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FUNCTIONALLY SUBSTITUTED PIPERIDINES VIA HETEROCYCLOADDITION[1].

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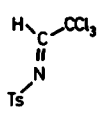
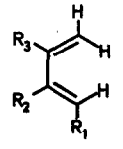
In continuation of our work[5] on the application of cycloaddition reactions to the synthesis of heterocyclic compounds we wish to report a new and stereoselective synthesis of α-substituted tetrahydropyridines[6] and piperidines. Although both types of structure occur frequently in compounds of biological interest relatively few general methods for its synthesis are known.



1



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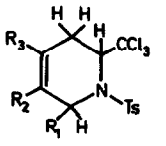
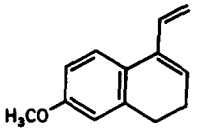


3

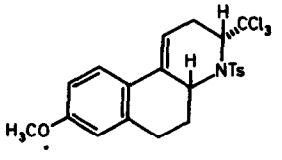
a $R_1=R_2=R_3=H$

b $R_1=R_2=H$; $R_3=OCH_3$

c $R_1=R_2=H$; $R_3=-C_6H_4-OCH_3$ (p)



2d



3d

Ts = $-SO_2-C_6H_4CH_3$ (p)

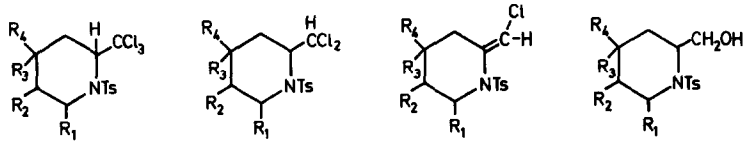
To demonstrate the scope and versatility of the method, the reaction of N-2,2,2-trichloroethylidene-p-toluene sulfonamide (1) with four selected dienes will be discussed.

Upon reactions of dienes 2a, 2b and 2c with the trichloromethylimine 1 the cycloadducts 3a (mp 92°-94° NMR: $\delta(CDCl_3)$ 5.60 (2H) =CH; 4.99 (1H) CH-CCl_3); 3b (mp 105°-107°; NMR: $\delta(CDCl_3)$ 5.00 (1H) =CH; 5.10 (1H) CH-CCl_3) and 3c (mp 98°-100°; NMR: $\delta(CDCl_3)$ 5.77 (1H) =CH; 5.16 (1H) CH-CCl_3) were obtained in good yields. The direction of the addition is in agreement with the polarisation in the imine[7] and the dienes used.

On the contrary reaction of diene 2d gave the adduct 3d (mp 188°-190° NMR: $\delta(CDCl_3)$ 5.90 (1H) =CH; 5.10 (1H) CH-CCl_3) in which the direction of the addition is reversed, presumably as a consequence of the steric demands of the trichloromethylgroup. The structure and stereochemistry of the tetrahydro pyridines 3 were established via extensive NMR-analysis[8]. The most important result from this analysis is the rigid half-boat conformation of the adducts 3, with the trichloromethylgroup in pseudo-axial position. Due to the voluminous nature of this substituent severe restrictions are posed on the conformational mobility of the heterocyclic ring.

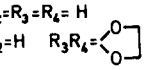
In considering the ease of formation of 3, as well as the variation possible in the diene and the remarkable regio- and stereoselectivity of the addition the method could find useful synthetic application, provided a selective conversion of the trichloromethyl substituent into a suitable functional group could be accomplished.

Hydrolysis experiments of 3 under a variety of conditions did not give useful results[10]. A successful approach, however, proved to be the following: catalytic (Pt) hydrogenation of 3a and the ketal 4b (mp 134°-136° NMR: $\delta(CDCl_3)$ 5.14 (1H) CH-CCl_3) - obtained via hydrolysis of 3b and subsequent ketalization - in ethanol in the presence of triethylamine gave the dichloromethyl products 5a (mp 113°-115°C NMR: $\delta(CDCl_3)$ 6.0

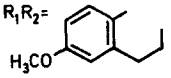


4 5 6 7

a $R_1=R_2=R_3=R_4=H$

b $R_1=R_2=H$ $R_3R_4=$ 

c $R_1=R_2=R_3=H$ $R_4=-C_6H_4OCH_3(p)$

d $R_3=R_4=H$ $R_1R_2=$ 

$-C\underline{H}Cl_2$ and 5b (mp 128°-130° NMR: $\delta(CDCl_3)$ 6.25 $-C\underline{H}Cl_2$) in nearly quantitative yields. The adducts 3c and 3d could be dechlorinated via treatment with Ra-Ni in a 1:1 mixture of acetic acid and ethyl acetate; additional Pd/C hydrogenation resulted in the dichloromethylpiperidines 5c (mp 130°-132° NMR: $\delta(CDCl_3)$ 6.06 $-C\underline{H}Cl_2$) and 5d (mp 158°-160° NMR: $\delta(CDCl_3)$ 5.92 $-C\underline{H}Cl_2$). HCl-elimination from the dichloromethylcompounds 5 proceeded smoothly by means of 1,5-diazabicyclo[4.3.0]-5-nonene to produce mostly a mixture of isomeric vinylchlorides 6[11] (6a mp 68°-70° NMR: $\delta(CDCl_3)$ 6.32 $=C\underline{H}$ (isomer δ6.10); 6b mp 150°-153° NMR: $\delta(CDCl_3)$ 6.46 $=C\underline{H}$ (isomer δ6.19); 6c mp 117°-119° NMR: $\delta(CDCl_3)$ 6.46 $=C\underline{H}$; 6d mp 159°-161° NMR: $\delta(CDCl_3)$ 6.40 $=C\underline{H}$ (isomer mp 201°-204°, δ6.21).

The conversion of 6 into alcohol 7 was accomplished via addition of diborane either to the pure vinylchloride or to the isomer mixture followed by H_2O_2-oxidation (yield 70%). Contrary to reported results with simple vinylchlorides[12] no aldehydic products could be detected, although the alcohols 7 could be oxidized to the corresponding aldehydes via oxidation with DMSO/Ac_2O. The relative stereochemistry of the C_α-substituent in 7 is reversed as compared with the starting trichloromethylpiperidines 3; this is more specifically discussed for 7d in the accompanying communication. Further transformations of the alcohol 7 as well as the results in a number of other diene systems will be reported in our full paper.

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