

A Convenient Synthesis of 2*H*-1,4-Benzoxazines, 3*H*-Indol-3-ones, and 2,3-Dihydrobenzoxazoles

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3,5-Di-*tert*-butyl-1,2-benzoquinone 1-oxime (**1b**) reacted with ester ylides **2a,b** to give the corresponding 2*H*-1,4-benzoxazin-2-ones **9a,b** along with the 3*H*-indol-3-one **11**, whereas with keto ylides **12a,b**, 2,3-dihydrobenzoxazoles **13a,b** were isolated. Conversely, the reaction of **1b** with moderated phosphonium salt **15** proceeded under phase-transfer catalysis conditions to afford the 2*H*-1,4-benzoxazine derivative **19**, instead of the expected Wittig reaction product.

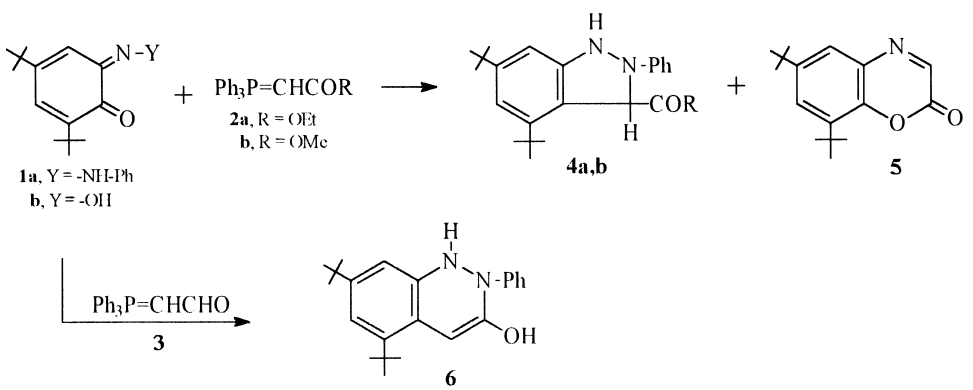
We reported earlier[1] that 3,5-di-*tert*-butyl-1,2-benzoquinone reacted with trialkyl phosphites to give pentaoxyphosphoranes, as presumably observed with *o*-quinones, whereas with dialkyl phosphonates an anomalous behavior was shown, whereupon a ring attack occurred to give phosphonate adducts. We also found that the dione system in the quinone in question behaved differently toward Wittig[2a,b] and Wittig-Horner reagents.[2c]

Later on, in a continuing exploration of the attack of alkylidenephosphoranes on carbon–nitrogen systems,[3] we described[3g] the synthesis of substituted 2,3-dihydro-1*H*-indazoles **4a,b**, 2*H*-1,4-benzoxazin-2-one **5** and 1,2-dihydrocinnoline **6** by applying phosphorus ylides **2** or **3** on 3,5-di-*tert*-butyl-1,2-benzoquinone 1-phenylhydrazone (**1a**) (e.g. Scheme 1). It has been pointed out that the substitution pattern in **1** is such as to obstruct (for steric hindrance reasons) a nucleophilic approach by a ylide phosphorane to the aryl-carbonyl in **1a**. The effect of the neighboring *t*-Bu moiety on the C–2(O) group would be expected to be quite unfavorable.

