THE FORMATION OF 3-CHLORO-1,2,5-THIADIAZOLES FROM α-OXIMIDONITRILES. OPTIMIZATION AND MECHANISTIC INSIGHTS

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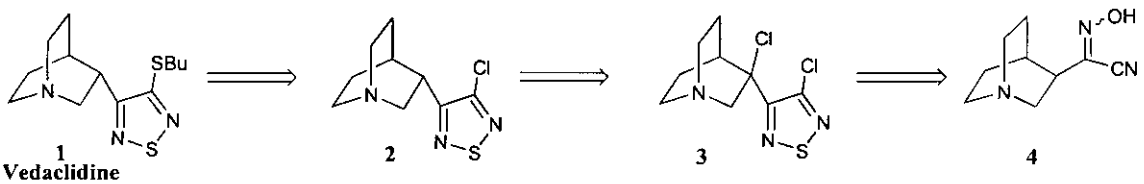
Abstract - The optimized formation of substituted 3-chloro-1,2,5-thiadiazoles (**2**) and (**3**) from the α-oximidonitrile (**4**) is described. New mechanistic insight into the formation of 3-chloro-1,2,5-thiadiazoles comes from the identification of a reaction intermediate in the thiadiazole ring-forming reaction.

INTRODUCTION

A new class of muscarinic antioceptive agents containing a substituted 1,2,5-thiadiazole ring has been reported.[2] These compounds have shown high affinity for muscarinic receptors and have demonstrated analgesic activity in animal models. The most active member of these muscarinic analgesic is the 1,2,5-thiadiazole (**1**) which is known as vedaclidine. As previously reported, vedaclidine is prepared from the 3-chloro-1,2,5-thiadiazole (**2**) which is derived by removal of the tertiary chloride (H_2, 5% Pd/C) from the α-chloro-3-chloro-1,2,5-thiadiazole (**3**) (Scheme 1).[2] Critical to the synthesis is the formation of the chlorothiadiazole ring system from the α-oximidonitrile (**4**). Although this chemistry represents a novel route of chlorothiadiazole construction, it required optimization prior to its use in preparing large quantities of **1**. This report focuses on our findings specific to the thiadiazole ring formation. Included in the discussion is the optimized chemistry for the preparation of α-chloro-3-chloro-1,2,5-thiadiazole (**3**) (dichlorothiadiazole) from the α-oximidonitrile (**4**), the identity of a reaction intermediate in the chlorothiadiazole formation, and a proposed mechanism for the formation of dichlorothiadiazole (**3**) and chlorothiadiazole (**2**).

Sulfur chlorides are generally considered the most useful reagents for the synthesis of 1,2,5-thiadiazoles because they are strongly electrophilic and can form N-S bonds with a wide range of substrates. Weinstock has described a general synthetic method for preparing 1,2,5-thiadiazoles, in which an acyclic NCCN grouping at any of several oxidation states is treated with sulfur monochloride (S_2Cl_2)[3] or sulfur dichloride (SCl_2)[4] to form the corresponding thiadiazole ring.[5] Using this methodology, it has been



1 Vedaclidine **2** **3** **4**

demonstrated that geminal diamines form unsubstituted 1,2,5-thiadiazoles upon treatment with SCl_2 or S_2Cl_2, while amide-containing substrates form 3-hydroxy-1,2,5-thiadiazoles and cyano-containing substrates form 3-chloro-1,2,5-thiadiazoles.[5,6] The optimum solvent for thiadiazole formation proved to be DMF and the desired stoichiometry was 3-6 equivalents of S_2Cl_2.[5] The reactions were generally carried out at room temperature.

There are few examples of the synthesis of 1,2,5-thiadiazoles from oxime substrates. Treatment of *o*-benzoquinone dioxime with S_2Cl_2 gaves a mixture of the corresponding 2,1,3-benzothiadiazole and its *N*-oxide, illustrating the necessary reduction of the oxime N-O bond in order to form the desired product.[7] The work most relevant to our chemistry is the combination of S_2Cl_2 with α-phenyl-oximidonitrile to form 3-chloro-4-phenyl-1,2,5-thiadiazole, albeit in 15% yield.[5] This is the only literature example of 3-chlorothiadiazole formation from an α-oximidonitrile, and it should be noted that the substrate contains no β-hydrogens (i.e. phenyl substituted oximidonitrile).

