librium and the ΔG (at 25 °C) decreased from 95% (ΔG = 1.745 kcal/mol) to 86% (ΔG = 1.028 kcal/mol) to 55% (ΔG = 0.119 kcal/mol). This result is due to the ability of dimethyl sulfoxide to compete with a carbonyl group for the NH hydrogen bond. In addition, dimethyl sulfoxide may associate with the carbonyl group.[23] Acetone shows less ability to break the NH···O hydrogen bond in the cis isomer because the carbonyl group in acetone is not as polarized as the sulfoxide group in dimethyl sulfoxide. The results of these studies are consistent with the effect of solvents on the proportions of cis and trans isomers of the Schiff bases of monoalkylamines and ethyl acetoacetate where the cis/trans ratio varies from 15:1 in CCl_4 to 10:1 in $CDCl_3$ to 7:5 in Me_2SO.[19]

The activation energy for isomerization (13.6 kcal/mol) in Me_2SO is consistent with either a mechanism involving isomerization about the double bond or a mechanism involving a ketimine intermediate. Rotation barriers as low as 9.1 kcal/mol have been observed for dialkenylamino ketones.[24] This low rotation barrier is apparently due to the fact that the transition state for isomerization resembles one of the possible charge-separated resonance structures. In order to test whether a ketimine was present, we measured the exchange of the olefin hydrogen atom of I in Me_2SO/D_2O. This hydrogen atom did exchange but at a much slower rate than isomerization, ruling out a mechanism involving only isomerization via the ketimine.

In conclusion, this paper illustrates another example of a useful approach to the analysis of conformationally (configurationally) mobile systems. This approach involves initial crystallographic analysis and subsequent solution studies. When information from these studies (crystallographic and solution) is combined, a complete picture of conformationally mobile systems is obtained.

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Registry No. **Ia**, 21759-74-0; **Ib**, 21731-13-5.

Supplementary Material Available: Table II, final temperature factors; Table III, bond lengths; Table IV, bond angles; Table V, intermolecular contacts (3 pages). Ordering information is given on any current masthead page.

(24) Y. Shvo and H. Shanan-Atidi, *J. Am. Chem. Soc.*, **91**, 6684 (1969).
(25) The X-Ray System (Version of June 1972, Update April 1974, Technical Report TR-192 of the Computer Science Center, Univerity of Maryland, June 1972) was used for all crystallographic computations reported.

4-Alkoxybenzonitriles from *O*-Alkyl-4-nitrobenzaldoximes: An Elimination–Aromatic Substitution Reaction

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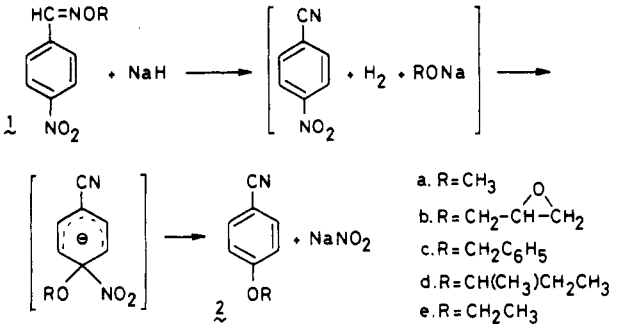
It has been reported that, in dipolar aprotic solvents, an aromatic nitro group activated by a single ortho or para carbonyl-type function can be replaced by nucleophiles ranging from hydroxyl or alkoxyl anions[1] to mercaptides[2,3] and oximate anions.[4] The latter nucleophile reacts with 4-nitrobenzonitrile to give an *O*-aryl aldoxime that undergoes elimination to the corresponding nitrile: these transformations constitute a "one pot" method for the conversion of aldoximes into nitriles.[4] In an extension of this work,[5] (*E*)-4-nitrobenzaldoxime was found to give 4-hydroxybenzonitrile upon alkaline treatment in Me_2SO solution containing a small amount of 4-nitrobenzonitrile. The proposed reaction pathway[5] involves a nitro displacement to afford *O*-(4-cyanophenyl)-4-nitrobenzaldoxime, followed by a base-promoted elimination leading to 4-hydroxybenzonitrile (the leaving group) and the chain carrier, 4-nitrobenzonitrile.