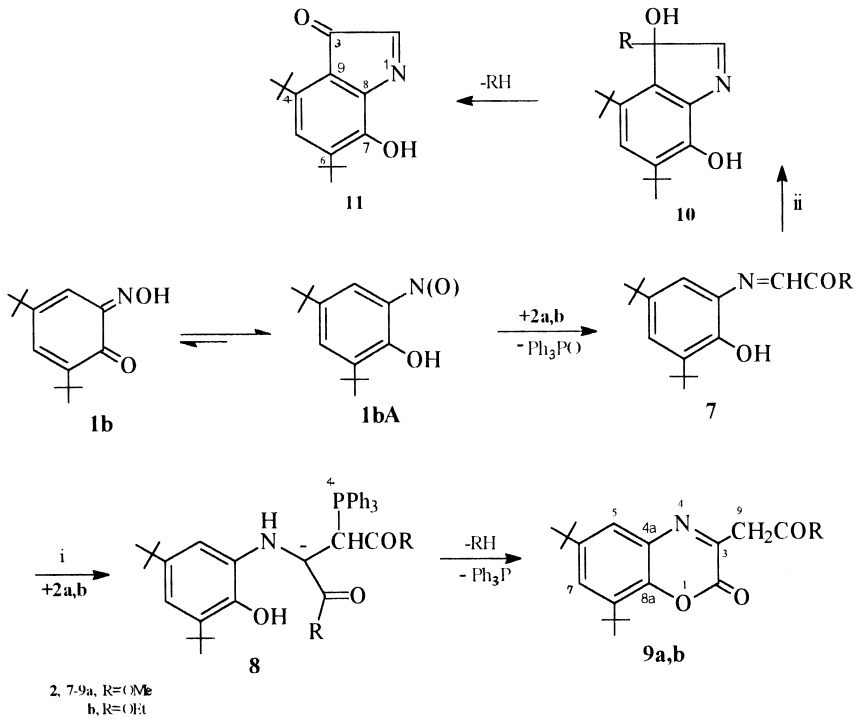
As a sequel, the work detailed herein describes the reactions of 3,5-di-*tert*-butyl-1,2-benzoquinone 1-oxime (**1b**) with stabilized ester-**2a,b** or keto-**12a,b** ylide phosphoranes and a moderate allyltriphenylphosphonium bromide **15**. The methodology has led to a facile synthesis of the title compounds, benzo[1,2-*b*]-fused *N*-heterocycles, which constitute an important class of compounds, many of which exhibit significant pharmaceutical and biological potency.[4,5]

Results and Discussion

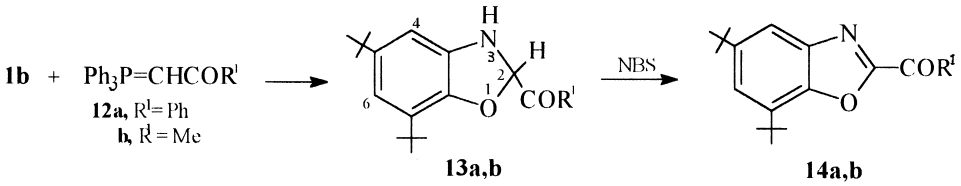
The required *o*-quinone monoxime **1b** was easily obtained in a reasonable yield (48%) from a reaction of the parent *o*-quinone with hydroxylamine hydrochloride in boiling ethyl alcohol for 24 h. The treatment of **1b** with (ethoxycarbonylmethylene)triphenylphosphorane (**2a**, 2 molar amounts) in boiling chloroform (or in toluene; best yield in chloroform) gave ethyl 6,8-di-*tert*-butyl-2-oxo-2*H*-1,4-benzoxazine-3-acetate (**9a**) (41%) along with unexpected 4,6-di-*tert*-butyl-7-hydroxy-3*H*-indol-3-one (**11**) (28%) (Scheme 2). A similar treatment of **1b** with (methoxycarbonylmethylene)triphenylphosphorane (**2b**) led to 2*H*-1,4-benzoxazin-2-one **9b** and 3*H*-indol-3-one **11** in 44 and 22% yields, respectively. The ^{1}H and ^{13}C NMR spectra of **9b** are similar to those of **9a**, except for the ester group, which displays characteristic resonances with appropriate chemical shifts. Repetition of the reaction between equimolar amounts of **1** and **2a,b** again afforded **9a,b** and **11** in addition to the unchanged **1b**. The structures **9** and **11** were assigned based on elemental analyses and spectral data. Thus, 2*H*-1,4-



Scheme 1.



Scheme 2.



