Oxidation of Alkynes in Aqueous Media Catalyzed by Diphenyl Diselenide

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Abstract: In this communication we propose a convenient methodology to effect the oxidation of alkynes using ammonium persulfate and diphenyl diselenide as catalyst. The reactions effected in aqueous media lead to 1,2-unprotected dicarbonyl derivatives or to hemiacetals starting from terminal alkynes.

Key words: selenium, oxidation, catalysis, alkynes, water chemistry

The development of improved and eco-friendly oxidation reactions is an area of great current interest in both academic and industrial laboratories. Recently we reported the use of diphenyl diselenide as a precatalyst in the ammonium persulfate as well as in the hydrogen peroxide mediated dihydroxylation of olefins.[1]

In the first case[1a] the reactions proceed through an hydroxyselenenylation followed by substitutive deselenenylation, whereas when using hydrogen peroxide as oxidant the mechanism has been demonstrated to involve an epoxidation promoted by the in situ formed perseleninic acid, followed by the attack of a molecule of water.

As an extension of our investigation concerning the use of organoselenium compounds as catalysts for greener synthetic procedures[2] we take in consideration the oxidation of carbon–carbon triple bond considering also the wide availability of alkynyl substrates. Diphenyl diselenide, in refluxing methanol in the presence of an excess of ammonium persulfate, converts alkynes into the corresponding di- or monoprotected α-dicarbonylic compounds.[3] In the same paper it has been reported an example in which a stoichiometric amount of diphenyl diselenide produces the unprotected derivatives when the solvent is a MeCN–H_2O mixture.

1,2-Dicarbonyl derivatives are known to be useful and versatile synthones.[4] Recently they were successfully employed in the synthesis of the imidazole core[5] present in a series of well-known drugs. Since their value as starting materials, many methods have been developed for the synthesis of these compounds: ruthenium tetroxide oxidation of acyloins,[6] α-bromoketones,[6] and carbon–carbon multiple bonds,[7] oxidative hydrolysis using silver salts of ketodithianes,[8] coupling reaction of acetic anhydride with aldehydes assisted by $CoCl_2$,[9] and oxidation of *vic*-diols.[10]

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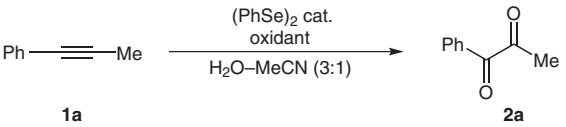
Particular attention has been devoted to the oxidation of alkynes, whereas this procedure is frequently complicated by the overoxidation affording the corresponding carboxylic acids.[11]

Here we report that ammonium persulfate in aqueous conditions can effect this oxidation and that diphenyl diselenide catalyzes the process leading directly to the formation of unprotected 1,2-dicarbonyl derivatives.



1a **2a**

Scheme 1 Oxidation of 1-phenyl-1-propyne

Preliminary experiments were carried out on 1-phenyl-1-propyne (**1a**) using several oxidants in the presence of a different concentrations of catalyst $(PhSe)_2$ and at different temperature (Scheme 1). The results summarized in Table 1 clearly demonstrate that H_2O_2 (35%), MCPBA, and peracetic acid (30%) are not suitable oxidants for this reaction. On the contrary ammonium persulfate at 60 °C slowly converts **1a** into the corresponding diketone **2a**, and the reaction can be accelerated by the presence of diphenyl diselenide.

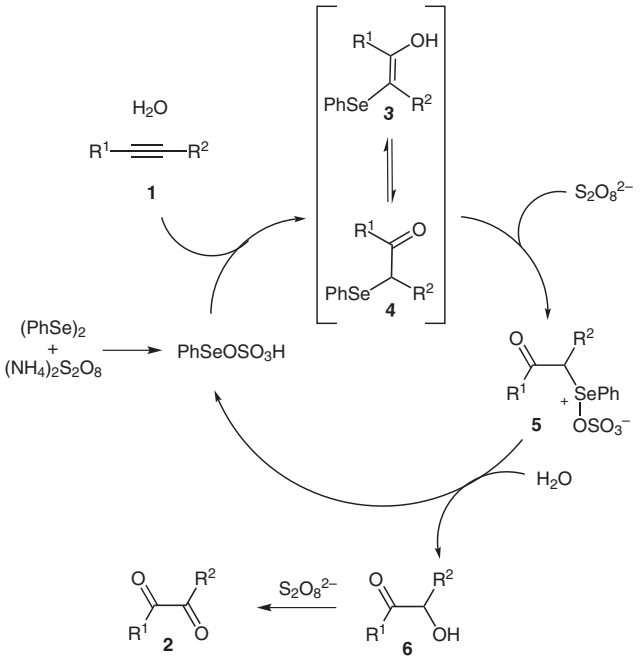
Table 1 Investigation of Reaction Conditions

