SYNTHESIS OF ETHOXALYL CYANIDE

A NOVEL HETERODIENO- AND HETEROENOPHILE

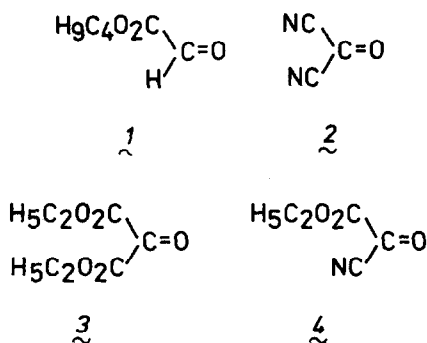O. Achmatowicz Jr. and J. Szymoniak

Institute of Chemistry and Agricultural Chemistry, Warsaw Agricultural University, 02-528 Warszawa, Poland

Abstract—The action of di-n-heptylsulphide on diethyl 2,3-dicyanooxiran-2,3-dicarboxylate yields ethoxalyl cyanide, a new dieno- and enophile with active CO group.

Amongst heterodienophiles those with an active CO group are of particular synthetic utility.[1] However ordinary ketones or aldehydes are weak dienophiles.[1] Their diene and ene reactions are possible only under extremely forcing conditions.[2] On the other hand compounds with a CO group activated by electronegative substituents, e.g. CN, CO_2R, $CX_3 - X = Cl$, F give smoothly Diels–Alder or ene adducts, e.g. reaction of butyl glyoxylate 1 with dienes opened a convenient route to the dihydropyrane system[3] whereas its ene reaction with alkenes, thermal or catalytic yielded esters of α-hydroxy-acids.[4]

$$H_9C_4O_2C \underset{H}{\overset{}{\diagdown}} C=O \qquad NC \underset{NC}{\overset{}{\diagdown}} C=O$$

$$\underset{\sim}{1} \qquad\qquad\qquad \underset{\sim}{2}$$

$$H_5C_2O_2C \underset{H_5C_2O_2C}{\overset{}{\diagdown}} C=O \qquad H_5C_2O_2C \underset{NC}{\overset{}{\diagdown}} C=O$$

$$\underset{\sim}{3} \qquad\qquad\qquad \underset{\sim}{4}$$

Even more reactive dienophiles (or enophiles) are carbonyl cyanide (2) and diethyl mesoxalate (3) in which the CO group is activated by two electron withdrawing substituents. Of the two carbonyl cyanide is by far more reactive. It reacts with dienes and olefins at room temperature,[5] whereas diethyl mesoxalate, particularly in the ene reaction with alkenes, requires elevated (120–140°) temperatures.[6] Apparently the carboalkoxy group has a weaker activating effect than the cyano group. It appeared of interest to examine dienophilic (enophilic) activity of ethoxalyl cyanide (4), a compound in which one cyano and one carboethoxy substituent is connected with the CO group. We expected that ethoxalyl cyanide (4) should be endowed with intermediate properties. Thus it should exceed diethyl mesoxalate in reactivity. On the other hand it was hoped that its ene addition would not be complicated by secondary reactions as is the case for carbonyl cyanide.[7] Moreover diene and ene adducts arising from ethoxalyl cyanide would have two different functional groups ($-CO_2C_2H_5$ and CN) enabling their further separate transformations, thus broadening the scope for the synthetic utility of these adducts relative to those of carbonyl cyanide or diethyl mesoxalate.

RESULTS and DISCUSSION

Based on the structural similarity of compounds 2, 3 and 4 for the synthesis of ethoxalyl cyanide (4) we applied the methods used for the preparation of diethyl mesoxalate (3)[8] and carbonyl cyanide.[9] First we examined the simpler possibility: oxidation of ethyl cyanoacetate with nitrogen dioxide analogous to that of diethyl mesoxalate (3).[8a] The reaction gave as the only isolated product the crystalline oxime 6 (Scheme 1) with m.p. corresponding to that reported in the literature[10] and the expected spectral data. It should be mentioned that earlier attempts at preparation of ethoxalyl cyanide (4) from ethyl cyanoacetate comprising oxidation with selenium dioxide and pyrolysis of 2-bromo-2-carboethoxycyanoacetate failed.[11]

The desired product was obtained by the route analogous to the preparation of carbonyl cyanide from 1,1,2,2-tetracyanooxirane.[9] Diethyl 2,3-dicyanooxiran-2,3-dicarboxylate (8) obtained according to the literature procedure[12,9] was treated with di-n-heptylsulphide[13] to give compound 4, with the satisfactory overall 59% yield, which after one redistillation had b.p. 32°/0.5 Torr, and m.p. ~ −62°.

