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Synthesis and Reactions of Chloroazodienes. A New and General Synthesis of Pyridazines.

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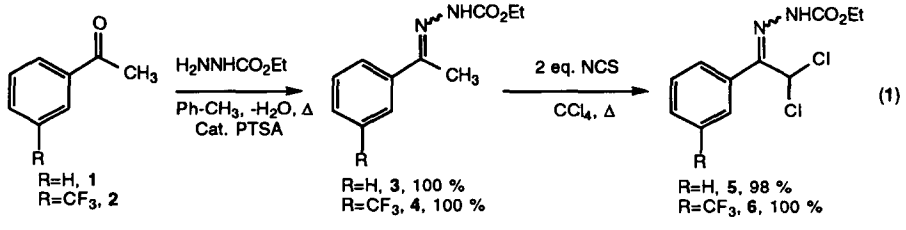
Abstract: The reaction of dichlorohydrazones with Hünig's base gives 4-chloroazodienes, which were found to combine with a variety of electron rich olefins to yield chloro-substituted tetrahydropyridazines. These chloroazodiene cyclizations are best characterized as inverse electron demand, 4+2 hetero Diels-Alder reactions that maintain a high degree of regio- and stereochemical control. The chloro-substituted tetrahydropyridazines that are formed give high yields of substituted pyridazines upon treatment with base. The sequence of a chloroazodiene cyclization to a tetrahydropyridazine followed by an aromatization constitutes a new and general synthesis of substituted pyridazines.

In recent years several reports have appeared describing the generation and reaction of non-halogenated azodienes with electron rich olefins.[1] It is clear from these reports that the full potential of these azodiene cyclizations for the preparation of variety of heterocycles has not been realized. These reactions lead mainly to the 6-membered tetrahydropyridazine products or to the 5-membered *N*-aminopyrrole products and are formal 4 + 2 or 3 + 2 cyclizations of an azodiene with an olefin. Previous attempts to introduce a labile group into the tetrahydropyridazine followed by an aromatization to give pyridazines are described, but these reactions are limited in scope.[2] We have an interest in pyridazines due to their unique biological activity[3] and sought to develop a new and general synthesis of these molecules. We envisioned introducing a labile group into the tetrahydropyridazine from a 4-chloroazodiene.[4] This labile chlorine could then be eliminated to produce the aromatized pyridazine providing that the other groups on the tetrahydropyridazine were stable to the reaction conditions. We have developed a new and convenient procedure for the preparation of pyridazines that relies on the cyclization of a 4-chloroazodiene with an electron rich olefin and a subsequent aromatization with a base. Unlike precedented syntheses of the pyridazine ring,[5] the azodiene route allows for the incorporation of many different types of functional groups. The sequence of a chloroazodiene cyclization to a chlorotetrahydropyridazine followed by an aromatization reaction constitutes a new and general synthesis of substituted pyridazines.

We found that high yields of dichlorohydrazones **5** and **6** were obtained from the acetophenones **1** and **2** by treatment with ethyl carbazate followed by two equivalents of NCS, eq. 1. The dichlorohydrazones usually existed as a mixture of *E* and *Z* isomers. When hydrazone **6** was treated with Hünig's base in an NMR tube,



R=H, **1**
R=CF_3, **2**

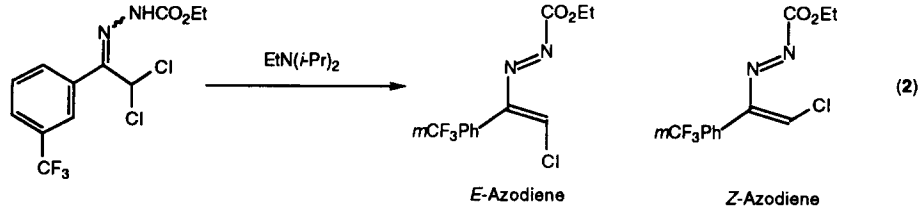
R=H, **3**, 100 %
R=CF_3, **4**, 100 %

R=H, **5**, 98 %
R=CF_3, **6**, 100 %

(1)

the solution turned deep red and gave what was presumed to be a 10 : 1 mixture of the *E*-azodiene to the *Z*-azodiene as shown in eq. 2. The 400 MHz NMR signal for the olefinic proton of the *E*-isomer was at 7.60 ppm while the *Z*-isomer was at 6.84 ppm.[4a] One would expect the proton of the *Z*-isomer to be at higher field

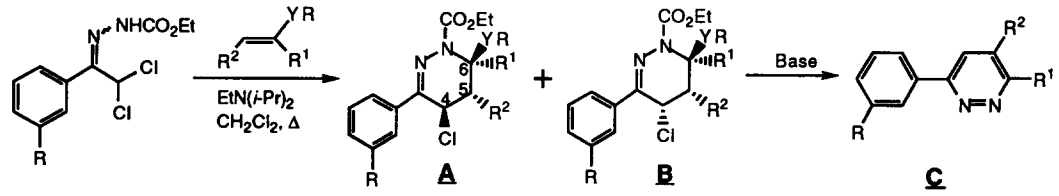
since it is in the shielding region of the phenyl ring. The next step was to study the reaction of the 4-chloroazodienes with electron rich olefins.



