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Novel Cyclization Reactions Of Dichloroazodienes

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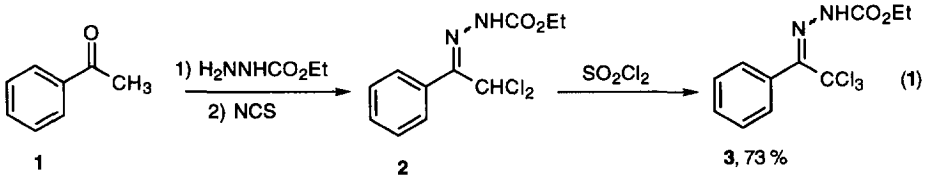
Abstract: The novel cyclization reactions of the *in-situ* generated 1-carboxyethyl-3-phenyl-4,4-dichloroazodiene were found to give *N*-aminopyrroles and pyridazines when combined with acyclic enamines , Table 1. However, reactions with cyclic enamines gave the *N*-aminopyrroles, pyridazines, a dihydropyridazine as products as well as the non-cyclized enamine intermediates, Table 2. The enamines **10c** and **11c** could be converted to the *N*-aminopyrroles **10a** and **11a** simply upon heating to higher temperatures indicating a stepwise mechanism. The examples described here are the first reported cyclization reactions for dichloroazodienes.

A number of non-halogenated azodienes have been studied which mainly give the saturated dihydropyrroles and the tetrahydropyridazines derived from a formal 3+2 or a 4+2 cyclization reaction with an electron rich olefin.[1] Derivatives prepared in this fashion are not set up for conversion directly to the corresponding aromatized *N*-aminopyrroles or pyridazines unless an external oxidant or strong base is utilized[2] which limits their utility for the preparation of these compounds. Since we are interested in the unique biological activity of 3-substituted pyridazines,[3] we recently developed a general way to prepare a variety of these compounds that relies on the concerted 4+2 reaction of a 4-chloro-3-phenylazodiene with an electron rich olefin to give a 4-chloro-substituted tetrahydropyridazine. These tetrahydropyridazines bear a chlorine in the 4-position of the ring, simply treating them with a base allows for the aromatization reaction to occur to give high yields of the corresponding pyridazine products.[4]

We wish to report here an extension of this methodology in the reactions of *in-situ* generated 1-carboxyethyl-3-phenyl-4,4-dichloroazodienes which yield *N*-aminopyrroles, pyridazines, a dihydropyridazine and non-cyclized enamine intermediates depending on the electron rich olefin that is used. No reports of successful cyclization reactions with these dichloroazodienes have appeared. However, several authors mention the preparation and addition elimination reactions of these compounds.[5]

The preparation of the trichlorohydrazone precursor necessary for the dichloroazodiene formation is shown in equation 1. The dichlorohydrazone **2** is prepared from acetophenone (**1**) by treatment with ethyl

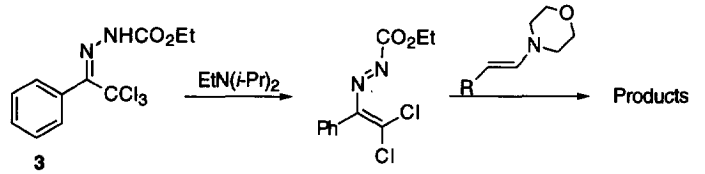


carbazate in refluxing toluene using a Dean-Stark trap to give the hydrazone in 97 % yield. Reaction of the hydrazone with NCS in carbon tetrachloride affords the dichlorohydrazone **2** in 89 % yield. The third chlorine is introduced using neat sulfuryl chloride to give trichlorohydrazone **3** in 85 % yield (73 % overall yield from acetophenone).

The highly colored dichloroazodiene is generated *in-situ* in the presence of the electron rich olefin from the trichlorohydrazone **3** by treatment with Hünig's base in methylene chloride at RT to reflux or in carbon tetrachloride at reflux to give the products shown in Table 1.[6,7] When the enamine contains a mono-substituted alkyl group as in Table 1 the products obtained from the reaction are both the *N*-aminopyrroles **4a** and **6a** and the pyridazines **4b** and **6b** in roughly equal amounts. When the enamine was substituted with a

phenyl group the main product (75 %) was the *N*-aminopyrrole **7a** and the minor product was the pyridazine **7b**. The methoxy-substituted enamine gave only the N-aminopyrrole product **5a**.

Table 1.



