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REACTIONS OF FUROXANS WITH PHOSPHORUS YLIDES

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Abstract: Benzofuroxan (1) reacts with phosphorus ylide 2 to give benzimidazole derivatives 8 and 10, whereas reaction of 1 with ylide 12 furnishes quinoxaline 17 via an initial Wittig-type reaction. Similarly the reaction between the furoxano[3,4-b]quinoxalines 19a or 19b and the ylide 2 yielded compounds 22a and 22b, respectively. In these reactions as well as in the reactions of the above furoxans with other phosphorus ylides, a significant deoxygenation of the furoxans to furazans with subsequent oxidation of the ylides is generally observed.

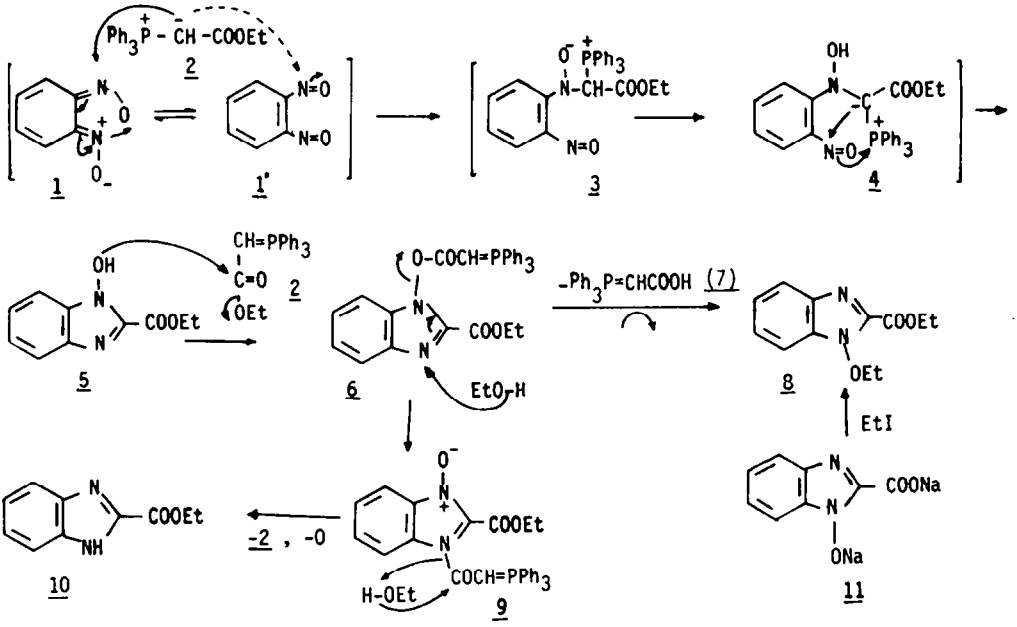
Tautomerism between the 2-oxides and 5-oxides is a consistent feature of furoxan chemistry. cis-Dinitrosoalkenes and o-dinitrosoarenes are likely intermediates although definitive evidence has not yet been presented[1]. A dinitroso intermediate has been postulated during the electrocatalytic reduction of benzofuroxan in aqueous acid solution on platinum surfaces modified with underpotential heavy metal monolayers[2]. The formation of the bisazoxy compound from benzofuroxan (1) and p-anisyl azide has, however, been rationalized in terms of such dinitroso species[3]. Enamines and enolate anions react readily with 1 to form quinoxaline dioxides, and this process is frequently referred to as the Beirut reaction. The reaction takes a different course when leaving groups such as CN^-, RSO_2^- and NO_2^- are present, leading to benzimidazole 3-oxides or 1,3-dioxides[1]. While not all aspects have yet been fully explained, it is generally accepted that the mechanism of these transformations involves nucleophilic attack at N(3) of the ground state of benzofuroxan (1) or less likely at one of the nitrogens of o-dinitrosobenzene (1') (Scheme 1).

Although it is known that nitroso compounds react with phosphorus ylides to give, through a Wittig-type reaction imines and triphenylphosphine oxide[4], reactions between phosphorus ylides and furoxans have not yet been reported. In connection with our previous work on Wittig reactions of dicarbonyl compounds[5], we now wish to report our results on the reactions of some alkylidenetriphenylphosphoranes with benzofuroxan (1), furoxano[3,4-b]quinoxalines 19a[6] and 19b, and 3,4-diphenyl-furoxan.

