Palladium-Catalyzed Deprotection of Hydrazones to Carbonyl Compounds

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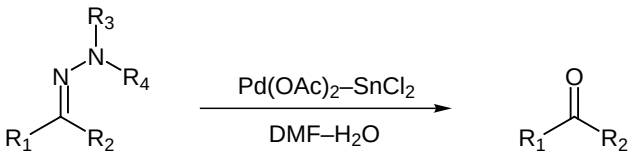
Abstract: Hydrazones of ketones and aldehydes undergo facile cleavage to the corresponding carbonyl compounds by a catalytic amount of $Pd(OAc)_2/SnCl_2$ in good yields.

Key words: hydrazones, aldehydes, ketones, palladium acetate, tin(II) chloride

Hydrazones have been found to be one of the most useful synthetic precursors of aldehydes and ketones.[1] In this method, a key point is the cleavage of the hydrazone moiety to the carbonyl group. Previously, a variety of such methods have been reported, including oxidative cleavage by ozonolysis at low temperature,[2] *N*-methylation of the hydrazone using methyl iodide followed by hydrolysis in a biphasic aqueous HCl–pentane system,[3] and copper-catalyzed hydrolysis.[4] The ozonolysis method provides nearly quantitative chemical yields under neutral conditions and short reaction times, but this method cannot be used if there are other ozone-sensitive groups such as alkenes in the molecule. Many other reagents have been used to cleave hydrazones and to regenerate carbonyl compounds from their *N*,*N*-dialkylhydrazones.[5] However, these methods require a stoichiometric or excess amount of cleavage reagents. The catalytic method of cleavage has only been reported using bismuth catalysis.[6] Therefore, we were interested in the catalytic methods of hydrazone cleavage. In the course of our study using palladium catalyst in organic synthesis,[7] we found that palladium acetate is effective for the catalytic cleavage of hydrazones **1–3** (Scheme).



1 - 3

1: R_1 = alkyl, aryl; R_2 = alkyl, aryl; $R_3 = R_4$ = Me
2: $R_1 = PhCH_2CH_2$; R_2 = Me; R_3 = alkyl, aryl; R_4 =alkyl
3: R_1 = alkyl; R_2 = H; $R_3 = R_4$ = Me

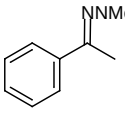
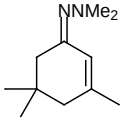
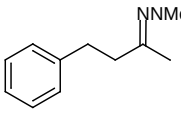
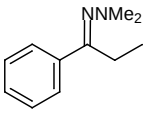
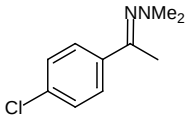
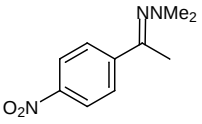
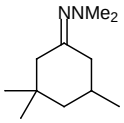
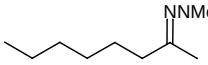
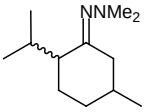
Scheme

This work reports the cleavage of hydrazones by Pd-catalyst. Representative results of the cleavage of aromatic, unsaturated, alicyclic and aliphatic ketone dimethylhydrazones are listed in Table 1.[8] When acetophenone dimethylhydrazone **1a** was treated with a catalytic amount of $Pd(OAc)_2$ and $SnCl_2$ as a co-catalyst in DMF/H_2O at 70 °C under an air atmosphere, the hydrolyzed compound acetophenone was obtained in good yield (Entry 1). However, when this reaction was carried out under an Ar atmosphere, acetophenone was obtained only in 48% yield after 96 h. When water was absent in this reaction, **1a** was not cleaved after 48 h under an air atmosphere, but when the reaction was carried out at 130 °C under the same conditions, the corresponding ketone was obtained in 27% yield after 24 h. Therefore, we believe that this reaction proceeded competitively by acidic and oxidative mechanisms. One of the characteristics of this reaction is that it proceeds under mild conditions without using stoichiometric acidic reagents or oxidative reagents. As shown in Entry 2, even α,β-unsaturated ketone dimethylhydrazone **1b** was hydrolyzed without rearrangement of the α,β double bond using this $Pd(OAc)_2/SnCl_2$ catalytic system. Functional groups such as the halogen or nitro group were also inert with this catalyst, and no by-product was observed by GLC (Entries 5 and 6).

The cleavage of benzylacetone hydrazones **2**, which derived from various *N*,*N*-bissubstituted hydrazines such as *N*,*N*-methylphenylhydrazine, *N*,*N*-dibenzylhydrazine, 1-aminohomopiperidine and *N*-aminomorpholine, proceeded easily with good yields (Table 2). When the cleavage of hydrazone **2a** was carried out, *N*-nitroso-*N*-methylaniline was identified using GLC by comparison of the retention time with those of authentic samples.

