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A New Route to 1,3-Benzoxazepines and 1,3-Benzodiazepines *via* Intramolecular Aza-Wittig Reaction

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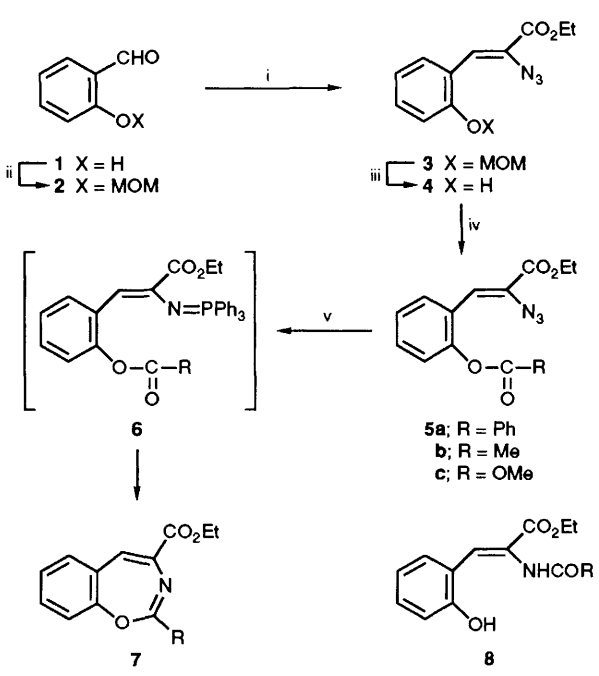
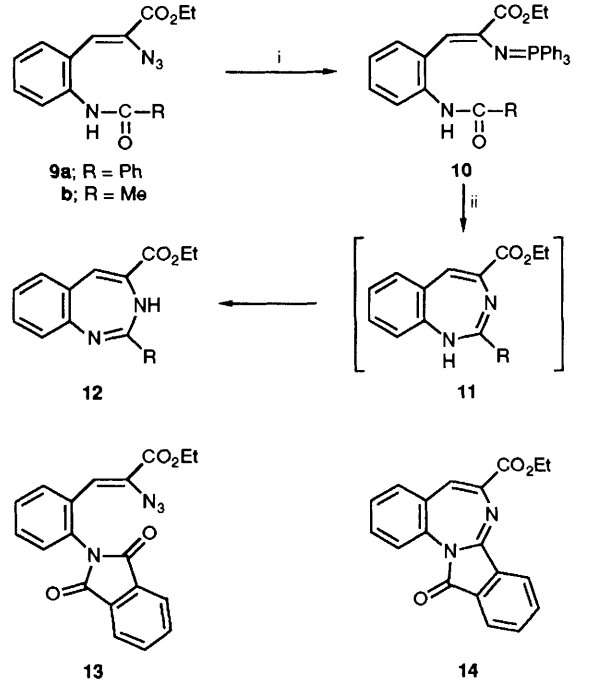
The reaction of triphenylphosphine with the *o*-acyloxy- **5** and *o*-acylamino-azidocinnamates **9**, prepared from salicylaldehyde and *o*-aminobenzaldehyde, results in ring closure to give the 1,3-benzoxazepines **7** and 1,3-benzodiazepines **12**, *via* the intramolecular aza-Wittig reaction of the iminophosphoranes **6** and **10** initially formed, respectively.

Fully unsaturated 1,3-dihetero seven-membered ring compounds (1,3-diheteroepines) have been prepared mainly by ring transformations of known heterocyclic rings. With regard to benzo compounds, 1,3-benzoxazepines[1,2] and 1,3-benzodiazepines[3] are synthesized by the photochemical rearrangement with ring expansion of isoquinoline *N*-oxides and quinoline *N*-imides, respectively. 3,1-Benzoxazepines are prepared by the photochemical rearrangement of quinoline *N*-oxides[2,4] or by the thermal ring expansion of 1-azidoisochromenes.[5] We report here a new synthetic route to 1,3-benzodiheteroepines involving no ring transformation.

Salicylaldehyde **1** was protected as the methoxymethyl (MOM) derivative **2**, which was condensed with ethyl azidoacetate to give the azidocinnamates **3**. After removal of the MOM group in **3**, the resulting phenolic compound **4** was treated with benzoyl chloride, acetic anhydride or methyl chloroformate giving the cinnamyl esters **5** in 30–40% yields from 1.† Treatment of **5** with triphenylphosphine in benzene



Scheme 1 *Reagents and conditions*: i, NaOMe, EtOH, $N_3CH_2CO_2Et$, 0–5 °C, 2 h, 60%; ii, NaOH, $Me(Octyl)_3N^+Cl^-$, H_2O, CH_2Cl_2, $ClCH_2OMe$, room temp., 1 h, 95%; iii, acetone, 10% HCl, room temp., 8 h, 85%; iv, PhCOCl, Ac_2O or $ClCO_2Me$, pyridine, room temp., 5–8 h, 60–80%; v, PPh_3, benzene, Ar, room temp., 3–4 h, 85–90%