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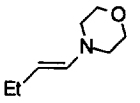
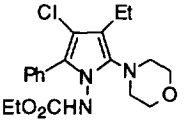
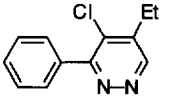
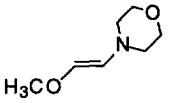
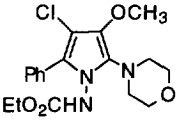
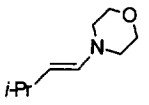
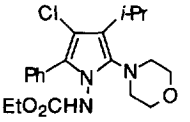
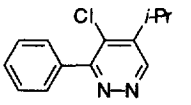
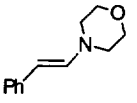
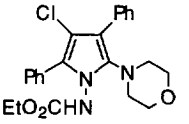
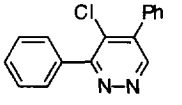
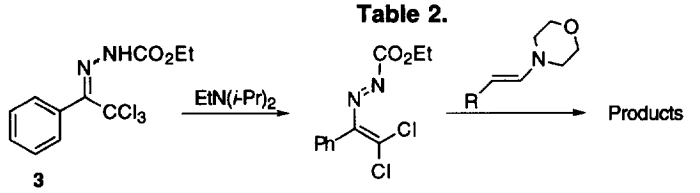
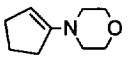
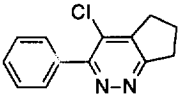
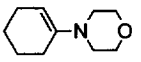
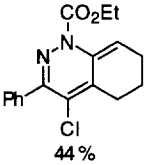
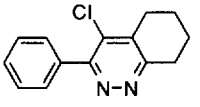
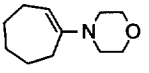
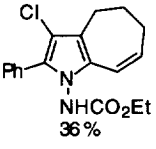
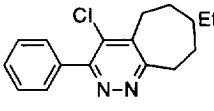
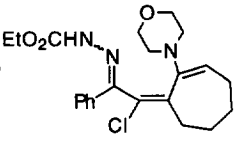
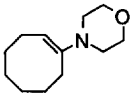
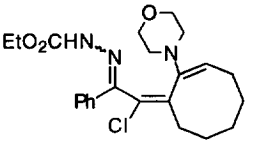
No.	Enamine	Products a	Products b
4		 15 %	 16 %
5		 11 %	
6		 23 %	 36 %
7		 75 %	 7 %

A similar set of products were obtained under the same reaction conditions when cyclic or disubstituted enamines were utilized in the reaction with the dichloroazodiene, Table 2.[6,7] Combination of the morpholinocyclopentene with the dichloroazodiene gave only the chloropyridazine product **8b** in 48 % yield. The reaction with morpholinocyclohexene gave a small amount (9 %) of the chloropyridazine **9b** as well as an unusual bicyclic *N*-carboxy substituted pyridazine (44 %) derivative **9a** that appears to have been formed by a ring closure reaction followed by a morpholine elimination. Morpholine elimination products were also obtained in the reactions of morpholinocycloheptene and morpholinocyclooctene, **10** and **11**. However, in these cases the *N*-aminopyrroles were formed and the double bond migrated away from the bridge head to give the products **10a** and **11a**.[8] The chloropyridazine **10b** was present in the reaction with the morpholinocycloheptene, but not with morpholinocyclooctene. In addition to the cyclic products that were isolated from these reactions, acyclic enamine intermediates were also isolated in the case of compounds **10c** and **11c**.[9] The structural assignments in Tables 1 and 2 were made on the basis of ^{1}H NMR, ^{13}C NMR, APT NMR, MS, and analytical data.[10]

Table 2.



3

No.	Enamine	Products a	b	c
8			 48 %	
9		 44 %	 9 %	
10		 36 %	 12 %	 31 %
11		 3 %		 31 %

It appeared that in reactions **9-11**, Table 2, that there were compounds isolated that were precursors to the pyridazine products. In an effort to test this hypothesis these compounds were subjected to more stringent reaction conditions. When compound **9a** was treated with acid in DMF at RT the pyridazine **9b** was formed in 81 % yield. Simply heating the open chain compounds **10c** and **11c** in DMF at 156 °C resulted in the formation of cyclic *N*-aminopyrroles **10a** and **11a** respectively. These experiments suggest that **9a** was an intermediate in the formation of **9b** and that **10c** and **11c** were precursors to **10a** and **11a**.

In summary, we have developed the synthesis and reaction chemistry of 1-carboxyethyl-3-phenyl-4,4-dichloroazodiene that gives a variety of products depending on the substitution pattern of the electron rich olefin. It is most likely that the compounds shown in Tables 1 and 2 are derived by a stepwise addition of the enamine to the dichloroazodiene since such a variety of products have been isolated and shown to be interconvertable. This is in contrast to what we observed in the reaction studies of the chloroazodienes which gave only the products derived from what appeared to be a concerted, inverse electron demand, 4+2 hetero Diels-Alder reaction.[4] We are currently studying this new reaction 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. (h) Attanasi, O. A.; Caglioti, L. *Org. Prep. Proceed. Int.* **1986**, *18*, 299.

