REACTIONS OF OXAZOLE WITH ACETYLENIC DIENOPHILES

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Received January 24th, 1975

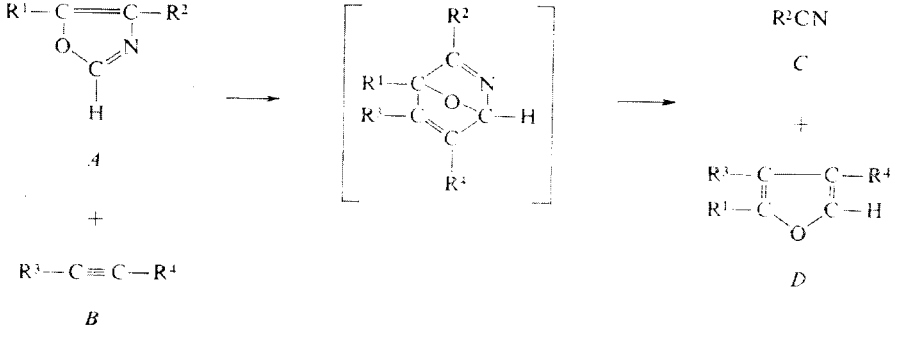
The reaction of 5-substituted oxazoles with acetylenic dienophiles has been studied as a route leading to some β-substituted furan derivatives.

Furan derivatives, substituted in the β-position, are not easily accessible. A simple route leading to such compounds is the reaction of an oxazole *A* with an acetylenic dienophile *B* which affords a nitrile *C* and a β-substituted furan derivative[1,2] *D*. Authors, who carried out this reaction previously, chose either symmetrical dienophiles (*B*: $R^2 = R^4 = COOCH_3$, C_6H_5)[1] or, though they used unsymmetrical dienophiles (*B*: $R^3 = H$, $R^4 = COOH$, $COCH_3$), condensed them with an oxazole, not substituted in position 4 (*A*: $R^1 = H$, $R^2 = C_6H_5$)[2]. Neither of these two cases can lead to two isomeric furan derivatives differing in the position of the substituents R^3 and R^4 on both β-carbon atoms. The only exception[1] is represented by the condensation of methyl phenylpropiolate (*B*: $R^3 = C_6H_5$, $R^4 = COOCH_3$) with 5-ethoxy-4-methyloxazole (*A*: $R^1 = OC_2H_5$, $R^2 = CH_3$), leading to a mixture of two isomeric furan derivatives which, however, were not isolated.

The question of the isomerism is interesting since the oxazoles, substituted in position 5 with benzyl (*A*: $R^1 = C_6H_5CH_2$), should react with propiolic acid or its esters (*B*: $R^3 = H$, $R^4 = COOH$, $COOCH_3$) under formation of benzylfuroic acids (*I*, *II*) or their esters (*III*, *IV*). We expected that thanks to the steric interaction of benzyl and carboxyl the preponderant products of the reaction will be the 2,4-isomers (*II* or *IV*) which are precursors of the important component of the pyrethroid insecticide, 2-benzyl-4-hydroxymethylfuran[3-5] (*V*). At the same time it was of interest to what extent the reaction course and the isomer ratio are affected by a substituent in position 4 of the oxazole ring, *i.e.* by a group which is splitted off together with the CN group in the form of the nitrile C.

Therefore, we prepared a series of 5-benzyloxazoles *VI*–*X*, together with one 4-benzyloxazole. 5-Benzyl-4-phenyloxazole (*VI*), 5-benzyl-4-methyloxazole (*VII*) and 4-benzyl-5-phenyloxazole (*XI*) were prepared from the corresponding bromo ketones by treatment with formamide or ammonium formate[6]. Ethyl 5-benzyl-4-oxazolecarboxylate (*VIII*) was obtained by condensation of ethyl isocyanoacetate

with phenylacetyl chloride in the presence of potassium tert-butoxide[7]. Hydrolysis of the ester *VIII* afforded the acid *IX*, decarboxylation of which gave 5-benzyloxazole (*X*), prepared already by a different route[7]. The UV spectrum of all the oxazole derivatives prepared in the present study exhibited a band near 212 nm, together with other substituent-dependent bands.



