# SYNTHESIS OF ETHYL 3-CYANO-2-ALKENOATES BY THE WITTIG CONDENSATION AND THEIR USE IN THE PREPARATION OF 2-SUBSTITUTED MALEINIMIDES

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Ethyl esters of 3-cyano-2-alkenoic acids may be prepared in high yields by the action of suitable acylation agents on hydrogen cyanide in the presence of excess ethoxycarbonylmethylentriphenylphosphorane (*I*). The esters *VIII*, *X*, and *XI* of the *cis* series were demonstrated to be useful in the preparation of 2-substituted maleinimides.

Investigations on the transport of showdomycin and some analogues through the cell wall and on their effects in various enzymatic systems[1] required to develop a general synthesis of 2-substituted maleinimides. Both the earlier syntheses of showdomycin[2,3] did not appear promising in this respect. Attention was therefore paid to the synthesis of the maleinimide cycle from the readily accessible monocarboxylic acids. Condensation of acyl cyanides* with ethoxycarbonylmethylenetriphenylphosphorane (*I*) to afford ethyl 3-cyano-2-alkenoates appeared attractive in this direction. Thus, the model condensation of benzoyl cyanide (*VI*) with the phosphorane *I* resulted in a high yield of the *cis* and *trans* isomers of ethyl 3-cyano-3-phenylacrylate (*cis-VIII* and *trans-VIII*). Application of this condensation to aliphatic and sugar acids could be regarded less promising because of the difficult accessibility and low stability of the starting acyl cyanides, particularly in the sugar series. This difficulty was successfully circumvented by preparing the required acyl cyanide *in situ* by the action of acylating agents on hydrogen cyanide in the presence of excess ethoxycarbonylmethylenetriphenylphosphorane (*I*) and condensing them without isolation with excess phosphorane *I* to the desired ethyl esters of 3-alkyl-3-cyanoacrylic acids. The chlorides *II*, *IV*, and *V* as well as the anhydride *III* may be used as acylating agents without any effect on the yield of the reaction. The course of the reaction is similarly not affected by the nature of the substituent R since the reaction is smooth both with the chloride of 2,3,4,5-tetra-O-acetyl-D-ribonic acid (*V*) and with the highly sterically

* The use of acyl cyanides in the Wittig condensation has also been proposed by Soulen and coworkers[4] and exemplified on condensation of aroyl cyanides with dichloromethylenetriphenylphosphorane.

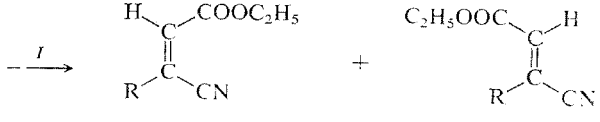
hindered pivaloyl chloride (*IV*). In the latter case, the first step of the reaction (acylation of hydrogen cyanide with the formation of the cyanide *VII*) was very fast and accompanied by evolution of considerable heat whereas the subsequent condensation of the resulting cyanide *VII* with excess phosphorane *I* was considerable slower and required for completion several days at room temperature or better, to be performed at a higher temperature. Concerning the steric course of the condensation, the required *cis* isomer always predominated and its content increased with increasing bulkiness of the substituent R. In the case of groups of low steric requirements, the *cis*/*trans* ratio was 7 : 3 (R = $C_6H_5$) and 7·2 : 2·8 (R = $CH_3$). With R equal to a bulkier D-*ribo*-1,2,3,4-tetraacetoxybutyl group, the *cis*/*trans* ratio was 9 : 1 and only the *cis* isomer was obtained when R = tert-butyl, *i.e.*, a group of high steric requirements.

$$RCOX \xrightarrow[(C_6H_5)_3P{=}CHCOOC_2H_5]{HCN} [RCOCN] + (C_6H_5)_3P^{(+)}CH_2COOC_2H_5\ X^{(-)} \longrightarrow$$

*I*

*II*, R = $C_6H_5$, X = Cl
*III*, R = $CH_3$, X = $CH_3COO$
*IV*, R = t-$C_4H_9$, X = Cl
*V*, R = D-*ribo*-1,2,3,4-tetraacetoxybutyl, X = Cl

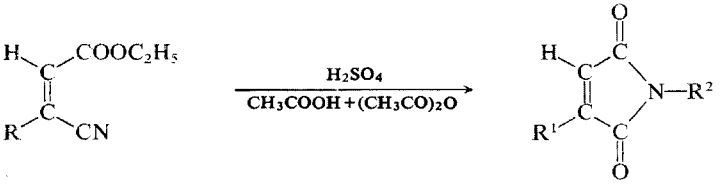
*VI*, R = $C_6H_5$
*VII*, R = t-$C_4H_9$