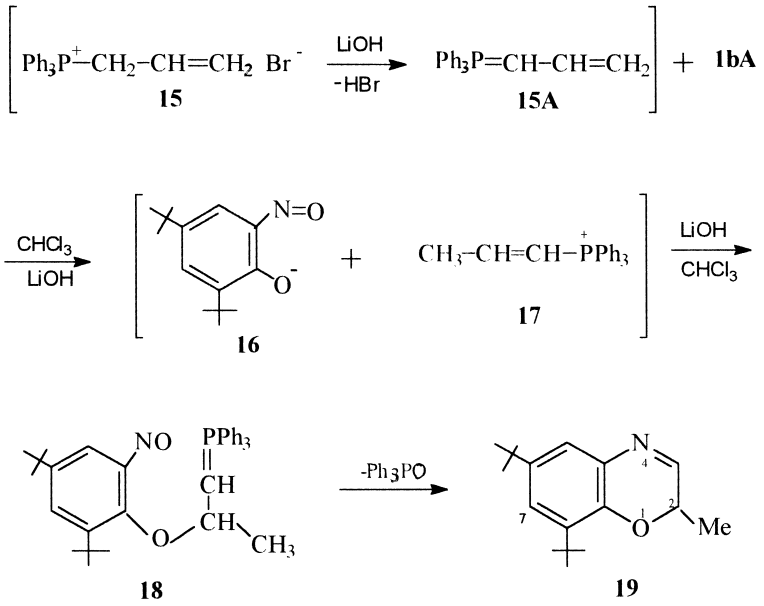
Scheme 3.

benzoxazin-2-ones **9a,b** showed strong absorptions at 1763 (**9a**) and 1772 cm^{-1} (**9b**), characteristic of the carbonyl groups in similar six-membered heterocyclic compounds (cf. δ lactones[6]). Other bands appeared at ~1720 [C(O), ester] and ~1590 cm^{-1} (C=N). The ^{1}H NMR spectra of compounds **9a,b** exhibit a singlet for their C-9-methylene protons around δ 2.6, in agreement with the suggested structure, and rule out the alternative arylidene form. Furthermore, the distinguishing features of the ^{13}C NMR spectra of **9a,b** were the presence of signals at δ ~28 (CH_2COR), ~160 [C(O), ester] and at ~172 [C-1-(O)].

The respective mechanism for the formation of **9** might involve an initial Wittig olefination of **1b** in its tautomeric nitroso form **1bA**,[7] leading to intermediate **7**, followed by the addition of a second ylide species, **2a** or **2b**. The further elimination of triphenylphosphine and δ-lactonization of the thusformed intermediate **8** yielded the final products **9a,b** accompanied by extrusion of an alcoholic moiety (Scheme 2-i). Meanwhile, according to a mechanism *suggested by the referee*, and outlined in Scheme 2-ii, the formation of compound **11** involved the intermediate **10**, which arose from an intramolecular Friedel–Crafts type condensation of intermediate **7**.[8] Further elimination of the appropriate alcoholic moiety from **10** afforded **11**. However, the latter step occurred through a carbabion mechanism, driven by the resulting gain of aromaticity. In favor of the assigned structure **11**, its ^{1}H NMR spectrum revealed the absence of a doublet at δ 6.23, assignable to the proton on C-6 in **1**,[9] or C-5 in **9** in their ^{1}H NMR spectra. Instead, signals at δ 6.05 (C-2-H), 6.87 (C-5-H) and 10.24 (OH) were present in the ^{1}H NMR spectrum of **11**. The absorption at ν_{max} 1733 cm^{-1} in the IR spectrum of **11** is also in better agreement with the carbonyl absorption (1725–1735 cm^{-1}) of several 3-oxoindoline derivatives.[10]

The monoxime **1b** reacted with benzoyl-**12a** and acetyl-**12b** methylenetriphenylphosphoranes in boiling toluene, giving the dihydrobenzoxazoles **13a,b** advantageously. The structure of **13** was assigned from its molecular weight, its single carbonyl peak at ν_{max} 1666 (**13a**) or 1675 (**13b**); its ^{1}H NMR absorption at δ ~3.7 [CH-C(O)] and δ ~11 (NH), and its conversion by *N*-bromosuccinimide (NBS) (Scheme 3) to **14** [78%, ν_{max} ~1595 cm^{-1}, C=N].