The structure. was confirmed by analytical and spectral data and chemical transformations. In the IR spectrum appeared bonds characteristic of the ester (1770 cm^{-1}) and cyanoformyl (1740 cm^{-1}) CO group as well as cyano group (2235 cm^{-1}). ^{1}H NMR spectrum of 4 gave only signals indicating the presence of an EtO group; however the ^{13}C resonance revealed the presence of five C atoms with chemical shifts (ppm) corresponding to two CO (160.4 and 155.9) cyano (112.1) and ethoxy (65.3 and 13.8) groups.

Ethoxalyl cyanide (4) is an yellowish viscous liquid which, like carbonyl cyanide (3), decomposes readily under the influence of the air moisture with evolution of hydrogen cyanide. Under the dry N_2 it could be stored without change for several months. Compound 4 treated with methanol in THF at room temperature gave ethylmethyl oxalate (9) whereas its reaction with aniline led to oxanilic acid (10). Catalyzed by BF_3 etherate condensation of cyanide 4 with phenol proceeded like the analogous reaction of carbonyl cyanide (2)[14] yielding ethyl bis(4-hydroxyphenyl)cyanoacetate (11).

Dienophilic and enophilic activity of ethoxalyl cyanide (4) was demonstrated by reacting it with 1,3-butadiene, 1-methoxy-1,3-butadiene and 1-hexene, respectively. For both dienes thermal addition led to the Diels–Alder products 12 and 13 respectively. Their structures were confirmed by analytical and spectral
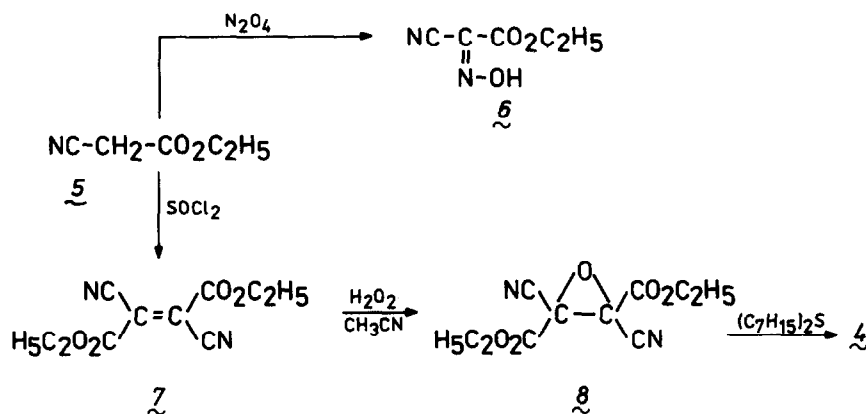
Scheme 1.

data. In the case of 1-methoxy-1,3-butadiene a single (tlc, ¹H NMR) diastereoisomer was obtained the configuration of which was not assigned.

Reaction of ethoxalyl cyanide (4) with 1-hexene both in thermal (130°) and catalytic (TiCl₄) conditions gave ene adduct 14 in good yield. The ratio of geometric isomers $E:Z$ of adduct 14 was 9:1 (glc) and E configuration of the major isomer followed from the ¹H NMR spectrum. The foregoing E–Z stereoselectivity is in accord with those observed in ene reactions of other heteroenophiles.[15]