A mechanism for the formation of monocyclic 3-chlorothiadiazole by the addition of S_2Cl_2 to an α-amino nitrile substrate has been proposed by Weinstock (Figure 1).[5,6] According to this mechanism, 2 equivalents of S_2Cl_2 are required for the reaction: 1 equivalent for insertion of the ring sulfur and 1 equivalent for the oxidation required to achieve aromaticity. In contrast, oximes require reduction of the N-O bond for formation of a 1,2,5-thiadiazole. Weinstock admits that "formation of thiadiazoles from oximes is less easily rationalized" than their formation from starting materials containing amine, amide or cyanide functionalities.[6] Our findings provide some insight into the formation of thiadiazoles from oximes, allowing us to rationalize the role of N-O bond reduction in the thiadiazole formation.

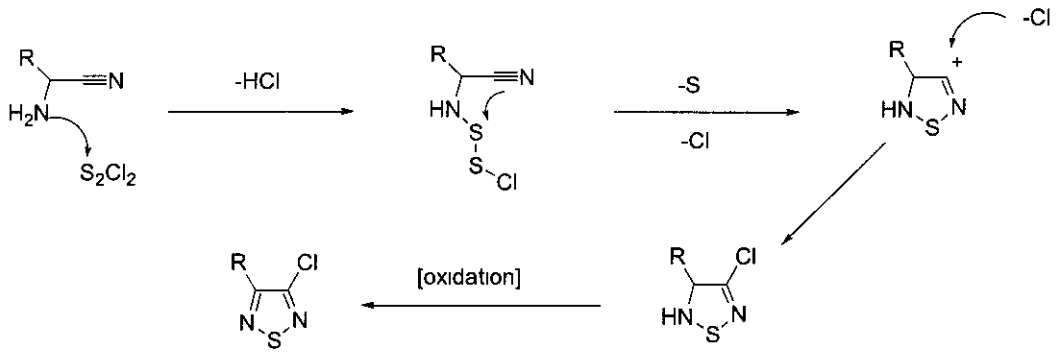
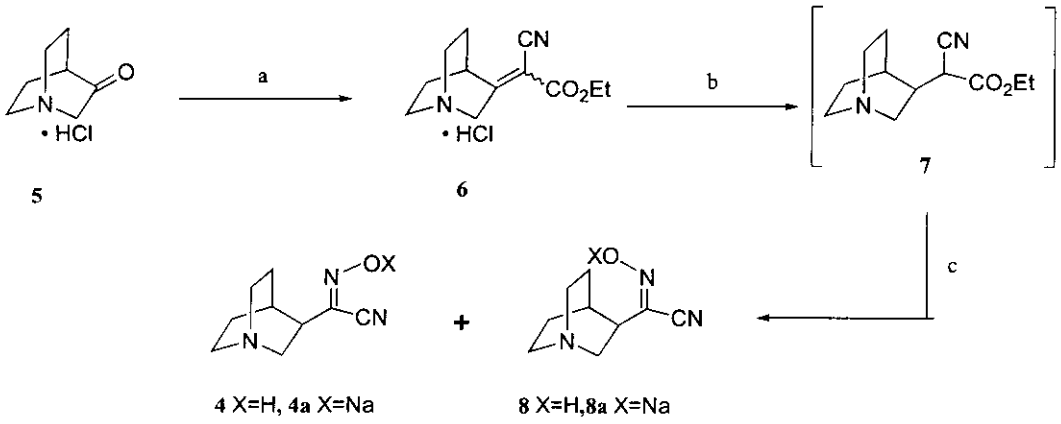


Figure 1. Weinstock's mechanism for the formation of 1,2,5-thiadiazoles from an α-amino nitrile.[5,6]

