Monatsh Chem 139, 617–623 (2008)
DOI 10.1007/s00706-007-0806-z
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

An efficient method for the synthesis of spiro and fused N-heterocyclic phosphor esters. Reactions of triketoindan-2-oxime with α-phosphonyl carbanions

Wafaa M. Abdou, Ashraf A. Sediek, Maha D. Khidre

Chemical Industries Division, National Research Center, Cairo, Egypt

Received 29 August 2007; Accepted 16 September 2007; Published online 19 May 2008

Abstract Treatment of triketoindan-2-oxime with α-phosphonyl carbanions in sodium ethanolate solution at reflux temperature led to a number of the corresponding substituted spiroisooxazole-, fused 1,3-oxazole, and 1,4-oxazine phosphor esters in moderate to high yields. Mechanisms for the formation of five- and six-membered rings are provided. A comparison of *Wittig-Horner* and *Wittig* reagent counterparts in reactions with the oxime is discussed. The various biological properties of selected examples of the synthesized products were studied.

Keywords Triketoindan-2-oxime; α-Phosphonate carbanions; Spiroisooxazoles; N-Five- and 6-membered rings.

Introduction

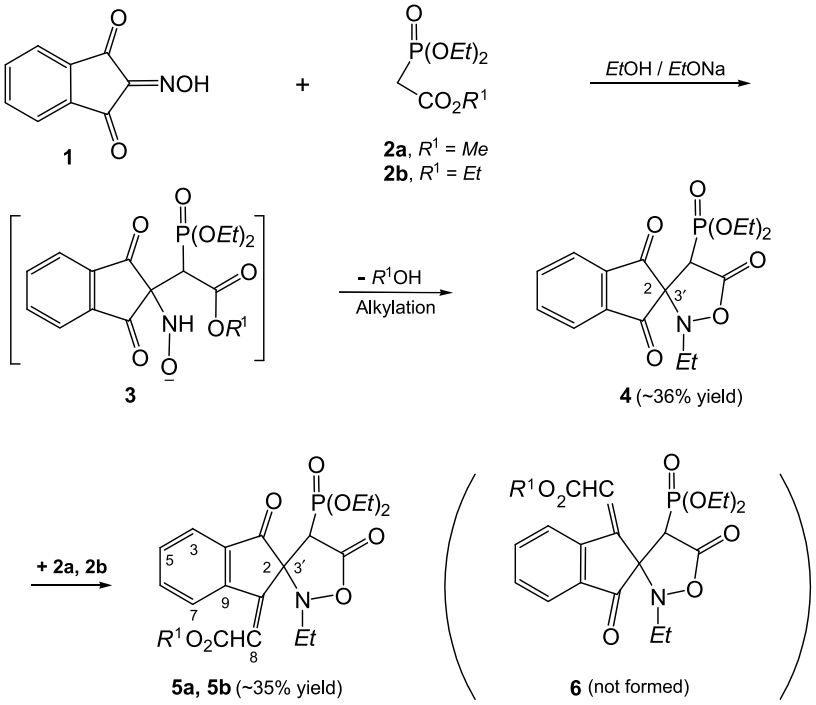
Over the last two decades we investigated reactions of phosphorus ylides [1] and phosphonate carbanions [1e, 2] with α-imino carbonyl compounds (oximes and hydrazones). The final products obtained depend on the nature of the above reactants. *Wittig* olefination products were formed either as stable compounds [1b, 1e] or as intermediates [1, 2], which were further transformed to stable spiro, linear, or fused heterocyclic derivatives. In some cases, "*Wittig-type*" reaction [1f–h] of the oximino group, or participation [1a–c, e, 2] of the 1,4-oxaza-1,3-diene system leading to the formation of oxazole derivatives were observed. However, it has been found that some α-imino carbonyl compounds [1c, 1i] reacted exclusively in the nitroso tautomeric structure whereby the attack by the nitroso-oxygen atom on the alkylidenephosphoranes was the first step.

One of our research programs has centered on the synthesis of spiro-oxazole- and fused pyrrolo compounds from the reaction of 1,3-dioxo-$\Delta^{2,\alpha}$-indanmonoxime (**1**) with different types of alkylidenephosphoranes [1b]. As a sequel, the work detailed here involves further studies of reactions of **1** with some α-phosphonyl carbanions with the objective of finding new routes for the synthesis of new derivatives of heterocyclic systems bearing a phosphonate substituent with expected biological potency. The reactions studied and the products obtained are depicted in Schemes 1–4. Similarities and differences in the reactivity of α-phosphonate carbanions and phosphorane counterparts toward oxime **1** are also discussed. Selective examples of the synthesized products were pharmacologically screened.

Results and discussion

We found that treatment of an ethanol solution of one equivalent of methyl diethyl phosphonoacetate (**2a**) with **1** in the presence of 2 equivalents of *Et*ONa, followed by heating the reaction mixture

Correspondence: Wafaa M. Abdou, Chemical Industries Division, National Research Center, Elbohouth St., D-12622 Dokki, Cairo, Egypt. E-mail: wabdou@intouch.com