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. (a) South, M. S.; Miller, M. J., U. S. Patent Application Pending. (b) South, M. S., U. S. Patent Application Pending. (c) South, M. S.; Moedritzer, K. A., U. S. Patent Application Pending. (d) South, M. S.; Jakuboski, T. L., U. S. Patent Application Pending.

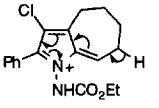
4. South, M. S.; Jakuboski, T. L. *Tetrahedron Letters* **1995**, 5703. Two reports of a cycloaddition reaction involving a chloroazodiene have appeared, but these products were not elaborated to pyridazines. (a) Gilchrist, T. L.; Sanchez Romero, O. A.; Wasson, R. C. *J. Chem. Soc., Perkin Trans. I* **1989**, 353. (b) Gilchrist, T. L.; Stevens, J. A. *J. Chem. Soc., Perkin Trans. I* **1985**, 1741.

5. Gilchrist, T. L.; Stevens, J. A. *J. Chem. Soc. Perkin Trans. I,* **1985,** 1737 and references cited therein.

6. The electron rich olefins in Table 1 and 2 were available commercially or 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. 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 ^{1}H NMR, ^{13}C NMR, and elemental analyses.

8. A potential intermediate in the *N*-aminopyrrole formation:



9. The regiochemistry of the double bonds is not known.

10. Data for **6a**: Tan solid, mp=176-178 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.12 (s, 1-H), 7.5-7.34 (m, 5-H), 4.25-4.10 (m, 2-H), 3.71 (bs, 4-H), 3.21 (septet, J=7.2 Hz, 1-H), 3.11 (bs, 4-H), 1.40 (d, J=7.2 Hz, 6-H), 1.26 (t, J=7.2 Hz, 3-H); APT ^{13}C NMR (75 MHz, Acetone-d_6) δ positive peaks, 156.0, 135.0, 129.8, 126.0, 119.0, 106.0, 68.0, 61.0, 52.0; δ negative peaks, 130.0, 128.0, 127.0, 25.0, 21.5, 14.0; GC-MS (EI) 391 (M^+).
Anal. Calcd. for $C_{20}H_{26}N_3O_3Cl$: C, 61.30; H, 6.69; N, 10.72. Found: C, 61.15; H, 6.62; N, 10.58.
Data for **6b**: White solid, mp=80-82 °C from EtOAc/cyclohexane; ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.21 (s, 1-H), 7.79-7.74 (m, 2-H), 7.60-7.55 (m, 3-H), 3.54 (septet, J=7.0 Hz, 1-H), 1.43 (d, J=7.0 Hz, 6-H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 159.96, 149.37, 145.60, 136.95, 135.89, 130.25, 129.85, 128.69, 31.01, 21.34; GC-MS (EI) 232 (M^+).
Anal. Calcd. for $C_{13}H_{13}N_2Cl$; C, 67.10; H, 5.63; N, 12.04. Found: C, 67.17; H, 5.66; N, 12.08.
Data for **10a**: White solid, mp=177-178 °C from hexane; ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.40 (s, 1-H), 7.46-7.34 (m, 5-H), 6.03 (dt, J=11.6, 1.8 Hz, 1-H), 5.72 (dt, J=11.6, 5.6 Hz, 1-H), 2.93-2.74 (m, 2-H), 2.46-2.41 (m, 2-H), 2.00-1.91 (m, 2-H), 1.18 (t, J=7.0 Hz, 3-H); APT ^{13}C NMR (75 MHz, Acetone-d_6) δ positive peaks, 154.5, 132.8, 129.5, 114.3, 114.2, 108.0, 61.0, 31.0, 28.0, 22.0; δ negative peaks, 129.6, 128.2, 127.7, 127.0, 119.2, 14.0; MS (CI) 331 ($M^+ + 1$).
Anal. Calcd. for $C_{18}H_{19}N_2O_2Cl$: C, 65.39; H, 5.79; N, 8.47. Found: C, 65.30; H, 5.81; N, 8.51.
Data for **10b**: White solid, mp=107-112 °C from hexanes; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.56-7.54 (m, 2-H), 7.38-7.36 (m, 3-H), 3.17-3.15 (m, 2-H), 3.02-2.99 (m, 2-H), 1.83-1.77 (m, 2-H), 1.66-1.56 (m, 4-H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 165.47, 158.99, 141.48, 137.62, 135.62, 130.37, 129.87, 128.86, 37.03, 32.40, 30.01, 27.01, 26.82; GC-MS (EI) 258 (M^+).
Anal. Calcd. for $C_{15}H_{15}N_2Cl$: C, 69.67; H, 5.85; N, 10.83. Found: C, 69.41; H, 5.83; N, 10.74.

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