Homolytic *C*-Alkylation of Aldoximes

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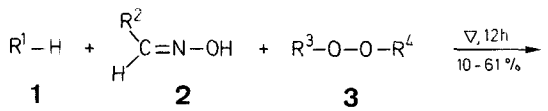
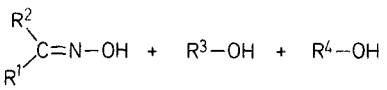
Thermal decomposition of alkyl peresters in hydrogen donor solvents (cycloalcanes or ethers) in the presence of aldoximes affords (*C*-*I*)-alkylated products. The reaction is favored by electron-withdrawing substituents on the oxime and involves free *C*-radical addition to the imine moiety.

C-Alkylation of aldoximes has hitherto not been observed. However, it is known that aldoximes are efficiently *C*-arylated by decomposing arenediazonium salts[1,2]. We have recently obtained evidence for the homolytic nature of this reaction[3]; this made us attempt the alkylation of aldoximes by using other sources of free *C*-radicals.

We report here that the thermal decomposition of alkyl peroxyesters **(3)** in hydrogen-donor solvents such as cycloalkanes or ethers **(1)** in the presence of aldoximes **(2)** represents an efficient method for the *C*-alkylation of aldoximes **(2)** to give ketoximes **(4)**.



1 **2** **3**



4

4	R^1	R^2	4	R^1	R^2
a	c-C_6H_{11}	$-CO-CH_3$	i		$-CO-CH_3$
b	c-C_7H_{13}	$-CO-CH_3$			
c	c-C_8H_{15}	$-CO-CH_3$			
d	c-$C_{12}H_{23}$	$-CO-CH_3$	j		$-COOCH_3$
e	c-C_6H_{11}	$-COOCH_3$			
f	c-C_6H_{11}	$-CO-C_6H_5$			
g	c-C_6H_{11}	$-CH_3$	k		$-CO-CH_3$
h	c-C_6H_{11}				

The monoximes of *vic*-diketones **(4a–d, f, i, k)** and of 2-oxoalkanoic esters **(4e, j)** prepared were found to have the (*E*)-configuration [^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ of OH = 12.2–12.6 ppm][4] whereas the ketoximes **4g** and **4h**, derived from simple ketones, have the (*Z*)-configuration.

Peresters [bis(4-*t*-butylcyclohexyl)-percarbonate (**3B**), di-*t*-butyl peroxalate (**3A**)] are the preferred peroxides owing to the relatively low decomposition temperature and the selective generation of free *C*-radicals from solvents. Less good results were obtained with diacyl or dialkyl peroxides [such as di-*t*-butyl peroxide (**3C**)]. The reactions were run for almost 10 half lives of the peroxide and the temperature was chosen so as to have an overall reaction time of 12 h.

Aldoximes **(2)** having electron-withdrawing groups (R^2 = $-CO-CH_3$, $-CO-C_6H_5$, $-COOCH_3$) were found to afford higher yields of ketoximes **4** than aldoximes **(2)** having electron-releasing groups (R^2 = CH_3, C_6H_5). This result parallels that observed for the arylation of aldoximes by arenediazonium salts[3] and strongly suggests that the reaction occurs via addition of a free *C*-radical to the imine group of the aldoxime, owing to the nucleophilic character of the alkyl and 1-oxyalkyl radicals involved[5], which favors the addition to the more electron-deficient substrate[5,6,7]. Only few examples of the addition of alkyl radicals to carbonyl groups in the absence of metal ions are known[8]; they are of limited synthetic value, probably with the exception of additions to *vic*-diketones[9].

Conversely, the homolytic alkylation of aldoximes appears to be somewhat more promising. The radical source **(3)** used here is of limited selectivity in the hydrogen abstraction from the solvent R^1-H **(1)**; it therefore applies favorably only to symmetric substrates or to substrates having quite different *C*—H bond energies. However, preliminary experiments indicate that the use of other radical sources can overcome these limitations, thus extending the potential scope of the method[10].

Ketoximes (4) from Aldoximes (2); General Procedure:

Under a nitrogen atmosphere, the aldoxime **2** (50 mmol) and the peroxide **3** (see Table 1; 50 mmol) are added at room temperature to the stirred solvent **1** (20 ml). The solution is heated at the temperature given in Table 1 for 12 h, then cooled to room temperature.

