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One-step selective deoxygenation of alcohols from acyloins†

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An efficient method for reducing primary, secondary and tertiary alcohols from α-keto alcohols was developed. The reduction of acyloins affords good product yields without affecting the carbonyl group.

Introduction

The reduction of alcohols is very useful in organic synthesis. Since the hydroxyl group is a poor leaving group, it should be generally activated before reduction.[1] This activation is commonly achieved by converting the –OH group into a better leaving group, which weakens the C–O bond.[2] These methods are generally incompatible with a carbonyl group, since the latter is also reduced under these conditions.

Some transformations require toxic or expensive reactants and are not useful for all types of alcohols. For instance, the Barton–Mc Combie[3] deoxygenation using xanthate is well known, mainly for secondary alcohols.[4]

The reduction of the hydroxyl group involves also the formation of different ester derivatives by photoinduced electron transfer (ET) reactions.[5] For instance, photosensitized deoxygenation using benzoate esters has a higher reactivity toward secondary or tertiary alcohols than toward primary alcohols.[6]

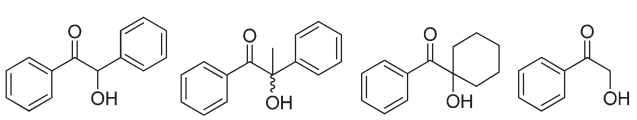
In contrast, the reduction of acyloins such as α-hydroxyketones, remains little explored. Acyloins are building blocks for synthesis due to their versatile functional groups, which may be easily transformed to other functionalities, *e.g.*, diols, halo or amino derivatives, and epoxides.[7] However, there are currently few methods for transforming acyloins to ketones. One example is the polar reduction of benzoin benzoates with 1,3-propanedithiol.[8] Marino *et al.* have also reported the 3-trifluoromethylbenzoyl group as an efficient activating group for the deoxygenation of sugars.[9] In addition, the reductive cleavage of C–O bond in acyloin derivatives has been performed using an electron donor.[10] Electrochemical reductions of acetophenones bearing a leaving anionic group in the α-position, such as, halogen, NR_2, OR and SR groups have been reported.[11] Furthermore, the cleavage of several α-substituted acetophenones by homogeneous electron donor has also been investigated.[12]

Our interest in this area began when we described the reactivity of α-keto radicals with diverse nucleophiles,[13] showing that conjugated radicals can slow down coupling reactions due to their stability, independently of the leaving group on the substrate. In view of this, the reduction of alcohols without affecting the carbonyl group would have significant synthetic applications. Here we report the deoxygenation of α-keto alcohols (Scheme 1, **1–4**) providing an efficient new approach to alcohol reduction.

The photostimulated reaction of **1** with Ph_2P^- ions during 1 or 3 h afforded the reduction product (**5**) in 43% or 48% yields, respectively. However, using higher dilutions of **1**, the reduction rendered a 97% yield in only 1.5 h (eqn 1) (Table 1, entries 1–3). In the dark, this reaction slowed down (26% yield). The photostimulated reaction was inhibited by *m*-dinitrobenzene (*m*-DNB), a well-known inhibitor of ET reactions (Table 1, entries 4–5).[14]

When $(EtO)_2PO^-$ ions were used, **1** reacted yielding both **5** (48%) and 2,3-diphenyloxirane (**6**) (29%) (Table 1, entry 6). The reduction is favored by the addition of KI,[15] which was described as an initial ET catalyst, which under these conditions increased the yield of **5** to 79% (eqn 1) (Table 1, entries 7 and 8). The reaction proceeds in the dark with this anion but it is inhibited by *m*-DNB (Table 1, entry 9), and, thus, a polar mechanism cannot be ruled out.[16]

After establishing that secondary (and benzylic) alcohol (**1**) was successfully reduced, we explored other substrates to test the scope of this reaction pathway.



1 2 3 4

Scheme 1

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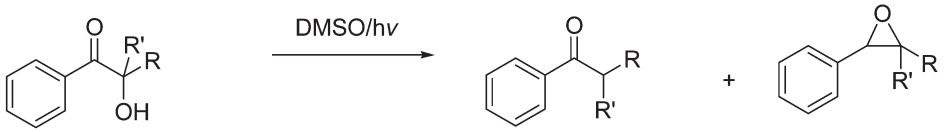
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopy data for all compounds. See DOI: 10.1039/c3ra40343b

Table 1 Deoxygenation reactions of **1**, **2**, **3** and **4** in DMSO[24]