Scheme 1

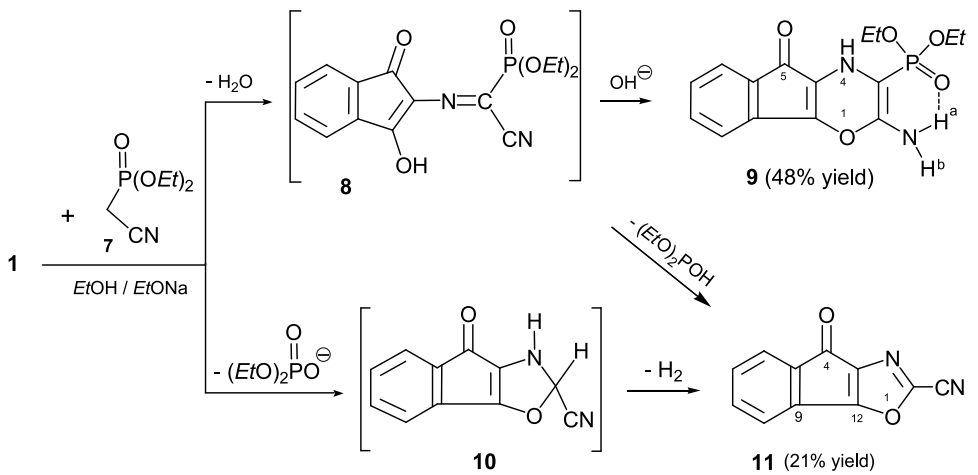
under reflux for 18 h afforded the phosphonates **4** (42%) and **5a** (22%) along with the substrate **1** (8%) (Scheme 1). Carrying out the reaction using two molar equivalents of the phosphonate anion **2a** instead of one, led to the formation of adducts **4** and **5** in equal yields (≈34%). Further treating **4** with one equivalent of **2a** in a boiling mixture of *Et*ONa/*Et*OH for 4 h, adduct **5a** was obtained in 88% yield.

A similar treatment of **1** with an equimolar amount of **2b** in sodium ethanolate solution at the reflux temperature gave **4** (46%) along with **5b** (16%), whereas a better yield (39%) of **5b** was obtained when **1** was reacted with 2 molar equivalents of **2b**.

The structure elucidation of **4** and **5** was based on their elemental analyses, molecular weight determinations (MS), and their spectroscopic data. The IR spectrum ($\bar{\nu}/\mathrm{cm}^{-1}$) of diethyl (2′-ethyl-1,3,5′-trioxo-1*H*,3*H*,5′*H*-trihydrospiro[indane-2,3′-4′*H*-isooxazol-4′-yl]phosphonate (**4**) showed the presence of 1- and 3-carbonyl stretching vibration bands at 1761 and 1733 cm^{-1}, thus excluding any cycloaddition reaction involving these moieties. The spectrum also exhibited the lactone-carbonyl frequency at 1782 cm^{-1} [3], as well as the phosphonate species at 1258 cm^{-1} (P=O) and at 1083 cm^{-1} (P–O–C). The ^{1}H NMR spectrum ($CDCl_3$) of **4** ($\delta_p = 25.6$ ppm) displayed signals at $\delta = 1.15$, 1.31 ppm (2dt, $J_{H-H} = 8.2$, $^4J_{P-H} = 4.6$ Hz, 2×3H, $2 \times H_3$C.C–O), and at 3.89, 4.18 ppm (2qt, $J_{P-H} = 13.5$ Hz, 4H, $2 \times H_2$CO) due to the phosphonate moiety [$P(OC_2H_5)_2$], whereas the *N*-ethyl moiety was located at 0.88 ppm (t, $J_{H-H} = 7.7$ Hz, 3H, H_3C.C–N) and at 3.67 ppm (q, $J_{H-H} = 7.2$ Hz, 2H, H_2CN). On the other hand, the doublet ($^2J_{P-H} = 21.4$ Hz, 1H) at 4.87 ppm was assigned to the oxazolinone H-4′. In the ^{13}C NMR ($CDCl_3$, δ ppm) spectrum [3] of **4** the phosphor-carbon (4′-*C*–P) appeared at 49.7 ppm (d, $^1J_{P-C} = 147$ Hz), while the spiro-carbon (3′-*C*) located at 74.8 ppm (d, $^2J_{P-C} = 33$ Hz). Other signals were displayed at 169.6 ppm (d, $^2J_{P-C} = 28$ Hz, 5′-*C*=O), 181.4, and 193.6 ppm (d, $^3J_{P-C} \approx 14$ Hz, 1-, and 3-*C*=O). These spectroscopic data indicate that **4** presents in the keto form and rule out the formation of its enol structure. Formation of **4** might involve an initial nucleophilic attack of the phosphonyl carbanion **2a** or **2b** on 2-hydroxyimino-carbon (2-C=NOH) in **1** yielding the phosphonate **3**. Subsequent ring closure the spiro product **4** would be obtained under elimination of an appropriate alcohol moiety with concomitant N-alkylation. Considering the N-alkylation by *WH*-reagents, an analogous process has been observed in their reactions with pyrimidines [4a], quinonimines [4b], pyrroles [4c, 4d], and thiazolidinones [4e].