A

VI; $R^1 = C_6H_5CH_2$, $R^2 = C_6H_5$
VII; $R^1 = C_6H_5CH_2$, $R^2 = CH_3$
VIII; $R^1 = C_6H_5CH_2$, $R^2 = COOCH_3$
IX; $R^1 = C_6H_5CH_2$, $R^2 = COOH$
X; $R^1 = C_6H_5CH_2$, $R^2 = H$
XI; $R^1 = C_6H_5$, $R^2C_6H_5CH_2$

D

I; $R^1 = C_6H_5CH_2$, $R^3 = COOH$, $R^4 = H$
II; $R^1 = C_6H_5CH_2$, $R^3 = H$, $R^4 = COCH$
III; $R^1 = C_6H_5CH_2$, $R^3 = COOCH_3$, $R^4 = H$
IV; $R^1 = C_6H_5CH_2$, $R^3 = H$, $R^4 = COOCH_3$
V; $R^1 = C_6H_5CH_2$, $R^3 = H$, $R^4 = CH_2OH$
XII; $R^1 = C_6H_5$, $R^3 = COOH$, $R^4 = H$
XIII; $R^1 = C_6H_5CH_2$, $R^3 = R = COOCH_3$

As expected, the reaction of the oxazoles *VI*, *VII*, *VIII* and *X* with propiolic acid or its methyl ester afforded 2-benzylfuroic acids (*I* and *III*). The yields (<15%) were somewhat lower than that obtained by other authors in analogous reactions[1,2]. Contrary to the expected sterically induced regioselectivity of the reaction, the NMR spectrum showed that the product consisted of comparable amounts of 2-benzyl-3-furoic (*I*) and 2-benzyl-4-furoic (*II*) acids or their methyl esters *III* and *IV*. The overall yields were better when an excess of the oxazole was used[2]; otherwise the reaction afforded greater amount of non-isolable side products which probably arose by further condensation of furan derivatives with the dienophiles. The substituents in position 4 of the oxazole ring do not affect markedly either the yield or the isomer ratio. The acid *IX* represents an exception because it did not react under the conditions employed.

Condensation of the oxazole *XI* with methyl propiolate afforded 2-phenyl-3-furoic acid (*XII*) as the only isolable product. The reaction of 5-benzyl-4-methyloxazole

(*VII*) with dimethyl acetylenedicarboxylate (*B*: $R^3 = R^4 = COOCH_3$) was similar to that with propiolate and gave dimethyl 2-benzylfuran-3,4-dicarboxylate (*XIII*).

In some cases, the nitriles which are the second products of the studied reaction were identified in the reaction mixture. Thus, benzonitrile (*C*: $R^2 = C_6H_5$) and benzyl cyanide (*C*: $R^2 = C_6H_5CH_2$) were detected by thin-layer chromatography in the reaction products of the oxazole *VI* and *XI*, respectively. Acetonitrile (*C*: $R^2 = CH_3$) was identified in the reaction product of the oxazole *VII* using gas–liquid chromatography, and hydrogen cyanide (*C*: $R^2 = H$) was detected by ferric chloride in the reaction product of the oxazole *X*.

Similarly to results of other authors[2], we also failed to isolate the anticipated primarily formed Diels–Alder adduct of the dienophile to the oxazole. However, among the products of the reaction of propiolic acid with 5-benzyloxazole (*X*) we found, beside benzylfuroic acids, an acid, m.p. 175°C, the elemental analysis of which corresponds to the formula $C_{13}H_{13}NO_4$. *i.e.* the sum of both starting molecules plus molecule of water. We assume that this compound is an adduct which was hydrolysed during the isolation.

