Woollins Reagent: A Chemoselective Reducing Agent for 1,4-Enediones and 1,4-Ynediones to Saturated 1,4-Diones

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Abstract: Woollins reagent was found to act as a highly chemoselective reagent for the reduction of a wide range of 1,4-enediones and 1,4-ynediones in methanol to afford the corresponding saturated 1,4-diketones in good yields under mild reaction conditions.

Key words: Woollins reagent, chemoselective reduction, 1,4-enediones, 1,4-ynediones, 1,4-diketones

1,4-Diketones are important and valuable precursors for the synthesis of heterocyclic compounds like furan, pyrrole, and their derivatives. Literature study revealed that 1,4-diketone derivatives have good uterotrophic activity related to estradiol.[1] A variety of synthetic methodologies have been developed for the preparation of 1,4-diketones, but most of them require lengthy procedures, special reagents, and expensive transition-metal complexes.[2–4]

A number of synthetic methodologies and reagents have been developed to bring about chemoselective reduction of C–C double bonds in α,β-unsaturated carbonyl compounds[5,6] by using metal catalysts, such as osmium,[7] iridium,[8] ruthenium,[9] rhodium,[10] platinum,[11] palladium,[12] nickel,[13] and cobalt.[14] The chemoselective reduction of C–C double bonds in *cis*- and *trans*-1,2-diaroylethylenes and of triple bonds in 1,2-diaroylacetylenes are relatively little explored, except by Doi et al.[15] who used [RuHCl(CO)(PPh_3)$_3$] as an effective catalyst for the selective reduction of 2-ene-1,4-diones to 1,4-diketones in benzene using isopropanol as the hydrogen donor. Herein, we report the highly chemoselective reduction of the double bond in 1,2-diaroylethylenes **1a**–**e**, 1,2-benzoylacetylethylene (**5a**), and 1,2-diacetylethylene (**5b**), and of the triple bond in 1,2-diaroylacetylenes **4a**–**e** to the corresponding 1,2-dibenzoylethanes **2a**–**e**, 1,2-benzoylacetylethane (**6a**) and 1,2-diacetylethane (**6b**) by the most familiar selenium-containing reagent 'Woollins reagent' under mild reaction conditions.

2,4-Diphenyl-1,3-diselenadiphosphetane-2,4-diselenide ($(PhPSe_2)_2$), also known as Woollins reagent (WR),[16] is a selenium analogue of another well-known sulfur-containing reagent named Lawesson's reagent, $(4\text{-MeOPhPS}_2)_2$. After Woollins et al. reported the first time about this reagent, a number of advanced synthetic routes have been reported so far for the preparation of WR.[17–20] Researchers are finding it very convenient to use deep-red crystals of WR for selenation reactions in preference to other selenium-containing reagents, as it can be easily prepared, safely handled in air, and has a less unpleasant odor.[21] WR has been used for the synthesis of symmetrical *E*-olefins,[22] selenoketenyl complexes,[23] and novel phosphorous–selenium heterocycles.[24] In our endeavor to obtain selenophenes in one of our ongoing projects on bioactive molecules, we observed for the first time that the reaction of *trans*-1,2-dibenzoylethylene (**1a**) with WR in methanol gave the unexpected and chemoselective C–C double-bond-reduced product 1,2-dibenzoylethane (**2a**) in good yield along with the corresponding cyclized product 2,5-diphenylfuran (**3a**) in minor quantity. Interestingly, treatment of 1,2-dibenzoylacetylene (**4a**) with WR in methanol also afforded the same products **2a** and **3a** in nearly same yield. Then we have extended this relatively simple methodology to reduce other analogues of *trans*-1,2-diaroylethylenes **1b**–**e** and 1,2-diaroylacetylenes **4b**–**e** to yield the corresponding 1,2-diaroylethanes **2b**–**e** (Scheme 1 and Scheme 2). The results are listed in Table 1 and Table 2. WR works equally well with *cis*-1,2-dibenzoylethylene[25] as that of its *trans* isomer **1a** to furnish **2a** and **3a** in 67% and 16% yields, respectively.