Scheme I



In relation to the above results, we now report that in dipolar aprotic solvents (dimethylformamide or dimethyl sulfoxide), the *O*-alkyl ethers of 4-nitrobenzaldoxime react with bases to give the corresponding 4-alkoxybenzonitriles in good yields.

The starting oxime ethers **1a–d** were obtained in excellent yields by alkylation of 4-nitrobenzaldoxime sodium salt with the appropriate alkyl halide in DMF solution.[6] Treatment of a DMF solution of the above oxime ethers with an excess of sodium hydride at room temperature afforded the 4-alkoxybenzonitriles **2a–d**, which were identified by their melting points and spectroscopic characteristics. Thus, the IR spectra of **2a–d** showed a strong absorption at 2235 cm^{-1}, due to the cyano group stretching. Comparison of the NMR spectra of **2a–d** with those of the oxime ethers **1a–d** showed the disappearance of the aldoxime proton signal near δ 8.0 and an upfield shift of 0.6–0.8 ppm for the aromatic signals. Mass spectrometry was used to confirm the structure of **2b**.

The above elimination–aromatic substitution reactions were also carried out in an NMR tube with hexadeuterated Me_2SO as a solvent; similar results were then obtained. **2a–c** were formed very fast (less than 1 min after the addition of NaH) whereas in the case of **2d** the reaction was completed after 3 h. Unfortunately, the reaction kinetics could not be established, since the hydrogen evolved during the process caused a loss of resolution of the NMR signals.

We propose a reaction pathway for the formation of 4-alkoxybenzonitriles **2a–d** involving an intial elimination of the alkoxide moiety from the oxime ethers **1a–d**, followed by a displacement of the nitro group (as nitrite anion) by the nucleophilic attack of the alkoxide anion (Scheme I).

The second step takes place readily because of the activating effect of the dipolar aprotic solvent. The replacement of the nitro group on 4-nitrobenzophenone by

(1) Gorvin, J. H. *Chem. Ind. (London)* **1967**, 1525.
(2) Beck, J. R. *J. Org. Chem.* **1972**, *37*, 3224.
(3) Beck, J. R. *J. Org. Chem.* **1973**, *38*, 4086.
(4) Knudsen, R. D.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.
(5) Knudsen, R. D.; Morrice, A. G.; Snyder, H. R. *J. Org. Chem.* **1975**, *40*, 2878.
(6) Leclerc, G.; Bieth, N.; Schwartz, J. *J. Med. Chem.* **1980**, *23*, 620.

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sodium methoxide does not occur in dioxane.[1] Moreover, alkaline treatment of alkyl and aryl ethers of 4-nitrobenzaldoxime in water–dioxane solution leads to 4-nitrobenzonitrile, without a trace of nitro substitution.[7]

The alkylation of the oxime and the elimination–substitution reactions can be carried out in a single operation, synthetically useful for the preparation of 4-alkoxybenzonitriles from 4-nitrobenzaldehyde. Thus, treatment of 4-nitrobenzaldoxime with benzyl bromide (1 equiv) and NaH (3 equiv) in DMF at room temperature afforded the nitrile **2c** in good yields. However, the method has some limitations; thus, reaction of 4-nitrobenzaldoxime with the tertiary alkyl halide ethyl 2-bromo-2-methylpropionate did not afford the expected ethyl 2-(4-cyanophenyl)-2-methylpropionate but instead formed 4-ethoxybenzonitrile (**2e**, 68% yield). This compound can arise from nitro substitution by sodium ethoxide, probably formed in the autocondensation of the initial intermediate, sodium 2-(ethoxycarbonyl)-2-methylethoxide.

Experimental Section

NMR spectra were determined on a Perkin-Elmer R-24B (60 MHz) instrument by using internal Me_4Si as a reference. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Melting points were determined in a Büchi apparatus and are uncorrected. The mass spectrum was determined on a Hewlett-Packard 5930A mass spectrometer. Microanalyses were performed by Instituto de Quimica Bio-Orgânica, Barcelona.