Qualitative comparison of the temperature, time and yields of diene and ene reactions of ethoxalyl cyanide (4) with those reported for diethyl mesoxalate (3) and carbonyl cyanide (2) as could be expected, indicate that cyanide 4 has an intermediate reactivity. E.g. reaction of carbonyl cyanide 2 with 1,3-butadiene proceeds at room temperature with considerable exothermic effect[5a] whereas that of compound 4 takes place at elevated temperature. On the other hand cyanide 4 reacts smoothly with 1-methoxy-1,3-butadiene at room temperature in contrast to diethyl mesoxalate (3) which requires longer time and heating. Ethoxalyl cyanide (4) has one significant advantage over carbonyl cyanide (2),

which stems from its lower reactivity. Namely neither during catalytic nor thermal addition any secondary reactions take place of adduct 14 with cyanide 4, whereas cyanoformylation of OH group of the alkenecarbonyl cyanide adduct is often encountered.[7] The new dienophile (or enophile) 4 offers a ready access to the dihydropyrane system or tertiary alcohols both with synthetically convenient substituent (CN and CO₂Et). In each case the possibility is opened for an asymmetric induction[16] in the course of formation of the chiral center and/or further separate transformations of cyano and carboalkoxy group.
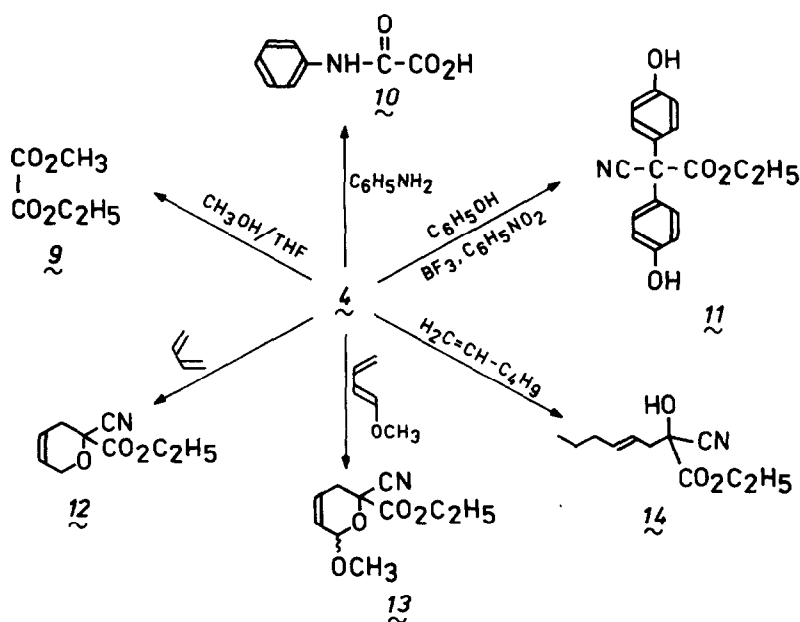
EXPERIMENTAL

Scheme 2.

400 mesh, E, Merck) was used. All solvents and reagents were freshly distilled before use.

Compound 7 was obtained from 5 by treatment with $SOCl_2$ (Scheme 1) according to the literature method[16]; however instead of distillation the product was filtered off from the cooled mixture and after recrystallization from ether–petroleum ether compound 7 (yield 87%) had reported[16] m.p., IR and ^1H NMR spectra. Compound 8 was obtained according to the literature procedure.[12]

Oxidation of ethyl cyanoacetate with nitrogen dioxide

Ethyl 2-(hydroxyimino)cyanoacetate (6). Ethyl cyanoacetate (14.1 g, 0.125 mol) was cooled in dry ice-acetone bath to −20 to −30° and saturated with nitrogen dioxide (13.0 g, 0.28 mol). The dark brown mixture was left for 3 days at 0–5° and then for 10 days at room temp when it turned yellowish. After evaporation of volatiles under reduced pressure the residue partially solidified. The crystals were filtered off and recrystallized from ether–ligroin to give 6 (1.3 g, 7%) m.p. 132–133° (lit.[10] m.p. 129–131°). (Found: C, 42.1; H, 4.3; N, 19.4. $C_5H_6O_3N_2$ requires: C, 42.3; H, 4.3; N, 19.7%). IR (KBr): 3200–3100 (OH), 2200 (C≡N), 1720 (C=O), 1030 (C–O) cm^{-1}. ^1H NMR (CDCl$_3$): δ4.45 (q, 2H), 1.40 (t, 3H, J = 7.2 Hz).