EXPERIMENTAL

Thin-layer chromatography was performed on a loose layer of silica gel with gypsum, column chromatography was carried out on silica gel deactivated with 20% of water. Melting points were taken on a Kofler block. UV spectra were measured in methanol on a Carl Zeiss-Jena Specord UV VIS spectrometer, NMR spectra were taken in hexadeuteriodimethyl sulphoxide (hexamethyldisiloxane as internal standard) on a Varian HA 100 instrument. IR spectra were taken in KBr pellet on a Carl Zeiss-Jena UR-100 apparatus.

5-Benzyl-4-phenyloxazole (*VI*)

A mixture of 2-bromo-1,3-diphenyl-1-propanone[8] (20 g, 0·07 mol), ammonium formate (30 g) and 99% formic acid (130 ml) was refluxed for 5 hours, poured into water (500 ml), made slightly alkaline with 20% sodium hydroxide and extracted with chloroform. The extract was dried over magnesium sulphate, the chloroform distilled off on a rotatory evaporator under diminished pressure and the residue distilled. Two distillations (bath temperature 122—128°C/0·015 Torr) afforded 11 g (67%) of the oxazole *VI*. UV spectrum: λ_{max} 211 nm, (ε 17000), λ_{max} 244 nm (ε 14000). For $C_{16}H_{13}NO$ (235·3) calculated: 81·68% C, 5·57% H, 5·95% N; found: 81·12% C, 5·38% H, 5·99% N.

5-Benzyl-4-methyloxazole (*VII*)

A solution of formamide (20 g) and conc. sulphuric acid[6] (10 g) was added dropwise at 150°C to a solution of 1-phenyl-2-bromo-3-butanone[9] (25 g; 0·111 mol) in formamide (50 g). The reaction mixture was kept at this temperature for 8 hours, cooled and poured into water (500 ml). The solution was neutralized and extracted with chloroform. Further work-up procedure was the same as described in the preceding experiment and yielded 13·5 g (71%) of the oxazole *VII*. UV spectrum: λ_{max} 213 nm (ε 8250). For $C_{11}H_{11}NO$ (173·2) calculated: 75·27% C, 6·40% H, 8·09% N; found: 75·89% C, 6·35% H, 7·82% N.

Ethyl 5-Benzyl-4-oxazolecarboxylate (*VIII*)

Ethyl isocyanoacetate[7,10] (12·5 g; 0·08 mol) was added dropwise at 0°C to a stirred suspension of potassium tert-butoxide (18 g; 0·16 mol) in tetrahydrofuran (120 ml), then phenylacetyl chloride (12·5 g; 0·08 mol) was added at a temperature below 5°C. The mixture was neutralized with 10% acetic acid (50 ml) under cooling and stirring and the tetrahydrofuran was distilled off. The residue was treated with water until the potassium salts dissolved. The solution was extracted with chloroform, the chloroform layer was dried over magnesium sulphate, taken down and the residue fractionated *in vacuo*. The fraction, boiling at 45—65°C/1 Torr, consisted of the nonreacted ethyl isocyanoacetate (7·5 g), the fraction, boiling at 110—120°C/0·05 Torr, was the ester *VIII* (12 g; 65%). UV spectrum: λ_{max} 212 nm (ε 9000), λ_{sh} 221 nm (ε 8400). For $C_{13}H_{14}NO_3$ (231·5) calculated: 67·52% C, 5·67% H, 6·06% N; found: 67·06% C, 5·60% H, 6·48% N.

5-Benzyl-4-oxazolecarboxylic Acid (*IX*)

The ester *VIII* (9 g; 0·04 mol) was saponified with 10% aqueous–ethanolic sodium hydroxide. The acid, which separated upon acidification, was taken into chloroform. The chloroform layer was dried over magnesium sulphate, taken down and the residue sublimed at 0·05 Torr, yielding 7·3 g (92%) of the acid *IX*, m.p. 155°C (subl.). For $C_{11}H_9NO_3$ (203·2) calculated: 65·02% C, 6·89% H, 4·46% N; found: 64·76% C, 6·85% H, 4·53% N.

