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THE RITTER REACTION IN THE SYNTHESIS OF ORTHO-FUSED NITROGEN-CONTAINING HETEROCYCLES

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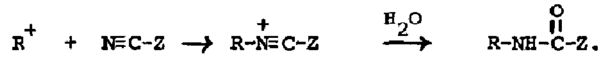
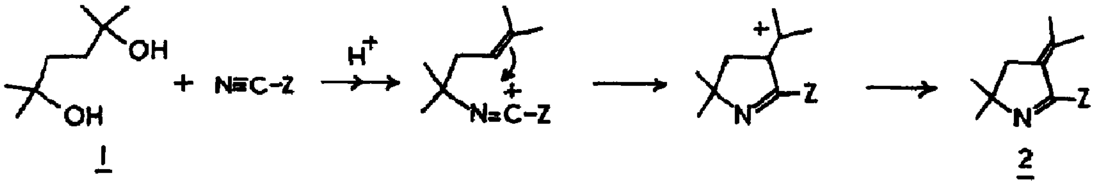
Abstract: The acid-catalysed condensation of a 1,4- and a 1,5-ditertiary diol with various arylated nitriles is shown to provide a simple and novel route to reduced benz[f]indoles, naphth[1,8a,8-fg]indoles, benzo[4,5]cyclohepta[1,2-b]pyrroles, and benzo[g]quinolines.

In the Ritter reaction(1) a nitrilium cation (generated by reaction of a nitrile with a carbonium ion) is captured by an external nucleophile, water, to give an N-substituted amide:



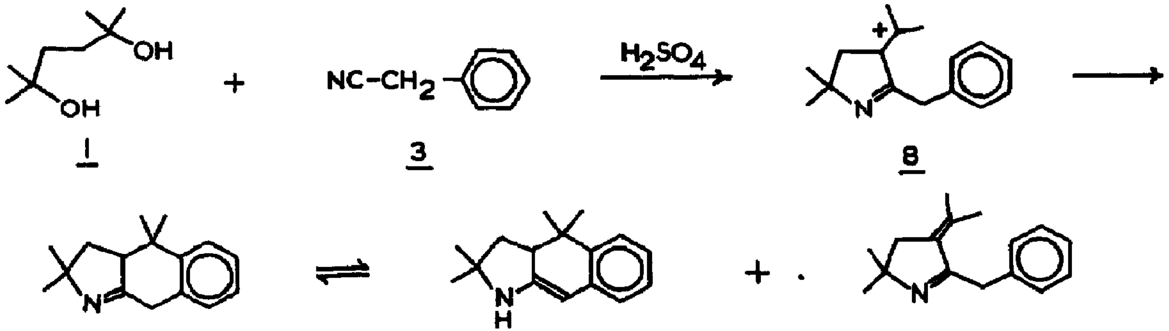
$$R^+ + N\equiv C\text{-}Z \longrightarrow R\text{-}\overset{+}{N}\equiv C\text{-}Z \xrightarrow{H_2O} R\text{-}NH\text{-}\overset{O}{\overset{\|}{C}}\text{-}Z.$$

If the carbonium ion precursor also contains a nucleophilic group then intramolecular capture of the nitrilium cation may occur to give a heterocycle.(1)(2) Thus Meyers and Ritter(3) showed that a wide variety of nitriles can be condensed with 2,5-dimethylhexane-2,5-diol, 1, to give 1-pyrrolines, 2, in 55-80% yield.



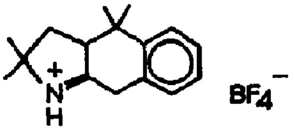
We wish to report that this type of condensation can lead to good yields of polycyclic heterocycles when the group Z contains a suitably positioned, and adequately reactive, aromatic ring which may further trap the carbonium ion. We present here four representative examples of the use of this reaction in a remarkably simple synthesis of ring systems which are either novel or preparable otherwise only by multi-stage syntheses.

Condensation of diol 1 with benzyl cyanide, 3, (1:1 moles, 0-20°, 4 hr), in sulphuric acid, gave a 72% yield of a tetrahydrobenz[f]indole, 4 (found to exist as a tautomeric mixture of 4a and 4b(4)), and a 15% yield of the expected pyrroline 5. Compound 4 was isolated and characterised as its tetrafluoroborate salt 6(5), mp. 165-166° (from ethyl acetate/ethanol) [$\bar{\nu}$ (nujol) 3200, 3120 (N-H), 1690 ($C=N^+$), 1080 broad (BF_4^-) cm^{-1}; δ ($CDCl_3$) 1.05, 1.48, 1.60, 1.66 (4 x s, 4 x CH_3), 2.08 (dd, J=9 and 14 Hz, -CHH-CH), 2.38 (dd, J=9 and 14 Hz, -CHH-CH-), 3.58 (t, J=9 Hz, $-CH_2-CH-$), 4.38 (broadened s, $ArCH_2$), 7.1-7.6 (m, 4 x ArH), 9.12 (broad, NH) : protons resonating at 4.38 and 9.12 δ exchange with D_2O].



