FURTHER STUDIES ON STEREOSELECTIVE SYNTHESIS OF VICINAL DIAMINES FROM 3,6-DIHYDROTHIAZINE-1-IMINES

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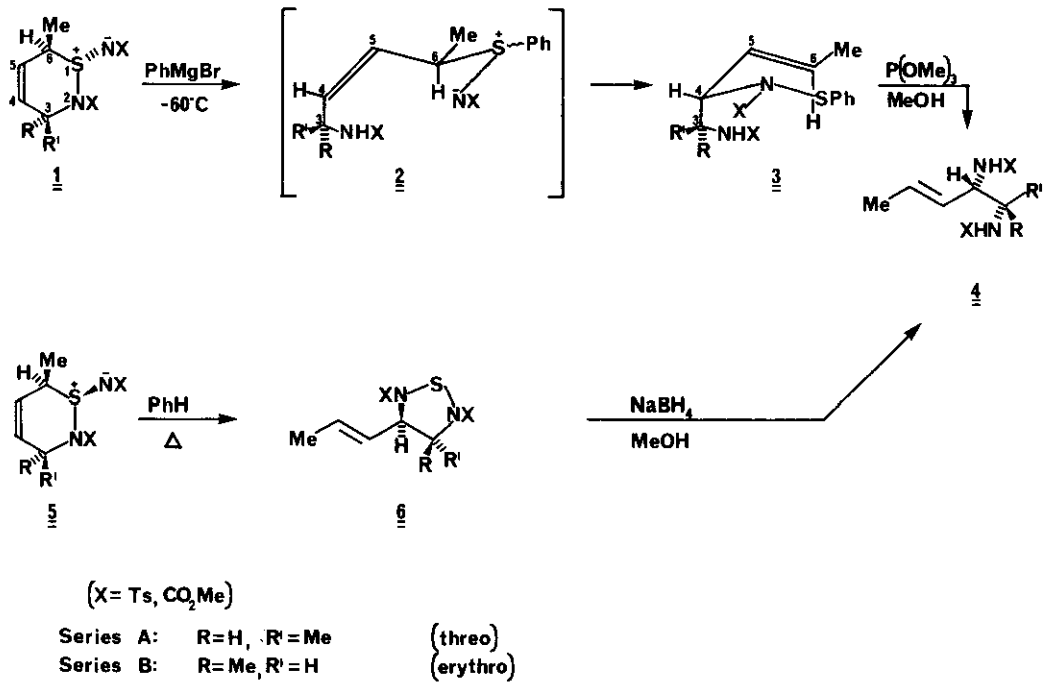
Abstract - 3,6-Dihydrothiazine-1-imines, prepared from a sulfur diimide and a 1-substituted 1,3-diene, can be transformed stereoselectively to either threo or erythro acyclic unsaturated vicinal diamine derivatives.

We recently described a strategy for stereoselective synthesis of unsaturated vicinal diamines from 3,6-dihydrothiazine-1-imines, which are readily available via [4+2] cycloadditions of various sulfur diimides and 1,3-dienes.[2] A summary of this methodology is shown in Scheme I. Diels-Alder adduct 1A, prepared from E,E-2,4-hexadiene, reacted with phenylmagnesium bromide to give an initial allylic sulfilimine 2A which underwent rapid [2,3] sigmatropic rearrangement to afford sulfenamide 3A as the exclusive stereoisomeric product. This rearrangement undoubtedly proceeds through an envelope-like transition state with the C-6 methyl substituent acting as a quasi equatorial anchor.[2,3] It is this effect that allows selective transfer of chirality from C-6 to C-4.[4] ^{1}H NMR studies showed that sulfenamide 3A was the only product present, and none of the sulfilimine 2A was detected. This result is opposite to what one observes in the corresponding allylic sulfoxide/sulfenate ester rearrangement.[4,5] Desulfurization of 3A cleanly afforded the threo vicinal diamine derivative 4A.