Next, we studied the reaction of **1b** with allyltriphenylphosphonium bromide **15**; the obtained product is depicted in Scheme 4. The treatment of **1b** with **15** in the presence of lithium hydroxide in $CHCl_3$ yielded 6,8-di-*tert*-butyl-2-methyl-2H-1,4-benzoxazine (**19**) (48%) (and unidentified products of



Scheme 4.

high melting points). Structure **19** was assigned from an elemental analysis and the spectral properties. Obviously, the highly reactive ylide **15A** is unlikely to react at the oxoimino nitrogen atom of **1b** and is much more likely to remove a proton from the OH group, to generate cation **17**. An attack of the oxygen anion **16** on **17** yields the ylide **18**, which would then undergo a Wittig reaction giving the final product **19**. Noteworthy, an analogous mechanism was previously reported for the reaction of vinylphosphonium salt with α-imino ketones.[11]

In summary, the present and previous studies[4g] clearly show that the α-imino carbonyl substrates **1a,b** react with alkylidenephosphoranes exclusively in the phenolic form, and not in the tautomeric *o*-quinone-imine structure, at least under the prevailing experimental conditions. Although the initial step in the reactions of **1b** with **2** or **12** involves a nucleophilic attack by the nitroso-oxygen atom on the phosphonium center of the reagent, the consequences of the initial step vary markedly according to the nature of the α-substituent of the ylidic carbon atom. Finally, the *N*-heterocycles prepared in the present work, might to be biologically active compounds based on known drug skeletons.

Experimental

All of the melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer model 297 (Grating) using a KBr disc. The ^{1}H and ^{13}C NMR spectra were run on a Varian Gemini 200 (200 MHz) instrument using TMS as an internal reference. The mass spectra were taken at 70 eV on an MS-50 Kratos (A.E.I.) spectrometer provided with a data system. Appropriate precautions in handling moisture-sensitive compounds were observed. Light petroleum refers to the 40–60 °C fraction.

I. Reaction of 3,5-Di-*tert*-butyl-1,2-benzoquinone 1-Oxime (1b) with Ester Ylides 2a,b: (A) Preparation of Compounds **9a** and **11**. A stirred solution of monoxime **1b** (0.8 g, 3.4 mmol) and (ethoxycarbonylmethylene)triphenylphosphorane (**2a**) (2.4 g, 6.8 mmol) in dry chloroform (25 mL) was boiled under reflux for 18 h. After removing the solvent, the residue was chromatographed on silica gel. Elution with hexane/$CHCl_3$ (9:1, v/v) afforded yellow crystals of ethyl 6,8-di-*tert*-butyl-2-oxo-2*H*-1,4-benzoxazine-3-acetate (**9a**) (480 mg, 41%), mp 131.5–133 °C (CH_2Cl_2); Anal. Found: C, 69.66; H, 7.82; N, 3.93%. Calcd for $C_{20}H_{27}NO_4$ (345.44): C, 69.54; H, 7.88; N, 4.05%; IR (KBr) 1763 (C=O, lactone), 1722 (C=O, ester), 1595 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, J_{HH} = 6.5 Hz, OC–CH_3), 1.24, 1.28 (2 × 9H, 2s, $C(CH_3)_3$), 2.64 (2H, s, CH_2–), 4.05 (2H, q, J_{HH} = 6.5 Hz, OCH_2), 6.23, 6.82 (2 × 1H, 2d, J_{HH} = 4.2 Hz, Ar-*H*); ^{13}C NMR δ 18.4 ($OCCH_3$), 27.8 (CH_2–), 31.2, 32.4 [2 × $C(CH_3)$], 34.6, 35.8 (2 × $C(CH_3)_3$), 58.3 (OCH_2), 123.7, 125.5 (C-5 & C-7), 129.4 (C-4a), 133.1 (C-3), 142.0 (C-6), 144.2 (C-8), 151.5 (C-8a), 159.3 (C(O), ester), 171.5 (C-2-(O)); MS *m/z* (%) 345 (M^+, 55), 330 (11), 300 (15), 272 (19), 271 (100), 246 (23), 186 (5).