5-Benzyloxazole (*X*)

The acid *XI* (11 g; 0·055 mol) was slowly heated at normal pressure to 180—210°C and the distillate was collected. Redestillation *in vacuo* yielded 4·6 g (53%) of the oxazole *X*, b.p. 58 to 61°C/0·06 Torr[7]. UV spectrum: λ_{max} 214 nm (ε 9380).

4-Benzyl-5-phenyloxazole (*XI*)

This compound was prepared in the same manner as its isomer *VI*. 1-Bromo-1,3-diphenyl-2-propanone[8] (20 g; 0·07 mol) was transformed into the oxazole *XI* (10·1 g; 62%), m.p. 46°C (cyclohexane). UV spectrum: λ_{max} 212 nm (ε 20000), λ_{sh} 218 nm (ε 15000), λ_{max} 260 nm (ε 19000), λ_{sh} 278 nm (ε 11000). For $C_{16}H_{13}NO$ (235·5) calculated: 81·68% C, 5·57% H, 5·95% N; found: 81·59% C, 5·77% H, 5·92% N.

Condensation of the Oxazoles *VI*, *VIII* and *X* with Propiolic Acid

A mixture of the oxazole (0·02 mol) and propiolic acid (0·39 g; 0·005 mol) was heated under nitrogen in a sealed ampoule to 130°C for 8 hours. The reaction mixture was dissolved in chloroform (50 ml) and shaken with a sodium hydrogen carbonate solution. Upon evaporation of the chloroform the neutral portions were distilled, affording the unreacted oxazole. Acidification of the aqueous layer liberated the benzylfuroic acids which were taken into chloroform (50 ml). The extract was dried over magnesium sulphate, taken down and the residue (0·12—0·15 g; 12—15%) was set aside overnight in refrigerator where it partially crystallized. The solid portion was crystallized from ethyl acetate and sublimed, giving 30—40 mg of 2-benzyl-4-furoic acid (*II*), m.p. 117—120°C. NMR spectrum: 3·97 (s, 2 H, CH_2); 6·36 (n, H, $J_{3,5} = 0·75$, J_3, methylene < 10, $H_{(3)}$); 7·97 (d, H, $J_{5,3} = 0·75$, $H_{(5)}$). For $C_{12}H_{10}O_3$ (202·2) calculated: 71·28% C, 4·99% H; found: 71·58% C, 5·36% H. The non-crystalline portion contained approximately the same amount of the 2,4- and the 2,3-isomers. NMR spectrum: 4·37 (s, 2 H, CH_2); 6·70 (d, H, $J_{4,5} = 2·5$, $H_{(4)}$).

In the condensation of propiolic acid with 5-benzyloxazole (*X*), the treatment of the crude benzylfuroic acids with chloroform left some insoluble material (10 mg). Upon crystallisation from ethyl acetate the compound melted at 174–175°C. For $C_{13}H_{13}NO_4$ (247·2) calculated: 63·15% C, 5·30% H, 5·67% N; found: 63·05% C, 5·40% H, 5·72% N and 0·49% H*.

Condensation of the Oxazoles *VI*, *VII* and *X* with Methyl Propiolate

The oxazoles (0·02 mol) were condensed with methyl propiolate (0·42 g; 0·005 mol) under identical conditions as described for the reaction with propiolic acid. Upon addition of 5M-NaOH (1·5 ml) and sufficient amount of methanol to give a homogeneous solution, the reaction mixture was set aside overnight at room temperature, and then shaken between water (10 ml) and chloroform (50 ml). The chloroform solution of the neutral substances was dried and taken down, leaving the starting oxazole. Acidification of the alkaline aqueous portions afforded the acids *I* and *II*. Further work-up procedure and yields were the same as in the preceding experiments.