Oxidant	$(PhSe)_2$ (%)	Yield (%)
$(NH_4)_2S_2O_8$	10	75[a]
$(NH_4)_2S_2O_8$	100	80[a]
$(NH_4)_2S_2O_8$	0	27[a]
oxidant[b]	10	–
oxidant[b]	100	–
oxidant[b]	0	–

[a] All the reactions were carried out at 60 °C for 24 h.
[b] H_2O_2 (35%), MCPBA or peracetic acid (30%). The reactions were carried out at 25 °C for 48 h recovering quantitatively the starting material.

Nonappreciable differences have been observed between the reactions carried out with catalytic or stoichiometric amounts of diselenide. The catalytic role of the $(PhSe)_2$ is proposed in Scheme 2. The actual catalyst is the strongly

electrophilic PhSe-sulfate produced by the reaction of diphenyl diselenide with ammonium persulfate. Reasonably this electrophile, in the presence of water, promotes an hydroxyselenenylation on the triple bond leading to the enol **3** that exists in a tautomeric equilibrium with the ketone **4**. The excess of ammonium persulfate activates the phenylselenium moiety to the nucleophilic substitution by a molecule of water as we reported for the dihydroxylation of olefins. The formation of the α-hydroxyketone **6a** (R^1 = Ph, R^2 = Me) has been hypothesized on the basis of a GC-MS peak [M^+] (*m/z* = 150) observed in the analysis effected on the ongoing reaction. In the described experimental conditions it is reasonable to suppose a rapid oxidation of **6** to afford the corresponding 1,2-dicarbonyl compound **2**. Noteworthy these experimental evidences suggest that the reaction mechanism, in the presence of water, is different from those proposed in 1991 by Tiecco et al.[3] for similar reactions effected in methanol.



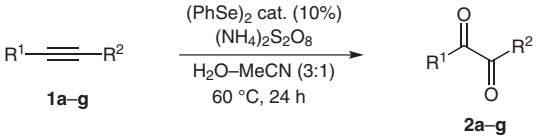
Scheme 2 Proposed mechanism

With the optimized conditions in hand we investigated the scope of this methodology starting from a series of substituted alkynes **1a**–**g**. The results are collected in Table 2. All the reactions were stopped after 24 hours, and the corresponding 1,2-dicarbonyl derivatives **2a**–**g** were purified by flash chromatography and fully characterized on the basis of GC-MS analysis, ^{1}H NMR and ^{13}C NMR spectral data. The yields, calculated on the amount of isolated compounds, range from moderate to good. Starting from the alkynes **1b**–**f** (entries 2–6) we demonstrated that longer reaction time produces a positive effect on the yields. Even if for a reaction time longer than 200 hours the over-oxidation seems to be the main process. The alkynes **1a**,**d**,**e**,**g** were quantitatively converted into benzoic acid in seven days. In all the cases after purification on silica gel column chromatography the precatalyst $(PhSe)_2$ can be quantitatively recovered and reused.

Starting from the terminal alkyne **1g** the α-ketoaldehyde **2g** has not been isolated, and the ^{1}H NMR spectrum of the crude shows an equilibrium with the hydrated form **7g** (Scheme 3). After silica gel chromatography, using a CH_2Cl_2–MeOH (99:1) mixture as eluent the methoxy hemiacetal **8g** is recovered in 65% yield. It is reasonable to suppose that the equilibrium between **2g** and **7g** for the presence of methanol and the acidic catalysis of SiO_2 is shifted towards the more stable form **8g** (Scheme 3).

In all the cases the yields obtained in the absence of $(PhSe)_2$ are much lower.