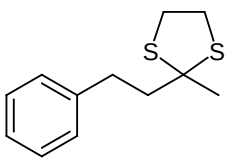
The results of the cleavage of various aldehyde dimethylhydrazones **3** are listed in Table 3. When octanal dimethylhydrazone **3a** was reacted using this catalyst system for 6 h, octanal was obtained as the main product (Table 3, Entry 1). However, when this reaction was carried out for 24 h, octanoic acid was obtained as the main product instead of the corresponding aldehyde (Entry 2). Consequently, it was necessary to optimize the reaction time. As shown in Entry 4, the α,β-unsaturated aldehyde dimethylhydrazone **3c** was cleaved slowly without the formation of the corresponding acid. Dimethylhydrazone **3d**, which was prepared from an air-sensitive aldehyde, gave a mixture of the corresponding aldehyde and acid (Entries 5 and 6).

Table 1 $Pd(OAc)_2$ / $SnCl_2$-Catalyzed Cleavage of Dimethylhydrazone **1**

Entry	Hydrazone **1**		Time (h)	Yield (%)[a,b]
1		**1a**	24	90(75)
2		**1b**	72	(53)[c]
3		**1c**	48	>98
4		**1d**	24	98
5		**1e**	24	>98
6		**1f**	24	>98
7		**1g**	72	>98
8		**1h**	24	96
9		**1i**	48	94

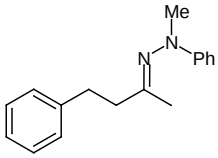
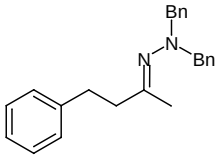
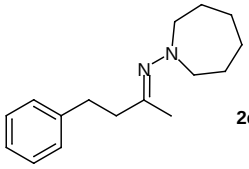
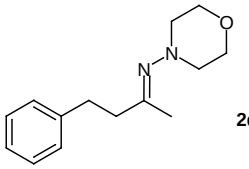
[a] GLC yields.
[b] Values in parentheses are isolated yields.
[c] 5 mol% of $Pd(OAc)_2$ and 2.5 mol% of $SnCl_2$ were used.

Cyclic thioacetals and ketals can also be used as carbonyl protecting groups instead of hydrazone.[5] Therefore, we investigated the deprotection of a cyclic thioketal such as



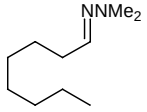
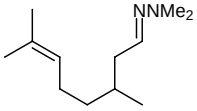
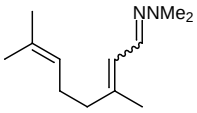
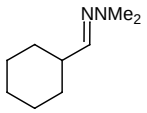
4

Table 2 $Pd(OAc)_2$ / $SnCl_2$-Catalyzed Cleavage of 4-Phenyl-2-butanone Hydrazone **2**

Entry	Hydrazone **2**		Time (h)	Yield (%)[a]
1		**2a**	24	93
2		**2b**	24	>98
3		**2c**	24	>98
4		**2d**	24	>98

[a] GLC yields.

Table 3 $Pd(OAc)_2$ / $SnCl_2$-Catalyzed Cleavage of Aldehyde Dimethylhydrazone **3**

Entry	Hydrazone **3**		Time (h)	Yield (%)[a,b]
1		**3a**	6	87(6)
2			24	24(75)
3		**3b**	6	76
4		**3c**	24	14
5		**3d**	6	44(13)
6			24	53(47)

[a] GLC yields.
[b] Values in parentheses are GLC yields of the correspounding acids.

1,3-dithiolane of 4-phenyl-2-butanone **4**. However, **4** was not cleaved to the corresponding ketone even though the reaction with $Pd(OAc)_2/SnCl_2$ catalyst was carried out for 120 h. Therefore, this Pd-catalyst shows chemoselectivity between 1,3-dithiolane and hydrazone moieties.

In conclusion, a $Pd(OAc)_2/SnCl_2$ catalyst has been successfully used for the cleavage of hydrazones to the corresponding carbonyl compounds.

All carbonyl compounds, hydrazines were obtained from commercial sources. The isolated carbonyl compounds or crude products were identified by ^{1}H NMR (400 MHz) and GC-MS or GLC by comparison of the t_R with those of authentic samples. Hydrazones **1-3** were prepared from the corresponding carbonyl compounds. *N*,*N*-dimethylhydrazine, *N*,*N*-methylphenylhydrazine, *N*,*N*-dibenzylhydrazine, 1-aminohomopiperidine and *N*-aminomorpholine were prepared according to the standard method.[9] Dithiolane **4** was prepared from benzylacetone and 1,2-ethanedithiol according to the standard method. [10,11] ^{1}H NMR spectra were obtained on $CDCl_3$ solutions.

