Reactions of triene-conjugated nitrile ylides: a route to 1,4-dihydro-1,4-prop-1′-enoisoquinolines from systems with α,β aromatic and γ,δ; ε,ζ olefinic unsaturation

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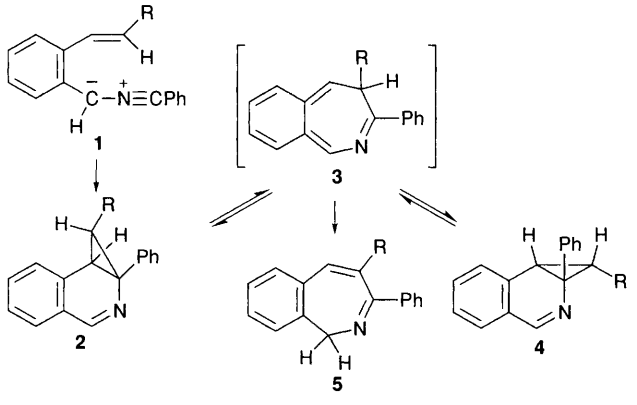
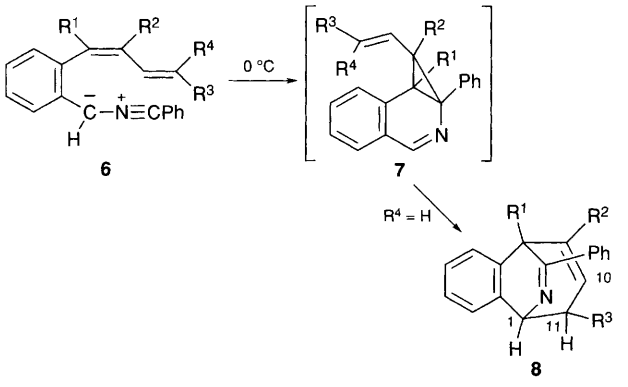
Triene-conjugated nitrile ylides with α,β aromatic and γ,δ; ε,ζ olefinic unsaturation undergo intramolecular cyclisation and rearrangement to give 1,4-dihydro-1,4-prop-1′-enoisoquinolines.

Recent work on the chemistry of diene-conjugated nitrile ylides with α,β aromatic and γ,δ olefinic unsaturation, *e.g.* **1** in Scheme 1, has shown that reaction at room temperature or below gives cyclopropa[*c*]isoquinolines, *e.g.* **2**, as the primary products.[1,2] It is not yet clear whether these products are formed by a single-step 1,1-cycloaddition reaction or *via* 1,7 electrocyclisation to give **3** followed by spontaneous ring contraction, but it has been shown that the reaction is wholly stereospecific in that the *trans* substituent at the terminal position in **1** goes into the *exo* position of the product **2**.[2] On heating, the cyclopropa[*c*]isoquinolines undergo an equilibration of the *exo*/*endo* isomers **2** and **4** *via* electrocyclic ring opening to give **3** followed by ring inversion and reclosure. In cases where there is a hydrogen atom at the C-1 position of the cyclopropa[*c*]isoquinoline this equilibration is accompanied by a slower [1,5] hydrogen migration in **3** to give the 2-benzazepine **5** as the final product. In other cases the system reacts *via* various skeletal rearrangements.[2]

Here we report the results of an exploratory study of the chemistry of the analogous all-*cis* triene-conjugated system **6**, Scheme 2. There are obviously many possible intramolecular reaction paths for such a system *via* electrocyclisation or cycloaddition reactions and the work was undertaken in order to find out whether any of them would be sufficiently dominant to be useful in a synthetic sense. The nitrile ylides were generated by the same method as used in earlier work, *i.e.* the base induced 1,3-dehydrochlorination of imidoyl chlorides in THF at 0 °C. The amides used as precursors to the latter were prepared by the Suzuki coupling of the appropriate bromodiene with 2-(benzylamidomethyl) phenylboronic acid.[3] The bromodienes were prepared *via* Arnold's bromoformylation reaction[4] and subsequent Wittig or Wadsworth–Emmons olefination. In the event it was found that almost all of the examples of **6** studied gave the 1,4-dihydro-1,4-prop-1′-enoisoquinolines **8**, Scheme 2, as the only isolated products (Table 1). These compounds are of interest in that they have the basic skeleton of the isopavine