Elution with hexane/$CHCl_3$ (8:2, v/v) afforded yellow leaflets of 4,6-di-*tert*-butyl-7-hydroxy-3*H*-indol-3-one (**11**) (245 mg, 28%), mp 155–157 °C (benzene); Anal. Found: C, 74.17; H, 8.24; N, 5.32%. Calcd for $C_{16}H_{21}NO_2$ (259.35): C, 74.09; H, 8.16; N, 5.4%; IR (KBr) 3425 (OH), 1733 (C-3-(O)), 1582 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 1.33, 1.46 (2 × 9H, 2s, $C(CH_3)_3$), 6.05 (1H, s, C-2-H), 6.87 (1H, s, C-5-H), 10.24 (1H, s_ω, –OH, exchangeable with D_2O); ^{13}C NMR δ 31.3, 32.6 (2 × $C(CH_3)$), 34.5, 35.4 (2 × $C(CH_3)_3$), 122.8 (C-5), 133.1 (C-2-H), 138.5 (C-9), 142.6 (C-4), 145.9 (C-6), 149.6 (C-8), 151.4 (C-7-OH), 171.3 (C-3-(O)); MS *m/z* (%) 259 (M^+, 100), 258 (4), 231 (16), 205 (3), 186 (11).

(B) Preparation of **9b** and **11**: A stirred solution of **1b** (0.8 g, 3.4 mmol) and (methoxycarbonylmethylene)triphenylphosphorane (**2b**) (2.3 g, 6.8 mmol) in dry $CHCl_3$ (20 mL) was boiled under reflux for 15 h (TLC). The product mixture was worked up according to the above-described procedure for ylide **2a**, yielding compounds **9b** and **11**.

Elution with hexane/$CHCl_3$ (9:1, v/v) yielded yellow crystals of methyl 6,8-di-*tert*-butyl-2-oxo-1*H*-1,4-benzoxazine-3-acetate (**9b**) (490 mg, 49%), mp 138–140 °C (CH_2Cl_2); Anal. Found: C, 68.74; H, 7.67; N, 4.18%. Calcd for $C_{19}H_{25}NO_4$ (331.42): C, 68.85; H, 7.60; N, 4.23%; IR (KBr) 1772 (C=O, lactone), 1718 (C=O, ester), 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 1.24, 1.28 (2

× 9H, 2s, $C(CH_3)_3$), 2.58 (2H, s, CH_2-), 3.84 (3H, s, OCH_3), 6.24, 6.79 (2 × 1H, 2d, J_{HH} = 4.2 Hz, Ar-*H*); ^{13}C NMR δ 28.3 (CH_2-), 31.4, 32.8 (2 × $C(CH_3)_3$], 34.3, 35.5 (2 × $C(CH_3)_3$), 54.5 (s, OCH_3), 123.4, 125.4 (C-5 & C-7), 129.8 (C-4a), 133.3 (C-3), 141.8 (C-6), 146.4 (C-8), 150.8 (C-8a), 161.5 (C(O), ester), 173.6 (C-2-(O)); MS *m/z* (%) 331 (M^+, 48), 316 (4), 300 (17), 272 (27), 271 (100), 246 (20), 186 (8).

Elution with hexane/$CHCl_3$ (8:2, v/v) afforded yellow leaflets of 3*H*-indol-3-one **11** (195 mg, 22%), mp 155–157 °C (benzene), and were shown to be identical to material prepared as described above by using **2a**.

(C) A reaction between equimolar amounts of **1b** and **2a** or **2b** in $CHCl_3$ was carried out, and the reaction mixture was worked up according to the above-described procedure for **2a,b**. The product mixture gave (with **2a**) **9a** (21%) and **11** (18%) and (with **2b**) **9b** (20%) and **11** (14%). Unreacted oxime **1b** was also isolated (∼25%) in each case.