Deprotection of 1–4;Typical Procedure
A solution of hydrazone (1.0 mmol) in DMF (2 mL) was added to a soln of $Pd(OAc)_2$ (0.02 mmol) and $SnCl_2$ (0.01 mmol) in H_2O (2 mL). The reaction mixture was stirred at 70 °C for 24 h and then diluted with EtOAc, washed with brine, and dried ($MgSO_4$). Evaporation of the solvents and bulb-to-bulb distillation or silica gel column chromatography gave the pure carbonyl compounds.

Acetophenone
^{1}H NMR: δ = 2.61 (s, 3H), 7.45-7.97 (m, 5H).

GC-MS: *m/z* (%) = 120 (M^+, 26), 105 (100), 77 (90), 51 (39).

bp: 65-67°C / 5 Torr.[12]

Isophorone
^{1}H NMR: δ = 1.04 (s, 6H), 1.94 (s, 3H), 2.17 (s, 2H), 2.20 (s, 2H), 7.28 (s, 1H).

GC-MS: *m/z* (%) = 138 (M^+, 14), 82 (100).

4-Phenylbutan-2-one
^{1}H NMR: δ = 2.14 (s, 3H), 2.75-2.78 (m, 2H), 2.88-2.91 (m, 2H), 7.14-7.30 (m, 5H).

GC-MS: *m/z* (%) = 148 (M^+, 68), 105 (100), 91 (78), 77 (32) and 51 (28).

Propiophenone
^{1}H NMR: δ = 1.23 (t, *J* = 7.3 Hz, 3H), 3.01 (q, *J* = 7.3 Hz, 2H), 7.44-7.48 (m, 2H), 7.53-7.57 (m, 1H), 7.96-7.98 (m, 2H).

GC-MS: *m/z* (%) = 134 (M^+, 12), 105 (100), 77 (59) and 51 (28).

4'-Chloroacetophenone
^{1}H NMR: δ = 2.59 (s, 3H), 7.42-7.46 (m, 2H), 7.90 (dt, *J* = 2.1, 8.9 Hz, 2H).

GC-MS: *m/z* (%) = 154 (M^+, 25), 139 (100), 111 (59), 75 (40).

4'-Nitroacetophenone
^{1}H NMR: δ = 2.69 (s, 3H), 8.10-8.14 (m, 2H), 8.32 (dt, *J* = 2.1, 8.9 Hz, 2H).

GC-MS: *m/z* (%) = 165 (M^+, 17), 150 (100), 104 (36), 92 (22).

3,3,5-Trimethylcyclohexanone
^{1}H NMR: δ = 0.88 (s, 3H), 1.01-1.06 (m, 6H), 1.27-1.33 (m, 1H), 1.57-1.61 (m, 1H), 1.86-1.93 (m, 1H), 1.98-2.08 (m, 2H), 2.15-2.34 (m, 2H).

GC-MS: *m/z* (%) = 140 (M^+, 13), 125 (7), 83 (100), 69 (59), 55 (46).

Octan-2-one
^{1}H NMR: δ = 0.88 (t, *J* = 6.7 Hz, 3H), 1.28 (br, 6H), 1.54-1.61 (m, 2H), 2.14 (s, 3H), 2.42 (t, *J* = 7.2 Hz, 2H).

GC-MS: *m/z* (%) = 128 (M^+, 3), 113 (3), 85 (60).

Menthone:
^{1}H NMR: δ = 0.85 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 1.32-1.40 (m, 2H), 1.88-2.15 (m, 6H), 2.33-2.37 (m, 1H).

GC-MS: *m/z* (%) = 154 (M^+, 17), 112 (70), 69 (100), 55 (98).

Octanal
GC-MS: *m/z* (%) = 100 (M^+-28, 5), 84 (30), 74 (58), 59 (100).

Octanoic Acid
GC-MS: *m/z* (%) = 115 (M^+-29, 3), 101 (11), 74 (47), 60 (100).

Citronellal
GC-MS: *m/z* (%) = 154 (M^+, 4), 139 (5), 121 (38), 111 (13), 69 (100).

Citral
GC-MS: *m/z* (%) = 152 (M^+, 2), 137 (4), 123 (4), 109 (6), 69 (100).

Cyclohexanecarboxaldehyde
GC-MS: *m/z* (%) = 112 (M^+, 3), 83 (28), 74 (54), 59 (100).

Cyclohexanecarboxylic Acid
GC-MS: *m/z* (%) = 128 (M^+, 3), 110 (2), 99 (3), 83 (25), 55 (100).

References and Notes

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(10) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945.
(11) ^{1}H NMR: δ = 1.84 (s, 3H), 2.18-2.28 (m, 2H), 2.81-2.91 (m, 2H), 3.30-3.43 (m, 4H), 7.15-7.32 (m, 5H); GC-MS: *m/z* (%) = 224 (M^+, 10), 119 (100), 91 (57).
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