Alkylation of 4-Nitrobenzaldoxime. To a suspension of 0.24 g (10 mmol) of sodium hydride (dispersion in oil, washed with hexane) in 25 mL of anhydrous DMF was added 1.66 g (10 mmol) of 4-nitrobenzaldoxime portionwise. The dark red solution was stirred at room temperature for 10 min, and a solution of 10 mmol of the alkylating agent (methyl iodide, epichlorohydrin, benzyl bromide or 2-butyl bromide, respectively, for **1a–d**) in 5 mL of anhydrous DMF was added dropwise. The mixture was stirred for 30 min, poured into 150 mL of water, and extracted with ether. The organic extracts were washed with water, dried, and evaporated to give the ethers **1a–d**, which were purified by vacuum distillation. ***O*-Methyl-4-nitrobenzaldoxime (1a)**: yield 89%; NMR ($CDCl_3$–CCl_4) δ 3.93 (s, 3 H, OCH_3), 7.57 (d, J = 8 Hz, 2 H, $H^{2,6}$), 7.91 (s, 1 H, CH=N), 8.07 (d, J = 8 Hz, 2 H, $H^{3,5}$). Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.57; H, 4.31; N, 15.72. ***O*-(2,3-Epoxypropyl)-4-nitrobenzaldoxime (1b)**: yield 90%; NMR ($CDCl_3$) δ 2.6–3.0 (AB part of an ABX, 2 H, CH_2 oxirane), 3.1–3.4 (m, 1 H, CH oxirane), 3.9–4.6 (AB part of an ABX, 2 H, OCH_2), 7.65 (d, J = 7.5 Hz, 2 H, $H^{2,6}$), 8.08 (s, 1 H, CH=N), 8.14 (d, J = 7.5 Hz, 2 H, $H^{3,5}$). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.90; H, 4.59; N, 12.87. ***O*-Benzyl-4-nitrobenzaldoxime (1c)**: yield 86%; NMR ($CDCl_3$) δ 5.13 (s, 2 H, CH_2), 7.25 (s, 5 H, C_6H_5), 7.56 (d, J = 8 Hz, 2 H, $H^{2,6}$), 8.00 (s, 1 H, CH=N), 8.07 (d, J = 8 Hz, 2 H, $H^{3,5}$). Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.74; H, 4.59; N, 11.01. ***O*-(2-Butyl)-4-nitrobenzaldoxime (1d)**: yield 91%; NMR (CCl_4) δ 0.94 (t, 3 H, CH_2CH_3), 1.25 (d, 3 H, $CHCH_3$), 1.3–1.8 (m, 2 H, CH_2), 4.15 (m, 1 H, OCH), 7.56 (d, J = 8 Hz, 2 H, $H^{2,6}$), 7.99 (s, 1 H, CH=N), 8.05 (d, J = 8 Hz, 2 H, $H^{3,5}$). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.65; H, 6.47; N, 12.64.

