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AN UNUSUALLY FACILE DIELS-ALDER REACTION WITH NOVEL 6-ALKYLTHIO DERIVATIVES OF 1,2,4-TRIAZINE

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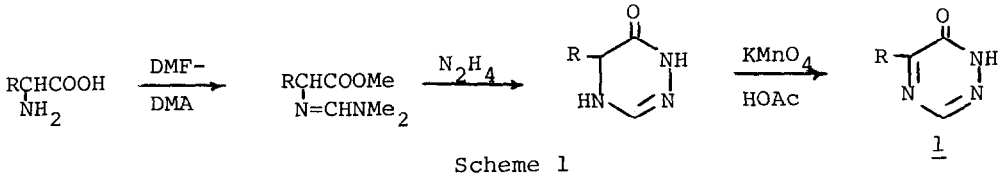
SUMMARY: Treatment of a series of 6-alkylthio-, 6-alkylsulfinyl- and 6-alkylsulfonyl-1,2,4-triazines with 1-pyrrolidinocyclopentene yields 3,4-cyclopentenopyridines. The observed rates of these cycloaddition reactions (sulfide < sulfoxide < sulfoxide) are consistent with an inverse electron-demand Diels-Alder reaction.

Inverse electron demand Diels-Alder reactions of 1,2,4,5-tetrazines (to give pyridazines and 1,2,4-triazines) and of 1,2,4-triazines (to give pyridines) are well documented and constitute useful synthetic routes to a variety of both simple and complex heterocyclic systems.[1,2] Conspicuous by their absence, however, are heterocyclic azadienes derived from 1,2,4-triazine-6-ones because no useful methods have been previously available for their preparation. We have recently developed a simple, versatile route to these previously unknown 1,2,4-triazine derivatives (Scheme 1),[3] and describe in the present paper their



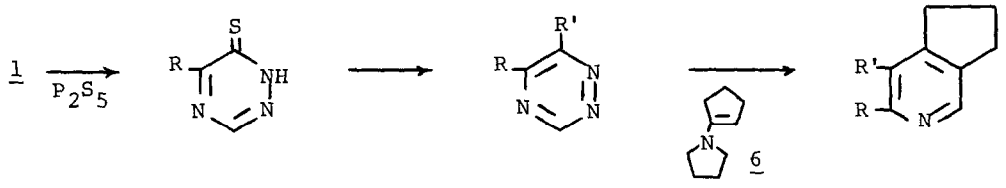
Scheme 1

utilization as azadienes for the preparation of pyridines by intermolecular Diels-Alder reactions. The accompanying paper describes a versatile entry to thieno[2,3-c]pyridines and thieno[2,3-b]pyridines by intramolecular Diels-Alder reactions.

The 1,2,4-triazine-6-ones (1), prepared as previously described, were converted to the corresponding 6-thiones (2) by reaction with P_2S_5 in refluxing

pyridine (yields 70-90%).[4] Use of the Lawesson reagent for this transformation proved to be much less satisfactory. S-Alkylation with benzylbromide gave the benzylthio derivatives (3) which were oxidized to the sulfoxides (4) and to the sulfones (5) in high yields by the use of one and two equivalents, respectively, of m-chloroperbenzoic acid.

We then examined the reaction of each of these azadienes with 1-pyrrolidino-1-cyclopentene (6). Reaction of the triazine 3a with 6 proceeded smoothly in refluxing dioxane to give the pyridine 7a in 95% yield. However, reaction of the sulfoxide 4a or the sulfone 5a with 6 was exothermic at room temperature, was accompanied by vigorous effervescence, and provided less than 20% of the anticipated Diels-Alder products 8a and 9a. The failure of these latter cycloaddition reactions under the above conditions is perhaps not surprising, however, in view of the propensity of these highly electron deficient heterocycles to add nucleophiles (in this case, either the enamine itself or pyrrolidine). Indeed, addition of the enamine 6 to a solution of the sulfoxide 4a in an anhydrous mixture of methylene chloride and glacial acetic acid led at room temperature to 8a in 88% yield after 6 hrs. Furthermore, addition of the enamine 6 to an anhydrous methylene chloride/acetic acid solution of the sulfone 5a resulted in complete consumption of the triazine within 20 minutes at 0°C, and formation of the pyridine 9a in 66% yield. Analogous results were obtained in cycloaddition reactions of the sulfide 3b, the sulfoxides 4b and 4c and the sulfone 5b with 6, with the formation of 7b, 8b, 8c, and 9b respectively (Scheme 2).



