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EQUILIBRIUM IN THE TRIETHYLAMINE-CATALYZED, EXTENDED BEHREND REARRANGEMENT OF N-(1-CYANOISOBUTYL)BENZYLIDENEAMINE N-OXIDES

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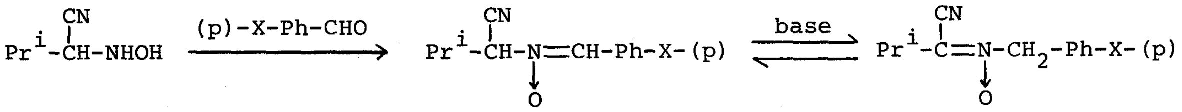
Triethylamine-catalyzed Behrend rearrangement of the title aldo-nitrones to the corresponding keto-nitrones in various solvents is an entropy-controlled, energetically unfavorable reaction but the position of the equilibrium significantly depends on the nature of solvent used.

KEYWORDS——base-catalyzed Behrend rearrangement; 1,3-prototropic isomerization; N-(1-cyanoalkyl)bezylideneamine N-oxide; equilibrium constant; solvent effect; substituent effect; thermodynamic parameter

A 1,3-prototropic isomerization of nitrones sometimes called the Behrend rearrangement has received little attention compared to the closely related isomerization of imines.[1-7] It has been accepted that the rearrangement occurs only in the presence of a strong base such as an alkoxide in ethanol.[6,7] Substrates which undergo the Behrend rearrangement under other base-solvent conditions have never been developed, and hence, quantitative information characterizing the Behrend rearrangement is unavailable except the indirect determination of the equilibrium constants for the aldo-aldo interconversion of α-phenyl N-benzylnitrones.[7]

We have found that functionalized nitrones, N-(1-cyanoisobutyl)benzylideneamine N-oxides (1), undergo the Behrend rearrangement under various base-solvent conditions to give the corresponding keto-nitrones (2). We first report herein the isolation of nitrones (1) and (2), and some quantitative approaches characterizing the equilibrium in the triethylamine-promoted Behrend rearrangement of these nitrones in various solvents.

Aldo-nitrones (1) were prepared by the condensation of 2-hydroxylamino-isovaleronitrile[8] with benzaldehydes in ethanol and purified from ethanol-n-hexane (Table I). On treatment with organic amines such as triethylamine, piperidine and pyridine in 1,4-dioxane, acetonitrile and methanol, or with sodium alkoxides and potassium carbonate in methanol, aldo-nitrones (1) were partially transformed into keto-nitrones (2). The keto-nitrones were column chromatographed on silica gel with benzene-ethyl acetate (5:1, v/v) as an eluent. The structures of (1) and (2) were characterized by their spectral data (Table I). The possibility of thermal E-Z interconversion of the nitrones or their thermal rearrangements to oxime-O-ethers was excluded on the basis of the following evidence: i). (2) showed a characteristic absorption maximum at 270 nm regardless of the substituent in the phenyl ring. ii). 1,3-dipolar cycloaddition of (2e) with fumaronitrile in benzene gave only one stable 1:1 adduct, an isoxazolidine derivative, exclusively.[10]



$$\mathrm{Pr^i\text{-}\overset{CN}{\overset{|}{C}H}\text{-}NHOH} \xrightarrow{\mathrm{(p)\text{-}X\text{-}Ph\text{-}CHO}} \mathrm{Pr^i\text{-}\overset{CN}{\overset{|}{C}H}\text{-}\underset{\underset{O}{\downarrow}}{N}{=}CH\text{-}Ph\text{-}X\text{-}(p)} \underset{}{\overset{\text{base}}{\rightleftharpoons}} \mathrm{Pr^i\text{-}\overset{CN}{\overset{|}{C}}{=}\underset{\underset{O}{\downarrow}}{N}\text{-}CH_2\text{-}Ph\text{-}X\text{-}(p)}$$

(1) (2)

Table I. Preparations and Spectral Data of Aldo-Nitrones (1) and Keto-Nitrones (2)

Compound[a]	X	mp(°C) or bp(°C/mmHg)	Yield(%)[b]	^{1}H-NMR (δ, ppm, in $CDCl_3$/TMS) $-\underline{C}H{=}N{\to}O$[c]	$-\underline{C}H\text{-}CN$[d]	$-\underline{C}H_2\text{-}Ar$[c]	λ_{max} nm (in MeOH)
(1a)	NO_2	125-126	89	7.80	4.71		338
(1b)	CN	117-118	85	7.72	4.66		313
(1c)	Cl	114-114.5	87	7.62	4.65		302
(1d)	H	113.5-114.5	88	7.63	4.65		297
(1e)	CH_3	114-115	84	7.57	4.57		302
(1f)	OCH_3	135-136	75	7.55	4.57		313
(2a)	NO_2	103-104	64			5.45	270
(2b)	CN	75	-			5.42	271
(2c)	Cl	49	-			5.21[e]	271
(2d)	H	87/0.6	40			5.35	270
(2e)	CH_3	40-41	62			5.13[e]	270
(2f)	OCH_3	100/0.4	51			5.17[e]	270