RESULTS AND DISCUSSION

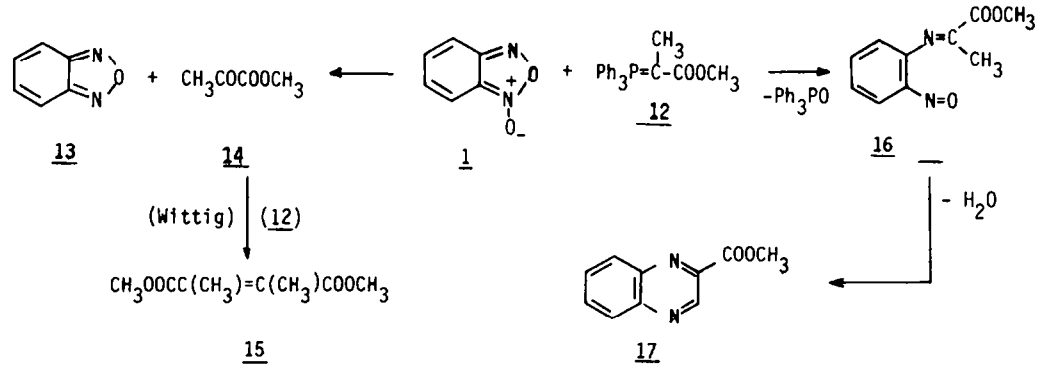
All the reactions were carried out, using two equivalents of the appropriate ylide. The reaction between benzofuroxan (1) and ethoxycarbonylmethylenetriphenylphosphorane (2) in boiling benzene for 30 h afforded ethyl 2-benzimidazole carboxylate (10), shown to be identical to that previously reported[7] and ethyl 1-ethoxy-2-benzimidazole carboxylate (8) in 18% and 16% yield respectively. The structure of compound 8 was confirmed by its elemental analysis and spectral data and, furthermore, by an independent synthesis from the known compound 11[8] and ethyl iodide

(Scheme 1). Formation of products 8 and 10 may be rationalized mechanistically as shown in Scheme 1. Nucleophilic attack of ylide 2 to 1 or 1' leads to betaine 3 which isomerizes to ylide 4. Intramolecular Wittig-type reaction of the ylidic moiety with the free nitroso group furnishes hydroxybenzimidazole 5. Nucleophilic attack of the hydroxy group of the latter to the carbonyl carbon of a second molecule of ylide 2 gives intermediate 6 which yields products 8 and 10. That is, direct attack by ethanol (formed in the reaction) at N(3) of 6 and elimination of the ylidic moiety (7) gives product 8. On the other hand, ethanolysis of the amidic bond of N-oxide 9 (which comes from 6) and deoxygenation furnishes product 10.



Scheme 1

Treatment of 1 with (1-methoxycarbonylethylidene)triphenylphosphorane (12) in boiling benzene for 6 h led to the formation of benzofurazan (13), diester 15, and methyl 2-quinoxaline-carboxylate (17)[9]. The latter was obtained in 4% yield (Scheme 2).



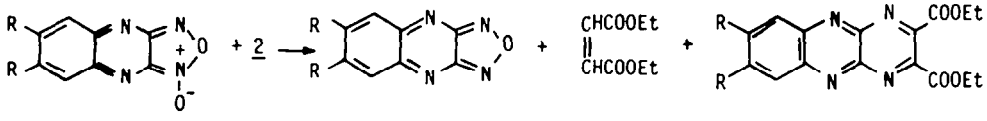
Scheme 2

A Wittig-type reaction between 1 and 12 to give intermediate 16, followed by an intramolecular dehydration of the latter, can account for the formation of compound 17, while oxidation of the ylide by the furoxan to the carbonyl compound 14 and further Wittig reaction between 14 and the

unreacted ylide 12, gave the predominant reaction products 13 and 15.

Attempted reaction between 1 and acetymethylenetriphenylphosphorane ($Ph_3P{=}CHCOCH_3$, 18) (boiling chloroform for 6 days) failed, as t.l.c. of the reaction mixture showed starting materials only.