R	R'	Substrate			
Ph	H,	1	Ph_2P^-	**5**, 97%	**6**, -
			$(EtO)_2PO^-$	79%	15%
Ph	CH_3,	2	Ph_2P^-	**7**, 91%	-
C_5H_{10}		3	Ph_2P^-	**8**, 88%	**9**, 9%
			$(EtO)_2PO^-$	68%	-
H	H,	4	Ph_2P^-	**10**, 45%	-
			$(EtO)_2PO^-$	60%	**11**,40

	Substrate (10^2 M)	Electron Donors (10^2 M)	Condition	Yield of products: reduction	Yield of products: epoxy
1[a]	**1** (3.3)	Ph_2P^- (3.3)	1 h, *hν*	**5**, 43 (57)[b]	—
2[c]	**1** (3.3)	Ph_2P^- (3.3)	3 h, *hν*	**5**, 48 (46)[b]	—
3	**1** (1.7)	Ph_2P^- (1.7)	1.5, *hν*	**5**, 97[d]	—
4	**1** (1.7)	Ph_2P^- (1.7)	1.5, dark	**5**, 26 (67)[b]	—
5	**1** (1.7)	Ph_2P^- (1.7)	1.5, *hν*[e]	**5**, - (98)[b]	—
6[a]	**1** (1.7)	$(EtO)_2PO^-$ (1.7)	30 min, *hν*	**5**, 48 (23)[b]	**6**, 29
7[a]	**1** (2.0)	$(EtO)_2PO^-$ (2.0)	30 min, *hν*/KI[f]	**5**, 69	**6**,30
8[c]	**1** (2.0)	$(EtO)_2PO^-$ (2.0)	30 min, *hν*/KI[g]	**5**, 79	**6**,15
9	**1** (2.0)	$(EtO)_2PO^-$ (2.0)	30 min, dark/KI[g]	**5**, — (92)[e]	—
10[c]	**2** (1.7)	Ph_2P^- (1.7)	1 h, *hν*	**7**, 91	—
11[c]	**3** (1.7)	Ph_2P^- (1.7)	5 min, *hν*	**8**, 88	**9**, 9[h]
12[c]	**3** (1.7)	Ph_2P^- (1.7)	5 min, dark	**8**, 11(82)	**9**, 5[h]
13	**3** (1.7)	Ph_2P^- (1.7)	5 min, dark[e]	**8**, 2 (92)[b]	—
14	**3** (1.7)	Ph_2P^- (1.7)	5 min, *hν*[e]	**8**, 2 (91)[b]	—
15	**3** (1.7)	—	15 min, *hν*	— (96)[b]	—
16[c]	**3** (2.0)	$(EtO)_2PO^-$ (2.0)	30 min, *hν*/KI[g]	**8**, 68 (23)[b]	—
17[a]	**3** (2.0)	$(EtO)_2PO^-$ (2.0)	1.5 h, *hν*/KI[g]	**8**, 47 (8)[b]	—[i]
18	**3** (2.0)	—	1.5 h, *hν*/KI[g]	— (68)[b]	—[i]
19[a]	**4** (3.3)	Ph_2P^- (3.3)	10 min, *hν*	**10**, 45 (35)[b]	—[j]
20[c]	**4** (2.0)	$(EtO)_2PO^-$ (2.0)	1.5 h, *hν*/KI[g]	**10**, 26 (70)[b]	—
21[a]	**4** (1.2)	$(EtO)_2PO^-$ (1.2)	1.5 h, *hν*/KI[g]	**10**, 60[d]	**11**,40
22	**4** (1.2)	$(EtO)_2PO^-$ (1.2)	1.5 h, *hν*[e]KI[g]	— (93)[b]	—
23[c]	**4** (1.2)	$(EtO)_2PO^-$ (1.2)	1.5 h, dark/KI[g]	**10**, 51[d]	**11**,35

