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Intramolecular Diels-Alder Reactions from Trichloro-1,2,4-triazine and 1,5- and 1,6-Dienes

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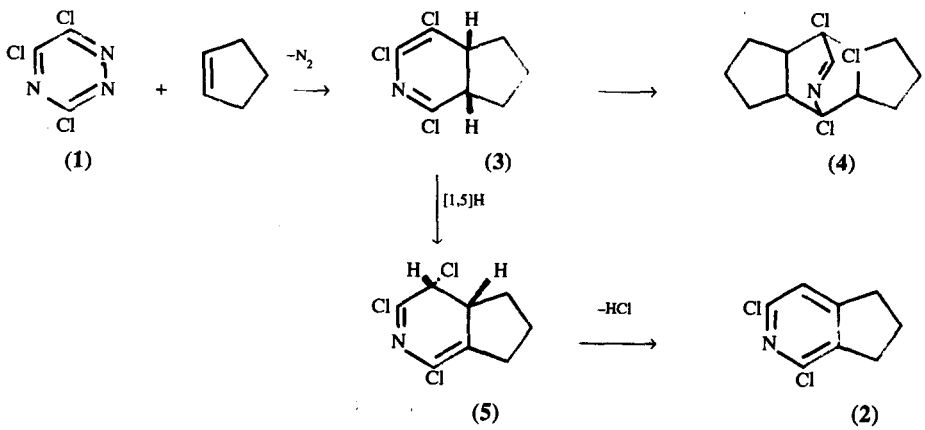
Abstract The initial dihydropyridines from Diels-Alder addition of dienes to trichloro-1,2,4-triazine, and loss of N_2, undergo intramolecular addition with hexa-1,5-diene and cyclo-octa-1,5-diene, also [1,5]H sigmatropic shift with diallyl ether, and [1,5]H shift and partial aromatisation with cyclododeca-1,5,9-triene.

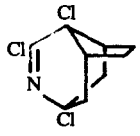
Trichloro-1,2,4-triazine (**1**) acts as an electron-deficient diene in the Diels-Alder reaction,[1] undergoing ready reaction with olefins such as cyclopentene, where the dichloropyridine derivative (**2**) is the major product (77%). It was suggested that this was formed by initial Diels-Alder reaction and loss of nitrogen to give the dihydropyridine (**3**), which mainly underwent [1,5] sigmatropic shift of hydrogen, and loss of HCl to give (**2**), while a second [4 + 2] addition of cyclopentene occurred to a limited extent (3%), forming di-adduct (**4**). Good evidence for the intermediacy of compounds such as (**5**) has now been obtained from a study of reactions of (**1**) with non-conjugated dienes and trienes.



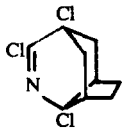
(**1**) (**3**) (**4**) (**5**) (**2**)

Intramolecular Diels-Alder reactions have been widely used in natural product synthesis,[2] and because of favourable entropy factors they often proceed more readily than their intermolecular counterparts. Appropriate dienes should give intermediates analogous to compounds (**3**) and (**5**), capable of such an intramolecular reaction.

Triazine (**1**)[3] and hexa-1,5-diene (1:8 molar ratio) underwent reaction at 70 °C during 9 days to give adducts (**6**) and (**7**) (78% yield; ratio 6:1 by NMR), easily hydrolysed to the corresponding amides (**8**)[4] and (**9**)[5] by water, or attempted dry column flash chromatography (DCFC) on silica gel.



(6)



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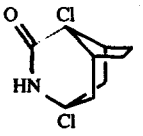

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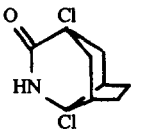
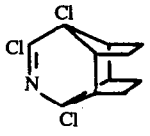
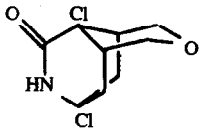


(9)

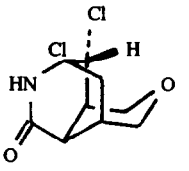
Cyclo-octa-1,5-diene (7 moles) reacted analogously, giving adduct (**10**; m.p. 118 °C; 85%) after 7 days at 70 °C, which was also easily hydrolysed to the corresponding cyclic amide (m.p. 245 °C). No products which involved [1,5] sigmatropic hydrogen shift were observed.