3, R' = SCH_2Ph
4, R' = $SOCH_2Ph$
5, R' = SO_2CH_2Ph

7, R' = SCH_2Ph
8, R' = $SOCH_2Ph$
9, R' = SO_2CH_2Ph

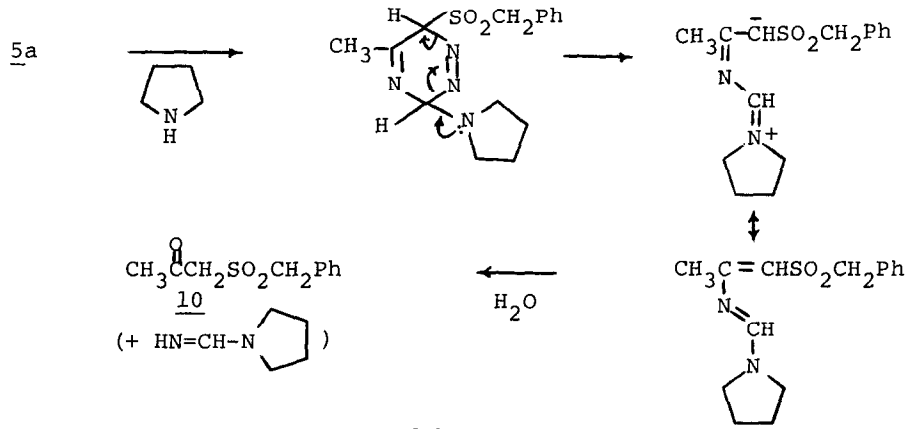
a, R = CH_3

b, R = Ph

c, R = $CH(CH_3)_2$

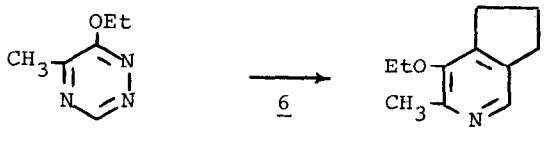
Scheme 2

The susceptibility of 5 to possible destruction by pyrrolidine, alluded to above, was briefly examined. Addition of pyrrolidine to a solution of 5a in methylene chloride resulted in vigorous effervescence, with isolation (after silica gel chromatography) of benzylsulfonylacetone (10) (43%). This facile triazine ring destruction appears to be the result of nucleophilic addition of pyrrolidine to C-3, the least hindered site in this electron-deficient triazine sulfone system, followed by ring fission with loss of nitrogen and subsequent hydrolysis (Scheme 3).



Scheme 3

Displacement of benzylmercaptan (or methylmercaptan) from 6-benzylthio- (or 6-methylthio)-5-methyl-1,2,4-triazine (3a) with sodium ethoxide in ethanol proceeded smoothly in good yield, but the resulting 5-methyl-6-ethoxy-1,2,4-triazine (11) proved to be considerably less reactive as an azadiene with 1-pyrrolidino- (or morpholino)-1-cyclopentene (Scheme 4). 3,4-Cyclopenteno-5-ethoxy-6-methylpyridine (12) was formed in only modest yields (as high as 40%), with considerable recovery of unchanged starting material. However, the structural similarity of 11 to pyridoxine (Vitamin B_6) has encouraged us to examine catalysis of this latter cycloaddition reaction; results of this investigation will be reported independently.



Scheme 4

The above 6-substituted 1,2,4-triazine derivatives thus follow the "normal" reactivity pattern for inverse electron demand Diels-Alder reactions, where the rate of reaction with an electron-rich dienophile increases with increasing electron deficiency of the azadiene.[1] This generalization does not hold true, however, for some intramolecular reactions of this 1,2,4-triazine system, as documented in the accompanying paper.

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2. Neunhoeffer, H.; Wiley, P.F. "Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines and Pentazines", Vol. 33 in the series "The Chemistry of Heterocyclic Chompounds", Weissberger, A.; Taylor, E.C. (eds), Wiley-Interscience, New York, 1978.

3. Taylor, E.C.; Macor, J.E. J. Heterocyclic Chem., in press.

4. The structures of all new compounds reported herein were confirmed by examination of their IR, ^{1}H and ^{13}C NMR spectra and by microanalytical data.

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