Condensation of Methyl 5-Benzyl-4-oxazolecarboxylate (*VIII*) with Methyl Propiolate

The ester *VIII* (4·5 g; 0·02 mol), was heated with methyl propiolate (0·42 g; 0·005 mol) under nitrogen in a sealed ampoule to 130°C for 8 hours. The reaction mixture was chromatographed on a column packed with silica gel (500 g) deactivated with 20% water. Benzene fractions (1 500 to 2000 ml) contained the excess ester *VIII* (about 0·01 mol), chloroform fractions (1000 ml) afforded 0·1–0·13 g (9–12%) of a mixture of methyl 2-benzyl-3-furoate (*III*) and methyl 2-benzyl-4-furoate (*IV*) (*III* : *IV* = 3 : 2), which distilled at bath temperature 120–130°C/0·05 Torr. IR spectrum: ν(C=O) 1719 cm^{-1}, ν(ring) 1602, 1521 cm^{-1}. NMR spectrum: 2,4-isomer: 6·25 (broad s, H, $J_{3,5} = 1{\cdot}0$, $H_{(3)}$), 7·79 (broad s, H, $H_{(5)}$), 3·8 (s, 2 H, CH_2), 3·7 (s, 3 H, $COOCH_3$); 2,3-isomer: 6·55 (d, H, $J_{4,5} = 2{\cdot}0$, $H_{(4)}$), about 7·15 (overlap with aromatic protons, $H_{(5)}$), 4·28 (s, 2 H, CH_2), 7·20 (broad signal, 5 H, C_6H_5). For $C_{13}H_{12}O_3$ (216·2) calculated: 72·21% C, 5·95% H; found: 71·86% C, 5·30% H.

5-Benzyl-4-oxazolecarboxylic acid (*IX*) was heated with methyl propiolate in toluene (5 ml) under the same conditions as described for other oxazoles. The reaction mixture was washed with a solution of sodium hydrogen carbonate. Acidification of the aqueous layer liberated the unchanged acid *IX*. The neutral portions did not contain the benzylfuroates *III* and *IV* (according to gas–liquid chromatography).

2-Phenyl-3-furoic Acid (*XII*)

The condensation of 4-benzyl-5-phenyloxazole (*XI*) with methyl propiolate and the subsequent alkaline hydrolysis were carried out as already described. Evaporation of solvent from the chloroform extract, containing the neutral compounds, gave the starting oxazole *XI*. Acidification of the alkaline aqueous layers liberated the acid *XII* (0·16 g; 17%) which upon recrystallisation from diisopropyl ether and sublimation *in vacuo* melted at 186°C. NMR spectrum: 6·89 (d, H, $J_{4,5} = 2{\cdot}1$ $H_{(4)}$); about 7·4 ($H_{(5)}$, in aromatic multiplet); 7·38–7·50 (m, 3 H, arom.); 7·90–8·02 (m, 2 H, arom.). For $C_{11}H_8O_3$ (188·2) calculated: 70·21% C, 4·29% H; found: 70·26% C, 4·24% H.

Methyl 2-Benzyl-3,4-furancarboxylate (*XIII*)

The oxazole *VI* was condensed with dimethyl acetylenedicarboxylate in the same manner as described for its reaction with propiolate. The reaction mixture was divided into five parts, each of which was subjected to preparative thin-layer chromatography (20 × 45 × 0·3 cm loose layer of

silica gel deactivated with 20% water; chloroform). The chromatogram had three main chromatographic bands, absorbing UV light: the principal band was the unreacted oxazole *VI*, the second was identified as benzonitrile (thin-layer chromatographic comparison with an authentic specimen), and the third belonged to the product. It was combined with the same bands from the other four chromatographic plates. The material thus obtained was extracted with ethyl acetate, the solvent evaporated and the product distilled *in vacuo*, yielding 0·18 g (13%) of the diester *XIII*, which distilled at the bath temperature 135–140°C/0·1 Torr. IR spectrum: 3166 cm^{-1} ($C_{(5)}$—H, furan), 1745, 1723 cm^{-1} (CO), 1556 cm^{-1} (ring). For $C_{15}H_{14}O_5$ (274·3) calculated: 65·69% C, 5·15% H; found: 65·75% C, 5·11% H.

The author is indebted to Dr M. Synáčková for the NMR measurements and to Dr P. Fiedler for taking the IR spectra. His thanks are due also to the staff of the Analytical Department of this Institute (Dr J. Horáček, Head).

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Translated by M. Tichý.