Adduct 5A, also prepared from E,E-hexadiene but which is epimeric to 1A at sulfur, proved unreactive towards Grignard reagents.[2] However, upon heating 5A rearranged via a novel [2,3] sigmatropic process to stereoselectively afford thiadiazolidine 6A. Cleavage of 6A with sodium borohydride yielded threo vicinal diamine 4A in excellent yields.

Very similar results were obtained with adducts 1B and 5B derived from E,Z-2,4-hexadiene. Dihydrothiazine-1-imine 1B reacted with phenylmagnesium bromide, followed by trimethyl phosphite, to give erythro product 4B. Similarly, adduct 5B was unreactive towards Grignard reagents but rearranged thermally to give 6B, which could be converted to the erythro carbamate series 4B.

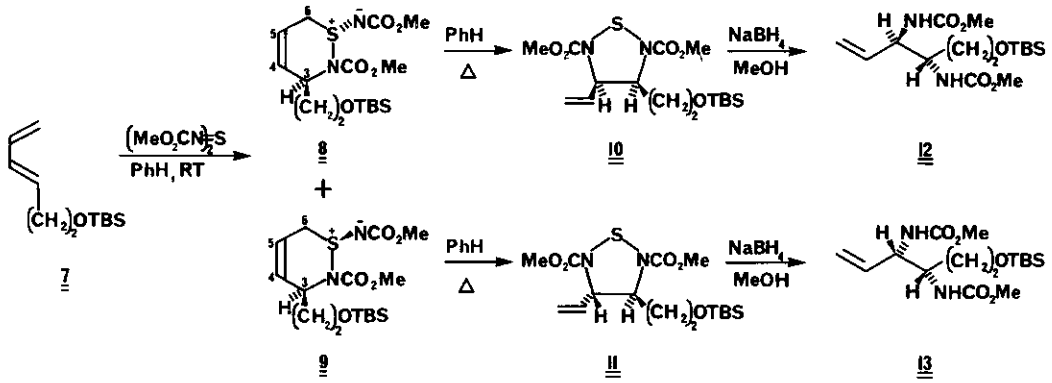
Scheme I



We have been involved recently in explorations of the scope of this methodology and in learning more about the allylic sulfilimine [2,3] sigmatropic rearrangement. Interestingly, although this reaction was discovered over thirty years ago,[6,7] relatively little is known about the process. This paper describes some of our results in this area using 3,6-dihydrothiazine-1-imines which are unsubstituted at C-6.

Diene 7[8] reacted with dicarbomethoxysulfur diimide at room temperature to afford approximately a 10/1 mixture of epimeric cycloadducts 8 and 9 which were only partially separable (84%) (Scheme II). By comparison with the ^{1}H NMR spectra of hexadiene adducts 1 and 5,[2] and based upon subsequent reactions (vide infra), we have assigned structures 8 and 9 to the major and minor epimers, respectively. When this mixture of adducts was refluxed in benzene, a mixture of thiadiazolidines 10 and 11 was produced. Reductive cleavage of the mixture afforded a