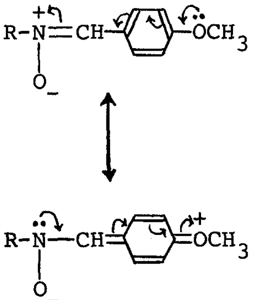
a) All compounds are new and they gave satisfactory results in microanalyses and mass spectra. b) Isolated yield. (2) were obtained from (1) by the rearrangement in 1,4-dioxane with triethylamine. (2b) and (2c) were separated by preparative TLC, and their yields were not recorded. c) Singlet. d) Doublet, J= ca.7 Hz. e) In CCl_4.

In order to obtain quantitative information on the equilibrium, the extended Behrend rearrangement of the nitrones was investigated with triethylamine in methanol.[9)] The equilibrium constants obtained for the formation of (2) from (1) are shown in Table II. In every case, aldo-nitrone (1) is favored over the isomeric keto-nitrone (2). The more electron-withdrawing the para-substituent becomes, the more favourable is the formation of (2). A linear free energy relationship on the logarithm of the equilibrium constants against Hammett σ_p values has been found to hold with a slope $\rho = 0.18$ ($\gamma = 0.998$, s = 0.005). This eliminates an electronically amphoteric capability of the nitrone function for conjugation,[1,7)] and suggests that the nitrone function in (1) behaves as an electron-acceptor rather than as an electron-donor and electron-releasing substituents alone can stabilize the nitrone function by the resonance illustrated below.

Table II. Equilibrium Constants for the Behrend Rearrangement of (1) to (2) in Methanol at 50°C

Compound (1),(2)	Equilibrium constant K = [2]/[1]
a	0.194
b	0.186
c	0.153
d	0.140
e	0.133
f	0.125

$[Et_4NCl] = 6.2 \times 10^{-1}M.$



(1f): $R=Pr^{i}-\overset{CN}{\overset{|}{C}}H-$

Table III. Thermodynamic Parameters for the Triethylamine-Catalyzed Behrend Rearrangement of (1a) to (2a) in Various Solvents (at 23°C)

Solvent	K	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (e.u.)
1,4-Dioxane	1.178	-0.097	1.97	6.98
Acetonitrile	0.387	0.560	2.96	8.11
Methanol	0.093	1.40	4.75	11.32

The equilibrium constant for the Behrend rearrangement of (1a) to (2a) increased linearly from 0.070 (at 13°C) to 0.194 (at 50°C) with an increase in temperature. From the least-squares slope of the logarithmic plot of the equilibrium constants against the reciprocal of the absolute temperature, ΔH = 4.75kcal/mol was obtained. The values of ΔS are constant (11.32 ± 0.1 e.u.) over the range of temperature used.

Table III shows the thermodynamic data for the extended Behrend rearrangement of (1a) in different solvents. From the data it is obvious that the Behrend rearrangement of aldo-nitrone (1) to the corresponding keto-nitrone (2) is, though it is unfavourable energetically, an entropy-controlled reaction despite the apparent steric hindrance in (2).

These analyses and the observation of a smaller K value in going to a more polar solvent mean that the aldo-nitrone is more solvated than the keto-nitrone, and alteration of solvent to a less polar one can shift the position of the equilibrium toward the formation of (2); a larger K value can be expected in a less-polar or less solvating solvent. The change in ΔG caused by the alteration of solvent from methanol to 1,4-dioxane, $\delta\Delta G$ = 1.5kcal/mol, is much larger than that caused by the change of substituent in the phenyl ring from nitro to methoxy group, $\delta_X\Delta G$ = 0.28kcal/mol. Solvation is, therefore, the most important factor controlling the aldo-keto equilibrium in the present Behrend rearrangement. The conclusions obtained here will be applicable generally to the Behrend rearrangement involving an aldo-keto interconversion of nitrones, because there would be little difference in the bond energy between the two C-N bonds responsible for the rearrangement.

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9) The concentrations of the nitrones and triethylamine were adjusted to 10^{-5}M and 10^{-2}M, respectively, and the ionic strength of the solution was maintained constant by the addition of tetraethylammonium chloride (0.62M). An equilibrium mixture was obtained in each case by approaching the equilibrium from either side. The equilibrium composition at an infinite time was directly determined spectrophotometrically with good precision. The composition did not vary with the concentration of triethylamine.

10) 2-Tolylmethyl-3-isopropyl-3,4,5-tricyanoisoxazolidine was obtained: ^{1}H-NMR (in CCl_4) δ 4.02 (d, 1H, J=3.4Hz, H-4); 5.12 (d, 1H, J=3.4Hz, H-5); 4.22 (s, 2H, N-CH_2-Ar).

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