On the other hand, the spectroscopic analysis of the second product clearly demonstrated that the olefinated products **5a** and **5b** were formed. The structure of which was established to be **5** rather than the regio-isomer **6** based on the NMR data as well as by analogy with structure **4**. The ^{1}H NMR ($CDCl_3$) spectrum of methyl [4′(diethoxyphosphonyl)-2′-ethyl-3,5′-dioxo-1*H*,3*H*,5′*H*-spiro[indane-2,3′-4′*H*-iso-oxazol]-1-ylidene]acetate (**5a**) ($\delta_p = 24.8$ ppm) showed the presence of a singlet at 7.34 ppm assignable to C8-olefinic proton. Furthermore, the structure **5** was investigated by nuclear *Overhauser* effect (N*O*E) experiments, which were also useful for the assignment of the ^{13}C NMR signals. The irradiation of the H7-proton (7.64 ppm) resulted only in the enhancement of the C8-doublet (d, $^4J_{P-C} = 4.6$ Hz, 1-C=*C*H) at 113.6 ppm, and the C1-doublet (d, $^3J_{P-C} = 14$ Hz, 1-*C*=CH) at 144.8 ppm. Irradiation of the exocyclic olefinic H8-proton (7.34 ppm) produced an N*O*E at the C1-doublet (144.8 ppm), C8-doublet (124.4 ppm), and C9-doublet (146.3 ppm) indicating the *syn*-configuration of the H7 and the olefinic H8-proton. The diastereomer **5** obtained as a sole product would be, however, the favored one from the kinetic and thermodynamic viewpoints. From the viewpoint of kinetics we presume that the substitution pattern in **4** is such to obstruct (for steric hinderence reasons) a nucleophilic approach by the phosphoryl carbanions to the 1-carbonyl. The effect of the neighboring phosphonate moiety on 4′-C would be expected to be quite unfavorable [5]. From the viewpoint of thermodynamies, structure **5** is the favored one, because the substitution on the methine carbon in the 4′-position with electron withdrawing carbonyl-, and phosphonate-groups results in an increased acidity of the corresponding methine proton H4′ that would be enough acidic to epimerize under the reaction conditions. Considering the earlier report [1b], the mechanism of the reaction of the alkylidenephosphorane counterparts ($Ph_3P{=}CHCO_2R^1$) with **1** had suggested similar initial nucleophilic attack. However, subsequent transformations were quite different.

By treatment of compound **1** with diethyl cyanomethylphosphonate (**7**) in a way analogous to the one described for **2**, diethyl (2-amino-5-oxo-4,5-dihydroindeno-[1,2-*b*][1,4]oxazin-3yl)phosphonate (**9**, 48%) together with 4-oxo-4*H*-indeno[2,1-*d*][1,3]-oxazole-2-carbonitrile (**11**, 21%) were obtained (Scheme 2). The ^{1}H NMR ($CDCl_3$) spectrum of **9** ($\delta_p = 22.7$ ppm) showed two types of the NH_2-protons [δ (H^a) = 6.55 (br, 1H) and δ (H^b) = 10.08 (br, 1H)]. The different chemical shifts of the NH_2-protons are the spectroscopic evidence for the presence of intramolecular hydrogen bond between one of the hydrogens of the NH_2-protons and the oxygen atom of the P=O bonding in the phosphonate group [6]. The 3-*C* atom appeared as a doublet ($^1J_{P-C} = 205$ Hz) at 103.5 ppm in the ^{13}C NMR spectrum of **9**. Furthermore, the lack of N*O*E between NH-proton and NH_2 in **9** can be explained by preferential conformation due to the intramolecular hydrogen bonding between one of the NH_2-protons and the phosphonate-oxygen atom. Therefore, the oxazine-NH proton is too far from NH_2 to give an observable N*O*E even with the difference spectroscopy technique.



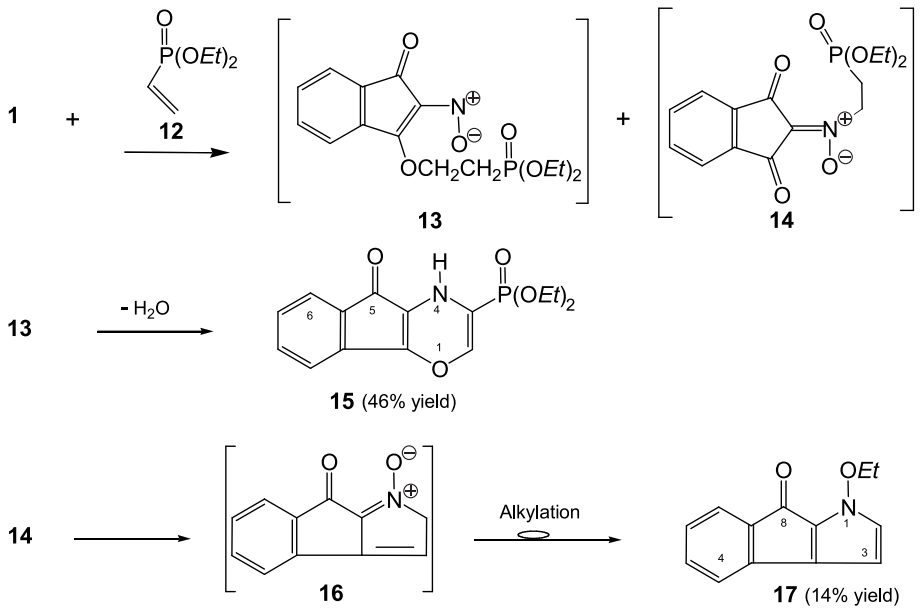
Scheme 2

Fused oxazine **9** was formed most probably through cyclization and transformation of the cyano group of initially formed condensation intermediate **8**. A similar observation was previously reported by *Coppola et al*. [7] for the reaction product of *N*-methylisatoic anhydride with *Wittig-Horner* (*WH*) reagent **7** as well as it was evoked by *Neidlein et al*. [8] and by us [2, 9] on similar instances. On the other hand, elimination of $[OP(=O)(OEt)_2]$ moiety from initially formed addition intermediate (to give 2,3-dihydro-oxazole **10**) followed by autooxidation could provide **11**. However, formation of **11** from **8** *via* extrusion of diethyl phosphonate cannot be overlooked.