Scheme II

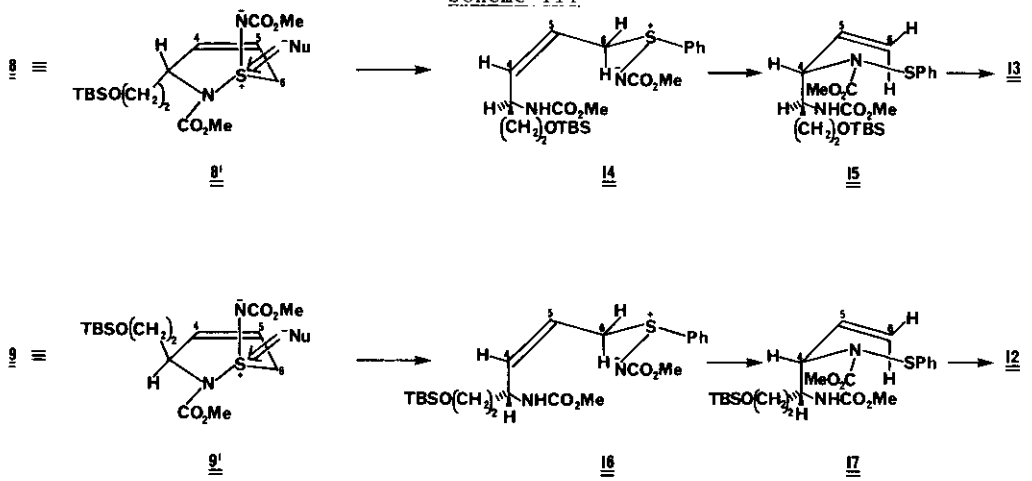


chromatographically separable 13/1 mixture of erythro/threo vicinal carbamates 12 and 13 (71% total yield from the mixture of 8 and 9).[9] Assuming that the thiadiazolidines are formed from the dihydrothiazine imines via a concerted [2,3] sigmatropic rearrangement, one would expect that isomer 8 should give erythro product 10 and 9 should afford the threo compound 11. It was possible to purify a small amount of major adduct 8 by repeated chromatography. Upon heating, compound 8 was, in fact, converted cleanly to erythro thiadiazolidine 10. We believe that rearrangement of epimeric adduct 9 is equally stereoselective, but the assumption could not be proven experimentally since 9 was not obtainable in pure form.

Rather interesting results were obtained when adducts 8 and 9 were subjected to the Grignard methodology outlined above in Scheme I. Treatment of the 10/1 mixture of Diels-Alder adducts with phenylmagnesium bromide at -60°C, followed by trimethyl phosphite in methanol at room temperature, gave a 1/13 mixture of erythro/threo compounds 12 and 13 (72%). A pure sample of major adduct 8 was found to give exclusively threo vicinal carbamate 13 when carried through this sequence of steps.

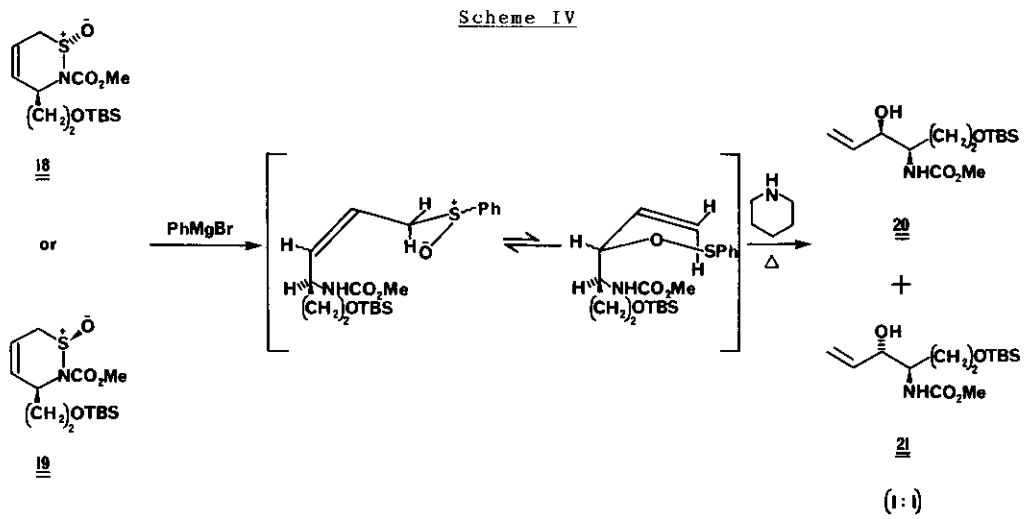
The high stereoselectivity in these rearrangements was quite surprising, since these dihydrothiazine imines are not substituted at C-6 (cf 2 → 3). We believe these observations can best be rationalized as shown in Scheme III. Based upon our previous studies, it seems reasonable that 8 and 9 exist in conformations 8' and 9', respectively, having quasi axial N-S bonds.[2] Assuming that ring opening of the dihydrothiazine imines by the Grignard reagent occurs with inversion of configuration at sulfur,[10] adduct 8 would afford allylic sulfilimine 14. If this

Scheme III



intermediate underwent a [2,3] sigmatropic rearrangement through an envelope-like transition state with the S-phenyl group quasi equatorial, threo sulfenamide 15 would be produced. Similarly, adduct 9 would yield sulfilimine 16, which affords erythro isomer 17 upon rearrangement.