Scheme 2 *Reagents and conditions*: i, PPh_3, benzene, Ar, room temp., 2 h, 95%; ii, xylene, reflux, 15 h, 40–50%

† Direct conversion of unprotected **1** into **4** by treatment with ethyl azidoacetate has been unsuccessful. Similar azidocinnamates obtained by the condensation of benzaldehydes with ethyl azidoacetate are known to be *Z*-forms (T. L. Gilchrist, C. W. Rees and J. A. R. Rodrigues, *J. Chem. Soc., Chem. Commun.*, 1979, 672; D. M. B. Hickey, C. J. Moody and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1982, 1419). Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds reported.

Selected data for **5a**: m.p. 95–96 °C; IR (KBr) 2128 (N_3), $\nu_{C=O}$ 1752 and 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 and 4.20 (3H, t, and 2H, q, *J* 7 Hz, CO_2Et), 7.02 (1H, s, alkenic H), 7.2–7.6 and 8.1–8.3 (7H, m, and 2H, m, Ph-H); **5b**: m.p. 66–68 °C; **5c**: m.p. 58–59 °C.

at room temperature resulted in ring closure to form the desired 1,3-benzoxazepines **7** in 85–90% yields, probably *via* the intramolecular aza-Witting reaction of the initially formed iminophosphoranes **6**, which could not be isolated, however (Scheme 1).‡ The 2-phenyl-oxazepine **7a** is stable and was isolated in 90% yield, however, the other oxazepines **7b,c** were readily hydrolysed to the ring-opened compounds **8** during isolation by chromatography and thus were purely isolated only in 30–40% yields, together with **8** (50–60%). 1,3-Benzodiheteroepines are known to readily undergo hydrolysis under mild conditions.[1–3]

On the other hand, in the reaction of triphenylphosphine with the *o*-acylaminoazidocinnamates **9** prepared from *o*-aminobenzaldehyde *via* two steps, the iminophosphoranes **10** were isolated as stable crystals almost quantitatively. Heating the phosphoranes **10** in refluxing xylene resulted in aza-Wittig reaction to form the 3*H*-1,3-benzodiazepines **12** in 40–50% yields, presumably *via* the 1*H*-isomers **11** initially formed (Scheme 2).§ It is known that *N*-unsubstituted 1*H*-1,3-benzodiazepines are unstable and tautomerize rapidly to the 3*H*-isomers.[6] Similarly, the tetracyclic diazepine **14** was also obtained from the phthalimido compound **13** in 60% yield.

These results indicate that the intramolecular aza-Wittig reaction to the ester carbonyl occurs at below room temperature, whereas a higher temperature is required for that to the amide carbonyl; this difference in reactivity between esters and amides is analogous to those observed in a variety of nucleophilic reactions. Although the aza-Wittig reactions have recently been utilized in the syntheses of nitrogen heterocycles, especially five- and six-membered rings,[7] the present result is the first example of utilization for the synthesis of seven-membered heterocyclic rings.

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‡ *Selected data* for **7a**: oil, IR (film) $\nu_{C=O}$ 1722 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 and 4.32 (3H, t, and 2H, q, *J* 8 Hz, CO_2Et), 7.1–7.5 (7H, m, Ph-H), 7.57 (1H, s, 5-H) and 8.2–8.3 (2H, m, Ph-H); **7b**: oil; **7c**: oil.

§ *Selected data* for **10** and **12–14**: **10a**: m.p. 164–166 °C; **10b**: m.p. 154–156 °C; **12a**: m.p. 117–118 °C; IR (KBr) ν_{NH} 3368 and $\nu_{C=O}$ 1692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 and 4.32 (3H, t, and 2H, q, *J* 7 Hz, CO_2Et), 6.47 (1H, s, 5-H), 6.61 (1H, br, NH) and 6.7–7.8 (9H, m, Ph-H). The above spectroscopic data show that the ester carbonyl IR absorption appeared at a lower wavelength and the NH proton NMR spectral signal also appeared at a lower field. These lower shifts may be a consequence of hydrogen bonding forming a five-membered ring chelate between the NH and the ethoxycarbonyl oxygen, by analogy with *N*-unsubsituted 2-methoxycarbonyl-1*H*-1,4-benzodiazepines (H. Sashida, M. Kaname and T. Tsuchiya, *Chem. Pharm. Bull.*, 1990, **38**, 2919); strongly suggesting that the diazepines **12** are the 3*H*-isomers. **13**: m.p. 183–185 °C; **14**: m.p. 137–138 °C; IR (KBr) $\nu_{C=O}$ 1740 and 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 and 4.30 (3H, t, and 2H, q, *J* 7 Hz, CO_2Et) and 7.1–8.1 (9H, m, ring H).

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