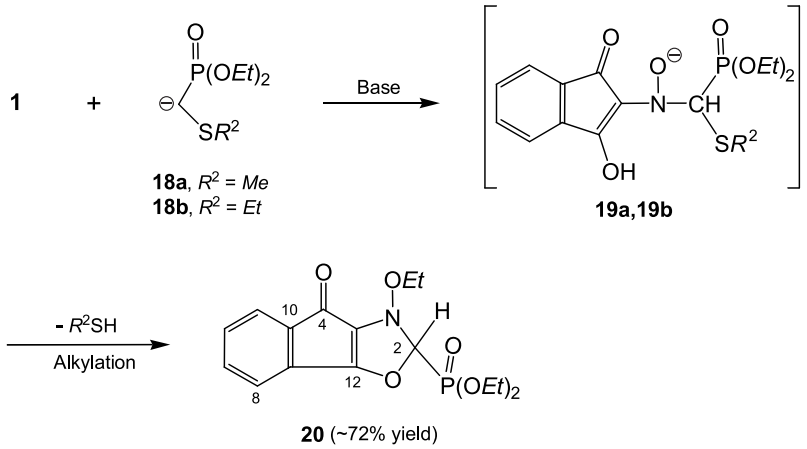
A noteworthy contrast exists between the present behavior of *WH* reagent **7** with oxime **1** and that reported previously [1b] for the behavior of resonance stabilized phosphorus ylide, cyanomethyltriphenylphosphorane. Thus, the results of the former investigation [1b] pointed out that the ylide $[Ph_3P{=}CHCN]$ reacted exclusively at the carbonyl group or further with the other carbonyl group in the oxime **1** to give the corresponding mono- and diolefines whereas compounds derived from an addition-elimination reaction at the oximino-species were the products of the reaction of **1** with the *WH*-reagent **7**.

The behavior of oxime **1** towards the unsaturated phosphonyl carbanion, diethyl vinylphosphonate (**12**), was next undertaken under similar reaction conditions to give diethyl (5-oxo-4,5-dihydroindeno[1,2-*b*][1,4]oxazin-3-yl)phosphonate (**15**, 46%) along with 1-ethoxy-8-oxo-8*H*-indeno[*a*]pyrrole (**17**, 14%). According to the mechanism outlined in Scheme 3, the addition of **12** to **1** affords the intermediates **13** and **14**. Under elimination of a molecule of water from **13**, oxazinephosphonate **15** would be formed. On the other hand, the pyrrole **17** is regarded as a product of an intramolecular *WH* reaction of **14** [10]. However, the dealkylated derivative of the pyrrole **17** was exclusively obtained from the reaction of vinyltriphenylphosphonium bromide with the substrate **1** [1b].

Furthermore, the reactions of oxime **1** with diethyl [(alkylthio)methyl]phosphonates **18a** and **18b** were investigated. Compound **1** was treated with an equivalent amount of diethyl [(methylthio)methyl]phosphonate (**18a**) in an alcoholic *Et*ONa solution at room temperature. Subsequent heating the reaction mixture at the reflux temperature for 6 h gave diethyl (3-ethoxy 4-oxo-4-hydroindeno[2,1-*d*][1,3]oxazol-2yl)phosphonate (**20**, 72%), and unidentified materials (Scheme 4). Compound **20** is somewhat compromised as occurring through the intermediate **19**, initially formed. Further elimination of R^2SH ($R^2 = Me$) molecule and ring closure with concomitant alkylation the fused oxazole derivative **20** would be formed. The preferential extrusion of R^2SH (as it is monitored by the distinct smell) than H_2O molecule [11] was driven from the result of the reaction of **1** with diethyl [(ethylthio)methyl)]phosphonate



Scheme 3



Scheme 4

(**18b**). Thus, when **1** was reacted with **18b**, compound **20** was again obtained.

The structures suggested for all new compounds are in good agreement with their analytical and spectral data (experimental section).

Biological screening

The synthesized phosphorylated compounds **4**, **5**, **9**, **15**, and **20** were screened against bacteria, such as *Bacillus polymixa*, *Bacillus subtilis* (*Gram* positive), and *Proteus vulgaris* (*Gram* negative) by using the filter paper disc diffusion technique [12]. Compounds **4**, and **9** showed feeble activity against *Gram* positive bacteria but are non-toxic to *Gram* negative bacteria. Other compounds **5**, **15**, and **20** displayed no activity against bacteria tested. The same compounds were also evaluated against fungi, such as *Dreschlera specifera* and *Fusarium oxysporum* by adopting the food poisoning technique [13]. Compounds **5a**, **5b**, and **15** are moderately active against *D. specifera* at 780 $\mu g/cm^3$ while compounds **4**, **9**, and **20** are more active against the same fungi at the same dose level. Compounds **4**, **9**, and **20** registered 100% spore germination inhibition of *F. oxysporum* at 320 $\mu g/cm^3$.

Conclusion

From the foregoing observations, the four studied reactions of **1** with *WH*-reagents **2**, **7**, **12**, and **18** lead to a methodology for the synthesis of 5- and 6-membered heterocyclic phosphor esters of potential fungicidal activity.