The furoxano[3,4-b]quinoxalines 19(a,b) reacted in methylene chloride solution with phosphoranes 2, 12 and 18 at room temperature, almost instantaneously. The reaction between 19a and the ylide 2 afforded furazan 20a[6] in 16% yield, diester 21 and a product with molecular formula $C_{16}H_{14}N_4O_4$ (m.p. 176-178 °C) in 6% yield, for which structure 22a is proposed (Scheme 3). Although the elemental analysis and the recorded spectral data of the compound in question are consistent with the proposed structure, the reported[10] m.p. for the diethyl pyrazino[2,3-b]-quinoxaline-2,3-dicarboxylate is 252-253 °C. We prepared compound 22a by condensation of 2,3-diaminoquinoxaline with ethyl dioxosuccinate, according to the reported method[10], and found it identical to that obtained by the reaction between compounds 19a and 2, with a m.p. 176-178 °C. The i.r. and ^1H nmr spectra of this compound prepared by both methods are identical. Similarly the reaction between furoxan 19b and the ylide 2 gave furazan 20b, diester 21 and diester 22b (7%), (Scheme 3).

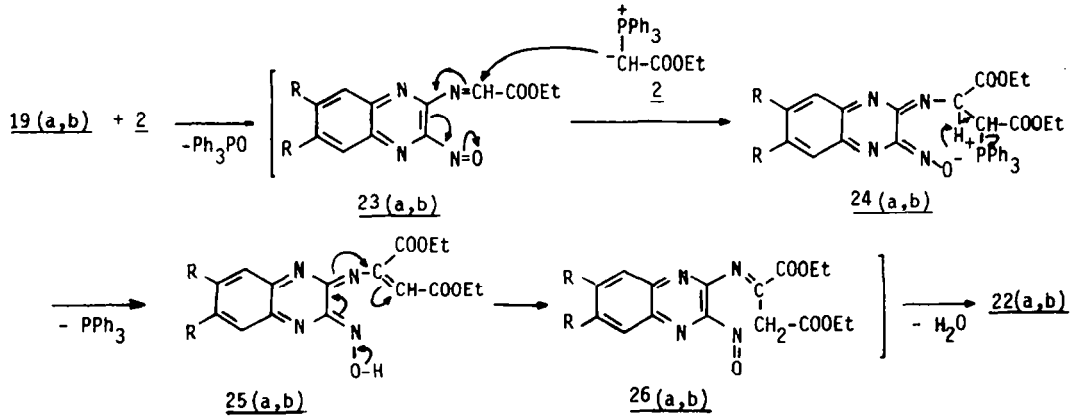


19 (a,b) 20(a,b) 21 22(a,b)

19,20,22 a:R = H
b:R = CH_3

Scheme 3

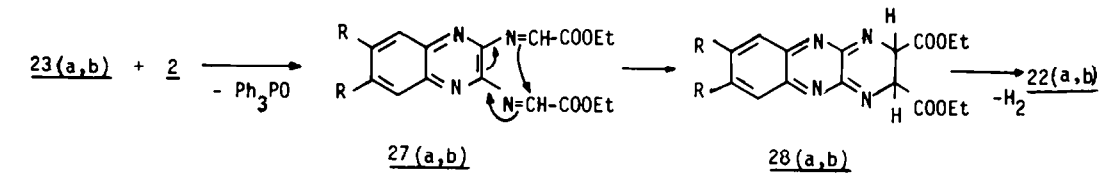
Obviously, compounds 20(a,b) and 21 were formed on the manner proposed for compounds 13 and 15. The formation of compounds 22(a,b) can be accounted for by a multistep mechanism involving a Michael addition of a second ylide species 2 to the initially formed, through a Wittig-type reaction, intermediate 23. Intramolecular abstraction of the β-hydrogen by the $N\text{-}O^-$ group in the phosphonio-intermediate 24 with subsequent Hoffman elimination of triphenylphosphine leads to 25. Tautomerization of 25 to 26 and dehydration of the latter can afford compounds 22(a,b) as suggested in Scheme 4.



a: R = H, b: R = CH_3

Scheme 4

An alternative pathway to compounds 22(a,b) is presented in Scheme 5. According to that, a second ylide species attacks the nitroso group of intermediate 23 in a Wittig-type manner to give the bis-imine 27, and subsequently the dihydro-derivative 28. Oxidation of 28 by furoxan 19, by analogy to the oxidation reported for some dihydroquinoxaline dioxides[11-13], can lead to the products obtained 22(a,b).



Scheme 5

Although the benzofuroxan (1) reacts with 1,3-butadienes to give the corresponding quinoxaline-N,N'-dioxides [11,13], formation of compounds 22(a,b) through condensation of 19(a,b) with the diester 21, and the further deoxygenation of the possible pyrazino[2,3-b]quinoxaline dioxide intermediate was excluded, since in a control experiment no reaction was observed between 19a and 21 under similar conditions as indicated by t.l.c.

