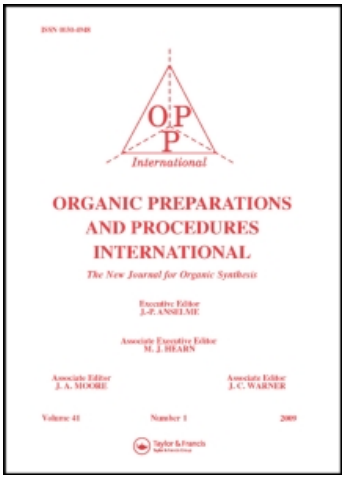

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A FACILE AND EFFICIENT METHOD FOR THE REGENERATION OF CARBONYL COMPOUNDS FROM HYDRAZONES AND OXIMES BY OXONE® UNDER HETEROGENEOUS CONDITIONS

Submitted by (04/01/98)

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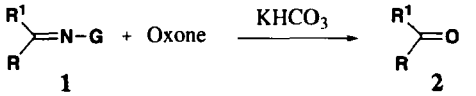
Highly crystalline hydrazone and oxime derivatives constitute a very efficient method for the isolation, purification and characterization of aldehyde and ketone compounds. Thus the regeneration of the aldehydes and ketones from such derivatives constitutes an important synthetic process. The classical method for the conversion of hydrazones to the corresponding carbonyl compounds involves hydrolysis under acidic conditions and is not suitable for acid sensitive and asymmetric compounds.[1] Several other reagents[2-8] have been developed, to supplement acid hydrolysis. We now report that the reaction of potassium peroxymonosulfate (oxone®) in acetone or acetonitrile and aqueous potassium bicarbonate[9] with derivatives of carbonyl compounds **1** under reflux gave the corresponding carbonyl compounds.

The reagent was examined on a wide array of derivatives of carbonyl compounds (**1**) and the results show that phenylhydrazones, *p*-nitrophenylhydrazones, 2,4-dinitrophenylhydrazones, semicarbazones, azines and oximes are converted to the corresponding aldehydes and ketones with no over-oxidation to the carboxylic acids (Table 1). β-Keto sulfoxides are very important starting material in asymmetric synthesis[10] and although these compounds can be synthesized by cleavage of C=N of N,N-dimethyl hydrazone of β-keto sulfoxides,[11] the optical purity for this conversion by the classical



1 **2**

a) R = R^1 = C_6H_5, G = NHPh
b) R = C_6H_5, R^1 = Me, G = NHPh
c) R = 3,4-$(MeO)_2C_6H_3$, R^1 = Me, G = NHPh
d) R = *p*-PhC_6H_4, R^1 = Me, G = NHPh
e) R = 2-pyridyl, R^1 = C_6H_5, G = NHPh
f) R = 2-pyridyl, R^1 = Me, G = NHPh
g) R = *p*-$MeOC_6H_4$, R^1 = Me, G = NHPh
h) R = *o*-$MeOC_6H_4$, R^1 = Me, G = NHPh
i) R = R^1 = C_6H_5, G = $NHC_6H_4NO_2$-*p*
j) R = *p*-$MeOC_6H_4$, R^1 = H, G = $NHC_6H_4NO_2$-*p*
k) R = *p*-ClC_6H_4, R^1 = Me, G = $NHC_6H_4NO_2$-*p*
l) R = *p*-PhC_6H_4, R^1 = Me, G = $NHC_6H_4NO_2$-*p*
m) R = C_6H_5CH=CH, R^1 = Me, G = $NHC_6H_4NO_2$-*p*
n) R = R^1 = C_6H_5, G = NMe_2
o) R = C_6H_5, R^1 = Me, G = NMe_2
p) R = 3,4-$(MeO)_2C_6H_3$, R^1 = Me, G = NMe_2
q) R = *p*-$MeOC_6H_4$, R^1 = Me, G = NMe_2
r) R = C_6H_5, R^1 = H, G = $NHCONH_2$
s) R = C_6H_5, R^1 = Me, G = $NHCONH_2$
t) R = *p*-$MeOC_6H_4$, R^1 = Me, G = $NHCONH_2$
u) R = 3,4-$(MeO)_2C_6H_3$, R^1 = Me, G = $NHCONH_2$
v) R = C_6H_5CH = CH, R^1 = H, G = $NHCONH_2$
w) R = R^1 = $(CH_2)_5$, G = OH
x) R = R^1 = $(CH_2)_6$, G = OH
y) R = C_6H_5, R^1 = Me, G = OH
z) R = $C_6H_5CH_2$, R^1 = Ph, G = OH

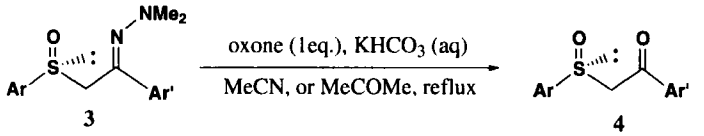
Scheme 1. *Conversion of Hydrazones and Oximes 1 to Carbonyl Compounds 2*