Table 1 Reduction of *trans*-1,2-Diaroyl Ethylenes to 1,2-Diaroyl Ethanes by WR

Entry	R^1	R^2	Time (h)	Yield (%)[a]	
1	H	H	1.5	**2a** 67[27]	**3a** 15[33]
2	Me	H	1	**2b** 64[30]	**3b** 16[33]
3	Cl	H	1	**2c** 60[31]	**3c** 15[33]
4	Br	H	2	**2d** 68[32]	**3d** 17[33]
5	Me	Cl	1	**2e** 60	**3e** 16

[a] Isolated yield.

Similarly, the unsymmetrical alkenone (*E*)-1-phenylpent-2-ene-1,4-dione (**5a**)[26] underwent reduction to yield 1-phenylpentane-1,4-dione (**6a**)[27] in 42% yield along with 2-methyl-5-phenylfuran (**7a**) in 18% yield (Scheme 3). Reduction of *trans*-hex-3-ene-2,5-dione (**5b**)[28] where two carbonyl groups are flanked by methyl groups under the same reaction conditions yielded hexane-2,5-dione (**6b**)[29] (Scheme 3, Table 3) along with 2,5-dimethylfuran (**7b**) in 46% and 17% yields, respectively. On the other hand,

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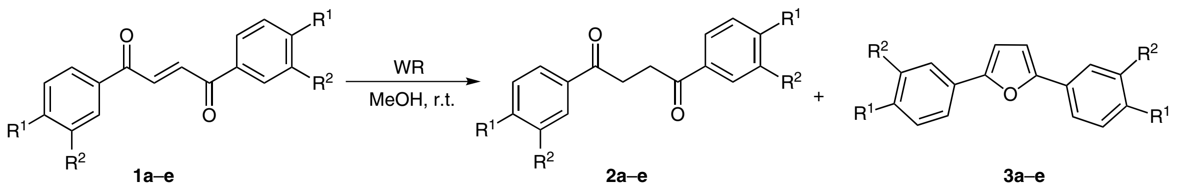
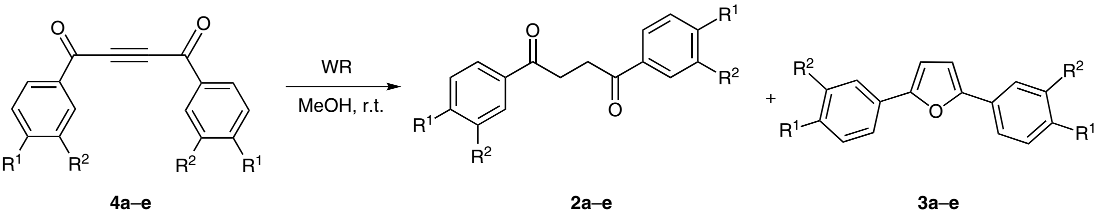


Scheme 1 Reduction of *trans*-1,2-diaroylethylenes to 1,2-diaroylethanes by WR



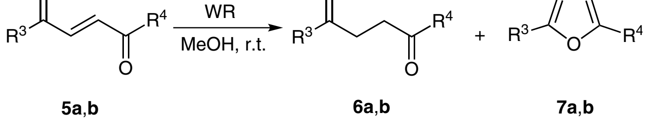
Scheme 2 Reduction of 1,2-diaroylacetylenes to 1,2-diaroylethanes by WR

simple olefins/acetylenes (e.g., 3-nitrostyrene, 3-bromopropyne, and heptyne) and α,β-unsaturated esters (e.g., ethyl cinnamate, ethyl propionate) did not undergo reduction under the present reaction conditions.

Table 2 Reduction of 1,2-Diaroyl Acetylenes to 1,2-Diaroylethanes by WR

Entry	R^1	R^2	Time (h)	Yield (%)[a]	
1	H	H	1	**2a** 61[27]	**3a** 16[33]
2	Me	H	1	**2b** 65[30]	**3b** 15[33]
3	Cl	H	1.5	**2c** 60[31]	**3c** 18[33]
4	Br	H	2	**2d** 62[32]	**3d** 16[33]
5	Me	Cl	1	**2e** 60	**3e** 16

[a] Isolated yield.



Scheme 3 Reduction of arylalkyl and dialkyl enediones by WR

Table 3 Reduction of Arylalkyl and Dialkyl Enediones by WR

Entry	R^3	R^4	Time (h)	Yield (%)[a]	
1	Ph	Me	1.5	**6a** 42[27]	**7a** 18[34]
2	Me	Me	1.5	**6b** 46[29]	**7b** 17[35]

[a] Isolated yield.