E : *Z* Ratio is 10 : 1

The dichlorohydrazones **5** and **6** were treated with Hünig's base to generate the 4-chloroazodiene *in-situ,* which, in the presence of a variety of electron rich olefins,[6] react to afford the tetrahydropyridazine adducts, Table 1.[7] These sequences were found to usually give two diastereomers of the corresponding tetrahydropyridazine or in some cases the pyridazines directly from the reaction mixture. A subsequent aromatization of the tetrahydropyridazines with a base gave the corresponding pyridazines in high yields.

Table 1[a], Synthesis of Pyridazines *Via* Chloroazodienes.



Entry	R	YR	R^1	R^2	% Yield A	B	C
1[b]	H	OEt	H	H	69	10	95
2[c]	H	Morpholino		-$(CH_2)_4$-	34	-	92
3[b]	H	OEt	H	Me	66	26	68
4[c]	H	Piperidino	H	Et		67[d]	34
5[b]	CF_3	Morpholino	H	Ph	46	39	82
6[b]	CF_3	Morpholino	H	*i*-Pr	65	10	38
7[b]	H	Morpholino	H	CF_3	54	15	51
8[b,e]	CF_3	Morpholino	H	CO_2Et	-	55[f] -	79[g]
9[c,e]	H	Morpholino	Me	Et	-	-	22
10[h]	H	OMe	Me	H	-	-	13

a) The reactions were run with 5 eq. of enol ether or 1.1-2.5 eq. of enamine in refluxing CH_2Cl_2 for 4-24 h with equal amounts of Hünig's base present in the reaction mixture. b) KOH in EtOH was used for the aromatization reaction. c) *t*-BuOK in *t*-BuOH was used for the aromatization reaction. d) Isolated as a 2 : 1 mixture of diastereomers A : B. e) After workup, the tetrahydropyridazine intermediates were used directly in the aromatization reaction and were not isolated. f) The product isolated was the dihydropyridazine that was obtained from the loss of HCl. g) The pyridazine could be isolated as the carboxylic acid after treatment of the reaction with base. h) The pyridazine was isolated directly from the reaction of the azodiene with the electron rich olefin.

Combination of the azodiene derived from **5** with a mono-substituted olefin, ethyl vinyl ether (entry 1, Table 1), gave a 69 % yield of the *cis*-tetrahydropyridazine and a 10 % yield of the *trans*-isomer. The *cis*-isomer in the 4,6-disubstituted pyridazine was distinguished from the *trans*-isomer as described for below. Aromatization of these tetrahydropyridazine isomers with KOH in EtOH (entry 1) led to the pyridazine in 95 % yield. Reaction of the choroazodienes with 1,2-disubstituted olefins (entries 3-8) with a number of different functional groups led to good yields of the tetrahydropyridazine isomers and moderate to good yields of the pyridazines after aromatization. A somewhat lower yield of the tetrahydropyridazines were obtained when the olefin was tri-substituted (entries 2 and 9) and were difficult to isolate and characterize without aromatization occurring spontaneously. However, fair to good yields of the pyridazine products could be obtained in these cases by treatment of the crude reaction mixture with a base. The tetrahydropyridazine was not observed at all when the olefin was 1,1-disubstituted (entry 10) and the aromatized pyridazine was obtained directly from the reaction mixture.