Experimental

All melting points are measured on an Electrothermal melting point apparatus. The IR spectra were recorded on a Perkin Elmer 317 Grating IR spectrophotometer, using KBr pellets. The ^1H and ^{13}C NMR spectra were measured on a Joel E.C.A-500 MHz instrument using SiMe_4 as an internal reference. The ^{31}P NMR spectra were recorded with the same instrument, relative to external H_3PO_4 (85%). The mass spectra were performed on a Joel JMS-A X 500 spectrometer. Elemental analyses were carried out at the Microanalysis Laboratory, Cairo University, Cairo, Egypt. Their values agreed favorably with the calculated ones. The appropriate precautions in handling moisture-sensitive compounds were observed. Solvents were dried by standard techniques. TLC: Merck 0.2 mm silica gel 60 F154 anal aluminium plates. Column chromatography (CC): silica gel (Kieselgel 60 mesh, particle size 0.2–0.5 mm; E. Merck, Darmstadt). The substrate 1,3-dioxo-$\Delta^{2,\alpha}$-indanmonoxime (**1**) was prepared according to the reported method [14].

*Treatment of 1,3-dioxo-$\Delta^{2,\alpha}$-indanmonoxime (**1**) with diethyl phosphonoacetates (**2a**, and **2b**). Synthesis of compounds **4**, **5a**, and **5b***

*Et*ONa, 0.7 g, (10 mmol) dissolved in 25 cm^3 absolute *Et*OH, was added to a stirred mixture of 4.7 mmol of **2a** (or **2b**) and 0.8 g **1** (4.57 mmol). After heating under reflux for ≈18 h (TLC control), the crude mixture was concentrated, poured into 100 cm^3 of dist H_2O, acidified with conc HCl and extracted with $CHCl_3$ ($2 \times 100\,cm^3$). The combined organic extracts were washed with 50 cm^3 of dist H_2O and dried. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (*n*-hexane/*Ac*O*Et*) yielding **4** and **5a** or **4** and **5b**.

*Reaction of **1** with **2a** afforded **4**, and **5a***

n-Hexane/*Ac*O*Et* (up to 8/2, *v*/*v*), afforded yellowish green crystals of unchanged substrate **1**, 64 mg (8% yield), mp 203–205°C (*Et*OH) (Ref. [14] 205°C).

Diethyl (2′-ethyl-1,3,5′-trioxo-1H,3H,5′H-spiro[indane-2,3′-4′H-isooxazol-4′-yl)phosphonate (**4**, $C_{17}H_{20}NO_7P$)
Eluent: *n*-hexane/*Ac*O*Et* (3:7, *v*/*v*), straw-yellow crystals (735 mg, 42% yield), mp 176–178°C (acetone); IR: $\bar{\nu}$ = 1782, 1761, 1733 (C=O), 1258 (P=O), 1083 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J_{H-H} = 7.7$ Hz, 3H, H_3CC.N); 1.15, 1.31 (2dt, $J_{H-H} = 8.2$, $J_{P-H} = 4.6$ Hz, $2 \times 3H$, $2 \times H_3$CC.O), 3.67 (q, $J_{H-H} = 7.7$ Hz, 2H, H_2CN), 3.89, 4.18 (2qt, $J_{H-H} = 8.2$, $J_{P-H} = 5.3$ Hz, 4H, $2 \times H_2$CO), 4.87 (d, $^2J_{P-H} = 21.4$ Hz, 1H, 4′-C*H*), 7.46, 7.74 (2m, 3H, *H–Ar*), 8.33 (dd, $J = 2$, 7 Hz, 1H, *periH*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.5$ (*C*H_3C · N), 16.3 (*C*H_3C · O), 44.4 (N*C*H_2), 49.7 (d, $^1J_{P-C} = 147$ Hz, 4′-*C*–P), 62.6 (O*C*H_2), 74.8 (d, $^2J_{P-C} = 33$ Hz, 3′-*C-spiro*), 122.6, 127.7, 129, 133.2, 134.8 (*C*-Arom.), 169.6 (d, $^2J_{P-C} = 28$ Hz, 5′-*C*=O), 181.4 (d, $^3J_{P-C} = 14$ Hz, 1-*C*=O), 193.6 (d, $^3J_{P-C} = 14$ Hz, 3-*C*(O)] ppm; ^{31}P NMR ($CDCl_3$): $\delta = 25.6$ ppm; EI-MS: *m*/*z* (%) = 380 (33) [M^+-1], 362 (12), 333 (17), 305 (22), 276 (25), 194 (67), 172 (100), 137 (29), 77 (55).