4-Alkoxybenzonitriles 2a–d. A solution of 5 mmol of the appropriate oxime ether **1** in 10 mL of anhydrous DMF was added to a suspension of 8 mmol of NaH in 20 mL of DMF. The mixture was stirred at room temperature for 1 h (4 h in the case of **1d**). The workup was carried out as above. **4-Methoxybenzonitrile (2a)**: yield 92%; mp 57–59 °C (lit.[8] mp 58–59 °C); IR ($CHCl_3$) 2235 cm^{-1} (CN); NMR (CCl_4) δ 3.77 (s, 3 H, OCH_3), 6.80 (d, J = 9 Hz, 2 H, $H^{3,5}$), 7.39 (d, J = 9 Hz, 2 H, $H^{2,6}$). **4-(2,3-Epoxypropoxy)benzonitrile (2b)**: yield 82%; mp 64–66 °C (lit.[9] mp 67 °C); IR ($CHCl_3$) 2235 cm^{-1} (CN); NMR (CCl_4) δ 2.5–2.9 (AB part of an ABX, 2 H, CH_2 oxirane), 3.0–3.3 (m, 1 H, CH oxirane), 3.7–4.4 (AB part of an ABX, 2 H, OCH_2), 6.86 (d, J = 7.5 Hz, 2 H, $H^{3,5}$), 7.46 (d, J = 7.5 Hz, 2 H, $H^{2,6}$); mass spectrum, m/e (relative intensity) 175 (74, M^+), 119 (91, McLafferty rearrangement), 57 (100, oxiranylmethyl cation). **4-(Benzyloxy)benzonitrile (2c)**: yield 87%; mp 91–93 °C (lit.[8] mp 94 °C); IR ($CHCl_3$) 2235 cm^{-1} (CN); NMR ($CDCl_3$) δ 4.99 (s, 2 H, CH_2), 6.85 (d, J = 8 Hz, 2 H, $H^{3,5}$), 7.25 (s, 5 H, C_6H_5), 7.40 (d, J = 8 Hz, 2 H, $H^{2,6}$). **4-(2-Butoxy)benzonitrile (2d)**: yield 89%; bp 120 °C (1 mmHg) [lit.[10] bp 109–111 °C (1.3 mmHg)]; IR (NaCl) 2235 cm^{-1} (CN); NMR (CCl_4) δ 0.95 (t, 3 H, CH_2CH_3), 1.26 (d, 3 H, $CHCH_3$), 1.4–1.9 (m, 2 H, CH_2), 4.22 (m, 1 H, OCH), 6.73 (d, J = 8 Hz, 2 H, $H^{3,5}$), 7.46 (d, J = 8 Hz, 2 H, $H^{2,6}$).

Direct Synthesis of 2c from 4-Nitrobenzaldoxime. Over a suspension of 30 mmol of NaH in 25 mL of anhydrous DMF was added 10 mmol of the oxime portionwise. The mixture was stirred at room temperature for 10 min, and then 10 mmol of benzyl bromide in 5 mL of DMF was added dropwise. After 30 min of stirring and the usual workup, nitrile **2c** was isolated in 85% yield.

Registry No. 1 (R = H), 1129-37-9; **1a**, 33499-32-0; **1b**, 86120-18-5; **1c**, 86120-19-6; **1d**, 86120-20-9; **2a**, 874-90-8; **2b**, 38791-92-3; **2c**, 52805-36-4; **2d**, 86120-21-0; **2e**, 25117-74-2; ethyl 2-bromo-2-methylpropionate, 600-00-0; methyl iodide, 74-88-4; epichlorohydrin, 106-89-8; benzyl bromide, 100-39-0; 2-butyl bromide, 78-76-2.

(7) Hegarty, A. F.; Tuohey, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1313.
(8) Vowinkel, E.; Bartel, J. *Chem. Ber.* **1974**, *107*, 1221.
(9) Petrow, V.; Stephenson, O. *J. Pharm. Pharmacol.* **1953**, *5*, 359.
(10) Cooper, F. C.; Partridge, M. W. *J. Chem. Soc.* **1953**, 255.

Use of Phosphorus Pentoxide: Esterification of Organic Acids†

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With a view to developing a method of esterification at room temperature on a vertical column, we chose phosphorus pentoxide as the packing reagent, which was diluted with anhydrous copper sulfate and sodium sulfate to avoid the blocking of the column. Anhydrous copper sulfate served as a water scavenger and also as an indicator for the progress of the reaction and the duration of the reactivity of the column through its color change, while anhydrous sodium sulfate retained the desired porosity and was useful for the sustained activity of the column with its water-absorbing property.

Phosphorus pentoxide has been frequently used in diverse types of organic reactions, but surprisingly only one example of its use in esterification reaction has been reported.[1] Coupled with this fact, this solid acidic oxide, possessing an extraordinary dehydrating capacity, made itself a unique material of choice for the present investigation. Thus, several primary aliphatic carboxylic acids were converted into the corresponding ethyl esters in varying yields (see the Experimental Section). A striking feature of this method was that aromatic acids could be recovered unchanged. But the process was slow; moreover, there was sufficient indication through arresting the acid-catalyzed reaction that it occurred partly (20–25%) on the column and partly (40–50%) during the removal of the excess alcohol from the steam bath. Therefore, the reaction was studied at room temperature for varying time

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