Ethoxalyl cyanide (4). Into a 3-neck flask equipped with magnetic stirrer, droping funnel, thermometer and Vigreux column, epoxide 8 (80 g, 33.6 mmol) was added to diethyl phthalate (16 mL) under N_2. The pressure was reduced to about 0.5 Torr, the flask warmed to 50° and to the stirred soln di-n-heptylsulphide was added dropwise in the course of 30 min. The temp was raised to 65–70° and maintained for 3 hr, the product was collected as a white solid in the receiver and kept at −70°. After filling the apparatus with N_2 and warming up the receiver to room temp compound 4 was obtained as a yellow-greenish mobile liquid (38 g, 89%) b.p. 32°/0.5 Torr, m.p. ~ −62°. MS: 128(13), 100(32), 98(51), 84(337), 73(54), 72(70). IR (film): 2235 (C≡N), 1770, 1740 (C=O) cm^{-1}. ^1H NMR (CDCl$_3$): δ4.50 (q, J = 7.0 Hz) –CH$_2$–, 1.38 (t, J = 7.0 Hz) –CH$_3$. ^{13}C NMR (CDCl$_3$): 160.4 (C=O), 155.9 (–CO$_2$–) 112.1 (CN), 65.3 (CH$_2$), 13.8 (CH$_3$). UV (hexane): λ_{max} 232 (ϵ = 2190), 351 (ϵ = 122) nm.

Methanolysis of ethoxalyl cyanide (4)

Ethyl-methyl oxalate (9). A soln of anhydr MeOH (0.065 g, 2 mmol) in THF (2 mL) was added to a soln of 4 (0.24 g, 1.9 mmol) in THF (5 mL) and left for 12 hr at room temp. Then solvents were evaporated to give ethyl-methyl oxalate (0.175 g, 70%), b.p. 58°/0.1 Torr whose IR and ^1H NMR spectra were identical with the literature data.

Reaction of ethoxalyl cyanide (4) with aniline

Oxanilic acid (10). Cyanide 4 (0.42 g, 3.3 mmol) was added to a soln of aniline (0.42 g, 4.5 mmol) under N_2. When the exothermic reaction subsided the mixture was refluxed for 1 hr. The ppt which had formed after cooling was collected and recrystallized from benzene to give 10 (0.35 g, 64%), m.p. 149–150°, whose IR and ^1H NMR spectra were identical with the literature data.

Condensation of ethoxalyl cyanide (4) with phenol

Ethyl bis(4-hydroxyphenyl)cyanoacetate (11). To a stirred soln of phenol (1.85 g, 19.6 mmol) in nitrobenzene (5 mL) chilled to −10°, under N_2, a solns of BF_3 etherate (0.56 g, 3.9 mmol) and 4 (0.50 g, 3.9 mmol) in nitrobenzene (5 mL) each were added successfully. The mixture was stirred at room temp for 16 hr, neutralized with Et_3N and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column in CHCl$_3$/EtOH = 93/7 to give 11 (0.81 g, 69%) as a homogeneous in tlc thick oil, b.p. 212°/5 × 10^{-2} Torr. (Found: C, 68.0; H, 5.0; N, 4.7. $C_{17}H_{15}NO_4$ requires: C, 68.7; H, 5.1; N, 4.7%). IR (film): 3550–3100 (OH), 2240 (C≡N), 1730 (C=O) cm^{-1}. ^1H NMR (acetone-d$_6$): δ 7.23 (d, J = 8.1 Hz, 4H), 6.9(d, J = 8.1 Hz, 4H) aromatic protons, 4.28 (q, J = 7.1 Hz, 2H) –CH$_2$–, 3.36 (b.s., 2H), 1.25(t, J = 7.1 Hz, 3H) –CH$_3$.