1 3 8

4a 4b 5



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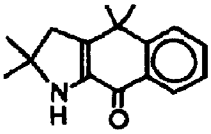

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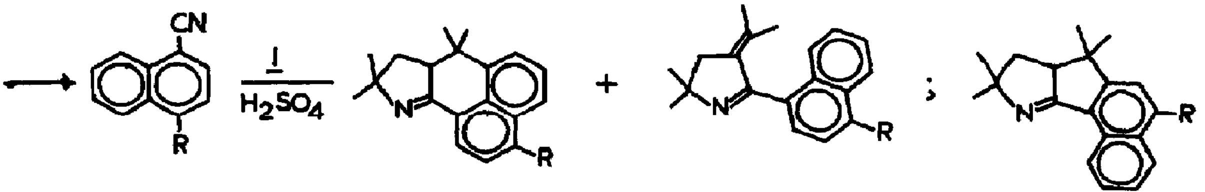
Exposure of the crude mixture of 4 and 5 to air (methanol, 8 hr, ~25°) led to rapid autoxidation of 4, and gave the yellow α-amino-enone 7(5), mp. 105-107.5°, which was isolated by recrystallisation (from petroleum ether/propan-2-ol) [$\tilde{\nu}$ (CCl_4) 3380 sharp, 3330 broad (both N-H), 1655 (C=O) cm^{-1}; δ ($CDCl_3$) 1.32 (s, 2 x CH_3), 1.43 (s, 2 x CH_3), 2.70 (s, CH_2), 3.45 (broad, NH; exchanges with D_2O), 7.2-7.7 (m, 3 x ArH), 8.31 (m, ArH ortho to C=O)]. Distillation of the oil remaining after removal of 7 afforded 5(5)(6) bp. 98°/0.2 mm. Since pyrroline 5 is not (<5%) cyclised to 4 on treatment with sulphuric acid (4 hr, 0-5°) we interpret the formation 4 and 5 as involving competitive partition of ion 8(7).

A number of alternatives to diol 1 as carbonium ion precursor were investigated. 2,5-Dichloro-2,5-dimethylhexane, 2,2,5,5-tetramethyltetrahydrofuran, and 2,5-dimethylhex-4-en-2-ol(8) all proved satisfactory, giving good yields of 4 + 5 (69, 93, 86% respectively) each rich in tricycle (80, 85, 78% of the basic fraction, respectively).

Condensation of diol 1 with 1-naphthalenecarbonitrile, 9, gave the pyrroline 11(5)(6), mp. 100° (from petroleum ether), (62% yield), and the tetracycle 10(5), bp. 145°/0.2 mm (31% yield) which contains the novel naphth[1,8a,8-fg]indole nucleus.