RESULTS AND DISCUSSION

The α-oximidonitrile (**4**) was prepared by the methods outlined in Scheme 1 as previously described.[2] Knoevenagel condensation of quinuclidone hydrochloride (**5**) with ethyl cyanoacetate yielded acrylate (**6**) (88%). Hydrogenation of the double bond over 5% Pd/C yielded the saturated cyanoacetate (**7**) which was reacted further without isolation. Nitrosation of **7** by the action of isopentyl nitrite and NaOEt occurred with concomitant extrusion of diethyl carbonate. The reaction yielded a 3.5:1 mixture of

Scheme 1[a]



[a] (a) ethyl cyanoacetate, Et_3N, 75 °C; (b) H_2, 5% Pd/Carbon, EtOH; (c) NaOEt (2.2 equiv), EtOH, 0 °C, then isopentyl nitrite (1.1 equiv), 25°C.

cis:trans oxime isomers (**4** and **8**) which proved to be the thermodynamic ratio. The crude sodium salts (**4a** and **8a**) of the oxime mixture were obtained by concentration of the reaction mixture to dryness. Alternatively, adjustment of the reaction mixture to pH 8-8.5 by the addition of 1 M HCl precipitated the major oxime isomer (**4**) in high purity (>99% pure, 72% Yield). The minor isomer (**8**) remained in the filtrate. The isolated *cis*-oximidonitrile (**4**) was used exclusively for the thiadiazole formations described in this paper.

Treatment of the oximidonitrile (**4**) under the conditions prescribed by Weinstock (3.5 equivalents S_2Cl_2, DMF)[5] yielded a 55% *in situ* yield of the dichlorothiadiazole (**3**). In addition 5-7% of the 3-chloro-thiadiazole (**2**) was found in the reaction mixture. In reactions performed *via* this protocol, the oxime starting material (**4**) was never consumed. For these reasons, alternate reaction conditions were sought. The thiadiazole forming reaction performance in various solvents was compared to that of reactions in DMF (Table 1). The various solvents included CH_2Cl_2, 1,2-dichloroethane, toluene, THF, ethyl acetate, acetonitrile (ACN), and dimethylacetamide (DMAC). Little or no reaction was observed in many of the solvents screened (CH_2Cl_2, 1,2-dichloroethane, toluene, THF, and ethyl acetate). This was likely due to the low solubility of **4** or the precipitation of the oxime upon addition of S_2Cl_2. Compared to reactions in DMF, higher *in situ* yields were observed when reactions were carried out in ACN or DMAC (Table 1). The best yields were seen in the DMAC reactions but the mixtures were thick gelatinous slurries which

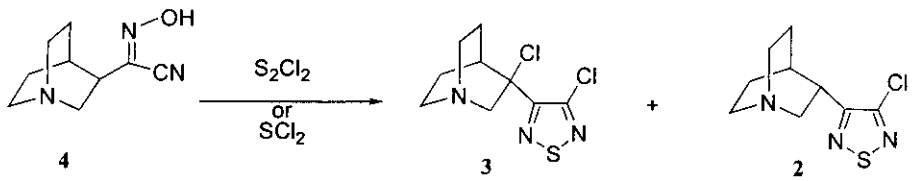


Table 1. **Solvents in the formation of dichlorothiadiazole (3).**

Reaction Solvent[a]	Reaction Temp °C	*In Situ* Yield of **3**[b] (%)	*In Situ* Yield of **2**[b] (%)
DMF	40	48	9
ACN	40	80	< 0.5
DMAC	25	85	6
ACN/DMF (3:1)	40	57	3
ACN/DMAC (3:1)	40	83	5

[a] The experiments were performed with 3.5 equivalents of S_2Cl_2.

[b] Yields were determined by HPLC analysis of a solution of **3** versus an external reference standard, see general experimental methods for details.

were difficult to agitate. Reactions in ACN gave good *in situ* yields (80%) but the reaction progressed at a slower rate than in DMAC solvents.

