Tetrahedron Letters,Vol.26,No.20,pp 2419-2422,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

NOVEL INTRAMOLECULAR DIELS-ALDER REACTIONS WITH ALKYNYLTHIO DERIVATIVES OF 1,2,4-TRIAZINES. NEW ROUTES TO THIENO[2,3-b]PYRIDINES AND THIENO[2,3-c]PYRIDINES

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SUMMARY: S-Alkylation of 1,2,4-triazine-6-thiones with 4-iodobutyne, followed by oxidation to the sulfoxide and intramolecular cycloaddition (at room temperature), gives 2,3-dihydrothieno[2,3-c]pyridines, which are readily dehydrated with acetic anhydride to thieno[2,3-c]pyridines. The same series of reactions carried out on 1,2,4-triazine-3-thiones leads to thieno[2,3-b]pyridines.

In the preceding Communication we described the utilization of a series of novel 6-alkylthio derivatives of 1,2,4-triazine as azadiene partners in an inverse electron demand Diels-Alder reaction with enamines.[1] In accordance with previous observations on the reactivity of tetrazines and triazines, the rate of cycloaddition with enamines increased with increasing electron deficiency in the triazine; i.e., the rate increased in the order of the substituents sulfides < sulfoxides < sulfones. We report in this Communication a parallel series of cycloaddition reactions with 1,2,4-triazines carrying sidechain dienophiles in which the above order of relative reactivity is dramatically violated. These novel intramolecular Diels-Alder reactions[2] provide a facile route to thieno[2,3-c]pyridines and to thieno[2,3-b]pyridines.

Treatment of the 1,2,4-triazine-6-thiones 1[1] with 4-iodobutyne gave a series of 5-substituted 6-(3-butynylthio)-1,2,4-triazines (2);[3] the related sulfoxides 3 and sulfones 4 were then prepared *in situ* by oxidation of the corresponding sulfides with one and with two equivalents, respectively, of m-chloroperbenzoic acid, and subjected to the cyclization conditions described below.

Heating the sulfide 2a for 21 hours in refluxing dioxane gave 7-methyl-2,3-dihydrothieno[2,3-c]pyridine (5a) in 69% yield. The sulfone 4a proved to be somewhat more amenable to an intramolecular Diels-Alder reaction; 7-methyl-2,3-dihydrothieno[2,3-c]pyridine 1,1-dioxide 7a was obtained in 75% yield after

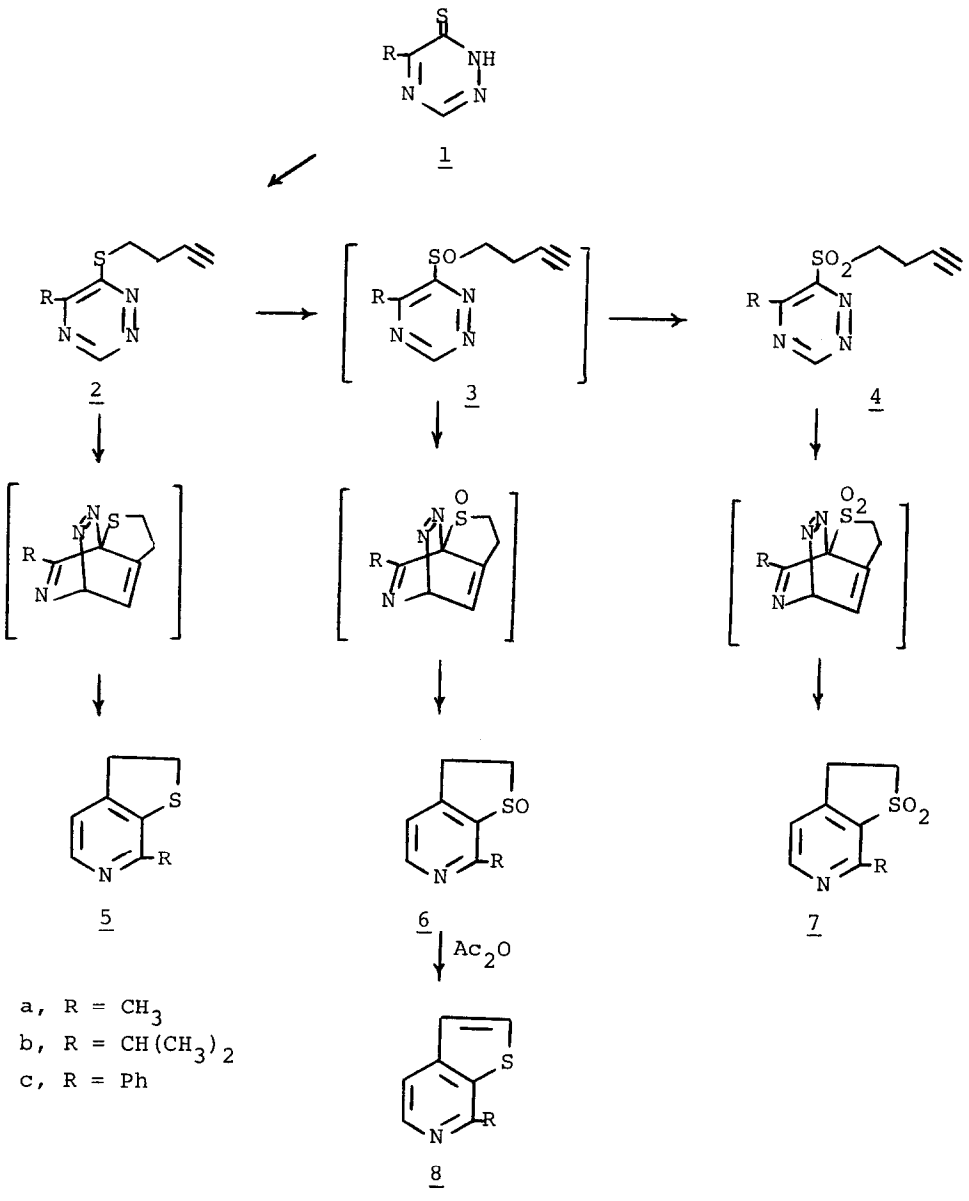
27 hours of heating at 67°C. We then turned to the sulfoxide 3a. It was anticipated that the rate of this latter reaction would prove to be intermediate between that of the sulfide 2a and the sulfoxide 4a. We were therefore astonished to observe, during an attempt to chromatograph the crude sulfoxide 3a on silica gel, that an almost explosive evolution of nitrogen took place. Under more controlled conditions, the intramolecular Diels-Alder reaction of 3a (produced in situ) leading to 7-methyl-2,3-dihydrothieno[2,3-c]pyridine 1-oxide (6a) was complete at room temperature in methylene chloride solution after 27 hours (69%), or at 39°C after 5 hours (60%). Refluxing 6a in acetic anhydride resulted in smooth dehydration to give 7-methylthieno[2,3-c]pyridine (8a)[4] in 88% yield.