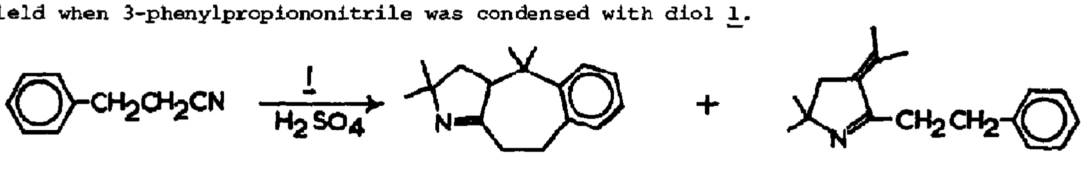


9 R=H 10 R = H 11 R = H 12 R = H

13 R=CH_3 14 R = CH_3 15 R = CH_3 16 R = CH_3

The proportion of 10 in the mixture of 10 + 11 could be increased from 33% to 75% by heating the mixture in polyphosphoric acid (PPA; 2 days, 180°). Removal of the remaining pyrroline was achieved by treating the enriched mixture with a large excess of iodomethane in ether, which led to precipitation of the pyrroline methiodide$^{(5)(6)}$, mp. 146° (from ethyl acetate/acetone), compound 10 remaining largely unchanged in solution. Structure 10, whose formation requires cyclisation at the peri position of the naphthalene ring, was supported by spectroscopic data [$\bar{\nu}$ (CCl_4) 1628 (C=N) cm^{-1}; δ ($CDCl_3$) 0.94, 1.27, 1.44, 1.51 (4 x s, 4 x CH_3), 1.72 (dd, J=9.5 and 13 Hz, -C$\underline{H}$H-), 1.96 (dd, J=9 and 13 Hz, -CH$\underline{H}$-), 3.25 (dd, J=9 and 9.5 Hz, -C$\underline{H}$-CH_2-), 7.2-8.0 (m, 5 x ArH), 8.33 (dd, J=1.5 and 7 Hz, ArH ortho to C=N)]. An isomeric structure, 12, arising from cyclisation at the carbon ortho to the nitrile group in 9, was ruled out on the basis of results obtained with 4-methyl-1-naphthalenecarbonitrile, 13. Compound 13, like the unsubstituted nitrile 9, gave with diol 1 a mixture of pyrroline, 15 (39%), and tetracycle, 14,$^{(5)(6)}$ bp. 130°/0.1 mm (39%). With the exception of the additional aromatic methyl resonance (at 2.62 δ), the 0-4δ region of the ^1H nmr spectrum of 14 could be virtually superimposed on that of 10, suggesting that the two heterocycles belonged to the same structural series. However, the aromatic resonance at lowest field (that associated with the proton ortho to the C=N group) appeared as a simple doublet (8.27δ, J=7.5 Hz), in contrast to the doublet of doublets for the analogous proton in 10. These results are in accord with structures 10 and 14 for the tetracycles, but not with 12 and 16.

The benzo[4,5]cyclohepta[1,2-b]pyrrole 17 was formed in 16% yield, and the pyrroline 18 in 49% yield when 3-phenylpropiononitrile was condensed with diol 1.

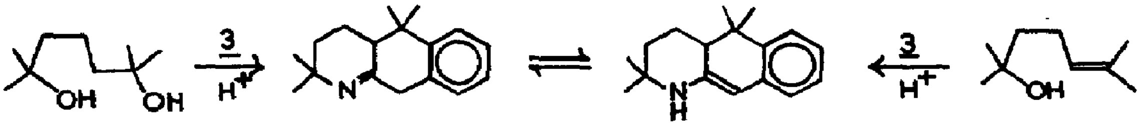


17 18

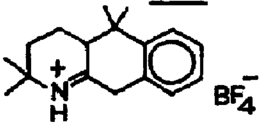
Compound 18 was readily isolated from the mixture of bases as its picrate salt$^{(5)(6)}$, mp. 148-9° (from ethanol). To obtain the tricyclic base, the base mixture was first heated with PPA (17 hr, 175°) under nitrogen to increase the percentage of 17 in the mixture (to 83%, in 59% recovery). Compound 17 was then isolated as the tetrafluoroborate salt$^{(5)}$, mp. 143-4° (from ethyl acetate) [$\bar{\nu}$ (nujol) 3180, 3100 (N-H), 1678 ($C{=}N^+$), 1070 broad (BF_4^-) cm^{-1}; δ ($CDCl_3$) 1.34, 1.47, 1.51, 1.59 (4 x s, 4 x CH_3), 1.8-3.8 (complex, 7 aliphatic H), 7.0-7.6 (m, 4 x ArH)].$^{(9)}$

Yields of basic material from the reaction of the homologous diol 19 with benzyl cyanide, 3, were low (14%) when the conditions used successfully for 1 with 3 were employed. However, a change to methanesulphonic acid as solvent, and use of a 100% excess of nitrile, together with a somewhat higher reaction temperature (diol added to nitrile/solvent over 30 min at 0-10°, then 4 hr at 15-25°) led to a 61% yield of the air-sensitive benzo[g]quinoline 20$^{(10)(11)}$, which, like 4, could be conveniently characterised and stored as the tetrafluoroborate salt 21$^{(5)}$, mp. 214-5° (from propan-2-ol) [$\bar{\nu}$ (nujol) 3230, 3150 (N-H), 1677 ($C{=}N^+$), 1090 broad (BF_4^-) cm^{-1}; δ ($CDCl_3$) 1.07, 1.49, 1.54, 1.59 (4 x s, 4 x CH_3), 1.7-2.2 (m, -CH_2-CH_2-), 2.6-3.1 (m, CH-$C{=}N^+$), 4.32 (broadened s, ArCH_2), 6.9-7.5 (m, 4 x ArH); ^{13}C δ ($CDCl_3$) 16.5 (t, $\underline{C}H_2$-CH), 24.4, 24.4, 26.9, 27.9 (4 x q, 4 x $\underline{C}H_3$), 32.9 (t, $\underline{C}H_2$-CH_2-CH), 36.0 (t, $\underline{C}H_2$Ar), 38.9 (s, Ar-$\underline{C}(CH_3)_2$), 46.9 (d, CH_2-CH_2-$\underline{C}$H), 57.6 (s, N-$\underline{C}(CH_3)_2$), 123.7, 127.6, 127.6, 128.5 (4 x d, 4 x $\underline{C}_{Ar}$-H), 127.6

(s, CH_2-$\underline{C}_{Ar}$), 143.2 (s, $\underline{C}_{Ar}$-$C(CH_3)_2$), 191.9 (s, $C=N^+$)].