*cis-VIII* *trans-VIII* R = $C_6H_5$
*cis-IX* *trans-IX* R = $CH_3$
*cis*-X — R = t-$C_4H_9$
*cis-XI* *trans-XI* R = D-*ribo*-1,2,3,4-tetraacetoxybutyl

Attempts were then made to convert the thus-obtained esters *cis-VIII*, *cis-X*, and *cis-XI* to the corresponding 2-substituted maleinimides. One route in this direction could consist in hydrolysis of the above esters to the corresponding maleic acids and transformation of these acids to imides analogously to the synthesis of showdomycin[2]. This route failed in our case because of the great stability of the nitrile function in alkaline media. (As it has been found later on, the esters of 2-cyano-2-alkenoic acids can be converted to the corresponding maleic acids by a two-step hydrolysis; the free cyano acid is obtained by alkaline hydrolysis and then subjected to the acid-catalysed hydrolysis with the formation of the required maleic acid). The cyclisation of the ester-nitriles *cis-VIII*, *cis-X*, and *cis-XI* was finally accomplished with the

use of a procedure consisting in heating the starting material in a mixture of acetic acid, acetic anhydride, and sulfuric acid[5]. After decomposition with water, a mixture of the appropriate maleinimide and its N-acetyl derivative is obtained; consequently, in order to obtain satisfactory yields of the required imides, the N-acetyl group must be removed by acidic hydrolysis. Since the *trans* isomers are stable under the cyclisation conditions and may thus be readily separated from the more polar imides after completion of the cyclisation, it is advantageous from the preparative standpoint to perform the cyclisation with a mixture of the *cis* and *trans* isomers and circumvent in this manner the separation of the geometrical isomers by chromatography. The present synthesis of 2-substituted maleinimides has been successfully applied to the preparative synthesis of the C-nucleosidic antibiotic showdomycin[6].




*XII*, $R^1 = C_6H_5$, $R^2 = CH_3CO$
*XIII*, $R^1 = C_6H_5$, $R^2 = H$
*XIV*, $R^1 = t\text{-}C_4H_9$, $R^2 = H$
*XV*, $R^1$ = D-*ribo*-1,2,3,4-tetraacetoxybutyl, $R^2 = CH_3CO$
*XVI*, $R^1$ = D-*ribo*-1,2,3,4-tetraacetoxybutyl, $R^2 = H$
*XVII*, $R^1$ = D-*ribo*-1,2,3,4-tetrahydroxybutyl, $R^2 = H$

## EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). The IR spectra were recorded of a double-beam UR 10 photometer (Carl Zeiss, Jena). The $^1$H-NMR spectra were measured on a Varian HA 100 spectrophotometer. Thin-layer chromatography was performed on the Merck $GF_{254}$ (type 60) silica gel. Spots were detected by a spray with aqueous potassium permanganate (olefinic compounds), by a spray with a 10% solution of sulfuric acid in methanol and the subsequent carbonisation (sugars) or by viewing under UV light. Analytical samples were dried at 20°C/0·05 Torr for 10 h. Organic solutions were dried over anhydrous magnesium sulfate and taken down under diminished pressure on a rotatory evaporator at 40°C.

Ethyl 3-Cyano-3-phenylacrylate (*cis-VIII* and *trans-VIII*)

*A*. The phosphorane *I* (3·52 g; 10 mmol) was added portionwise to a solution of benzoyl cyanide (*VI*; 1·31 g; 10 mmol) in ether (10 ml) and the mixture was kept at room temperature for 20 h under occasional swirling. The precipitate of triphenylphosphine oxide was filtered off and washed with ether. The filtrate and washings were combined and evaporated. The residue was chromatographed on a column (2 × 16 cm) of siliga gel in light petroleum–ether (9 : 1).

The product-containing fractions were determined by thin-layer chromatography of samples and spray with aqueous potassium permanganate. Evaporation yielded 1·80 g (90%) of the 7 : 3 mixture of *cis-VIII* and *trans-VIII*, as determined by gas–liquid chromatography (QF1 at 180°C). The sample for analysis was redistilled at 0·1 Torr and 150°C (bath temperature).

