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# INTRAMOLECULAR DIELS-ALDER REACTIONS OF 1,2,4-TRIAZINES: SYNTHESIS OF TRICYCLIC CONDENSED PYRIDINES AND PYRAZINES[1]

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**Abstract:** Syntheses of several 6,6,6-tricyclic condensed pyridines and pyrazines utilizing intramolecular Diels-Alder reactions of 1,2,4-triazines with alkyne and nitrile dienophiles are detailed. The cyclizations are facilitated by the presence of conformationally restrictive planar aromatic rings in the chain tethering the diene and the dienophile.

The ability of heterocyclic azadiene systems, particularly 1,2,4,5-tetrazines and 1,2,4-triazines, to participate in inverse electron demand Diels-Alder reactions with electron-rich dienophiles is well documented.[2] Exploitation of the entropic advantage inherent in intramolecular reactions has allowed extensions of such cyclizations to include less reactive dienophiles such as terminal alkynes and alkenes. Recent publications from our laboratory describe successful applications of this concept to the preparation of various bicyclic fused pyridines (inter alia, thieno[3,2-c]pyridines, thieno[2,3-b]pyridines, furo[2,3-b]pyridines) from appropriately substituted 1,2,4-triazines.[3] We report herein applications of this strategy which provide convenient routes to a variety of tricyclic condensed pyridines and pyrazines.

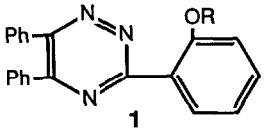
5,6-Diphenyl-3-(o-hydroxyphenyl)-1,2,4-triazine was prepared from salicylhydrazide, benzil and ammonium acetate according to the procedure of Atkinson and Cossey.[4] Alkylation with propargyl bromide provided 1a. 5,6-Diphenyl-3-(o-aminophenyl)-1,2,4-triazine[4] was acylated with trifluoroacetic anhydride, and the resulting highly acidic amide was alkylated with propargyl bromide to afford 2a. Hydrolysis of this latter compound gave the secondary amine 2b.

Heating the 3-(o-propynyloxy)triazine 1a in refluxing benzene afforded 2,3-diphenyl-5H[1]benzopyrano[4,3-b]pyridine 3 in 64% yield. Similarly, 5,6-dihydro-2,3-diphenyl-6-trifluoroacetylbenzo[H]-1,6-naphthyridine (4) was obtained in 74% yield from 2a in refluxing toluene.[5] Intramolecular cyclization of the secondary amine 2b required refluxing bromobenzene, and under these rather harsh conditions, air oxidation of the initially formed 5,6-dihydro derivative occurred to give the fully aromatic 1,6-naphthyridine 5 (43%).

The above reactions were then successfully extended to the use of nitrile dienophiles. 5,6-Diphenyl-3-(o-hydroxyphenyl)-1,2,4-triazine and 5,6-diphenyl-3-(o-trifluoroacetamidophenyl)-1,2,4-triazine were alkylated with bromoacetonitrile to afford 1b and 2c respectively. When heated neat at 225-235 °C under nitrogen, 1b cyclized in modest (45%) yield to 2,3-diphenyl-5[H][3,4-b]benzopyranopyrazine 6. In analogous fashion, 2c cyclized in refluxing diphenyl ether to give a mixture of 2,3-diphenyl-5,6-dihydro-6-trifluoroacetylpyrazino[2,3-c]quinoline (7) (36%) and the deacylated, fully aromatic system 8 (47%). These transformations are worthy of particular note because of the normal recalcitrance of electron-deficient nitriles to undergo Diels-Alder reactions with electron-deficient azadienes.[6] Access to pyrazines via the Diels-Alder reaction has previously been severely limited by a paucity of reactive 1,4-diazadienes;[7] utilization of a nitrogen-containing dienophile in a cycloaddition reaction with a suitable azadiene offers an attractive alternative. The conversion of 2c to 7 and 8 represents the first synthesis of a pyrazino[2,3-c]quinoline.

In intramolecular Diels-Alder reactions, the length of the chain connecting the diene with the dienophile can exert a profound effect on the reaction rate. Entropic considerations dictate that 3-atom chains (which lead to fused 5-membered rings) offer the optimum intramolecular advantage;[8] temperature requirements for cyclization of substrates with 4-atom bridges (which lead to fused 6-membered rings) are usually substantially higher.[9] Conformational restraints in the connecting chain - ideally achieved by incorporation into the chain of a planar aromatic ring, thus providing a biphenyl-like cycloaddition precursor - augment these intramolecular advantages,[10] as can be seen from the facility with which the above cycloaddition reactions occur.

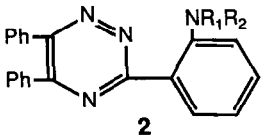
We are currently exploring the use of other and potentially more reactive nitrogen-containing dienophiles in an attempt to extend the synthetic utility of this potentially general route to condensed pyrazines.



1

a, R = $CH_2C{\equiv}CH$

b, R = $CH_2CN$

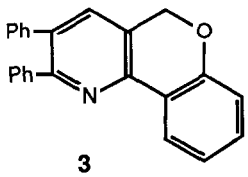


2

a, $R_1 = CH_2C{\equiv}CH$, $R_2 = COCF_3$

b, $R_1 = CH_2C{\equiv}CH$, $R_2 = H$

c, $R_1 = CH_2CN$, $R_2 = COCF_3$



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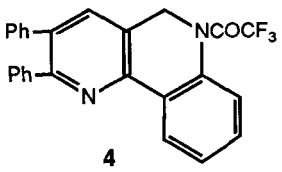

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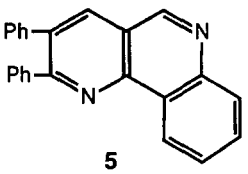

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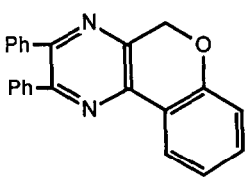

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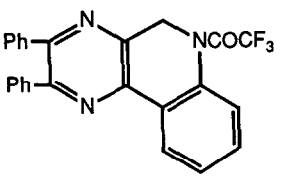

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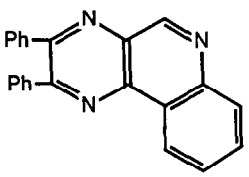

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## References and Notes

1. We are greatly indebted to Eli Lilly & Company, Indianapolis, Indiana, for support of this research.

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3. (a) Taylor, E. C.; Macor, J. E. Tet. Lett., **1985**, *26*, 2415, 2419; (b) Taylor, E. C.; Macor, J. E. Tet. Lett. submitted for publication.

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5. The cycloaddition proceeded slowly in refluxing benzene.

6. A single example of an intramolecular nitrile-pyrimidine cycloaddition has been described, although no yield was reported: Davies, L. B.; Leci, O. A.; Sammes, P. G.; Watt, R. A. J. Chem. Soc. Perkin Trans. 1, **1978**, 1293.

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