The role of methanol and other protic solvents in the present methodology has been investigated. It is found that methanol appears to be the solvent of choice (Table 4).[15]

Table 4 Effect of Solvent in the Reduction of *trans*-1,2-Dibenzoylethylene (**1a**) by WR

Solvent	Time (h)	Yield (%)[a]
MeOH	1.5	67
i-PrOH	3	40
i-PrOH–H_2O (7:3)	2	15
THF	5	n.r.
DMF	5	n.r.
CH_2Cl_2	5	n.r.
$CHCl_3$	5	n.r.

[a] Isolated yield; n.r. = no reaction.

It is well known that WR is in equilibrium with a diselenaphosphorane ($PhPSe_2$, **A**), which is the true reactive species in solution.[36] This undergoes reaction with *trans*-1,2-dibenzoylethylene (**1a**) and methanol giving the phenylphosphonodiselenoate complex **B**. Upon attack by another molecule of methanol at phosphorus, the complex **B** undergoes cleavage to yield the reduced product 1,2-dibenzoylethane (**2a**, Scheme 4).

In order to support the proposed mechanism (Scheme 4), wherein we have shown that the source of the protons is from methanol, 1,2-dibenzoylacetylene (**3a**) was treated with WR by using CD_3OD as solvent. Both ^1H NMR and MS analyses of the resultant product confirmed the incorporation of deuterium into **2a** (Figure 1).

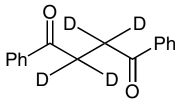
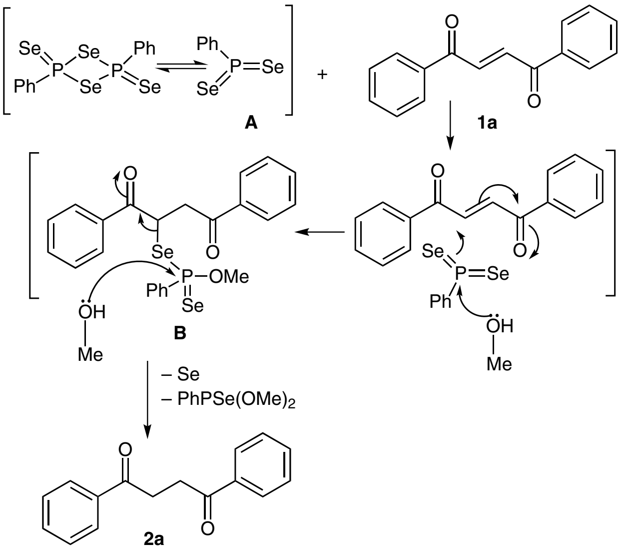


Figure 1 Deuterated product of **2a**



Scheme 4 Proposed mechanism for the reduction of *trans*-1,2-dibenzoylethylene (**1a**) to 1,2-dibenzoylethane (**2a**) by WR

It is pertinent to mention that reduction of 1,2-dibenzoylacetylene (**4a**) to 1,2-dibenzoylethane (**2a**) occurred via formation of *trans*-1,2-dibenzoylethylene (**1a**) under the same experimental conditions. The progress of this reaction has been followed by ^{1}H NMR analysis, which showed that within the first ten minutes, the triple bond in **4a** was completely reduced to a double bond along with the formation of the fully reduced product 1,2-dibenzoylethane (**2a**, 24%). This observation also suggests that the reduction of the triple bond is faster than that of the double bond to a single bond in such systems.

All the substrates have been prepared by following synthetic procedures reported earlier from this laboratory,[37] except the unsymmetrical alkenone **5a**[26] and diacetylethylene **5b**.[28] All the reduced products **2a**–**d**,[27,30–32] **6a**,[27] **6b**,[29] and the 2,5-disubstiuted furans **3a**–**e** and **7a**,**b** were characterized from their spectral data (mainly NMR and mass spectra) and further corroborated with the authentic spectral data available in the literature.

In conclusion, we have disclosed a new dimension in the application of a well-known selenium containing reagent 'Woollins reagent' for chemoselective reduction of C–C multiple bonds in the presence of a carbonyl group by using methanol as the proton source.

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