Reactions performed in 3:1 ACN:DMAC solvent mixture produced **3** in 82-86% *in situ* yield after 7 h at 40 °C with 5-8% of **2** also being produced (Table 1). These reactions afforded greater than 90% mass balance of **2** and **3**, and reaction mixtures were not as thick as with pure DMAC, and the slurry was adequately stirrable. With 3:1 ACN:DMF, the yield was 57% after 7 h at 40 °C, as compared to 48% yield for the reaction in pure DMF. The presence of DMF appeared to retard the consumption of **4**. Interestingly, reactions in ACN gave the lowest amounts of the 3-chlorothiadiazole (**2**), but the reactions with DMAC showed increased reaction rates and higher, more consistent yields of both thiadiazole products. For these reasons 3:1 ACN:DMAC solvent mixture was adopted as the preferred reaction solvent for thiadiazole formation.

Stoichiometries of S_2Cl_2 between 1.0 equivalent and 4.0 equivalents were evaluated in the reaction. The larger amounts of S_2Cl_2 gave greater *in situ* yields. For example, the *in situ* yield for the reaction in 3:1 ACN:DMAC with 2.0 equivalents of S_2Cl_2 was 65% as compared to 83% for reactions with 3.5 equivalents of S_2Cl_2. There were no differences in the reactions with S_2Cl_2 stoichiometries between 3 and 4 equivalents. Theoretically, only one equivalent of S_2Cl_2 was needed for conversion of **4** to the 3-chloro-thiadiazole ring system. However, reactions with one equivalent S_2Cl_2 gave precipitation and clumping of an oily residue and very little product was detected by HPLC analysis of the reaction mixture. Any amount greater than 3.0 equivalents of S_2Cl_2 relative to the oximidonitrile (**4**) gave comparable results.

The reactions were generally performed at a very high concentration, typically ~1 M in oxime (6 mL solvent/g oxime). Reactions in 3:1 ACN:DMAC carried out at half the concentration (12 mL solvent/g oxime) gave slightly reduced *in situ* yields (72%) after 7 h at 40 °C.

The reaction of the oximidonitrile with S_2Cl_2 was found to be very exothermic. Calorimetry measurements made during the reaction identified the occurrence of three separate exothermic events, one upon addition of S_2Cl_2, one upon warming the reaction mixture to ambient temperature, and the last occurred slowly during the duration of the reaction at 30 °C (Table 2). The first exotherm (31.9 kcal/g•mol) was observed during the addition of the oxime slurry to S_2Cl_2. An equivalent exothermic event (32.2 kcal/g•mol) resulting in a 47.5 °C adiabatic temperature rise was observed during the addition of the first 0.5 equivalent of S_2Cl_2 to a slurry of the oxime. Quenching the reaction mixture at the end of the reagent addition and the corresponding heat generation gave only recovered oximidonitrile. Attempts to control the initial exothermic event by slow addition of S_2Cl_2 to a slurry of **4** in ACN:DMAC gave decomposition of the starting oxime when less than 1 equivalent of S_2Cl_2 had been added and lower than normal *in situ* and isolated yields. This was consistent with the observed decomposition that occurs in reactions with 1 equivalent of S_2Cl_2. Thus, in order to avoid the decomposition, the first temperature rise had to be controlled by the slow addition of the oxime in ACN:DMAC to S_2Cl_2 in ACN:DMAC at a rate to maintain the temperature below 0 °C.

***Table 2.* Heat of reaction data for the formation of dichlorothiadiazole (3).[a]**

Exothermic Event	Operation	Heat of Reaction (kcal/g•mol)	Adiabatic Temperature Rise (°C)
1	Addition of oxime (**4**) to S_2Cl_2	31.9	42.5
2	Heating the mixture to 30 °C	49.2	65.7
3	Stirring the mixture at 30 °C	55.1	73.4

[a] The experiments were performed with 3.5 equivalents of S_2Cl_2 in 3:1 ACN:DMAC.