Table 1. Conversion of Hydrazones and Oximes **1** to Carbonyl Compounds **2**

Compd	Yield [a, b] and Time				mp./°C or bp./°C/torr (lit.[12,15])
	in MeCN		in Me_2CO		
	%	min	%	min	
2a	98	60	98	45	127-130/760 (127-130)
2b	95	45	95	30	154-156/760 (154-156)
2c	93	80	93	40	177/760 (179)
2d	97	30	97	15	240/760 (240)
2e	91	60	91	30	42-44 (41-44)
2f	96	45	96	30	204/760 (203)
2g	97	45	97	30	49-52 (50-52)
2h	97	45	97	25	55-57 (55-57)
2i	55	80	55	80	58-60 (58-60)
2j	55	80	55	45	80-83 (80-83)
2k	40	80	30	45	232/760 (234)
2l	44	80	58	40	117-119 (117-118)
2m	50	80	45	40	39 (39-40)
2n	95	40	98	15	48 (47-49)
2o	90	60	95	20	84/760 (83-85)
2p	100	30	100	15	48-49 (47-50)
2q	98	30	96	15	37-39 (37-39)
2r	60	80	55	45	178-179/760 (177-179)
2s	40	80	35	45	84-85 (83-85)
2t	45	80	45	45	38 (37-39)
2u	50	80	55	45	47-49 (47-50)
2v	45	60	50	30	127/760 (125-128)
2w	95	30	98	15	128/760 (127-130)
2x	95	30	95	15	125/760 (125-128)
2y	90	40	95	30	203/760 (204)
2z	94	35	98	20	56 (56-57)

a) Confirmed by comparison with authentic sample (IR and NMR). b) yield of isolated product.

method is low. We have also found that cleavage of C=N bond of *N,N*-dimethylhydrazone of β-keto sulfoxides **3**,[11] is rapid (20-30 min in acetone and 30-60 min. in acetonitrile), and proceeds in nearly quantitative yield with high optical purity. In all cases, the crude product was judged to be of > 95% purity based on ^{1}H NMR and TLC analysis; the corresponding sulfones are not formed in these reactions. The enantiomeric purity of **4** was determined from ^{1}H NMR chiral shift studies using (-)-*(R)*-*N*-(3,5-dinitrobenzoyl)-a-phenylethylamine as a chiral shift reagent[10] and comparing the optical rotation of the products with known compounds (*Scheme 2*).[10-13]



3 4

a) Ar = Ar' = C_6H_5 b) Ar = C_6H_5, Ar' = 3,4-$(MeO)_2C_6H_3$
c) Ar = 4-MeC_6H_4, Ar' = C_6H_5 d) Ar = 4-MeC_6H_4, Ar' = 3,4-$(MeO)_2C_6H_3$
e) Ar = 2-$MeOC_{10}H_6$, Ar' = C_6H_5 f) Ar = 2-$MeOC_{10}H_6$, Ar' = 3,4-$(MeO)_2C_6H_3$

Scheme 2. *Conversion of Dimethylhydrazones 3 to β-Ketosulfoxides 4*

In conclusion, we have developed a novel, efficient, rapid and inexpensive method for the regeneration of carbonyl compounds from phenylhydrazones, *p*-phenylhydrazones, *p*-nitrophenylhydrazones, semicarbazones, azines and oximes, which is superior to previously reported methods[2-8] in terms of optical purity, yields and purity of products.

Table 2. Conversion of Dimethylhydrazones **3** to β-Ketosulfoxides **4**

Cmpd	Yield (%)	e.e.	Time (min) in MeCN	Time (min) in Me_2CO
4a	98	95	30	20
4b	100	96	30	20
4c	96	96	55	25
4d	99	98	55	25
4e	95	98	60	30
4f	95	100	60	30

EXPERIMENTAL SECTION

β-Ketosulfoxide hydrazones **3** were prepared by published method.[14,16] All products were identified by comparison with an authentic sample (IR, NMR, mp., bp.).[12,15] All mps. were taken on a Gallenkamp. melting apparatus and are uncorrected. Elemental analysis was performed by Research Institute of Petroleum Industry, Tehran, I. R. Iran. ^{1}H NMR spectra were recorded on a Varian EM-390 NMR Spectrometer operating at 90 MHz, or a Varian Unity 400 Fourier Transform NMR Spectrometer operating at 400 MHz. The spectra were measured in $CDCl_3$ unless otherwise stated, relative to TMS (0.00 ppm). The enantiomeric purity of **4** was determined by mixing it with one equivalent of (-)-*(R)-N*-(3,5-dinitrobenzoyl)-α-phenylethylamine in the NMR tube. Optical rotations were recorded with a JASCO, DIP-370, Digital Polarimeter. Oxone is a registered trademark of E. I. du Pont de Nemours & Co.