With cycloalkanes as solvent, the solution is directly chromatographed on silica gel (40–63 mesh; 150 g) eluting with hexane and

Table 1. Ketoximes **4** prepared

4	Reaction Conditions		Yield [%]	m.p. [°C]	Molecular Formula[b] or m.p. [°C] reported
	Radical Source 3[a]	Temperature [°C]			
4a	3A	60	61	91–92	$C_6H_{15}NO_2$ (133.2)
	3B	80	52		
	3C	120	43		
4b	3B	80	48	80–81	$C_{10}H_{17}NO_2$ (183.25)
4c	3B	80	50	66–67	$C_{11}H_{19}NO_2$ (197.3)
4d	3A	60	40	129–130	$C_{15}H_{27}NO_2$ (253.4)
4e	3A	60	34	126–127	$C_9H_{15}NO_3$ (169.2)
4f	3B	85	50	96–97	$C_{14}H_{17}NO_2$ (231.3)
4g	3B	85	10	64	64–65.5[11]
4h	3B	85	16	158–159	160[12]
4i	3A	60	50	85–86	$C_7H_{11}NO_4$ (173.2)
4j	3A	60	39	125–126	$C_6H_{11}NO_5$ (177.15)
4k	3B	80	30	66–67	$C_7H_{11}NO_3$ (157.2)

[a] 3A = di-*t*-butyl peroxalate; 3B = bis[4-*t*-butylcyclohexyl]percarbonate; 3C = di-*t*-butyl peroxide.

[b] The microanalyses were in satisfactory agreement with the calculated values: C ±0.25, H ±0.16, N +0.18.

Table 2. Spectral Data of Compounds **4**

4	U.V. (ethanol) λ_{max} [nm] (ε)	^{1}H-N.M.R. (90 MHz, $CDCl_3/TMS_{int}$) δ [ppm]
a	221 (8100)	1.0–2.0 (m, 10H, $5CH_2$); 2.28 (s, 3H, CH_3); 3.1 (m, 1H, CH); 8.4 (br., 1H, OH)
b	226 (9100)	1.3–2.1 (m, 12H, $6CH_2$); 2.28 (s, 3H, CH_3); 3.2 (m, 1H, CH); 8.9 (br., 1H, OH)
c	225 (10000)	1.1–2.2 (m, 14H, $7CH_2$); 2.3 (s, 3H, CH_3); 3.3 (m, 1H, CH); 8.3 (br., 1H, OH)
d	227 (9000)	1.1–2.1 (m, 22H, $11CH_2$); 2.28 (s, 3H, CH_3); 3.4 (m, 1H, CH); 8.3 (br., 1H, OH)
e	215 (7500)	1–2.0 (m, 10H, $5CH_2$); 3.15 (m, 1H, CH); 3.78 (s, 3H, OCH_3); 9.9 (br., 1H, OH)
f	257 (9800)	1–1.9 (m, 10H, $5CH_2$); 3.03 (m, 1H, CH); 7.2–7.6 (m, $5H_{arom}$); 8.7 (br., 1H, OH)
i	224 (10000)	2.35 (s, 3H, CH_3); 3.82 (m, 6H, $3CH_2$—O); 5.12 (dd, 1H, CH—O); 9.8 (br., 1H, OH)
j	214 (8000)	3.4–3.9 (m, 9H, CH_2—O, OCH_3); 5.1 (dd, 1H, CH—O); 10.3 (br., 1H, OH)
k	225 (9000)	1.8–2.3 (m, 4H, $2CH_2$); 2.43 (s, 3H, CH_3); 3.6–3.8 (m, 3H, 3CH—O); 10.0 (br., 1H, OH)

collecting fractions of 50 ml). After the cycloalkane and small amounts of oxygenated compounds, products **4** can be obtained practically pure. They are further purified by crystallization from hexane/diethyl ether.

With ethers as solvent, silica gel (40–63 10^{-2} mm; 13 g) is added to the reaction mixture and the solvent evaporated using the rotary evaporator at 50°C. The residue is chromatographed with hexane/ethyl acetate (2% gradient) mixtures. Products 4i, j, k are crystallized from hexane.

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