The 4, 5, 6-trisubstituted tetrahydropyridazine isomers were characterized based on their 400 MHZ ^{1}H NMR spectra. The group in the 6-position prefers to be in an axial position and the tetrahydropyridazine adopts a half-chair conformation.[1b] In all of the examples shown in Table 1, the *trans* stereochemistry of the olefin is retained in the product. For illustrative purposes the tetrahydropyridazines in entry 3 of Table 1 will be discussed. In the *cis* isomer (Cl and OEt are *cis*) the H-4 proton is in the equatorial position and appears as a singlet at δ 4.31. The H-5 equatorial proton is at δ 2.65 and is a quartet coupled only to the adjacent methyl group (J=7.4 Hz). The H-6 equatorial proton is at δ 5.28 and is also a singlet. The equatorial H-4, H-5, and H-6 protons are not coupled to each other since their dihedral angles are nearly 90°. This situation then places all of the non-hydrogen substituents in axial positions. In the *trans* isomer (Cl and OEt are *trans*) the H-4 proton is in an axial position and is a doublet (δ 5.14, J=6.3 Hz) coupled to the equatorial H-5 proton. The equatorial H-5 proton is at δ 2.39 and is a qdd (J=6.9, 6.3, 3.2 Hz) coupled to the adjacent methyl group and to the axial H-4 proton (J=6.3 Hz) and the equatorial H-6 proton (δ 5.33, J=3.2 Hz). This places the Cl-group in an equatorial position, the methyl group in an axial position, and the OEt group in an axial position. This analysis is consistent for all of the 4, 5, 6-trisubstituted tetrahydropyridazines presented in Table 1. A more detailed analysis of the NMR data for these tetrahydropyridazines will appear elsewhere.

In summary, the reactions of chloroazodienes with a variety of electron rich olefins produces tetrahydropyridazines with a high degree of stereochemical and regiochemical control. This indicates that these cyclizations are concerted, 4 + 2 hetero Diels-Alder reactions with a high degree of *endo* character. The chloro-substitute tetrahydropyridazines were aromatized in moderate to high yields to pyridazines. This sequence constitutes a new and general synthesis of substituted pyridazines that is superior to the methodology currently available for the preparation of these molecules. We are currently studying this new pyridazine synthesis in more detail to be published at a later date.

References and Notes

1. (a) Clarke, S. J.; Gilchrist, T. L. *J. Chem. Res.* (S) **1985**, 310; *J. Chem. Res.* (M) **1985**, 3371. (b) Clarke, S. J.; Davies, D. E.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. I* **1983**, 1803. (c) Gilchrist, T. L.; Richards, P. *Synthesis* **1983**, 153. (d) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. I* **1979**, 249. (e) Sommer, S. *Tetrahedron Letters* **1977**, 117. (f) Sommer, S.*Chem. Letters* **1977**, 583. (g) Sommer, S. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 58. (h) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Chem. Commun.* **1976**, 581.

2. Several attempts have been made to aromatize a tetrahydropyridazine to a pyridazine, but none involve the use of a chloroazodiene as an intermediate. (a) Clarke, S. J.; Gilchrist, T. L. *J. Chem. Res.* (S) **1985**, 310; *J. Chem. Res.* (M) **1985**, 3371. (b) Vors, J. *J. Heterocyclic Chem.* **1990**, *27*, 579. (c) Cocco, M. T.; Congiu, C.; Maccioni, A.; Plumitallo, A. *Gazz. Chim. Ital.* **1988**, *118*, 187.

3. Substituted pyridazines exhibit "bleaching" herbicidal activity. South, M. S.; et. al. US Patent Applications Pending.

4. Two reports of a cycloaddition reaction involving a chloroazodiene have appeared, but these products were not elaborated to pyridazines. (a) Gilchrist, T. L.; Sanchez Romero, O. A.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. I* **1989**, 353. (b) Gilchrist, T. L.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. I* **1985**, 1741.

5. Mason, J. W., *Heterocyclic Compounds*; Vol. 28, Castle, R. N., ed., John Wiley and Sons, Inc., New York NY, 1973, p 407.

6. The electron rich olefins in Table 1, entries 1-3 and 10 are commercially available. The olefins in entries 4-6 and 9 were prepared *via* published procedures that involve refluxing 1 eq. of the appropriate aldehyde or ketone with an excess of the secondary amine in toluene or benzene over a Dean-Stark trap until the theoretical amount of water was collected. See: March, J., *Advanced Organic Chemistry*; 3rd Ed., John Wiley and Sons, New York, NY, p 689, 796-798. The olefins in entries 7 and 8 were prepared by stirring 1 eq. of the appropriate alkyne precursor with 1 eq. of morpholine in CH_2Cl_2 for 30 min. to 1 h at RT followed by reflux for a short period of time. These enamines prepared in this way were used without isolation or purification. All of the electron rich olefins had the *trans* geometry as evidenced by the large coupling constant of the vinyl protons of 10-16 Hz.

