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RING-EXPANSION BY A WITTIG-PRÉVOST SEQUENCE

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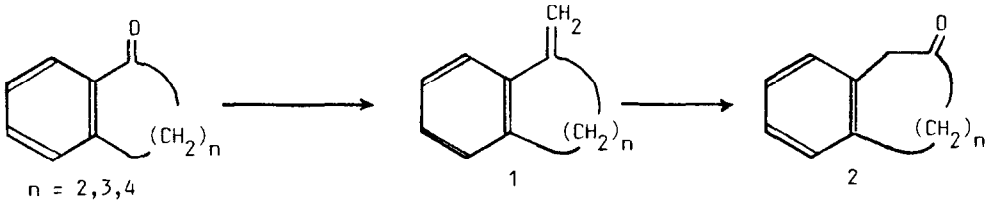
α-Tetralones and an N-tosyl-tetrahydroquinol-4-one undergo 1-carbon ring-expansion on being subjected to the Wittig reaction followed by Prévost reaction ($AgNO_3/I_2$/MeOH).

Preparatively useful ring expansions, which involve carbenium ion rearrangements, can encompass several variations such as, for example, the Demyanov reaction.[1] In particular, the sequence outlined in equation 1, in which the Wittig products (1) from cyclic aryl ketones undergo ring expansion on treatment with thallium(III) nitrate in methanol, has been developed.[2] By the inclusion of trimethyl orthoformate, the products can be diverted to the corresponding acetal. A mechanistically similar transformation[3a] has been invoked for



Eq. 1

the thallium(III) nitrate mediated rearrangement of aryl ketones to arylacetic acids.[3b] In the latter case, the 'Prévost' reaction conditions ($AgNO_3/I_2$/MeOH) have been shown to be an adequate and convenient replacement for thallium ion. It occurred to us, therefore, that the ring expansion step in equation 1 might also be brought about advantageously under Prevost conditions. The ketone (2) would be of considerable synthetical interest in connection with bridged ring nitrogen heterocyclics.[4]

α-Tetralones were readily converted into the corresponding exo-cyclic alkenes (1a)-(1e) using modifications of literature methodology.[5] In most cases, some of the endo-isomer (3) was also obtained. Exo-cyclic unsaturated esters [e.g. (1f)] were much more troublesome to prepare and, although detected, could not be isolated in acceptable yields.

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All new compounds gave satisfactory elemental analyses and were further identified by n.m.r. and mass spectroscopy.

Treatment (of 1a) under Prévost conditions afforded a mixture of two products, an acetal and an enol ether, in 65% yield. Subsequent hydrolysis of the mixture gave a single, crystalline product whose spectroscopic properties were consistent with either structure (1h) or (4b). Since these alternatives could not be satisfactorily differentiated by the usual spectroscopic methods, single crystals of the compound were subjected to X-ray crystallographic analysis.[6] Thus the hydrolysis product, as depicted in figure 1, was unambiguously identified as the ring-expanded enol (4b) which is derived ultimately from both the acetal (5) and enol ether (4a). Presumably the reaction proceeds via an intermediate such as 6.

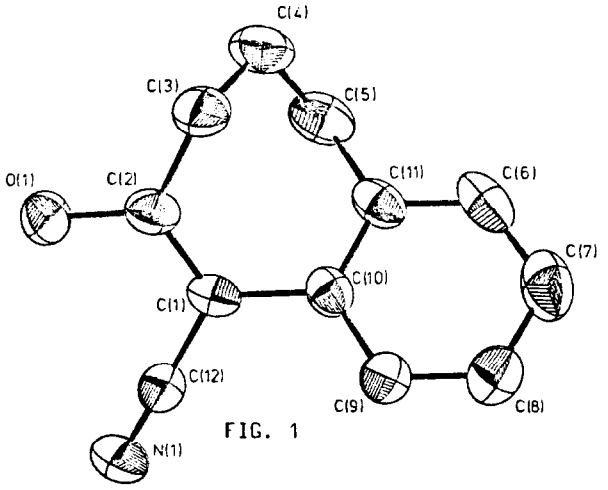


FIG. 1

The scope of the ring-expansion procedure has been investigated more extensively and the results are summarised in Table 1. From our work, several general observations can

TABLE 1

Product	2a	2b	2c	2d	2e
Yield %	25	80	57	72	83

be made. Except where X or Y (1) =CN, ketones (2) were obtained directly. Optimum yields were obtained using dry methanol as solvent (other alcohols gave poorer results), a reactant ratio $AgNO_3$:I_2:substrate of 2:1:1 was desirable, and the $AgNO_3$ (finely ground) had to be refluxed with methanol for 1 h prior to the addition of the other reactants. Reaction times of the order of 5 h were normally required (tlc monitoring). In only one case (2c) the product was iodinated: the reason for this is not fully understood but is being further investigated. Application of the ring expanded products in further synthetic work will be reported later.