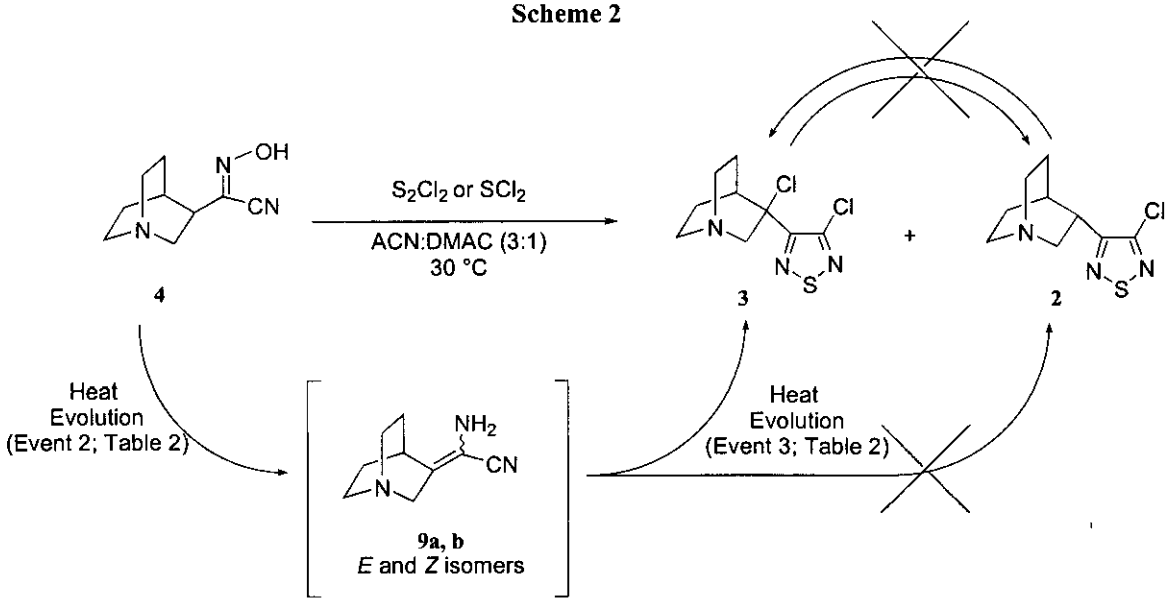
Following the addition, the reactor temperature was increased from -10 °C to 30 °C over 1 h. A sharp rise in heat generation (49.2 kcal/g•mol) was observed at approximately 15-20 °C. The heat generation leveled off at a steady, low value approximately 20 minutes after it peaked and persisted until the maximum *in situ* yield was obtained (15 h). The second exothermic event was controlled by slowly heating the mixture to 20 °C and allowing the reaction to heat itself to 30-35 °C, while cooling the mixture such as to not exceed this temperature. The reaction was completed by maintaining the temperature at 30 °C for 15 h.

HPLC analysis of a quenched reaction aliquot taken at the completion of the second exothermic event showed the consumption of oximidonitrile (**4**), the appearance of chlorothiadiazole (**2**) and dichlorothiadiazole (**3**), and the presence of two unidentified peaks (Peaks A and B). The amount of **2** (~5-7%) did not change after the completion of the second exotherm. When subjected to the reaction conditions, isolated chlorothiadiazole (**2**) did not convert to the dichlorothiadiazole product. Likewise, when isolated **3** was subjected to the reaction conditions none of the monochlorothiadiazole product was observed.

The unidentified peaks in the HPLC chromatogram, present in approximately a 3:1 ratio of peak A to B, slowly disappeared as the reaction progressed and the concentration of **3** increased. The maximum yield of **3** was not obtained until the completion of the third exothermic event (Table 2) at which point the unidentified peaks had disappeared. This behavior suggested that peaks A and B represent reaction intermediates. The reaction showed no change in the amount of **2** as the intermediates disappeared thus it was concluded that the monochlorothiadiazole product did not form from these intermediates as the dichlorothiadiazole product did, and must form by a divergent mechanism.

A pure sample of the major unidentified intermediate (peak A) was isolated from a reaction which was quenched at the completion of the second heat evolution. The structure was determined to be that of the α-cyano enamine (**9a**) (Scheme 2). An assignment of the double bond geometry of **9** was not accomplished. Although the minor unidentified intermediate (**9b**, peak B) was not isolated pure from peak A, NMR and GC-MS data suggested it was the double bond isomer of **9a**. When a purified sample of **9a** was subjected to the reaction condition (S_2Cl_2, ACN:DMAC 3:1, 30 °C), the dichlorothiadiazole (**3**) was produced exclusively. Clearly, the existence of these reaction intermediates indicated that the N-O bond reduction occurs early in the transformation of the oximidonitrile (**4**) to the thiadiazoles (**2**) and (**3**),

Scheme 2



and provided an explanation for the chlorination alpha to the thiadiazole ring producing **3** as the major product. This data also suggested that formation of the chlorothiadiazole (**2**) was due to a mechanistic divergence at the N-O bond reduction stage of the reaction.