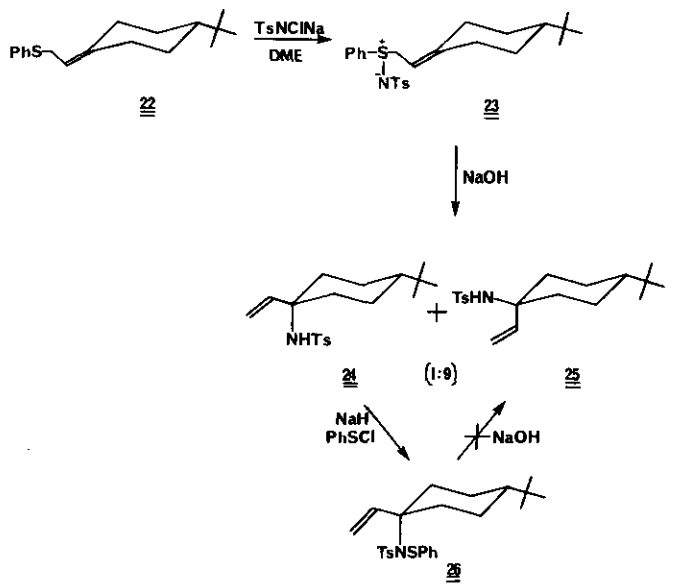
Scheme IV



The fact that sulfur chirality was transferred so efficiently to C-4 was unexpected, since in the corresponding rearrangement of allylic sulfoxides this transfer is usually non-stereoselective.[4] To test this point, adducts 18 and 19 were prepared from diene 7 and methyl N-sulfinylcarbamate and were individually treated with phenylmagnesium bromide followed by piperidine.[3] In both cases approximately a 1/1 mixture of threo 20 and erythro 21 was formed. The intermediate in this process is an allylic sulfoxide, which as anticipated, reversibly rearranges to a sulfenate ester (Scheme IV) with non-selective chirality transfer from the sulfoxide sulfur to carbon.[3,4]

It seems reasonable that the difference in the stereochemical outcome between the [2,3] sigmatropic rearrangements of allylic sulfilimines vs allylic sulfoxides is due to a lack of reversibility in the former reaction. This supposition was tested in a simple model system (Scheme V).[11] Allylic sulfide 22 was converted to allylic sulfilimine 23 with Chloramine-T. This intermediate was not isolated, but under hydrolytic reaction conditions (NaOH, DME, RT) afforded a 9/1 mixture of

Scheme V



equatorial 25 and axial 24 allylic sulfonamides, respectively (75%). The minor axial sulfonamide 24 was converted to sulfenamide 26 with phenyl sulfenyl chloride. Compound 26 showed no tendency to rearrange to a mixture of axial and equatorial allylic sulfonamides, even upon refluxing in DME. Thus, it is clear

that 26 does not reversibly rearrange to allylic sulfilimine 23. We thus suggest that [2,3] sigmatropic rearrangements of allylic sulfilimines to sulfenamides may generally be irreversible processes.

The research described here demonstrates that a 3,6-dihydrothiazine-1-imine prepared from a 1-substituted diene can be converted stereoselectively to either acyclic threo or erythro unsaturated vicinal diamine derivatives. The particular stereoisomer obtained is dependent upon the configuration at sulfur in the Diels-Alder adduct and upon the sequence of steps (cf Scheme II vs Scheme III) used for the rearrangement process.

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