19 20a 20b 23



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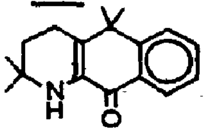

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When the basic fraction from the reaction of 3 and 19 was exposed to air (neat, or in methanol) the only product detectable (^1H nmr) was the ketone 22. There was no indication of any 2-benzyl-3-isopropylidene-6,6-dimethyl-3,4,5,6-tetrahydropyridine, the counterpart of the pyrrolines 5, 11, 15, and 18 obtained from diol 1.$^{(12)}$ The structure of compound 22$^{(5)}$, mp. 65-6° (from petroleum ether) followed from its spectroscopic properties, which paralleled those of 7 [$\bar{\nu}$ (CCl_4) 3400 (N-H), 1645 (C=O) cm^{-1}; δ ($CDCl_3$) 1.17 (s, 2 x CH_3), 1.46 (s, 2 x CH_3), 1.70 (t, "J"=7 Hz, $C\underline{H}_2$-CH_2-C=C), 2.46 (t, "J"=7 Hz, CH_2-$C\underline{H}_2$-CH), 4.5 (broad, NH), 7.1-7.7 (m, 3 x ArH), 8.20 (m, ArH ortho to C=O)]. The use of the unsaturated alcohol 23, in place of diol 19, provided an even better synthesis of tricycle 20. Yields of 82% were obtained using methanesulphonic acid as solvent, and a procedure identical to that used for reaction between 3 and 19.

The chemistry and pharmacology of these, related, and derived compounds are the subjects of forthcoming publications. We gratefully acknowledge the award of Research Assistantships (to M.S. and P.W.S.) by Kirklees Metropolitan Council.

REFERENCES and FOOTNOTES

1. L.I. Krimen and D.J. Cota, Organic Reactions, 1969, 17, 213.
2. F. Johnson and R. Madronero, Advances in Heterocyclic Chemistry, 1966, 6, 95.
3. A.I. Meyers and J.J. Ritter, J.Org.Chem., 1958, 23, 1918.
4. Ratio of 4a:4b = 3:1 ($CDCl_3$, 34°; $Ar\underline{CH}_2$ 3.80δ, N-C=C$\underline{H}$-Ar 5.25δ).
5. Acceptable microanalytical results (±0.33%) were obtained for this compound.
6. The spectroscopic properties of this compound were in full agreement with the assigned structure.
7. A study of the condensation of diol 1 with a series of α- and ring-substituted benzyl cyanides has shown that the ratio of pyrroline to tricycle is controlled by electronic and steric factors which, in extreme cases, can lead to exclusive formation of either the pyrroline (as in the case of p-nitrobenzyl cyanide; 60% yield) or the tricycle (as in the case of α,α-dimethylbenzyl cyanide; 80% yield).
8. Material prepared (in 4% yield) by dehydration of diol 1 according to T.A. Favorskaya and N.P. Ryzhova, Zhur.Obshchei Khim., 1956, 26, 423 [Chem.Abs., 1956, 50, 13861] was used. ^1H nmr analysis showed that it contained 33% of 2,5-dimethylhex-5-en-2-ol.
9. Only one example of this ring system has been reported hitherto: Y. Hayashi and T. Sakan, Nippon Kagaku Zasshi, 1960, 81, 1894 [Chem.Abs., 1962, 56, 2397a].
10. In contrast, condensation of diol 1 with benzyl cyanide (1:1 moles) in methanesulphonic acid gave only a 16% yield of basic material together with a 72% yield of the bis-amide$^{(5)(6)}$ [$C_6H_5CH_2CONH$-$C(CH_3)_2$-$CH_2]_2$, mp. 238.5-239.5° (from acetic acid).
11. Ratio of 20a:20b = 1:1 ($CDCl_3$, 34°; $Ar\underline{CH}_2$ 3.72δ, N-C=C$\underline{H}$-Ar 5.31δ).
12. This result is in keeping with the lower strain-energies associated with 6:6 ring fusion in comparison with 5:6 fusion (see, eg., N.L. Allinger et al., J.Amer.Chem.Soc., 1971, 93, 1637).

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