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Intramolecular Diels-Alder Reactions of 1,2,4-Triazines: Exploitation of the Thorpe-Ingold Effect for the Synthesis of 2,3-Cyclopentenopyridines and 5,6,7,8-Tetrahydroquinolines

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Summary: *Intramolecular inverse electron-demand Diels-Alder reactions of 1,2,4-triazines assisted by the Thorpe-Ingold effect have been utilized in novel syntheses of 2,3-cyclopentenopyridines and 5,6,7,8-tetrahydroquinolines.*

We have previously described unusually facile intramolecular Diels-Alder reactions of electron-deficient 1,2,4-triazines to form fused pyridines (thieno[2,3-c]pyridines, thieno[2,3-b]pyridines, and furo[2,3-b]pyridines),[1] and related reactions of 1,2,4-triazines with dienophilic sidechains tethered through a planar aromatic ring;[2] the resulting "entropic assistance" makes possible the utilization of unactivated acetylenes and even nitriles as dienophiles. We describe in this paper an alternate strategy for facilitation of these intramolecular reactions which exploits the Thorpe-Ingold ("gem-dimethyl" or "scissors") effect[3] and leads to a novel and effective synthesis of 2,3-cyclopentenopyridines and 5,6,7,8-tetrahydroquinolines. The former compounds are of considerable interest as C-3' quaternizing groups for cephalosporins; previous methods for their synthesis (generally from cyclopentanones) have been reviewed.[4] By contrast, the synthesis described herein utilizes an aliphatic unit, introduced by a nucleophilic displacement reaction unto the 1,2,4-triazine ring, to provide both the cyclopenteno ring and two of the ring carbons of the annulated pyridine ring. In principle, a wide variety of substituted cyclopentenopyridines should be available by utilization of appropriately functionalized aliphatic sidechains. Homologation of the aliphatic sidechain by one carbon atom leads to 5,6,7,8-tetrahydroquinolines.

Condensation of 1,2-dicarbonyl compounds with S-methylthiosemicarbazide hydrogen iodide gives 3-methylthio-1,2,4-triazines,[5] which are efficiently oxidized with MCPBA to 3-methylsulfonyl-1,2,4-triazines (1).[1b] Dimethyl malonate, ethyl cyanoacetate and malononitrile were alkylated with 4-iodo-1-butyne,[6] and the

resulting mono-alkylated derivatives 2 were converted to their respective carbanions and reacted with the above 3-methylsulfonyl-1,2,4-triazines in anhydrous THF at r.t. Displacement of methylsulfinate[7] took place to give the 3-(4-pentynyl)-1,2,4-triazines 3. Characterization of these compounds was complicated by their propensity to cyclize to the functionalized cyclopentenopyridines 4, even at r.t. Although isolation of 3 was not as a consequence effectively achieved in every case, it nevertheless is clear that the efficiency of the displacement reaction is inversely related to increasing bulk in the X and Y groups in the nucleophiles 2. The crude reaction mixtures were therefore heated (in THF) for several hours to complete the intramolecular Diels-Alder reaction. Results are sumarized in Table 1. The Diels-Alder reaction itself (i.e., 3 4) proceeded in essentially quantitative yield, as judged by a comparison of the NMR spectrum of crude 3 with that of the product 4; the yields of 4 given in Table 1 are primarily a reflection of the initial displacement reaction leading to 3.

Alkylation of malononitrile, ethyl cyanoacetate and dimethyl malonate with 5-iodo-1-pentyne[6] gave the homologous monoalkylation products 5, which were converted to their anions and reacted with 6-(4-chlorophenyl)-3-methylsulfonyl-1,2,4-triazine. The displacement products 6a,b, which could readily be isolated, were then heated in refluxing chlorobenzene (132 °C, 36 hr) to give the 5,6,7,8-tetrahydroquinolines 7a,b (see Table 2). The deleterious effect of increasing size of the nucleophile on the effectiveness of the displacement reaction (here leading to 6) is even more dramatic in this homologous series; the subsequent intramolecular Diels-Alder reaction, by contrast, clearly proceeds well regardless of the nature of the X and Y groups in 5.

Since 5,6,7,8-tetrahydroquinolines are not accessible from quinolines (reduction of the latter leads to 1,2,3,4-tetrahydro derivatives), their ready availability from 1,2,4-triazines by the two-step procedure described here may merit further exploration.

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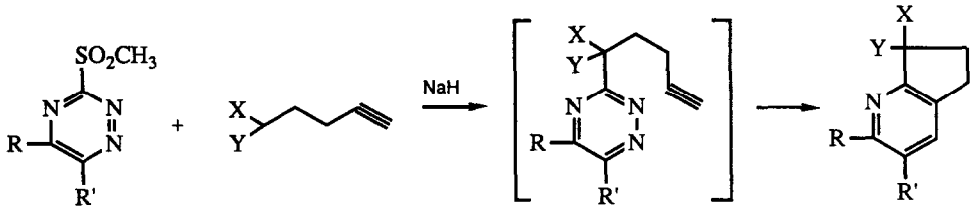
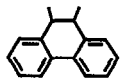
TABLE 1. Synthesis of 2,3-Cyclopentenopyridines



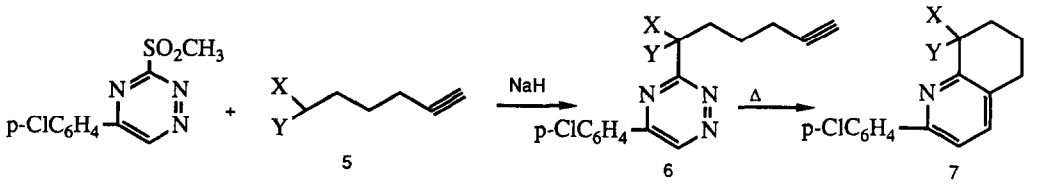
1 2 3 4

Cmpd	R	R'	X	Y	Yield,%
a	C_6H_5	H	COOMe	COOMe	41
b	p-ClC_6H_4	H	COOMe	COOMe	49
c			COOMe	COOMe	10[a]
d	p-ClC_6H_4	H	COOEt	CN	49
e	p-ClC_6H_4	H	CN	CN	80
f	p-ClC_6H_4	H	COOEt	$COCH_3$	trace[b]

[a] As judged by nmr, the yield of 3c was only 12%; the intramolecular cycloaddition reaction proceeded in 84% yield

[b] The displacement reaction gave only a trace of 3f

TABLE 2. Synthesis of 5,6,7,8-Tetrahydroquinolines



Cmpd	X	Y	Yield,%	
a	CN	CN	70	84
b	CN	COOEt	36	74
c	COOMe	COOMe	0	-

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7. See Konno, S.; Yokoyama, M.; Kaite, A.; Yamatsuta, I.; Ogawa, S.; Mizugaki, M.; Yamanaka, H. Chem. Pharm. Bull. Jpn., **1982**, *30*, 152, which describes the oxidation of 3-methylthio-5,6-diphenyl-1,2,4-triazine with potassium permanaganate to the 3-methylsulfonyl derivative, and displacement of methyl sulfinate from this intermediate by a number of nucleophiles, including the carbanions derived from ethyl cyanoacetate and ethyl acetoacetate.

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