In order to shed more light into the mechanism in question, we treated furoxan 19a with ylide 12, considering that formation of a dimethyl derivative as that of 28a, for example, could be evidence in favour of the proposed mechanism in Scheme 5. However, since furazan 20a and the diester 15 were detected as the sole reaction products, it is deduced that no nucleophilic attack of the ylide to the furoxan ring took place, the favoured pathway being oxidation of the ylide. The same path, i.e. oxidation of the ylide, was also observed in the reaction between furoxan 19a and ylide 18. Thus, the mechanism towards formation of products 22(a,b) remains open to further investigation.

Efforts to bring about reaction between ylide 2 and 3,4-diphenyl-furoxan were unfruitful even under forced conditions such as refluxing in benzene or toluene for extended period of time.

From the above results it is concluded that products 8, 10, 17, 22a, 22b are formed via an initial nucleophilic attack of the ylide either at N(3) of the furoxan ring or at one of the nitrogens of the tautomeric dinitroso form, to give the corresponding betaine. In the case of reaction between 1 and 2, the initially formed betaine was isomerized to the corresponding ylide which subsequently underwent intramolecular Wittig-type reaction with the free nitroso moiety. In all other cases a typical Wittig-type sequence was followed. The formation of compounds 22(a,b) can also be rationalized in terms of a double Wittig-type reaction with both nitroso groups of furoxans 19(a,b), although more evidence is required for such consideration.
In most of reactions studied, the oxidation of the ylides by the furoxans is the predominant route at the expense of the Wittig-type process. We also found that the above ylides are easily oxidized by treatment with pyridine-N-oxide. The reactivity of furoxans used seems to be in accord with the expected order of their easier tautomerisation[14] and in agreement with the fact that only the rapidly equilibrating fused furoxans undergo the Beirut reaction[1].

Further work is in progress to investigate the reactions between furoxans and bis-ylides.

EXPERIMENTAL

M.p.S. are uncorrected and were determined on a Kofler hot-stage apparatus. I.r. spectra were obtained with a Perkin-Elmer 297 spectrophotometer as Nujol mulls. ^{1}H N.m.r. spectra were recorded with deuteriochloroform as the solvent on a Varian A60-A spectrometer, with tetramethylsilane as the internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6L mass spectrometer. The ionisation energy was maintained at 70 eV. Light petroleum refers to the fraction of b.p. 40-60 °C.

Preparation of 6,7-Dimethyl-furoxano[3,4-b]quinoxaline (19b) and 6,7-Dimethyl-furazano[3,4-b]quinoxaline (20b). Compounds 19b and 20b were prepared following the procedures reported for the preparation of compounds 19a[15,6] and 20a[6]. To a cold solution of 4,5-dimethyl-o-phenylenediamine (3.3 g, 24 mmol) and dichloroglyoxime (4 g, 30 mmol) a 2N sodium carbonate solution (100 ml) was added dropwise during 30 min. to give 6,7-dimethyl-2,3-bis[hydroxyimino]-1,2,3,4-

tetrahydroquinoxaline (5 g, 95%), m.p. 233-235 °C (from dioxane). Found: C, 54.7; H, 5.5; N, 25.5. $C_{10}H_{12}N_4O_2$ requires C, 54.54; H, 5.49; N, 25.44%.

To a suspension of the above bis-hydroxyimino-tetrahydroquinoxaline (2.2 g,10 mmol) in methylene chloride (80 ml) was added lead tetraacetate (10.2 g, 23 mmol) and the mixture was stirred at r.t. for 5 h. The reaction mixture was then filtered, the filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using chloroform as eluant to give compound 19b (red crystals, 1.76 g, 81.5%), m.p. 185-186 °C (dec.) (from chloroform). Found: C, 55.4; H, 3.82; N, 25.72. $C_{10}H_8N_4O_2$ requires C, 55.55; H, 3.73; N, 25.92%. ν_{max} (Nujol) 3020, 1630, 1585(s), 1545, 1530 cm^{-1}; δ ($CDCl_3$) 2.5 (6 H, s) and 7.6 (2 H, s); m/z 216 (M^+, 16%), 200 (8), 187 (100), 186 (73), 172 (42), 171 (8), 170 (18), 157 (15), 156 (92), 155 (23), 141 (73), 134 (17), 129 (15), 128 (18), 104 (12), 103 (13), 102 (18), 101 (11), 91 (17), 90 (10), 89 (12), 77 (28), 65 (18), 64 (15), 63 (19), 53 (10), 52 (17), 51 (30), 50 (18), 41 (18), 39 (43), 30 (98).