Addition of (4) with 1,3-butadiene

Ethyl 2-cyano-2H-3,6-dihydropyran-2-carboxylate (12). A

soln of 4 (0.40 g, 3.1 mmol) and 1,3-butadiene (0.41 g, 7.4 mmol) in CCl$_4$ (6 mL) was heated under N_2 in the sealed tube at 120° for 19 hr. Then the solvents were removed and the residual thick oil was chromatographed over silica gel (25 g) column. Elution with ether/ligroin (1/4) and distillation gave pure 12 (0.49 g, 86%), b.p. 68°/0.1 Torr. Found: C, 59.4; H, 6.4; N, 8.2. $C_9H_{11}NO_3$ requires: C, 59.7; H, 6.1; N, 7.7%) IR (film): 1780, 1760 (C=O), 1275, 1115 (C–O) cm^{-1}. ^1H NMR (CDCl$_3$): δ 5.87 (s, 2H) CH=CH, 4.50(m, 2H) OCH$_2$–, 4.35 (q, J = 7.0 Hz, 2H) CO$_2$CH$_2$–, 2.70(m, 2H) –CH$_2$–, 1.40(t, J = 7.0 Hz, 3H) –CH$_3$.

Addition of ethoxalyl cyanide (4) to 1-methoxy-1,3-butadiene

Ethyl 2-cyano-6-methoxy-2H-3, 6-dihydropyran-2-carboxylate (13). 1-Methoxy-1, 3-butadiene (0.60 g, 7.2 mmol) was added at room temp, with small exothermic effect, to a soln of 4 (0.47 g, 3.8 mmol) in CH$_2$Cl$_2$ (9 mL). After 30 min the reaction was complete yielding essentially a single product (tlc). The mixture was evaporated in vacuo and the residue chromatographed over silica gel (25 g). Elution with ether/ligroin (3/2) and distillation gave pure 13 (0.58 g, 72%) b.p. 82°/5 × 10^{-2} Torr. (Found: C, 56.9; H, 6.2; N, 6.6. $C_{10}H_{13}NO_4$ requires: C, 56.9; H, 6.2; N, 6.6%) IR (film): 1750 (C=O), 1260, 1115 (C–O) cm^{-1}. ^1H NMR (CDCl$_3$): δ 6.02(s, 2H)

CH=CH, 5.13(b.s., 1H) H–C$\overset{O}{\underset{O}{\diagup\diagdown}}$, 4.42 (q, J = 7.1 Hz, 2H) –CH$_2$–,

3.63(s, 3H) –OCH$_3$, 2.67(m, 2H)–CH$_2$–, 1.42(t, J = 7.1 Hz, 3H)–CH$_3$.

Ene addition of ethoxalyl cyanide (4) with 1-hexene

Ethyl 2-cyano-2-hydroxyoct-4-enoate (14)

(a) *Thermal reaction.* A soln of 4 (0.36 g, 2.8 mmol) and 1-hexene (0.47 g, 5.6 mmol) in CH$_2$Cl$_2$ (3 mL) was heated in the sealed tube at 130° for 12 hr. Then solvents were evaporated and the residue chromatographed over silica gel. Elution with ether/ligroin (1/4) and distillation gave 14 (0.37 g, 63%), b.p. 75°/5 × 10^{-2} Torr. (Found: C, 62.2; H, 8.2; N, 6.6. $C_{11}H_{17}NO_3$ requires: C, 62.6; H, 8.1; N, 6.6%). IR (film): 3460 (OH), 1760 (C=O), 1270 (C–O), 1270 (C–O) cm^{-1}. ^1H NMR (CDCl$_3$): δ5.68 (dt, J$_{45}$ = 14.9 Hz, J$_{34}$ = 6.4 Hz, 1H) H–4, 5.37 (dt, J$_{45}$ = 14.9 Hz, J$_{56}$ = 6.4 Hz, 1H) H–5, 4.42 (q, J = 7.1 Hz, 2H)–OCH$_2$–, 3.90 (b.s., 1H) OH, 2.78(m, 2H) H–3, H–3', 2.08(m, 2H) H–6, H–6', 1.2–1.6(m, 2H) H–7, H–7', 1.41(t, J = 7.1 Hz, 3H) –CH$_3$, 0.99(t, J = 7.0 Hz, 3H) 8–CH$_3$.