*B.* To a solution of the phosphorane *I* (8·0 g; 22·5 mmol) in chloroform (20 ml) hydrogen cyanide (2·0 ml) was added, followed by benzoyl chloride (*II*; 1·4 g; 10 mmol) in portions. The whole was kept at room temperature for 1 h, evaporated, and the residue triturated with a mixture of ether (20 ml), hydrochloric acid (5 ml) and water (15 ml). The ethereal layer was separated, washed with water, dried, and concentrated to the volume of about 10 ml. The triphenylphosphine oxide was filtered off and washed with ether. The filtrate and washings were evaporated and the residue processed analogously to paragraph *A*. Yield, 1·64 g (81%) of the 7 : 3 mixture of *cis-VIII* and *trans-VIII*. For $C_{12}H_{11}NO_2$ (201·2) calculated: 71·63% C, 5·51% H, 6·96% N; found: 71·74% C, 5·62% H, 7·32% N.

Ethyl 3-Cyano-3-methylacrylate (*cis-IX* and *trans-IX*)

To a solution of the phosphorane *I* (8·0 g; 22·5 mmol) in chloroform (20 ml) hydrogen cyanide (2·0 ml) was added, followed by acetic anhydride (*III*; 1·02 g; 10 mmol) in portions. The whole was kept at room temperature for 1 h, evaporated, and the residue processed analogously to the preparation of compounds *VIII* by procedure *B*. Yield, 0·80 g (58%) of the 72 : 28 mixture of *cis-IX* and *trans-IX*, as determined by gas–liquid chromatography (QF1 at 90°C). For analytical purposes, the product was redistilled at 15 Torr and 150° (bath temperature). For $C_7H_9NO_2$ (139·2) calculated: 60·42% C, 6·52% H, 10·07% N; found: 60·41% C, 6·64% H, 9·93% N.

Ethyl 3-Cyano-3-tert-butylacrylate (*cis-X*)

To a solution of the phosphorane *I* (8·0 g; 22·5 mmol) in chloroform (20 ml) hydrogen cyanide (2·0 ml) was added, followed by pivaloyl chloride (*IV*; 1·20 g; 10 mmol) in portions. The whole was kept at room temperature for 15 min, concentrated, and the concentrate heated at 100°C for 6 h. Ether (20 ml), water (15 ml), and hydrochloric acid (5·0 ml) were then added and the mixture processed analogously to the preparation of compound *VIII* by procedure *B*. Yield, 1·50 g (83%) of compound *cis-X*. The analytical sample was redistilled at 15 Torr and 150°C (bath temperature). For $C_{10}H_{15}NO_2$ (181·2) calculated: 66·27% C, 8·34% H, 7·73% N; found: 66·51% C, 8·44% H, 8·09% N.

Ethyl 3-(D-*ribo*-Tetraacetoxybutyl)-3-cyanoacrylate (*cis-XI* and *trans-XI*)

A suspension of 2,3,4,5-tetra-O-acetylribonic acid (3·34 g; 10 mmol), ether (6·0 ml), thionyl chloride (6·0 ml), and dimethylformamide (1 drop) was refluxed for 45 min, evaporated, and the residue coevaporated with two 20 ml portions of benzene. The residual chloride *V* (ref.[7]) was dissolved in chloroform (20 ml) and the solution added portionwise to a precooled (0°C) solution of the phosphorane *I* (8·0 g; 22·5 mmol) and hydrogen cyanide (2·0 ml) in chloroform (50 ml). The whole mixture was kept at room temperature for 1 h and evaporated. Ether (50 ml), water (45 ml), and hydrochloric acid (5·0 ml) were added to the residue, the ethereal layer separated, washed with water, dried, concentrated to the volume of about 15 ml, and the concentrate allowed to deposit triphenylphosphine oxide. The solid was filtered off, washed with ether, the combined filtrate and washings evaporated, and the residue chromatographed on a column (12 × 3·3 cm) of silica gel in the solvent system benzene–ethyl acetate (85 : 15). The product-containing fractions (detection with aqueous potassium permanganate) were pooled and evapo-

rated. Yield, 3·41 g (82·5%) of the 9 : 1 mixture of *cis-XI* and *trans-XI*, as determined by gas–liquid chromatography (QF1 220°C). The geometrical isomers *XI* may be separated by rechromatography into *cis-XI*, m.p. 58—60°C, $[\alpha]_D^{25}$ +20·9° (*c* 0·5 in chloroform), and *trans-XI*, $[\alpha]_D^{25}$ +35·5° (*c* 0·5 in chloroform). $R_F$ values on thin-layer chromatography in 85 : 15 benzene–ethyl acetate: 0·45 (*cis-XI*) and 0·53 (*trans-XI*). For $C_{18}H_{23}NO_{10}$ (413·3) calculated: 52·30% C, 5·61% H, 3·39% N; found (*cis-XI*): 52·57% C, 5·69% H, 3·73% N; found (*trans-XI*): 52·17% C, 5·66% H, 3·46% N.