7. Yields are not optimized. All new compounds presented here had satisfactory ^1H NMR, ^{13}C NMR, and elemental analyses. General procedure for the preparation of the tetrahydropyridazines and pyridazines in Table 1: The appropriate enol ether (5 eq.) or enamine (1.1-1.5 eq.) and Hünig's base (*N,N*-diisopropylethyl amine, 1.1-2.5 eq.) were stirred in CH_2Cl_2 (0.1 molar with respect to the dichlorohydrazone) at RT under N_2 while the appropriate dichlorohydrazone (0.015-.036 moles of either **5** or **6**) was added dropwise as a solution in CH_2Cl_2 (usually 25 % of the total solvent volume was used to dissolve the hydrazone) over 30 minutes. A transient deep red or orange color was noted. The mixture was then allowed to reflux for 4-24 h while monitoring the loss of the colored azodiene by TLC. The mixture was then cooled and poured into an extraction funnel containing EtOAc and water. The organic layer was washed 2-3 times with water, dried ($MgSO_4$), filtered through a pad of SiO_2, and the solvent was removed *in-vacuo* to give the crude tetrahydropyridazines as an oil. The tetrahydropyridazines were chromatographed on the Prep-500 and/or recrystallized where appropriate.

The tetrahydropyridazine or dihydropyridazine products were converted to the pyridazine products by treatment with 5 eq. of KOH in EtOH at reflux for 1-4 h, 5 eq. of KO*t*-Bu in *t*-BuOH at RT for 4-24 h, 5 eq. of NaOH in DMSO at 100 °C for 2-4 h, or heating in DMF at reflux for 0.5-2 h or DMSO at 175 °C for 0.5 h. This operation was followed by pouring the mixtures into water, followed by extraction several times with EtOAc. The organic layer was dried ($MgSO_4$), filtered through a pad of SiO_2, and evaporated *in-vacuo* to give the crude pyridazines. The pyridazines were chromatographed on the Prep-500 and/or recrystallized where appropriate.

Table 1, Entries 1A and 1B: These compounds were prepared according to the general procedure given for Table 1 above and were isolated from the azodiene reaction by Prep-500 chromatography. 1A was obtained as a white solid (7.79 g, 69 % yield, mp=80-82 °C from EtOAc/cyclohexane) and 1B was also obtained as a white solid (1.15 g, 10 % yield, mp=50-53 °C from EtOAc/cyclohexane).

Data for 1A: ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.85 (m, 2-H), 7.45-7.38 (m, 3-H), 5.80 (bs, 1-H, eq 6H), 4.93 (d, J=10.0 Hz, 1-H, eq 4H), 4.38 (q, J=11.0 Hz, 2-H), 3.68 (q, J=11.0 Hz, 2-H), 2.84 (d, J=19.0 Hz, 1-H, eq 5H), 2.31 (ddd, J=19.0, 10.0, 3.0 Ha, 1-H, ax 5H), 1.41 (t, J=11.0 Hz, 3-H), 1.22 (t, J=11.0 Hz, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.50, 144.50, 134.82, 129.53, 128.38, 126.30, 75.37, 63.82, 63.03, 40.49, 32.12, 14.99, 14.46.

Anal. Calcd. for $C_{15}H_{19}N_2O_3Cl$: C, 57.97; H, 6.16; N, 9.01. Found: C, 57.75; H, 6.21; N, 8.97.

Data for 1B: ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 2-H), 7.42-7.35 (m, 3-H), 5.75 (dd, J=3.0, 3.0, 1-H, eq 6H), 5.20 (dd, J=12.0, 8.0 Hz, 1-H, ax 4H), 4.45-4.25 (m, 2-H), 3.68-3.56 (m, 2-H), 2.81 (ddd, J=16.0, 8.0, 3.0 Hz, 1-H, eq 5H), 2.30 (ddd, J=16.0, 12.0, 3.0 Hz, 1-H, ax 5H), 1.41 (t, J=11.0 Hz, 3-H), 1.27 (t, J=11.0 Hz, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.50, 148.25, 135.59, 129.16, 128.02, 127.18, 78.13, 63.95, 62.98, 45.94, 35.46, 14.96, 14.44.

Anal. Calcd. for $C_{15}H_{19}N_2O_3Cl$: C, 57.97; H, 6.16; N, 9.01. Found: C, 58.24; H, 6.31; N, 8.98.

Table 1, Entry 1C. A mixture of 1A and 1B (1.36 g, 0.0044 moles) and KOH (0.86 g, 0.0153 moles) was refluxed under N_2 in EtOH (100 mL) for 1 h. The mixture was then partitioned between EtOAc/water and the organic layer was dried ($MgSO_4$), filtered, and evaporated *in-vacuo*. The compound was recrystallized from cyclohexane/EtOAc (0.65 g, 95 % yield) and was obtained as white crystals, mp=100-102 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, J=4.0 Hz, 1-H), 8.10-8.05 (m, 2-H), 7.85 (d, J=12.0 Hz, 1-H), 7.60-7.35 (m, 4-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.48, 149.90, 136.29, 130.10, 128.96, 127.10, 126.82, 123.93.

Anal. Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.96; H, 5.18; N, 17.85.

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