The above experiments were repeated with the 5-isopropyl- and the 5-phenyl-6-(3-butynylsulfinyl)-1,2,4-triazines 3b and 3c. The resulting 2,3-dihydrothieno[2,3-c]pyridine 1-oxides (6b,c) were then smoothly dehydrated with acetic anhydride to give the fully aromatic thienopyridines 8b and 8c. This series of straightforward reactions thus provides a facile route to thieno[2,3-c]pyridines (Scheme 1).

The above studies were extended to 5-phenyl-(3-butynylthio)-1,2,4-triazine (9) (which was readily prepared from thiosemicarbazide and phenylglyoxal, followed by S-alkylation of the resulting 5-phenyl-1,2,4-triazine-3-thione with 4-iodobutyne) and with the derived sulfoxide 10 and sulfone 11. Once again, the sulfoxide 10 underwent the intramolecular Diels-Alder reaction much more rapidly than the corresponding sulfone, which in turn reacted more rapidly than the starting sulfide 9. Heating 6-phenyl-2,3-dihydrothieno-[2,3-b]pyridine 1-oxide (13) with acetic anhydride led smoothly to the fully aromatic 6-phenylthieno[2,3-b]pyridine (15) (Scheme 2).

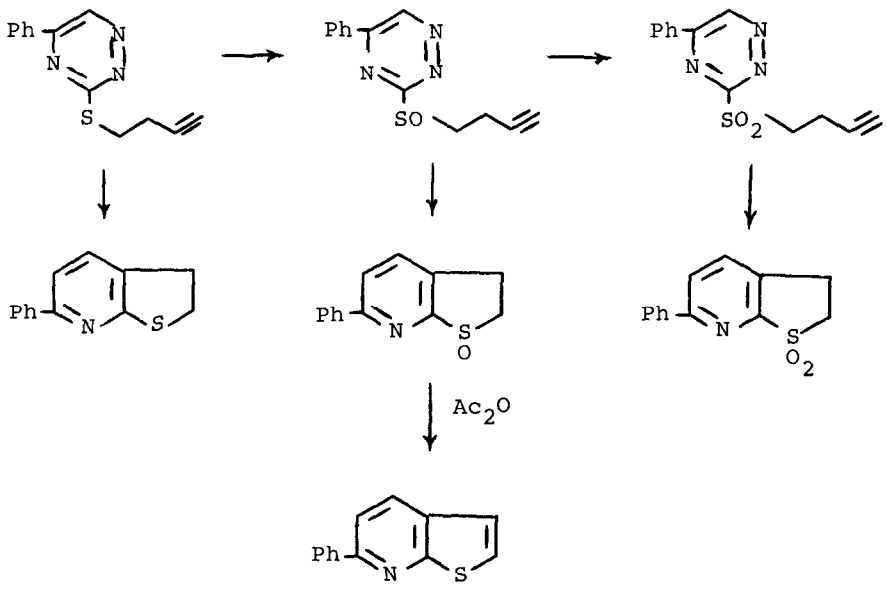
Thus, S-alkylation of 1,2,4-triazine-6-thiones with an appropriate dienophilic sidechain, followed by an intramolecular Diels-Alder reaction of the in situ-formed sulfoxide as described above, leads readily to thieno[2,3-c]-pyridines, while the same series of reactions carried out on a 1,2,4-triazine-3-thione leads to thieno[2,3-b]pyridines.

The above violations of the "normal" order of reactivity in an inverse electron-demand Diels-Alder reaction may be due either to steric considerations or to a fortuitous matching of the HOMO of the sidechain acetylenic dienophile with the LUMO of the azadiene sulfoxide; a theoretical investigation of this latter possibility is currently underway. We are currently examining further intramolecular Diels-Alder reactions of 1,2,4-triazines and other heterocyclic azadienes with dienophilic sidechains; results will be reported independently.



a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = Ph

Scheme 1



Scheme 2

REFERENCES

1. Taylor, E.C.; Macor, J.E. Tetrahedron Lett. . . .

2. To our knowledge, there is only one previous report of an intramolecular Diels-Alder reaction of a 1,2,4-triazine derivative: Seitz, G.; Dietrich, S. Archiv. Pharm, 1984, 317, 379.

3. 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.

4. The physical and spectral properties of this compound were in agreement with previously published data: Dressler, M.L.; Joullie, M.M. J. Heterocyclic Chem., 1970, 7, 1257.

(Received in USA 15 February 1985)