(D) A reaction between **1b** and 2 molar amounts of **2a,b** was repeated in dry toluene. The reaction mixture was heated under reflux for 40 h and afforded, after the usual working up, compounds **9a,b** (∼28%) and **11** (∼17), respectively.

II. Reactions of 1b with Keto Ylides 12a,b: Preparation of **13a,b** and **14a,b**: A mixture of **1b** (0.8 g, 3.4 mmol) and benzoyl-**12a** or acetyl-**12b** methylenetriphenylphosphorane (4 mmol) in dry toluene (20 mL) was refluxed for 40 h. The product mixture was chromatographed on silica gel using hexane/chloroform (8:2, v/v) as the eluent to give **13a** or **13b**, respectively.

2-Benzoyl-5,7-di-*tert*-butyl-2,3-dihydrobenzoxazole (**13a**) was obtained as pale-yellow flakes (722 mg, 63%), mp 118–120 °C (cyclohexane); Anal. Found: C, 78.35; H, 8.14; N, 4.20%. Calcd for $C_{22}H_{27}NO_2$ (337.46): C, 78.30; H, 8.06; N, 4.15%; IR (KBr) 3345 (NH), 1666 cm^{-1} C(O)Ph; ^{1}H NMR ($CDCl_3$) δ 1.23, 1.26 (2 × 9H, 2s, $C(CH_3)_3$], 3.68 (C-2-H), 6.23 (1H, d, J_{HH} = 4.2 Hz, C-4-H), 6.81 (1H, d, J_{HH} = 4.2 Hz, C-6-H), 7.35–7.77 (5H, m, Ph-*H*), 11.3 (1H, s, NH, exchangeable with D_2O); ^{13}C NMR δ 31.2, 32.6 (2 × $C(CH_3)_3$), 34.1, 35.5 (2 × $C(CH_3)_3$), 51.3 (C-2), 123.4, 124.4 (C-4 & C-6), 142.7 (C-5), 147.4 (C-7), 195.5 (C(O), benzoyl); MS *m/z* (%) 337 (M^+, 33), 335 (55), 307 (10), 232 (29), 230 (100), 186 (6).

2-Acetyl 5,7-di-*tert*-butyl-2,3-dihydrobenzoxazole (**13b**) was obtained as pale yellow needles (475 mg, 51%), mp 108–109 °C (pentane); Anal. Found: C, 74.23; H, 9.09; N, 5.18%. Calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.08%; IR (KBr) 3330 (NH), 1675 cm^{-1} (C(O)CH_3); ^{1}H NMR ($CDCl_3$) δ 1.24, 1.26 (2 × 9H, 2s, $C(CH_3)_3$), 2.55 (3H, s, (O)CH_3), 3.88 (C-2-H), 6.22 (1H, d, J_{HH} = 4.2 Hz, C-4-H), 6.76 (1H, d, J_{HH} = 4.2 Hz, C-6-H), 10.68 (1H, s, NH, exchangeable with D_2O); ^{13}C NMR δ 30.8, 31.3, 32.8 (C(O)*C*H_3 & 2 × $C(CH_3)_3$), 34.6, 35.2 (2 × $C(CH_3)_3$), 48.8 (C-2),123.8, 125.9 (C-4 & C-6), 142.3 (C-5), 146.4 (C-7), 192.5 (C(O), acetyl); MS *m/z* (%) 275 (M^+, 22), 273 (38), 258 (11), 245 (9), 230 (100), 186 (8).

Conversion of 13a,b to 14a,b: *N*-Bromosuccinimide (NBS) (54 mg, 0.3 mmol) and benzoyl peroxide (7 mg, 0.04 mmol) were added to a solution of **13a** (100 mg, 0.3 mmol) or **13b** (82 mg, 0.3 mmol) in 20 mL of dry CCl_4. The mixture was refluxed for 2 h and filtered while hot. Evaporation of the solvent left a residue, which was triturated with a small amount of light petroleum to give the dehydrogenated derivative, **14a** or **14b**.