The Wittig-Prévost sequence was also applied to the heterocyclic ketone (7).[7] Reaction with diethyl cyanomethylphosphonate yielded both the endo- (20%) and exo-isomers (60%), [(8) and (9) respectively], which were separated by chromatography and fractional crystallisation. The exo-isomers, either separately or in admixture, reacted with iodine

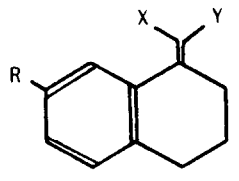
and silver nitrate in methanol to give the acetal (10a) [m.p. 161°C; 60%]. The latter could be methylated (LDA, MeI, THF) giving a mixture of (10b) [35%] and the enol ether (11a) [20%]. Hydrolysis of (10a) [conc. HCl/EtOH/80°/30h] afforded the enolic nitrile (11b). These products represent the first 1-benzazepine derivatives having effectively ketogroups at C-4.[8]

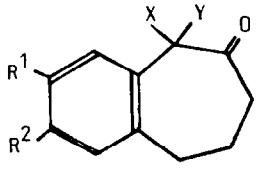
Typical procedure (for (2e)

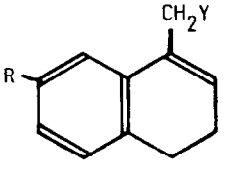
Silver nitrate (2.71 g) was crushed and suspended in dry methanol (75 cm^3). The suspension was refluxed and stirred until the silver nitrate had dissolved. Iodine (2.02 g) and the compound (1e, 1.50 g) were added simultaneously in methanol (50 cm^3) and the reaction mixture refluxed for 5 h.

The reaction mixture was then cooled in ice, after which the silver iodide was filtered off, and the filtrate diluted with water (200 cm^3) and extracted with ether (4 x 100 cm^3). The combined ethereal layers were washed with sodium metabisulphite solution (5 x 20 cm^3) and saturated sodium chloride solution (3 x 20 cm^3). After drying (Na_2SO_4), the solvent was removed in vacuo to yield a yellow gum (1.5 g, 92%). GLC (5% carbowax, 220°C) indicates the product consists of one major peak (90%) with minor peaks (10%).

Kugelrohr distillation (150°C, 0.2 mmHg) gave a white semi-solid: [Found: C,76.25; H,8.05%; M^+204.1137. $C_{13}H_{16}O_2$ requires C,76.45; H,7.9%; M,204.1105] $\nu_{max.}$(film) 1705 (C=O), 1 605 cm^{-1} (C=C). δ 1.41 (3H, d, CH_3), 1.95 (3H, m, 3-H and CH_2 + CH), 2.41-2.90 (4H, m, 2 x ring CH_2), 3.76 (3H, s, OCH_3), 6.60-7.05 p.p.m. (3H, m, aromatic).





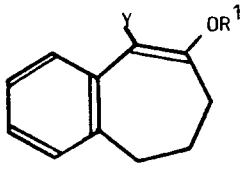


1a; R=X=H, Y=CN
b; R=X=Y=H
c; R=H, Y=Me, Y=CN
d; R=OMe, X=Y=H
e; R=OMe, X=H, Y=Me

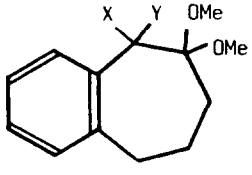
f; R=X=H, Y=CO_2Et
g; R=H, X=OMe, Y=CN
h; R=H, X=OH, Y=CN

2a; R^1=R^2=X=H, Y=CN
b; R^1=R_2=X=Y=H
c; R^1=OMe, R^2=I, X=Y=H
d; R^1=R^2=X=H, Y=Me
e; R^1=OMe, R^2=X=H, Y=Me

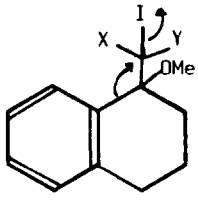
3



4a; R^1=Me, Y=CN
b; R^1=H, Y=CN



5; X=H, Y=CN



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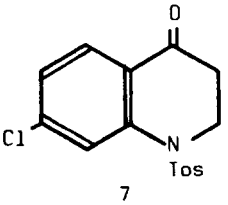

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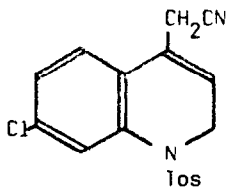

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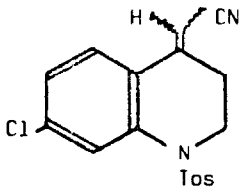

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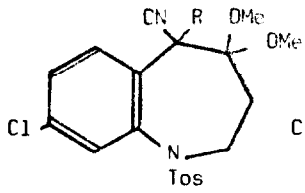
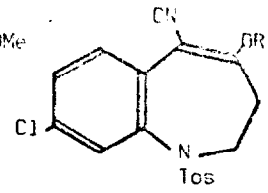


10 a; R=H
b; R=Me



11 a; R=Me
b; R=H

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6. Crystal Data: Compound (4), $C_{12}H_{11}NO$, M = 185.2 monoclinic, a = 9.478(3), b = 15.415(4), c = 13.880(8) Å, ß=99.42 (4)°, μ = 2000.6Å^3, space group $P2_1/n$(non-standard setting $P2_1/c$ No.14), Z = 8, D_c = 1.230 g cm^{-3}, (Mo-K_α) = 0.74 cm^{-1}, F(000) = 784. The intensity data were collected on a CAD-4 diffractometer (Mo-K_α radiation, ω-2θ scanning) and corrected for Lorentz and polarisation. Of 2435 unique data, 1468 had $I > 2\sigma(I)$. The structure was solved by direct methods (SHELX84) and refined (SHELX76) by block-matrix least squares methods (C,N,O anisotropic). The hydrogen atoms were located on difference-Fourier maps and included at idealised positions with fixed temperature factors (μ iso = 0.10Å^2) in the final stages of refinement. At convergence, R and R_ω were 0.045 and 0.056 respectively where $\omega = [\sigma^2(F) + 0.001\ F^2]^{-1}$ The bond distances were all within expected ranges (mean e.s.d.'s for bonds and angles were 0.005Å and 0.4° respectively). The crystal structure consists of two independent molecules of (4b) per asymmetric unit which differ little in terms of geometrical paramenters or conformation and are linked by an extended network of hydrogen bonding between -OH and -CN groups of neighbouring molecules.

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