Methyl [4′(diethoxphosphony)l-2′-ethyl-3,5′-dioxo-1H,3H,5′H-spiro[indene-2,3′-4′H-isooxazol]-1-ylidene]acetate
(**5a**, $C_{20}H_{24}NO_8P$)
Eluent = *n*-hexane:*Ac*O*Et* (2:8, *v*/*v*), yellow crystals (250 mg, 22% yield), mp 245–247°C ($CHCl_3$); IR: $\bar{\nu}$ = 1783, 1758 (C=O), 1638 (1-C=CH), 1256 (P=O), 1088 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J_{H-H} = 7.4$ Hz, 3H, H_3CC.N), 1.13, 1.36 (2dt, $J_{H-H} = 7.8$, $J_{P-H} = 4.6$ Hz, $2 \times 3H$, $2 \times H_3$CC.O), 3.42 (s, 3H, H_3CO, ester), 3.73 (q, $J_{H-H} = 7.4$ Hz, 2H, H_2CN), 4.04, 4.36 (2qt, $J_{H-H} = 7.4$, $J_{P-H} = 5.4$ Hz, 4H, $2 \times H_2$CO), 4.89 (d, $^2J_{P-H} = 18.4$ Hz, 1H, 4′-C*H*), 7.34 (s, 1H, 1-C=C*H*), 7.64, 7.88 (m, 3H, *H–Ar*), 8.41 (dd, $J = 2$, 7 Hz, 1H, *peri-H*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.8$ (*C*H_3C.N), 15.4 (*C*H_3C.O), 45.2 (*C*H_2N), 48.6 (d, $^1J_{P-C} = 147$ Hz, 4′-*C*–P), 61.6 (*C*H_2O), 76.4 (d, $^2J_{P-C} = 33$ Hz, 3′-*C-spiro*), 113.6 (d, $^4J_{P-C} = 8.6$, 1-C=*C*H), 124.2, 127.7, 129.3, 133.2 (*C*-Arom.), 144.8 (d, $^3J_{P-C} = 14$, 1-*C*=CH), 164.3 (*C*=O, ester), 167.9 (5′-*C*=O), 182.5 [d, $^3J_{P-C} = 15.5$ Hz, 3-*C*(O)] ppm; ^{31}P NMR ($CDCl_3$): δ = 24.8 ppm; EI-MS: *m*/*z* (%) = 437 (18) [M^+], 436 (17), 421 (9), 393 (11), 349 (36), 336 (48), 307 (24), 277 (29), 196 (77), 174 (100), 137 (27), 77 (58).

When oxime **1** was reacted with two molar amounts of the carbanion **2a** under the previous experimental conditions and the same working up, the products **4** (36% yield) and **5a** (34% yield) were again isolated.

*Reaction of **1** with **2b** afforded **1** (8%), **4** (800 mg, 46%), and **5b***

Ethyl [4′(diethoxphosphony)l-2′-ethyl-3,5′-dioxo-1H,3H,5′H-spiro[indene-2,3′-4′H-isooxazol]-1-ylidene]acetate
(**5b**, $C_{21}H_{26}NO_8P$)
Eluent: *n*-hexane/*Ac*O*Et* (2:8, *v*/*v*), straw-yellow crystals (256 mg, 16% yield), mp 233–235°C (*Et*OH); IR: $\bar{\nu} = 1778$ (5′-C=O), 1730 (3-C=O), 1632 (1-C=CH), 1262 (P=O), 1105 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.87$ (t, $J_{H-H} = 7.4$ Hz, 3H, H_3CC.N), 1.15–1.52 (3t (m), 9H, $3 \times H_3$CC.O), 3.64 (q, $J_{H-H} = 7.4$ Hz, 2H, H_2C–N), 3.89–4.36 (3q (m), 6H, $3 \times H_2$CO), 5.01 (d, $^2J_{P-H} = 18.4$ Hz, 1H, 4′-*H*C), 7.31 (s, 1H, 1-C=C*H*), 7.57, 7.88 (m, 3H, *H–Ar*), 8.46 (dd, $J = 2$, 7 Hz, 1H, *periH*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 12.8$ (*C*H_3C.N), 15.4, 16.3 (*C*H_3C.O), 46.2 (*C*H_2N), 48.8 (d, $^1J_{P-C} = 158$ Hz, 4′-*C*–P), 63.2 (*C*H_2O), 76.4 (d, $^2J_{P-C} = 33$ Hz, 3′-*C-spiro*), 116.6 (d, $^4J_{P-C} = 6.6$ Hz, 1-C=*C*H), 121.4, 123.7, 126.5, 129.3, 134.2, 137.4 (*C*-Arom.), 144.5 (d, $^3J_{P-C} = 14.5$ Hz, 1-*C*=CH), 163.9 (*C*=O, ester), 168.4 (d, $^2J_{P-C} = 38$ Hz, 5′-*C*=O), 185.6 [d, $^3J_{P-C} = 16$ Hz, 3-*C*(O)] ppm; ^{31}P NMR ($CDCl_3$): $\delta = 26.5$ ppm; EI-MS: *m*/*z* (%) = 450 (15) [M^+-1], 421 (9), 393 (16), 349 (31), 307 (55), 277 (26), 196 (62), 174 (100), 137 (27), 77 (44).

When oxime **1** was reacted with two molar amounts of the carbanion **2b** under the previous experimental conditions and the same working up, the products **4** and **5b** in 34 and 39% yields were again isolated.

*Conversion of **4** to **5***
A solution of 0.3 g **4** (0.78 mmol), and 0.8 mmol **2a** (or **2b**) in 15 cm^3 *Et*ONa was heated under reflux for 4 h. The product mixture was worked up in the usual manner and purification of the resulting crude product by crystallization from ethanol gave **5a** or **5b** in ≈ 88% yield.

*Reaction of oxime **1** with diethyl cyanomethylphosphonate **7**. Synthesis of **9** and **11***
A mixture of 0.8 g **1** (4.57 mmol), and 0.88 g **7** (5 mmol) in 20 cm^3 absolute *Et*OH containing *Et*ONa (~10 mmol) was heated under reflux for 12 h. After the usual workup, the residue was chromatographed with *n*-hexane/*Ac*O*Et* to give **11**, and **9**, respectively.