2-Benzoyl-5,7-di-*tert*-butylbenzoxazole (**14a**) was obtained as a pale-yellow substance (72 mg, 72%), mp 105–107 °C (pentane); Anal. Found: C, 78.65; H, 7.45; N, 4.07%. Calcd for $C_{22}H_{25}NO_2$ (335.45): C, 78.77; H, 7.51; N, 4.17%; IR (KBr) 1667 (C(O)Ph), 1605 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 1.23, 1.25 (2 × 9H, 2s, $C(CH_3)_3$], 6.23, 6.83 (2 × 1H, 2d, J_{HH} = 4.2 Hz, C-4-H & C-6-H), 7.35–7.77 (5H, m, Ph-*H*); MS *m/z* (%) 335 (M^+, 28), 307 (13), 231 (66), 230 (100), 185 (3).

2-Acetyl-5,7-di-*tert*-butylbenzoxazole (**14b**) was obtained as yellow crystals (57 mg, 70%), mp 89–90 °C (light petroleum); Anal. Found: C, 74.62; H, 8.58; N, 5.06%. Calcd for $C_{17}H_{23}NO_2$ (273.38): C, 74.69; H, 8.48; N, 5.12%; IR (KBr) 1675 (C(O)Me), 1598 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 1.22, 1.24 [2 × 9H, 2s, $C(CH_3)_3$], 2.57 (3H, s, (O)CH_3), 6.22, 6.79 (2 × 1H, 2d, J_{HH} = 4.2 Hz, C-4-H & C-6-H); MS *m/z* (%) 273 (M^+, 43), 258 (14), 245 (8), 230 (100), 186 (8).

III. Reaction of Monoxime 1b with Allylidenetriphenylphosphorane (16): Preparation of **19**: A solution of allyltriphenylphosphonium bromide (1.4 g, 3.6 mmol) and the monoxime **1b** (0.8 g, 3.4 mmol) in chloroform (40 mL) was stirred by a magnetic stirrer. Freshly prepared aqueous lithium hydroxide (0.5 M, 15 mL, 1 M = 1 mol dm^{-3}) was added in one portion to the mixture, and the two- phase system was stirred at room temperature for 1 h, then refluxed for 4 h. The product mixture was then extracted with $CHCl_3$ (2 × 50 mL) and dried; the solvent was removed under reduced pressure. The residue was chromatographed on silica gel using hexane/$CHCl_3$ 7:3, v/v to give 6,8-di-*tert*-butyl-2-methyl-2*H*-1,4-benzoxazine (**19**) (425 mg, 48%), mp 174–175 °C (acetonitrile); Anal. Found: C, 78.77; H, 9.67; N, 5.32%. Calcd for $C_{17}H_{25}NO$ (259.39): C, 78.71; H, 9.71; N, 5.40%; IR (KBr) 1600 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 1.24, 1.28 (2 × 9H, 2s, $C(CH_3)_3$), 1.68 (3H, d, J_{HH} = 8.2 Hz, C-2-CH_3), 3.84 (1H, d of q, J_{HH} = 5.8 Hz, C-2-H), 6.25 (1H, d, J_{HH} = 2.4 Hz, C-5-H), 6.87–6.95 (2H, m, C-3-H & C-7-H); ^{13}C NMR δ 22.2 (C-2-*C*H_3), 31.1, 32.4 (2 × $C(CH_3)_3$), 34.3, 35.3 (2 × $C(CH_3)_3$), 44.7 (C-2), 122.6, 123.3, 125.2 (C-3, C-5 & C-7), 129.8 (C-4a), 142.4 (C-6), 146.6 (C-8), 150.4 (C-8a); MS *m/z* (%) 259 (M^+, 57), 244 (100), 228 (21), 226 (11), 199 (7), 186 (10).

In the next fractions several polymeric unidentified products with mp > 300 °C were eluted.

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