To a solution of compound 19b (0.216 g, 1 mmol) in dry methylene chloride (20 ml) triphenylphosphine (0.262 g, 1 mmol) was added at room temperature. The red colour of the solution was discharged and all the furoxan was consumed, as monitored by t.l.c. The orange-yellow solution was then chromatographed on silica gel with methylene chloride as eluant to give orange-yellow crystals of compound 20b (0.164 g, 82%), m.p. 215-217 °C (dec.) (from chloroform). Found: C, 60.4; H, 4.3; N, 28.05. $C_{10}H_8N_4O$ requires C, 59.99; H, 4.03; N, 27.99% δ ($CDCl_3$) 2.5 (6 H, s) and 7.7 (2 H, s); m/z 200 (M^+, 54%), 170 (100), 143 (9), 118 (26), 116 (43), 102 (11), 91 (27), 89 (15), 77 (19), 65 (16), 30 (24).

Reaction of Benzofuroxan (1) with Ethoxycarbonylmethylenetriphenylphosphorane (2). Preparation of Ethyl 1-ethoxy-2-benzimidazole carboxylate (8) and Ethyl 2-benzimidazole carboxylate (10). A solution of 1 (0.34 g, 2.5 mmol) and 2 (1.74 g, 5 mmol) in benzene (20 ml) was boiled under reflux for 30 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with light petroleum-ethyl acetate (2:1) as eluant, 20-ml fractions being collected. Fractions 12-18 gave compound 8 (94 mg, 16%), oil. Found: C, 61.3; H, 5.9; N, 11.7. $C_{12}H_{14}N_2O_3$ requires C, 61.52; H, 6.02; N, 11.96%; ν_{max} (Nujol) 1715 cm^{-1}; δ ($CDCl_3$) 1.47 (3 H, t, J=7 Hz), 1.49 (3 H, t, J=7 Hz), 4.56 (4 H, q, J=7 Hz), 7.17-7.67 (3 H, m) and 7.73-8.05 (1 H, m); m/z 234 (M^+, 75%), 216 (6), 190 (22), 160 (22), 145 (50), 144 (42), 134 (92), 133 (18), 118 (100), 117 (13), 116 (20), 106 (42), 105 (58), 100 (32), 89 (21), 88 (19). Fractions 31-40 gave compound 10 (86 mg, 18%), m.p. 227-229 °C (from methylene chloride-light petroleum) (lit.[7], 228-230 °C). ν_{max} (Nujol) 3070, 1732 cm^{-1}; δ ($CDCl_3$) 1.43 (3 H, t, J=t Hz), 2.73 (2 H, q, J=7 Hz) and 7.23-8.0 (4 H, m); m/z 190 (M^+, 31%), 144 (26), 118 (100), 97 (8).

Preparation of Ethyl 1-ethoxy-2-benzimidazole carboxylate (8) (B Method). To a solution of the sodium salt 11 (0.4 g, prepared from 1 and barbituric acid according to the literature[8]) in dioxane (10 ml)-water (10 ml) was added ethyl iodide (2 ml). The mixture was refluxed for 3 h, then water (50 ml) was added and extracted with ether. The organic layer was dried (Na_2SO_4), concentrated under reduced pressure and the residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:2) as eluant to give compound 8 (15 mg, 4%).

Reaction of Benzofuroxan (1) with (1-methoxycarbonylethylidene)triphenylphosphorane (12). Preparation of Methyl 2-quinoxaline carboxylate (17). A solution of 1 (0.34 g, 2.5 mmol) and 12 (1.74 g, 5 mmol) in benzene (20 ml) was boiled under reflux. After 6 h almost all the furoxan was consumed, as monitored by t.l.c. The solvent was evaporated and the residue was chromatographed on silica gel with ethyl acetate-light petroleum (1:2) as eluant, 20-ml fractions being collected. Fractions 6-12 gave a mixture of furazan 13 and the diester 15 as it was shown by ^1H n.m.r. Repeated crystallizations of the mixture from hexane gave benzofurazan (13) (0.136 g, 45%), m.p. 52-53 °C, (lit.[16], 53 °C); δ ($CDCl_3$) 7.22-7.58 (2 H, m) and 7.62-8.0 (2 H, m). Concentration of the filtrate gave diester 15 (55mg, 13%). δ ($CDCl_3$) 2.05 (3 H, s) and 3.78 (3 H, s); m/z 172 (M^+), 140. The fractions 30-40 gave compound 17 (19 mg, 4%), m.p. 110-112 °C (subl.) (lit.[9], 111-112 °C); δ ($CDCl_3$) 4.15 (3 H, s), 7.75-8.01 (2 H, m), 8.1-8.4 (2 H, m) and 9.6 (1 H, s); m/z 188 (M^+).