Scheme 1



Scheme 2

Table 1 Reactions of the nitrile ylides **6** and **9**

Reactant	R^1	R^2	R^3	R^4	Product (%)	Mp/°C
6a	Me	Ph	Ph	H	**8a** (65)	181–182
6b	Me	Ph	Me	H	**8b** (46)	149–150
6c	Me	Ph	CO_2Me	H	**8c** (20)	oil
6d	$(CH_2)_3$		Ph	H	**8d** (63)	144–146
6e	$(CH_2)_3$		CO_2Me	H	**8e** (42)	oil
6f	Me	Ph	Me	Me	**7f** (20)	oil
9					**10** (65)	167–169

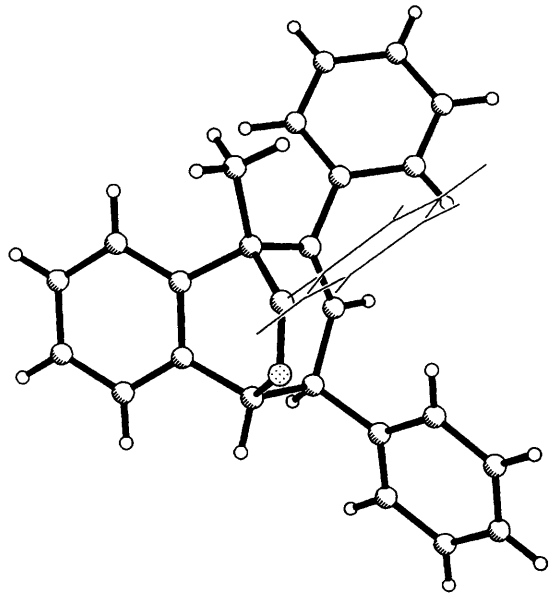
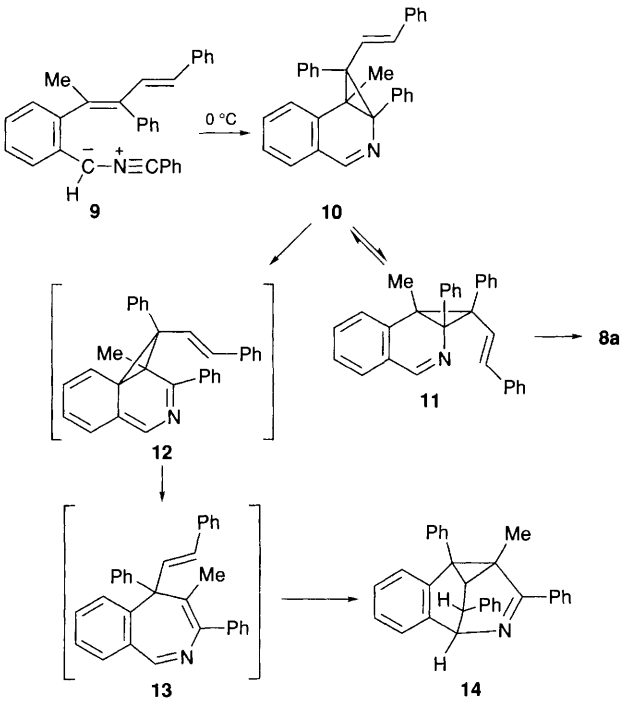


Fig. 1 Compound **8a**

alkaloids. The structures of the products were determined by X-ray crystallography on two of them, **8a** (Fig. 1) and **8d**,† and deduced for the others by comparison of ^{1}H NMR spectra. The characteristic features of the latter are the three multiplets for the protons at C-11, C-1 and C-10 which for **8a** occur at δ 3.90, 5.26 and 5.51, respectively. In view of the known chemistry of the analogous diene system, Scheme 1, it seems likely that the primary product is the cyclopropa[*c*]isoquinoline **7** which then undergoes a fast aza-Cope rearrangement at the reaction temperature (0 °C) to give the product. The only reactant which failed to follow the sequence in Scheme 2 was **6f** (R^1, R^3, R^4 = Me, R^2 = Ph) which gave a low yield of an unstable material which had ^{1}H and ^{13}C NMR spectra consistent with its formulation as the cyclopropa[*c*]isoquinoline **7f**.