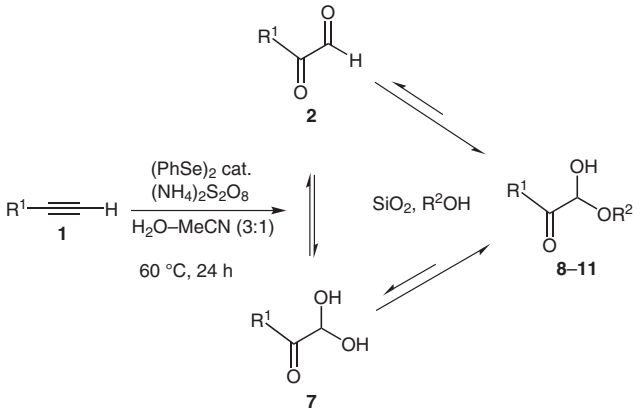
Table 2 Scope of the Reaction



1a–g **2a–g**

Entry	Substrate	Product	Yield (%)
1	Ph—≡—Me **1a**	**2a**	75
2	Pr—≡—Pr **1b**	**2b**	20 67[a]
3	Ph—≡ **1c**	**2c**	20 59[a]
4	Ph—≡—Pr **1d**	**2d**	30 77[a]
5	Ph—≡—Ph **1e**	**2e**	5 85[b]
6	$H_{17}C_8$—≡—Me **1f**	2f	30 57[a]
7	Ph—≡—H **1g**	**8g**	65[c]

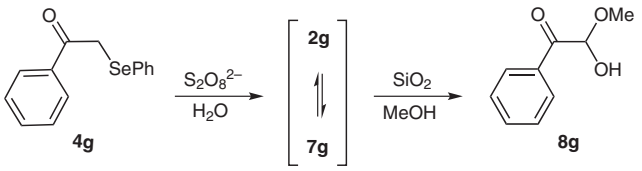
[a] Reaction time 48 h.
[b] Reaction time 72 h.
[c] After chromatography SiO_2 eluent: CH_2Cl_2–MeOH.



Scheme 3 Formation of hemiacetals **8–11**

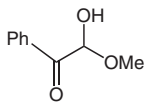
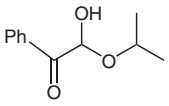
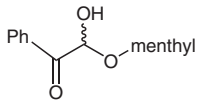
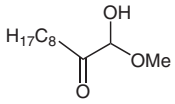
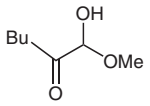
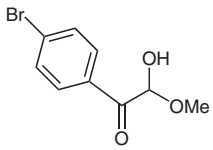
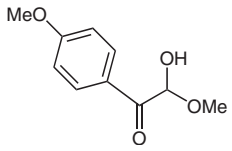
In order to prove the above proposed mechanism (Scheme 2) and the involvement of an α-selenoketone as intermediate, the selenide **4g** was prepared according to our recently reported procedures.[12]

Treatment of **4g** with an excess of ammonium persulfate in a refluxing mixture of MeCN–H_2O (1:3) afforded rapidly and quantitatively **8g** after purification on silica gel and methanol (Scheme 4). This reaction was not accelerated by the presence of a catalytic amount of diphenyl diselenide indicating that the deselenenylaton is mainly promoted by the oxidant and not by the electrophilic catalyst.



Scheme 4 Deselenenylation of **4g**

Table 3 Preparation of Hemiacetals

Entry	Substrate	R^2	Product	Yield (%)
1	Ph—≡—H **1g**	Me	 **8g**	65
2	**1g**	*i*-Pr	 **9g**	55
3	**1g**	*t*-Bu	–	–
4	**1g**	D-menthyl	 **10g–11g** (1:1)	30
5	$H_{17}C_8$—≡—H **1h**	Me	 **8h**	30
6	Bu—≡—H **1i**	Me	 **8i**	50
7	Br—C6H4—≡—H **1l**	Me	 **8l**	60
8	MeO—C6H4—≡—H **1m**	Me	 **8m**	65

Due to the synthetic versatility as well as to some reported pharmaceutical application of glyoxal derivatives[5,13] we investigated the selenium-catalyzed oxidation of a series of terminal alkynes **1g–m**. In order to isolate the corresponding hemiacethal **8–11** the crude mixtures were treated with different alcohols during the purification on silica gel column.

The results reported in Table 3 indicate that the sterical demand of the alcohol produces a negative influence on the yields (entries 2–4) and that an optically pure alcohol such as D-menthol does not produce a stereoselection during the formation of the chiral hemiacetalic carbon leading to a 1:1 mixture of the possible diastereoisomers **10g** and **11g** that cannot be separed by chromatography (entry 4).

The compounds **8g–m**, **9g**, **10g**, and **11g** were isolated by chromatography and were fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and resulted stable at 0 °C for several days.

Some selected reactions (on **1a**,**g**,**m**) were then carried out in 'on water' conditions observing that when starting from aryl-substituted alkynes results comparable to those observed in the presence of the co-solvent MeCN can be obtained.