Reaction of Furoxano[3,4-b]quinoxaline (19a) with Ethoxycarbonylmethylenetriphenylphosphorane (2). Preparation of Diethyl pyrazino[2,3,b]quinoxaline 2,3-dicarboxylate (22a). To a solution of furoxan 19a (0.188 g, 1 mmol) in dry methylene chloride (30 ml) was added the ylide 2 (0.646 g, 2 mmol) at room temperature. The red colour of the solution turned to orange-yellow, almost instantaneously and all the furoxan was consumed, as monitored by t.l.c. The solvent was evaporated and the residue was chromatographed on silica gel. The column was eluted with light petroleum containing increasing amounts of ethyl acetate (from 50 to 100%). A mixture of furazan 20a and diester 21 was first eluted. Addition of hexane (5 ml) to the concentrated mixture gave yellow crystals of compound 20a (28mg, 16%), m.p. 180-182 °C (lit.[6], 181-182 °C). Evaporation of the solvent left diester 21 (33 mg) as a mixture of isomers (cis-trans 15:85) as it was indicated by ^1H n.m.r. In the following fractions compound 22a (20 mg, 6%) was eluted, m.p. 176-178 °C (from ethanol). Found: C, 59.05; H, 4.4; N, 17.4. $C_{16}H_{14}N_4O_4$ requires C, 58.89; H, 4.32; N, 17.17%; ν_{max} (Nujol) 1745, 1730 cm^{-1}; δ ($CDCl_3$) 1.52 (6 H, t, J=7 Hz), 4.63 (4 H, q, J=7 Hz), 7.93-8.27 (2 H, m) and 8.33-8.67 (2 H, m); m/z 326 (M^+, 4%), 282 (3), 254 (14), 226 (1), 210 (6), 182 (13), 154 (9), 128 (8), 102 (14) and 44 (100). Further elution of the column gave triphenylphosphine oxide (0.49 g).

Reaction of 6,7-Dimethyl-furoxano[3,4-b]quinoxaline (19b) with Ethoxycarbonylmethylenetriphenylphosphorane (2). Preparation of Diethyl 7,8-dimethyl-pyrazino[2,3-b]quinoxaline-2,3-dicarboxylate (22b). The reaction between 19b (0.216g, 1 mmol) and 2 (0.646 g, 2 mmol) in dry methylene chloride was carried out and the reaction mixture was separated as described for the reaction of 19a to give: Compound 20b (10 mg, 5%), compound 21 (15 mg) and yellow crystals of compound 22b (25 mg, 7%), m.p. 187-189 °C (from ethanol). Found: C, 60.5; H, 5.2; N, 15.6. $C_{18}H_{18}N_4O_4$ requires C, 60.99; H, 5.12; N, 15.81% ν_{max} (Nujol) 1740, 1725 cm^{-1}; δ ($CDCl_3$) 1.5 (6 H, t, J=7.5 Hz), 1.8 (6 H, s), 4.6 (4 H, q, J=7.5 Hz) and 8.2 (2 H, s); m/z 354 (M^+, 35%), 324 (20), 310 (28), 282 (74), 238 (40), 223 (20), 210 (100), 183 (28), 182 (40), 141 (20), 130 (23), 105 (18), 104 (17), 103 (20), 77 (30) and 44 (37).

Reaction of Furoxano[3,4-b]quinoxaline (19a) with ylides (1-methoxycarbonylethylidene)triphenylphosphorane (12) and Acetylmethylenetriphenylphosphorane (18). The reaction as well as the separations of the reaction mixtures between 19a (0.188 g, 1 mmol) and the ylides 12 or 18 (2 mmol) were carried out as it was described above for the other reactions of 19a. From the reaction with 12 diester 15 (70 mg), furazan 20a (62 mg, 36%) and triphenylphosphine oxide (0.52 g) were obtained. From the reaction of 18 furazan 20a (38 mg, 20%) and triphenylphosphine oxide (0.38 g) were obtained.

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