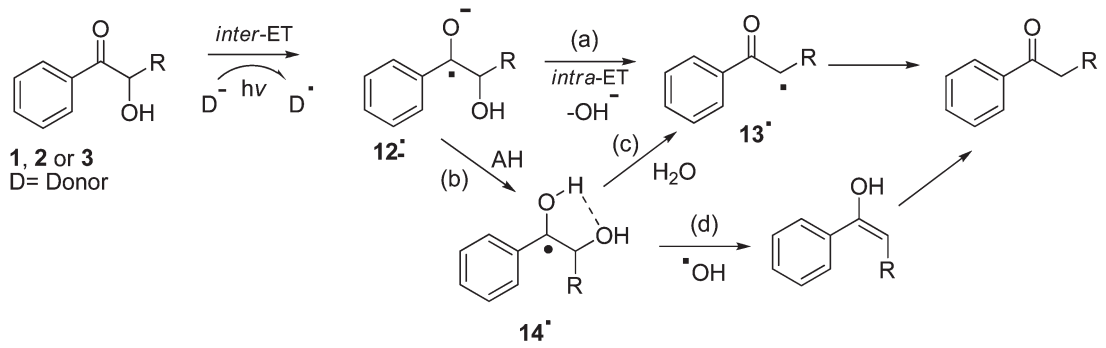
[a] Organic products were determined by GC using relative areas. [b] Recovered substrate. [c] Organic products, after extraction with ethyl ether and CH_2Cl_2, were determined by GC using internal standards. [d] Isolated yield. [e] With addition of 1.0 10^{-3} mol *m*-DNB. [f] With addition of 2.0 10^{-3} mol KI. [g] With addition of 5.0 10^{-3} mol KI. [h] Determined by GC-MS. [i] Cyclohexanone was found at 30–40%. [j] Ethyl benzene was found at 40%.

Thus, tertiary alcohols such as **2**[17] and **3** were examined. As shown in Table 1, these tertiary alcohols afforded satisfactory results. Thus, the photostimulated reaction of **2** with Ph_2P^- ions gave a 91% yield of **7**, while **3** afforded a 88% yield of **8**. In the dark, this reaction slowed down (Table 1, entries 10–12).

The reaction was inhibited (using either light or dark conditions) by *m*-DNB (Table 1, entries 13 and 14). Light catalysis and inhibition with *m*-DNB indicate that a photostimulated ET mechanism is involved. A reaction without Ph_2P^- was also tested to exclude a possible photolysis mechanism,[18] showing that the reduction product was not formed (Table 1, entry 15).

When $(EtO)_2PO^-$ was used as anion, **3** afforded a 68% yield of **8**. The same reaction, given more time, produced cyclohexanone. Cyclohexanone was also observed when an electron donor was not present, indicating that it was generated by photolysis of the substrate under this condition (Table 1, entries 16–18).[18]

Considering that some known methods are not efficient for reducing primary alcohol,[4] we decided to try these reductions using a primary alcohol, namely **4**. This substrate reacted with Ph_2P^- ions under light stimulation yielding both **10** (45%) and ethyl benzene as by-product. In contrast, when $(EtO)_2PO^-$ was used, **4** reacted slowly. However, using higher dilutions, the reduction rendered a 60% yield of **10** together with the oxirane **11** in 1.5 h. Although the reaction was inhibited by *m*-DNB, the dark reaction shows that the substrate **4** is reduced without photostimulation, which seems to indicate that this compound may be reduced by a polar mechanism (Table 1, entries 19–23).



Scheme 2

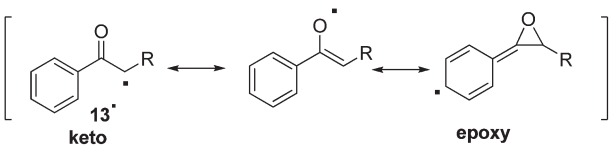
Note that none of the reactions of substrates **1–4** allowed observing products that evidence the classical nucleophilic or oxophilic behavior of phosphorus anions.[15]

On this basis, a plausible mechanism for these reductions could be proposed for compounds **1–3** with anion Ph_2P^-. As shown in Scheme 2, the substrate receives one electron from the donor through an *inter*-molecular ET (*inter*-ET), providing the radical anion **12**$^{-\bullet}$. Then, one *intra*-molecular ET takes place (*intra*-ET), allowing the elimination of anion HO^- and the formation of radical **13**$^\bullet$, which is protonated by the solvent. The driving force for the *inter*-ET is the formation of a stabilized radical anion. Other possible mechanisms of C–O bond fragmentation have been described for esters derived from acyloins.[19] In the presence of a proton donor, the radical anion **12**$^{-\bullet}$ can form the radical **14**$^\bullet$ (path (b)), which can undergo two alternative paths (paths c or (d)) to finally give the reduced compound. In contrast, for the reactions of anion $(EtO)_2PO^-$ more experiments would be necessary in order to describe the mechanism.

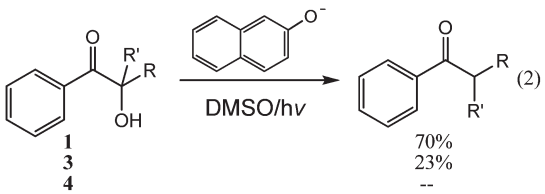
The presence of epoxides and ketones as products could be explained based on the possible resonance structures of radical **13**$^\bullet$,[20] as shown in Scheme 3.