In conclusion we reported an unprecedented oxidation of alkynes promoted by ammonium persulfate in aqueous medium stressing the catalytic effect of diphenyl diselenide. The proposed procedure[14] represents a convenient way to prepare 1,2-unprotected dicarbonyl derivatives. From terminal alkynes an interesting conversion of the resulting α-ketoaldehydes to the corresponding hemiacetals by treatment of the crude with silica gel and different alcohols has been observed.

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(14) In a typical procedure $(PhSe)_2$ (0.1 mmol) and $(NH_4)_2S_2O_8$ (3 mmol) were suspended in H_2O (5 mL) (or in a 3:1 mixure of H_2O–MeCN) and heated at 60 °C for 15 min. To the resulting red-orange reaction mixture alkyne (**1a**–**m**, 1 mmol) was added and stirred for the time reported in Tables 2 and 3. After the usual workup the crude was purified by a silica gel chromatography using CH_2Cl_2 or a mixture 1:99 R^2OH–CH_2Cl_2 as eluent.
All the compounds, after purification, were fully characterized by GC-MS, ^{1}H NMR, and ^{13}C NMR experiments. Physical and spectral data for the products not previously described in literature are reported below.
2-Hydroxy-2-isopropoxy-1-phenylethanone (9g)
Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, 2 H, *J* = 7.5 Hz), 7.64 (t, 1 H, *J* = 7.5 Hz), 7.51 (t, 2 H, *J* = 7.5 Hz), 5.79 (d, 1 H, *J* = 8.0 Hz), 4.57 (d, 1 H, *J* = 8.0 Hz), 4.27 (sept, 1 H, *J* = 6.4 Hz), 1.35 (d, 3 H, *J* = 6.4 Hz), 1.28 (d, 3 H, *J* = 6.4 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 194.5, 134.9, 133.4, 130.0, 129.1, 90.9, 71.0, 24.2, 22.2 ppm. GC-MS: *m/z* (relative intensity) = 192 (1), 121 (51), 105 (100), 77 (58), 51 (29).
1-Hydroxy-1-methoxydecan-2-one (8h)
Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.86 (d, 1 H, *J* = 9.2 Hz), 4.10 (d, 1 H, *J* = 9.0 Hz), 3.50 (s, 3 H), 2.78–2.71 (m, 1 H), 2.57–2.45 (m, 1 H), 1.71–1.62 (m, 2 H), 1.30–1.28 (m, 10 H), 0.89 (t, 3 H, *J* = 6.0 Hz) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 206.1, 95.5, 55.5, 37.9, 35.5, 31.7, 29.2, 23.0, 14.0 ppm. GC-MS: *m/z* (relative intensity) = 202 (1), 141 (100), 123 (33) 71 (94), 57 (94).
1-Hydroxy-1-methoxyhexan-2-one (8i)
Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.81 (d, 1 H, *J* = 9.0 Hz), 4.09 (d, 1 H, *J* = 9.0 Hz) 3.50 (s, 3 H), 2.78–2.65 (m, 1 H), 2.65–2.43 (m, 1 H), 1.65–1.53 (m, 2 H), 1.43–1.23 (m, 2 H), 0.90 (t, 3 H, *J* = 7.01 Hz) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.1, 95.5, 55.5, 37.5, 25.1, 22.2, 13.7 ppm. GC-MS: *m/z* (relative intensity) = 146 (13), 119 (10), 97 (36), 85 (60), 77 (50), 70 (55), 57 (100).
2-Hydroxy-2-methoxy-1-(4′-bromophenyl)-ethanone (8l)
Mp 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.85 (m, 2 H), 7.65–7.55 (m, 2 H), 5.57 (d, 1 H, *J* = 9.0 Hz), 4.55 (d, 1 H, *J* = 9.0 Hz), 3.55 (s, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 193.6, 132.6, 131.8, 131.4, 130.4

93.4, 55.0 ppm. GC-MS: *m/z* (relative intensity) = 242 (1), 183 (100), 157 (83), 75 (60), 50 (51).

2-Hydroxy-2-methoxy-1-(4′-methoxyphenyl)-ethanone (8m)

Mp 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.05 (m, 2 H), 7.05–6.95 (m, 2 H), 5.59 (s, 1 H), 4.75 (br s, 1 H), 3.90 (s, 3 H) 3.53 (s, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 192.6, 165.0, 132.5, 126.0, 114.5, 93.1, 55.9, 54.7 ppm. GC-MS: *m/z* (relative intensity) = 196 (1), 134 (100), 107 (80), 92 (83), 77 (86), 63 (51), 50 (29).