2-Phenylmaleinimide (*XIII*)

Acetic acid (5·0 ml), acetic anhydride (5·0 ml) and sulfuric acid (1·0 ml) were added to the ester-nitrile *VIII* (730 mg of the *cis/trans* mixture containing 2·5 mmol of *cis-VIII*). The mixture was heated at 100°C for 20 min, cooled down, decomposed with water (25 ml), and (after 5 min) extracted with ethyl acetate (25 ml). The extract was washed with water and saturated aqueous sodium hydrogen carbonate, dried, and evaporated. The residue (*A*) was dissolved in methanol and the solution treated with water until turbid to deposit 160 mg (32%, referred to *cis-VIII*) of N-acetyl-2-phenylmaleinimide (*XII*), m.p. 107—109°C. $^1$H-NMR spectrum (deuteriochloroform): $\delta$ 2·59 (s, 3 H; $CH_3CON$), 6·83 (s, 1 H; CH), 7·3—8·0 p.p.m. (m, 5 H, $C_6H_5$). For $C_{12}H_9NO_3$ (215·2) calculated: 66·97% C, 4·22% H, 6·51% N; found: 66·93% C, 4·00% H, 6·51% N. To obtain compound *XIII*, the above crude residue *A* was kept in a mixture of methanol (10 ml) and hydrochloric acid (0·30 ml) for 24 h at room temperature, evaporated, and the residue crystallised from methanol–water to afford 270 mg (62%, referred to *cis-VIII*) of compound *XIII*, m.p. 172—174°C (sealed capillary); reported[8], m.p. 167—168°C. $^1$H-NMR spectrum (deuteriochloroform): $\delta$ 6·72 (d, 1 H, $J_{CH,NH}$ = 1·2; CH), 7·3—8·0 p.p.m. (m, 5 H; $C_6H_5$). For $C_{10}H_7NO_2$ (173·2) calculated: 69·36% C, 4·07% H, 8·09% N; found: 69·23% C, 4·13% H, 8·27% N.

2-Tert-butylmaleinimide (*XIV*)

The *cis-X* isomer (450 mg; 2·5 mmol) was converted to the imide *XIV* and isolated analogously to the phenyl derivative *XIII*. Yield, 310 mg (81%) of the imide *XIV*, m.p. 154—156°C. IR spectrum (KBr): 1616, 1714, 1725, 1770, 3221 $cm^{-1}$. For $C_8H_{11}NO_2$ (153·2) calculated: 62·73% C, 7·24% H, 9·14% N; found: 62·89% C, 7·37% H, 9·36% N.

2-D-*ribo*-Tetrahydroxybutylmaleinimide (*XVII*)

The ester *XI* (1·15 g of the *cis/trans* mixture containing 2·5 mmol of *cis-XI*) was cyclised analogously to the ester *VIII*, the mixture decomposed with water, extracted with ethyl acetate, the extract washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated. The residue (containing compounds *XV* and *XVI*) was chromatographed on a column (2 × 8 cm) of silica gel in 9 : 1 benzene–acetone. The main sugar fraction ($R_F$ value of compounds *XV* and *XVI* on thin-layer chromatography in 9 : 1 benzene–acetone: 0·31) was evaporated and the residual sirup (750 mg) dissolved in methanol (10 ml). Hydrochloric acid (0·3 ml) was added, the mixture kept at room temperature for 24 h, evaporated, and the residue coevaporated with two 10 ml portions of 2-propanol. The final residue was dissolved in a little 2-propanol and the solution allowed to deposit crystals which were collected with suction and washed with 2-propanol. Yield, 256 mg (47%, referred to *cis-XI*) of compound *XVII*, m.p. 121·5—123°C, $[\alpha]_D^{25}$ +108·96° (*c* 0·5 in water). IR spectrum (KBr): 1633, 1707, 1721, 1769 $cm^{-1}$. For $C_8H_{11}NO_6$ (217·2) calculated: 44·24% C, 5·11% H, 6·45% N; found: 44·49% C, 5·16% H, 6·50% N.

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