(10)

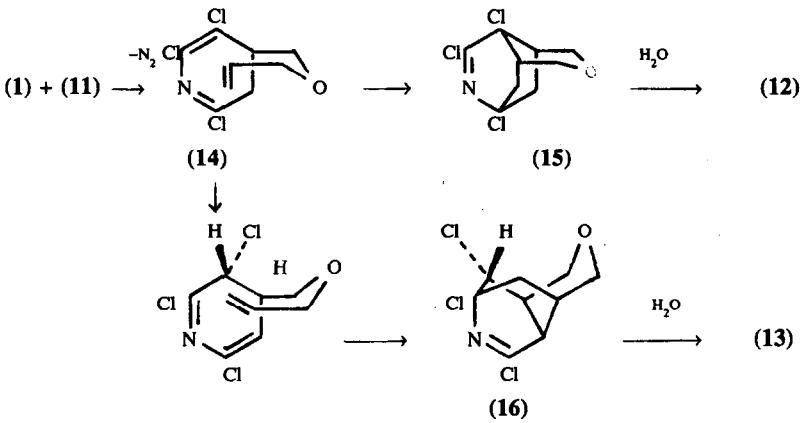


(12)



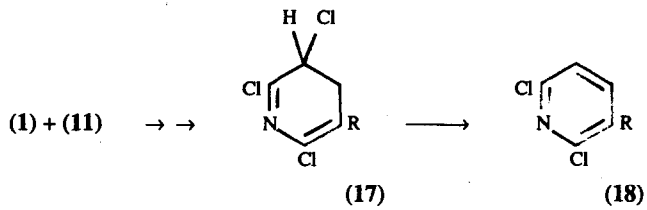
(13)

Diallyl ether (**11**) (6.5 mole) gave a much more complex and water sensitive reaction product. Extraction with diethyl ether left a residue, easily hydrolysed (H_2O/CH_2Cl_2) to a 6:1 mixture (26%) of amides (**12**; m.p. 228 °C)[4] and (**13**).[6] The extract yielded 2,6-dichloro-3-chloromethylpyridine (m.p. 80–82 °C; 31%),[7] together with a complex mixture, which appeared to contain components made up of at least two triazine and/or olefin residues. Addition of diallyl ether to triazine (**1**) can yield an intermediate (**14**), which largely undergoes [4 + 2] addition to give (**15**), but in part undergoes [1,5] hydrogen shift followed by [4 + 2] addition to give imidoyl chloride (**16**), the precusor to amide (**13**). The 2,6-dichloro-3-chloromethylpyridine

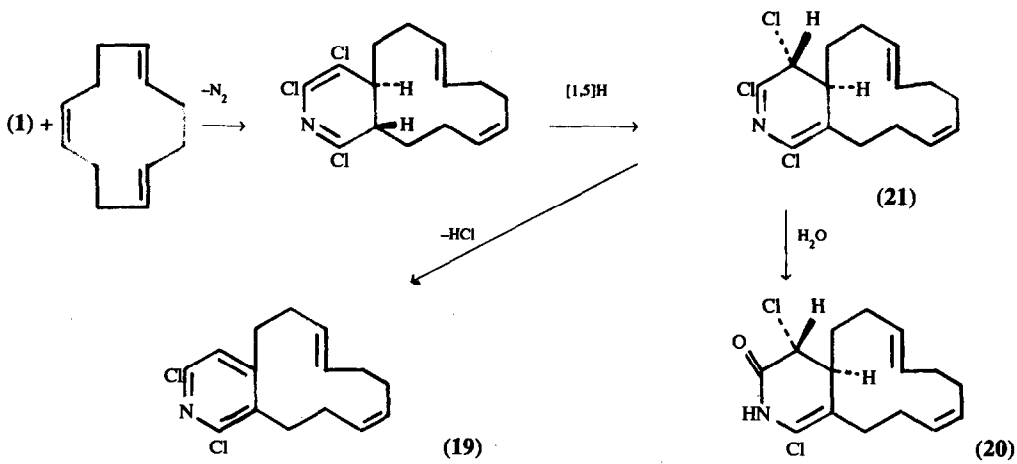


presumably arises *via* the alternative addition of (**11**) to (**1**) to give intermediate (**17**; R = $CH_2OCH_2CH{=}CH_2$) after [1,5] hydrogen shift. Here the side-chain is attached to an sp^2–carbon and [4 + 2] addition is more difficult, so aromatisation results to give (**18**; R = $CH_2OCH_2CH{=}CH_2$), the presumed precursor to the

chloromethyl derivative (**18**; R = CH_2Cl).[8]



The ring system in *trans, trans, cis*-cyclododeca-1,5,9-triene is relatively rigid, rendering intramolecular addition difficult. Its reaction with triazine (**1**) (3.5:1 molar ratio) at 70 °C during 4 days resulted in reaction with one of the *trans* C=C bonds[9] and gave HCl (39%), and, after DCFC on silica gel, recovered (**1**; 30%), and a mixture of *trans, cis*-1,3-dichloro-5,6,9,10,13,14-hexahydrocyclo-dodeca[*c*]pyridine (**19**), its *cis,trans*-isomer (42%; 2:1 molar ratio) and the novel *trans, cis*-amide (**20**), whose structure was confirmed by an X-ray crystallographic study,[4] together with its *cis, trans*-isomer. The suggested reaction pathway to the major isomers is shown below.