Oxidation of 1 to 2. General Procedure.- To a 250 mL flask containing a magnetic stirrer bar was added the appropriate compound **1** (1 mmol) in acetone or acetonitrile (15 mL) and potassium hydrogen carbonate (3.5 mmol, 0.35 g) in water (15 mL). The reaction mixture was stirred vigorously and a solution of oxone (1 mmol, 0.61 g) in water (10 mL) was added in one portion. The mixture was heated at reflux until TLC showed complete disappearance of starting material, (Table 1). The reac-

tion mixture was extracted with dichloromethane (3 x 10 mL) and the extract was dried ($MgSO_4$). Evaporation of the solvent gave the product. The product was purified by short-path distillation or column chromatography on silica gel using mixture of ethyl acetate and n-hexane as eluent (90:10).

Preparation of β-Ketosulfoxide 4. General Procedure.- To a 250 mL flask containing a magnetic stirrer bar was added the appropriate β-keto sulfoxide hydrazone **3** (1 mmol) in acetone or acetonitrile (15 mL) and potassium hydrogen carbonate (3.5 mmol, 0.35 g) in water (15 mL). The reaction mixture was stirred vigorously and a solution of oxone (1 mmol, 0.61 g) in water (10 mL) was added in one portion. The mixture was heated at reflux until TLC showed complete disappearance of starting material, (Table 2). The reaction mixture was extracted with dichloromethane (3 x 10 mL) and the extract was dried ($MgSO_4$). Evaporation of the solvent gave the product. The product could be further purified by column chromatography on silica gel using ethyl acetate as eluent.

(+)-(*R*)-2-(Phenyl-1'-sulfinyl)acetophenone (4a), mp. 70-71° lit.[12] 70.5-71.5°. ^{1}H NMR: δ 7.1-7.9 (m, 10H), 4.48, and 4.28 (AB quartet system, J = 13.8 Hz, 2 H). MS: m/z, 244.30 (80%. M^+), 105 (100%). $[\alpha]_D^{28}$ = +161.65 (c 1.2, $CHCl_3$).

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.70; H, 5.00

(+)-(*R*)-2-(Phenyl-1'-sulfinyl)3,4-dimethoxyacetophenone (4b), mp. 88-89° lit.[12] 88-89°. ^{1}H NMR: δ 7.1-7.9 (m, 8H), 4.48, and 4.28 (AB quartet system, J = 13.6 Hz, 2 H), 3.92 (s, 6 H, 2xOMe). MS: m/z, 304.36 (65%. M^+), 165 (100%). $[\alpha]_D^{28}$ = +146.65 (c 1.2, $CHCl_3$).

Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 63.00; H, 5.50

(+)-(*R*)-2-(Tolyl-1'-sulfinyl)acetophenone (4c), mp. 84-85°. lit.[13] 82-83.5°). 1H NMR: δ 7.0-7.9 (m, 9H), 4.52, and 4.28 (AB quartet system, J =1 4 Hz, 2 H), 2.35 (s, 1 H). [a]$_D^{28}$ = +180.20 (c 1.2, $CHCl_3$) {lit.[13] $[\alpha]_D^{26}$ = +227.70 (C 1.00, acetone)}.

(+)-(*R*)-2-(Tolyl-1'-sulfinyl)3,4-dimethoxyacetophenone (4d), mp. 96-98°. ^{1}H NMR: δ 7.1-7.9 (m, 7H), 4.95, and 4.39 (AB quartet system, J = 13.6 Hz, 2 H), 3.88 (s, 6 H, 2xOMe), 242 (s, 3 H). MS: m/z, 318.39 (70%. M^+), 165 (100%). $[\alpha]_D^{28}$ = +202.20 (c 1.2, acetone).

Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70 . Found: C, 64.20; H, 5.70

(+)-(*R*)-2-(2'-Methoxynaphthyl-1'-sulfinyl)acetophenone (4e), mp. 89-90°. ^{1}H NMR: δ 8.92 (d, 1H), 7.1-7.9 (m, 10H), 5.05, and 4.82 (AB quartet system, J = 13.2 Hz, 2 H), 3.90 (s, 3H, OMe). MS: m/z, 325.5 (80%. M^+), 226.3 (25%), 141 (100%). $[\alpha]_D^{28}$ = +97.5, (c 1.2, DCM).

Anal. Calcd for $C_{19}H_{16}O_3S$: C, 70.35; H, 4.97 . Found: C, 70.40; H, 4.90

(+)-(*R*)-2-(2'-Methoxynaphthyl-1'-sulfinyl)3,4-dimethoxyacetophenone (4f), mp. 119-121°. ^{1}H NMR: δ 8.95 (d, 1 H), 6.8-8 (m, 7 H), 5.02, and 4.85 (AB quartet system, J = 13.2 Hz, 2 H), 4.00 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 3.80 (s, 3 H, OMe). MS: m/z, 385.1 (50%, M^+), 288.3 (25%), 205 (100%). $[\alpha]_D^{28}$ +90.8, (c 1.3, DCM)

Anal. Calcd for $C_{21}H_{20}O_5S$: C, 65.61; H, 5.24 . Found: C, 65.70; H, 5.40

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