Scheme 3

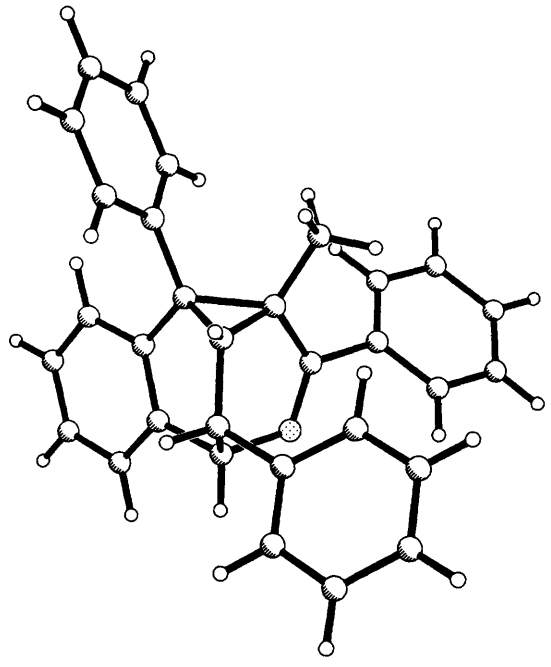


Fig. 2 Compound **14**

In an attempt to obtain further evidence for the mechanism, a similar reaction was carrier out with **9** (Scheme 3), the *Z,E* analogue of **6a**. Predictably, the isomeric cyclopropa[*c*]isoquinoline **10**, with its 1-alkenyl group now in the *exo* position, proved to be kinetically stable at the reaction temperature and was isolated and characterised. It was expected that, on heating, this compound would undergo *exo/endo* equilibration as discussed above, and that the *endo* isomer **11** would then spontaneously undergo the aza-Cope rearrangement to give compound **8a**. In practice, heating compound **10** at reflux in perdeuteriobenzene gave **8a** in only 35% yield and, unexpectedly, the major product (65%) was the new heterocyclic system 3,4-benzo-6-azatricyclo[3,3,1,$0^{2,8}$]nona-3,6-diene **14** (mp 116–118 °C), probably formed *via* the route shown. The structure of compound **14** was determined by X-ray crystallography, Fig. 2.†

This route to 1,4-dihydro-1,4-prop-1′-enoisoquinolines, Scheme 2, is the first one to this system, but the analogous 1,4-dihydro-1,4-prop-2′-enoisoquinolines have been prepared *via* an intramolecular reaction of α-azidocinnamates with 1,3-dienes.[6]

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Footnote

† *Crystal data* for $C_{31}H_{25}N$, **8a**: M = 411.52, monoclinic, $P2_1/n$, a = 10.3624(7), b = 19.1821(13), c = 11.1715(5) Å, α = 94.549(4)°, V = 2213.6 Å^3 [from 2 values for 94 reflections measured at ± (40 < 2 < 44°), = 1.54184 Å]. Z = 4, D_{calc} = 1.235 g cm^{-3}, F(000) = 872, T = 150 K, μ(Cu-K) = 0.538 mm^{-1}. Colourless lump, 0.35 × 0.31 × 0.06 mm^3.

Crystal data for $C_{32}H_{27}NCl_2$, **14**: CH_2Cl_2, M = 496.48, monoclinic, $C2/c$, a = 26.662(9), b = 9.496(6), c = 21.929(7) Å, α = 108.08(3)°, V = 5277.90 Å^3 [from 2 values for 31 reflections measured at ± (10 < 2 < 44°), = 1.54184 Å]. Z = 8, D_{calc} = 1.25 g cm^{-3}, F(000) = 2089.90, T = 220 K, μ(Cu-K) = 2.38 mm^{-1}. Colourless lump, 0.45 × 0.27 × 0.16 mm^3. Data were collected in the range 5 < 2 < 120° using Cu-K radiation and scans on a Stoe Stadi-4 four-circle diffractometer equipped with an Oxford Cryosystems low-temperature device.[7] The structures were solved by direct methods.[8] Full-matrix least-squares refinement was performed using SHELXTL for **8a** and CRYSTALS for **14**.[9] Hydrogen atoms were placed in calculated positions, and all non-hydrogen atoms were refined with anisotropic displacement parameters. In **14** one molecule of CH_2Cl_2 lies disordered over three orientations with occupancies 0.5, 0.25 and 0.25, each chlorine site being common to two such orientations. Conventional R indices [based on F and data with $I > 2(I)$] were 4.38% for **8a** and 7.79% for **14**. The final difference map maximum and minimum were +0.2/−0.2 for **8a** and +0.7/−0.4 eÅ^{-3} for **14**. The crystals of **8d** were of poor quality and resulted in higher uncertainties for the molecular geometry parameters.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/279.

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