4-Oxo-4H-indeno[2,1-d][1,3]oxazole-2-carbonitrile
(**11**, $C_{11}H_4N_2O_2$)
Eluent = *n*-hexane:*Ac*O*Et* (1:1, *v*/*v*), colorless needles (188 mg, 21% yield), mp 158–160°C (CH_2Cl_2); IR: $\bar{\nu}$ = 2218 (CN), 1728 (C=O), 1616 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.55$ Hz, 7.88 (2m, 3H, *H–Ar*), 8.32 (dd, $J = 2$, 7 Hz, 1H, *periH*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 108.6$ (*C*N), 120.2, 124.5, 126.3, 128.4, 130.6, 133.8 (*C*=C), 137.3 (2-*C*=N), 150.4 (12-*C*–O), 181.3 (4-C=O) ppm; EI-MS: *m*/*z* (%) = 196 (100) [M^+], 170 (26), 142 (36), 128 (24), 77 (72).

Diethyl (2-amino-5-oxo-4,5-dihydroindeno[1,2-b][1,4]-oxazin-3-yl)phosphonate (**9**, $C_{15}H_{17}N_2O_5P$)
Eluent = *n*-hexane:*Ac*O*Et* was obtained (1:9, *v*/*v*), yellow crystals (735 mg, 48% yield), mp 188–190°C (*Et*OH); IR: $\bar{\nu} = 3336w$ (NH, NH_2), 1728 (C=O), 1224 (P=O, bonded), 1084 (P–O–C) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.16$ Hz, 1.24 (2dt, $J_{H-H} = 6.7$, $J_{P-H} = 4.12$ Hz, 6H, $2 \times H_3$CC.O), 3.89, 4.17 (2qt, $J_{H-H} = 6.7$, $J_{P-H} = 4.8$ Hz, 4H, $2 \times H_2$CO), 6.55 (s, br, 1H, H^aN), 7.44, 7.82 (2m, 3H, *H–Ar*), 8.32 (dd, $J = 2$, 7 Hz, 1H, *periH*), 9.78 (s, br, 1H, 4-N*H*), 10.08 (s, br, 1H, H^bN) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.8$ (*C*H_3C.O), 59.6 (*C*H_2O), 103.5 (d, $^1J_{P-C} = 205$ Hz, 3-*C*), 111.3, 124.5, 126.2, 133.3, 142.4 (*C*-Arom), 136.4 (d, $^2J_{P-C} = 37$ Hz, 2-*C*), 183.1

(*C*=*O*) ppm; ^{31}P NMR ($CDCl_3$): $\delta = 22.7$ ppm; EI-MS: m/z (%) = 335 (15) [M^+-1], 321 (23), 184 (100), 159 (61), 137 (38), 77 (67).

*Reaction of oxime **1** with diethyl vinylphosphonate (**12**). Synthesis of **15** and **17***

A solution of 0.8 g **12** (4.8 mmol), and 0.8 g **1** (4.57 mmol) in 20 cm^3 *Et*ONa was heated under reflux for 12 h. The reaction mixture was worked up in the usual manner and separated by column chromatography, using *n*-hexane/*Ac*O*Et* as the eluents to give the products **17**, and **15**, respectively.

1-Ethoxy-8-oxo-8H-indeno[2,3-d]pyrrole (**17**, $C_{13}H_{11}NO_2$)

Eluent = *n*-hexane:*Ac*O*Et* was obtained (6:4, *v*/*v*), colorless crystals (362 mg, 42% yield), mp 115–118°C (cyclohexane); IR: $\bar{\nu} = 1728$ (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, $J = 7.7$ Hz, 3H, H_3CC.O.N), 3.78 (q, $J = 7.7$ Hz, 2H, CH_2ON), 6.36, 6.76 (2d, 2H, $J_{H-H} = 2.8$ Hz, 3-*H*C, 2-*H*C), 7.45, 7.78 (2m, 3H, *H–Ar*), 8.35 (dd, $J = 2$, 7 Hz, 1H, *peri-H*) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.2$ ($CH_3C \cdot O \cdot N$), 55.4 (CH_2ON), 106.6 (3-*C*), 135.5 (2-*C*), 121.4, 126.3, 129.1, 131.7, 133.8 (*C*=*C*), 180.2 (*C*=O) ppm; EI-MS: m/z (%) = 213 (12) [M^+], 168 (100) [M^+-OC_2H_5), 167 (42), 140 (17).

Diethyl (5-oxo-4,5-dihydroindeno[2,3-b][1,4]oxazin-3-yl)phosphonate (**15**, $C_{15}H_{16}NO_5P$)

Eluent = *n*-hexane:*Ac*O*Et* (1:9, *v*/*v*), straw yellow crystals (675 mg, 46% yield), mp 168–170°C (*Et*OH); IR: $\bar{\nu} = 3330$ (NH), 1734 (C=O), 1238 (P=O, bonded), 1100 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.16$ Hz, 1.28 (2dt, $J_{H-H} = 6.7$, $^4J_{P-H} = 4.3$ Hz, 6H, $2 \times H_3$C.C.O), 3.93, 4.18 (2qt, $J_{H-H} = 6.7$, $J_{P-H} = 5.8$ Hz, 4H, $2 \times H_2$CO), 7.47, 7.79 (2m, 3H, *H–Ar*), 8.32 (dd, $J = 2$, 7, 1H, *peri-H*), 9.81 (br, 1H, *H*N) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.8$ (CH_3C.O), 59.6 (CH_2O), 103.9 (d, $^1J_{C-P} = 211$ Hz, 3-*C*), 111.3, 121.8, 126.2, 130.3, 139.4 (*C*-Arom.), 131.4 (d, $^2J_{P-C} = 37$ Hz, 2-*C*), 180.1 (5-*C*=*O*) ppm; ^{31}P NMR ($CDCl_3$): $\delta = 22.7$ ppm; EI-MS: m/z (%) = 321 (8) [M^+], 320 (23), 183 (100), 158 (67), 137 (28), 77 (53).