Thus, the products distribution can be understood considering the relative stabilities of these structures. As expected, a greater amount of epoxide is produced from **4** (**13**$^\bullet$ is a primary radical) while a greater amount of ketone is produced from compounds **1**, **2** and **3** (these form more stable radicals).

Finally, considering the satisfactory results, we decided to extend this reaction pathway to another electron donor, one which can be solved in water, such as a naphthoxide ion.[21] Thus, the photostimulated reaction of **1** with 2-naphtoxide ions in DMSO afforded a 70% yield of **5** after 3 h, without evidence of epoxide as by-product (eqn 2).[22]



Scheme 3



The same reaction with compound **3** afforded a 23% yield of **8**, whereas for **4** a reduction product was not observed under these conditions (Table 2, entries 1–6). As can be observed, the reactivity under light catalysis towards a poor nucleophilic and non-oxophilic weak base, (2-naphtoxide anion), in conjunction with the absence of reaction in the dark, allowed us to corroborate that an electron transfer process may be feasible at least for a good electron donor such as Ph_2P^-. The reactivity trend is the expected when the rate-determining step is the fragmentation of the radical anion. Considering that the electron acceptor is the same (Ph–C(O)– group), the fragmentation depends on the stability of the radical produced. In fact, the best substrate for this ET process is **1**, forming a benzylic radical; then **3**, which reacts more slowly (tertiary aliphatic radical), while compound **4** is not reactive under these conditions based on the stability of the primary radical.

This last result is quite important because it allows extending this novel reduction to a more environmentally friendly solvent, like water, demonstrating that ET is feasible with a non-oxophylic reagent, at least for **1** and **3**.[23] These results are in agreement with the proposed ET mechanism for a good electron donor such as Ph_2P^-. In contrast, for anion $(EtO)_2PO^-$ the reduction could take place by a polar mechanism. Photophysical and photochemical studies will be performed in order to fully elucidate the mechanism of these reactions.

Conclusions

We report a general and useful method for selective dehydroxylation of α-keto alcohols. We have verified an efficient pathway for the reduction of primary, secondary and tertiary α-keto alcohols, without affecting the carbonyl group. So far, we have proposed a different mechanism by which reduction products are formed, showing that the difference in the stability of products from each

Table 2 Deoxygenation reactions of **1**, **3** and **4** in DMSO

	Substrate (10^2 M)	2-naphtoxide (10^2 M)	Condition[a]	Yield of reduction products[b]
1	**1** (1.25)	(1.25)	3 h, *hv*	**5**, 70 (24)[c]
2	**1** (1.25)	(1.25)	3 h, dark	**5**, — (96)[c]
3	**3** (1.25)	(1.25)	3 h, *hv*	**8**, 23 (69)[c]
4	**3** (1.25)	(1.25)	3 h, dark	**8**, — (96)[c]
5	**4** (1.25)	(1.25)	3 h, *hv*	**10**, — (97)[c]
6	**4** (1.25)	(1.25)	3 h, dark	**10**, — (98)[c]

[a] With addition of 5.0 10^{-3} mol KI. [b] Organic products, after extraction with ethyl ether and CH_2Cl_2, were determined by GC using internal standards. [c] Recovered substrate.

reaction can determine the facility of formation of each product. To achieve the best yield, it is important to set up the appropriate reaction conditions for each substrate employed, which mainly depends on the time and concentration used. Efforts to extend this reaction pathway to other stabilized radicals, expanding the scope for synthetic applications, are currently underway. To the extent of our knowledge this is the first report about the reduction of α-hydroxy ketones without activation of the hydroxyl group.

Acknowledgements

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22 Concentration of substrate and electron donor were 1.25 10^2 M.

23 This experiment also shows that phosphine proceeds as a reductant and not a phosphorylating agent.

24 The following procedure is representative. $NaPPh_2$ (1 mmol) and substrate 1 (1.0 mmol) were added to 3 mL dry and degassed DMSO under nitrogen; the reaction mixture was irradiated. The reaction was quenched with an excess of NH_4NO_3. The residue was dissolved with water and extracted with both diethyl ether and dichloromethane. The organic extract was analyzed by GC-MS. $(EtO)_2POH$ and *t*-buOK were used to form $(EtO)_2PO$– *in situ*. All products had the same retention time as authentic materials and the correct mass by GC-MS.