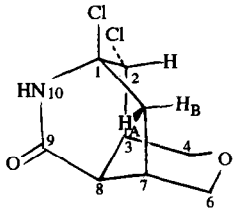


Suprafacial [1,5] hydrogen shift gives compound (**21**), where the rigidity of the cyclododecadiene ring hinders aromatisation to form (**19**) by a *syn*-coplanar elimination of HCl, and compound (**20**) appears to result from reaction of (**21**) with water upon chromatography on silica gel.[10]

References

1. Barlow, M.G.; Haszeldine, R.N.; Simpkin, D.J. *J. Chem. Soc., Perkin I* **1982**, 1245–1249.
2. *E.g.*, Carruthers, W *Some Modern Methods of Organic Synthesis*; Cambridge Univ. Press, 3rd. edit. 1986, p. 215.
3. Loving, B.A; Sydner, C.E.; Whittier, G.L.; Fountain, K.R. *J. Heterocyclic Chem.*, **1971**, *8*, 1095–1996.

4. The structure has been confirmed by X-ray crystallography: Barlow, M.G.; Pritchard, R.G.; Sibous, L.; Tipping, A.E., to be published in *Acta Cryst. (C)*.
5. The regioselectivity is in accord with that observed for reaction with hex-1-ene, where a 1:2 ratio of 3- and 4-*n*-butyl-2,6-dichloropyridine is obtained: Barlow, M.G.; Sibous, L.; Tipping, A.E. unpublished results.
6. We have so far been unable to obtain this completely free of its isomer (**12**). The structure shown is inferred from ^{1}H NMR (including COSY and selective decoupling) and ^{13}C NMR (including DEPT 135°) studies.



1,2-Dichloro-5-oxa-10-azatricyclo[5.3.1.$0^{3,8}$]-undecan-9-one
(**13**)

^{13}C NMR, $CDCl_3$: δ 172.8 (C–9), 77.2 (C–1), 69.5, 67.9 (C–4, 6), 66.1 (C–2), 43.0, 42.6 (C–3, 8), 41.1 (C–11) and 29.3 (C–7). ^{1}H NMR: δ 7.58 (broad, H–10, $^{4}J_{10-8}$ = 1 Hz), 4.28 (d, H–2, $^{3}J_{2-3}$ = 2.5 Hz), 4.01 (broad dd, H–4*e*, $^{2}J_{4-4}$ = 11.6, $^{3}J_{4e-3}$ 2.0, $^{4}J_{4e-6e} \leq$ 1Hz), 3.75 (broad dd, H–6*e*, $^{2}J_{6-6}$ = 11.5, $^{3}J_{6e-7}$ = 1.5, $^{4}J_{4e-6e} \leq$ 1 Hz), 3.46 (dd, H–4*a*, $^{2}J_{4-4}$ = 11.6, $^{3}J_{4a-3}$ = 1.7 Hz), 3.45 (dd, H–6*a*, $^{2}J_{6-6}$ = 11.5, $^{3}J_{6a-7}$ = 1.4Hz), 2.56 (dd, H–11A, $^{2}J_{11A-11B}$ = 14.0, $^{3}J_{11A-7}$ = 12.4), 2.54 (broad td, H–8, $^{3}J_{8-3}$, $^{3}J_{8-7} \approx 2$, $^{4}J_{8-10} \approx$ 1Hz), and 2.22 (broad d, H–11B, $^{2}J_{11B-11A} \approx$ 14 Hz) overlapping with 2.21 (broad d, H–7, $^{3}J_{7-11A} \approx$ 12 Hz). Noteworthy is the large magnitude of $^{3}J_{7-11A}$, corresponding to a near zero dihedral angle, which is absent from $^{4}J_{2-3}$, and the long-range couplings $^{4}J_{8-10}$ and *equatorial–equatorial* $^{4}J_{4-6}$, where the **W** pathway operates.

7. Fritz, H.; Weis, C.D.; Winkler, T, *Helv. Chim. Acta* **1976**, *59*, 179–190.
8. HCl is produced in the reaction and may be responsible for removal of the allyl ether grouping.
9. In reactions of (**1**) with cyclododecene, the *trans*-isomer is much more reactive than the *cis*-isomer: Barlow, M.G.; Sibous, L.; Tipping, A.E. unpublished results.
10. Spectroscopic data (IR, ^{1}H and ^{13}C NMR, mass) for the compounds described are listed in Sibous, L *Cycloaddition Reactions of 3,5,6-Trichloro-1,2,4-triazine*, University of Manchester, 1991, including the following ^{13}C NMR chemical shift data (ppm, 75 MHz in $CDCl_3$).
    6: 160.2 (C=N), 83.1, 71.5 (CCl), 47.5, 45.0 and 29.8.
    7: 161.5 (C=N), 84.4, 72.2 (CCl), 50.2, 44.4 and 30.8.
    8: 169.8 (C=O), 77.4, 72.2 (CCl), 50.9, 45.1 and 31.5.
    9: 171.2 (C=O), 85.0, 63.9 (CCl), 46.3, 45.1 and 29.3.
    10: 159.4 (C=N), 96.6, 77.6 (CCl), 50.7, 50.4, 25.6 and 25.1.
    12: 168.7 (C=O), 72.8, 69.1 (CCl), 66.4 (CH_2O), 44.1 (CH_2) and 37.4 (CH).

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