolate (Table 1, entry 17), the only case where a propiolate ester fails to react with an alcohol that does react with an acetylenedicarboxylate.

Although the photomediator, benzophenone, is used in substoichiometric quantities, the fact that its removal requires chromatography reduces the attractiveness of the procedure. As a result, the use of a supported photomediator, which can be removed by simple filtration and in principle re-used, has obvious potential. Three supported photomediators—an aminopropyl silica-bound benzophenone,[21] a propyl-linked 4-hydroxybenzophenone-silica[22] and a Merrifield polymer-bound benzophenone[23]—were prepared and their reactivity and recyclability were assessed using the reaction between 2-propanol and DMAD as a standard (Table 2). Following their initial use, the supported photomediators were recovered from the reaction mixture by filtration, and were washed in a Soxhlet thimble and dried in a vacuum oven prior to reuse. The performance of the silica supported photomediators was superior to that supported on the Merrifield resin. Overall, the propyl-linked 4-hydroxybenzophenone-silica was the most promising, combining reactivity with good recyclability.

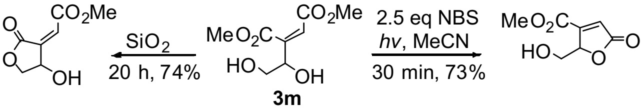
Table 2
Use of supported photomediators in the DMAD/2-propanol

	Time[a] (h)	Yield[b] (%)	**3a**:**5a**[c]
3-Aminopropylsilica-bound benzophenone			
Run 1	3.75	87	1:0.8
Run 2	4.5	82	1:0.8
Run 3	6.5	75	1:0.7
Propy-linked 4-hydroxybenzophenone-silica			
Run 1	0.75	86	1:1
Run 2	2	83	1:0.9
Run 3	3	67	1:0.8
Merrifield polymer-bound benzophenone			
Run 1	3.25	79	1:0.7
Run 2	10	65	1:0.6
Run 3	18	54	1:0.5

[a] Complete reaction of alkyne.
[b] Combined yield of **3a** and **5a** (GC).
[c] GC.



Scheme 4.



Scheme 5.

γ-Butenolides, including spirocyclic butenolides, are of synthetic importance because this structural unit occurs frequently in natural products with important biological activity. In this context the butenolides **5a**,[6,24] **5c**,[25] **5f**,[26] **5i** and **5j**[27] have been synthesized previously, using methods which are generally multistep and/or involve uncommon reagents. The formation of a γ-butenolide in many of these photomediated alkyne/alcohol reactions gives them a synthetic importance that would be further enhanced if the cis addition product **3** could be isomerized to **4** which readily forms a γ-butenolide.

Disappointingly, experiments indicated that photosensitized *E*/*Z* isomerization is not an option and although direct irradiation of **3h** at 254 nm does result in isomerization, further photoreaction of the γ-butenolide occurs competitively leading ultimately to the formation of a complex mixture of products. Irradiation (350 nm) in the presence of *N*-bromosuccinimide (NBS)[28] was, however, more successful (Scheme 4). Interestingly, the product resulting from the photoaddition of ethylene glycol to DMAD, **3m**, lactonizes on silica with a different regioselectivity to that obtained using NBS (Scheme 5).

The results presented here confirm the value of photomediation as a method of generating α-hydroxyalkyl radicals, and demonstrate that the reaction of acetylenic esters with such radicals, particularly when generated using silica-bound photomediators, has synthetic potential in relation to the synthesis of γ-butenolides.

Acknowledgement

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18. A nitrogen degassed solution of DMAD (3 mmol), 2-propanol (60 mmol) and benzophenone (1.2 mmol) in acetonitrile (60 ml) was irradiated in a Rayonet reactor (350 nm lamps) for 45 min. Solvent removal and chromatography on silica gave dimethyl (*Z*)-2-(1-hydroxy-1-methylethyl)but-2-enedioate **3a** (37%) and methyl 2,2-dimethyl-5-oxo-2,5-dihydrofuran-3-carboxylate **5a** (31%).
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20. The spectroscopic data obtained for **3g** and **5g** are representative. Dimethyl (*Z*)-2-(1-hydroxycyclobutyl)but-2-enedioate, **3g**: IR (cm^{-1}): 3443, 1719 and 1642; ^{1}H NMR (400 Mz, $CDCl_3$) (δ): 1.41 (s, 1H), 1.64 (m, 1H), 1.95 (m, 1H), 2.19–2.21 (m, 2H), 2.43–2.46 (m, 2H), 3.73 (s, 3H), 3.85 (s, 3H), 6.06 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm): 168.3, 165.6, 152.9, 117.5, 76.8, 52.7, 52.2, 35.1, 12.9. Anal. calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.86; H, 6.88. Methyl 6-oxo-5-oxaspiro[3,4]oct-7-ene-8-carboxylate, **5g**: IR (cm^{-1}): 1762, 1725 and 1626; ^{1}H NMR (400 MHz, $CDCl_3$) (δ): 2.11–2.15 (m, 2H), 2.57–2.59 (m, 2H), 2.77–2.81 (m, 2H), 3.91 (s, 3H), 6.53 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) (ppm): 169.8, 161.6, 157.6, 125.9, 89.1, 52.8, 31.8, 13.4. HRMS (CI): *m/z* calcd. for $C_9H_{11}O_4$ (M + H$^+$, 100): 183.0657; found; 183.0667.
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