*Reaction of **1** with (alkylthio)methyphosphonyl carbanions **18a** and **18b**. Synthesis of the phosphonate **20***

At −10°C, 0.7 g *Et*ONa (10 mmol) in 15 cm^3 *Et*OH was added to a stirred mixture of 5 mmol diethyl [(alkylthio)methyl]phosphonate **18a** (or **18b**) and 0.8 g **1** (4.57 mmol). After an additional hour at rt, and further for 6 h (TLC control) at the reflux temperature, the solvent was concentrated to half of its volume *in vacuo*, poured onto ice, acidified with *conc*. HCl, extracted with $CHCl_3$ and dried. After evaporation of the solvent, the crude residue was purified by column chromatography to give in each case compound **20**.

Diethyl (3-ethoxy-4-oxo-4H-indeno[2,1-d][1,3]oxazol-2-yl)phosphonate (**20**, $C_{16}H_{20}O_6NP$)

Eluent = *n*-hexane:*Ac*O*Et* (7:3, *v*/*v*), colorless crystals (≈72%, yield), mp 110–112°C (cyclohexane); IR: $\bar{\nu} = 1733$ (C=O), 1268 (P=O), 1128 (P–O–C) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta =$ 1.07 Hz, 1.15–1.34 (3t (m), 9H, $3 \times H_3$CC.O), 3.73, 4.04–4.21 (3q (m), 6H, $3 \times H_2$CO), 5.12 (d, $^2J_{P-H} = 24.1$ Hz, 1H, *H*C–P), 7.42, 7.78 (2m, 3H, *H–Ar*), 8.12 (dd, $J = 2$, 7 Hz, 1H, *periH*); ^{13}C NMR ($CDCl_3$): $\delta = 16.7$ (CH_3C.O), 57.7 (CH_2ON), 62.8 (CH_2O), 103.2 (11-*C*), 114.8 (d, $^1J_{P-C} =$ 196 Hz, 2-*C*), 121.1, 123.5, 126.2, 132.3, 136.9 (*C*-Arom.), 151.5 (12-*C*), 184.8 (4-*C*=O) ppm; ^{31}P NMR ($CDCl_3$): $\delta = 18.7$ ppm; EI-MS: m/z (%) = 353 (9) [M^+], 307 (39), 170 (100), 137 (35), 133 (28), 128 (16), 77 (46).

References

1. a) Abdou WM, Barghash RF (2005) Trends Heterocycles 10:57; b) Abdou WM, Salem MAI, Sediek AA (2003) Monatsh Chem 134:1373; c) Abdou WM, Salem MAI, Sediek AA (2002) Bull Chem Soc Jpn 75:2481; d) Abdou WM (2002) Phosph Sulfur Silicon 177:325; e) Abdou WM, El-Khoshnieh YO, Salem MAI, Barghash RF (2002) Synlett:1417; f) Abdou WM, Ganoub NAF, Shaddy AM (2000) Phosph Sulfur Silicon 165:171; g) Abdou WM (1997) Synth Communs 27:3599; h) Abdou WM, Ganoub NAF, Mohammed AA (1997) Heterocycl Commun 3:57; i) Mahran MR, Abdou WM, Ganoub NAF (1988) Phosph Sulfur Silicon 39:51
2. Abdou WM, Salem MAI, Barghash RF (2007) Arkivoc 15:45
3. Silverstein RM, Bassler GC, Morril TC (eds) (1981) Spectroscopic Identification of Organic Compounds, 4th edn. John Wiley and Sons, Inc., New York
4. a) Yakout ESMA, Giurgius DB, Boulos LS (1999) Phosph Sulfur Silicon 148:177; b) Boulos LS, Arsanious MHN, El-Din NK (1997) Phosph Sulfur Silicon 122:49; c) Mercey JM, Toube TP (1987) J Chem Research Synop: 62; Medium (M):680; d) Boulos LS, Arsanious MHN (1994) Phosph Sulfur Silicon 89:185; e) Abdou WA, Khidre MD (2004) Phosph Sulfur Silicon 179:1307
5. IBM Editorial Staff (1992) Alchemy III, 3D-Molecular Modeling Software Users Guide. Tripos Associates Inc., Subdivision of Evans and Sutherland
6. Neidlein R, Jochheim M, Krieger C, Kramer W (1994) Heterocycles 39:185
7. Coppola GM, Hardtmann GE, Pfister OR (1976) J Org Chem 41:825
8. Neidlein R, Hahn DU, Kramer W, Krieger C (1998) Heterocycles 47:221
9. a) Abdou WM, El-Khoshnieh YO (1999) Synth Communs 29:2657; b) Abdou WM, Ganoub NAF (2000) Heteroatom Chem 11:196
10. a) Schweizer EE, Kopay CM (1972) J Org Chem 37:1561; b) Yavari I, Djahaniani H, Maghsoodlau MT, Hazeri N (1999) J Chem Res Synop:382
11. Latham EJ, Murphy SM, Stanforth SP (1995) Tetrahedron 51:10385
12. Vincent JC, Vincent HW (1944) Proc Soc Extl Biol Med 55:162
13. Nene YL, Thapliyal PN (1965) Naturwissenschaften 52:89
14. Teeters WO, Shriner RL (1933) J Am Chem Soc 55:3026