(b) *Catalytic reaction.* A soln of TiCl$_4$ (0.056 g, 0.3 mmol) and 1-hexene (0.27 g, 3.2 mmol) each in CCl$_4$ (1.5 mL) were added successively to a stirred soln of 4 (0.23 g, 1.9 mmol) in CCl$_4$ under N_2 and kept at −5°. The stirring was continued for 1 hr till completion (tlc) of the reaction. The mixture was neutralized with ion-exchange resin (Dowex 8) filtered and evaporated. Distillation of the residue gave 14 (0.28 g, 71%) b.p. 75°/5 10^{-2} Torr identical (IR, ^1H NMR, tlc) with the sample obtained in the experiment (a).

REFERENCES

[1] 1,4-Cycloaddition Reactions. *The Diels-Alder Reaction in Heterocyclic Syntheses* (Edited by J. Hamer). Academic Press, New York (1967).
[2a] J. Jurczak, M. Chmielewski and S. Filipek, *Synthesis* 41 (1979); [b] J. A. Gladysz and S. Yu. Yeung, *J. Chem. Soc.* Chem. Comm. 599 (1978).
[3] Yu. A. Arbuzov, E. M. Klimov and E. J. Klimova, *Dokl. Akad. Nauk SSSR* 142, 341 (1962).
[4] E. J. Klimova and Yu. A. Arbuzov, *Ibid.* 167, 1066 (1966).
[5a] O. Achmatowicz and A. Zamojski, *Bull. Acad. Polon. Sci.* Cl. III 5, 927 (1957); [b] O. Achmatowicz and F. Werner-Zamojska, *Ibid.* 923 (1957).
[6] O. Achmatowicz and O. Achmatowicz, Jr., *Roczniki Chem.* 36, 1791 (1962).
[7a] R. Małachowski and L. Jurkiewicz, *Ibid.* 24, 88 (1950); [b] O. Achmatowicz, M. Leplawy and A. Zamojski, *Ibid*, 30, 215 (1956); [c] O. Achmatowicz and F. Zamojska, *Ibid.* 35, 221 (1961); [d] O. Achmatowicz and K. Belniak, *Ibid.* 39, 1685 (1965).
[8a] B. B. Corson and R. K. Hazen, *Org. Synth.* 10, 54 (1930); [b] R. Muller, *Ber. Dtsch. Chem. Ges.* 66, 1668 (1933); [c] R. Anschutz and E. Parlato, *Ibid.* 25, 3614 (1892).
[9a] E. L. Martin, *Org. Synth.* 51, 70 (1971); [b] W. I. Linn, O. W.

Webster and R. E. Benson, *J. Am. Chem. Soc.* **87**, 3651 (1965).

[10]C. O. Parker, *Tetrahedron* **17**, 109 (1962).

[11]D. G. J. Felton, *J. Chem. Soc.* 515 (1955).

[12]C. J. Ireland and J. S. Pizey, *Ibid.* Chem. Comm. 4 (1972).

[13]Recommended in the literature procedure[9] di-n-butylsulphide could not be used because of the higher b.p. of **4** than **2**. We have noticed that it is also advantageous to use di-n-heptysulphide in the preparation of carbonyl cyanide since then only one fractionation is required.

[14a]E. G. Banucci, *Synthesis* 671 (1973); [b]E. G. Banucci and N. Y. Scotia U.S. patent 3,810,933 (1974).

[15a]O. Achmatowicz, Jr. and J. Szymoniak, *J. Org. Chem.* **45**, 1228 (1980); [b]O. Achmatowicz, Jr. and J. Szymoniak, *Ibid.* **45**, 4774 (1980); [c]O. Achmatowicz, Jr. and M. Pietraszkiewicz, *J. Chem. Soc.* Perkin Trans. I, in press.

[16a]J. Jurczak and A. Zamojski, *Tetrahedron* **28**, 1505 (1972); [b]O. Achmatowicz, Jr. and B. Szechner, *J. Org. Chem.* **37**, 964 (1972).