The same intermediates were observed by HPLC when **4** was treated with SCl_2 instead of S_2Cl_2. The initial exotherm with SCl_2 (-10 to 80 °C) was much larger than with S_2Cl_2 (-10 to 0 °C), probably due to the greater reactivity of SCl_2. No second exotherm was observed with SCl_2. The same relative amounts of the chlorothiadiazole products (**2**) and (**3**) were formed regardless of which S_xCl_2 reagent was used.

The dichlorothiadiazole (**3**) was isolated by quenching the reaction mixture with a small amount of water (7 equivalents with respect to **4**), precipitating the product as the hydrochloride salt and elemental sulfur. Acetone was added to reduce the yield loss and to improve the agitation of the mixture of precipitated solids. The resulting slurry was filtered cold, yielding a crude product contaminated with elemental sulfur. The wetcake containing **3** hydrochloride and sulfur was reslurried in hot water (pH 2) and filtered to remove sulfur. Addition of acetone to the filtered aqueous solution and cooling produced crystalline dichlorothiadiazole hydrochloride monohydrate (**3**) in 72% yield with a purity of at least 82.5% by HPLC analysis.[8] The yield reduction resulted from product loss in the reaction mixture filtrate (4-6%) and the final isolation filtrate (5-7%).

To date, there have been no reported mechanisms for the formation of 3-chloro-1,2,5-thiadiazoles from α-oximidonitriles. Based on our observations, the isolated intermediate, and corresponding heat data, we propose the mechanism shown in Figure 2 for the formation of the 3-chlorothiadiazoles (**2**) and (**3**). This mechanism accounts for the divergent nature of the N-O bond reduction which must occur in the formation of thiadiazoles from oximidonitriles. First, the oxime oxygen attacks the S_2Cl_2 with loss of chloride to form an R-O-SSCl intermediate, which is consistent with the initial exotherm observed. Reaction of the oximidonitrile in which the oxime was protected as a mesylate with S_2Cl_2 gave no initial exotherm and no reaction, thus supporting the formation of an RN-O-SSCl intermediate. Reaction with 1.0 equivalent of S_2Cl_2, instead of 3.5 equivalents, resulted in the same initial exotherm, indicating that the initial exotherm was caused by a one-to-one addition of S_2Cl_2 to the oxime. Quenching the reaction with water after the initial exotherm yielded only recovered starting material.

Quaternization of the oxime nitrogen with a second equivalent of S_2Cl_2 leads to a reaction intermediate from which point we propose the mechanism can diverge (intermediate (**11**), Figure 2). Allowing the reaction to warm to ambient temperature leads to a second observed exotherm (Table 2), which corresponds to the consumption of starting material. Quenching the reaction after the second exotherm yields a mixture of thiadiazoles (**2**) and (**3**) as well as the enamine reaction intermediates **9**.

Mechanistically, the formation of the chlorothiadiazole (**2**) is explained by the breaking of the N-O bond (pathway B), leading to intermediate (**14**) (Figure 2). Presumably the attack of a latent nucleophile such as chloride on the sulfur adjacent to the chlorine results in cleavage of the N-O bond. In a mechanism identical to that proposed by Weinstock, the cyclization of intermediate (**14**) leads to the unsubstituted 3-chlorothiadiazole (**2**). Intermediate (**14**) has not been observed by any spectral means.

Alternatively, the formation of the dichlorothiadiazole (**3**) occurs by elimination of the α-hydrogen in intermediate (**11**) and neutralization of the positive charge on nitrogen at the point of diversion (pathway A, intermediate (**11**), Figure 2). Quenching of intermediate (**12**) leads to the isolated cyano enamines (**9**).

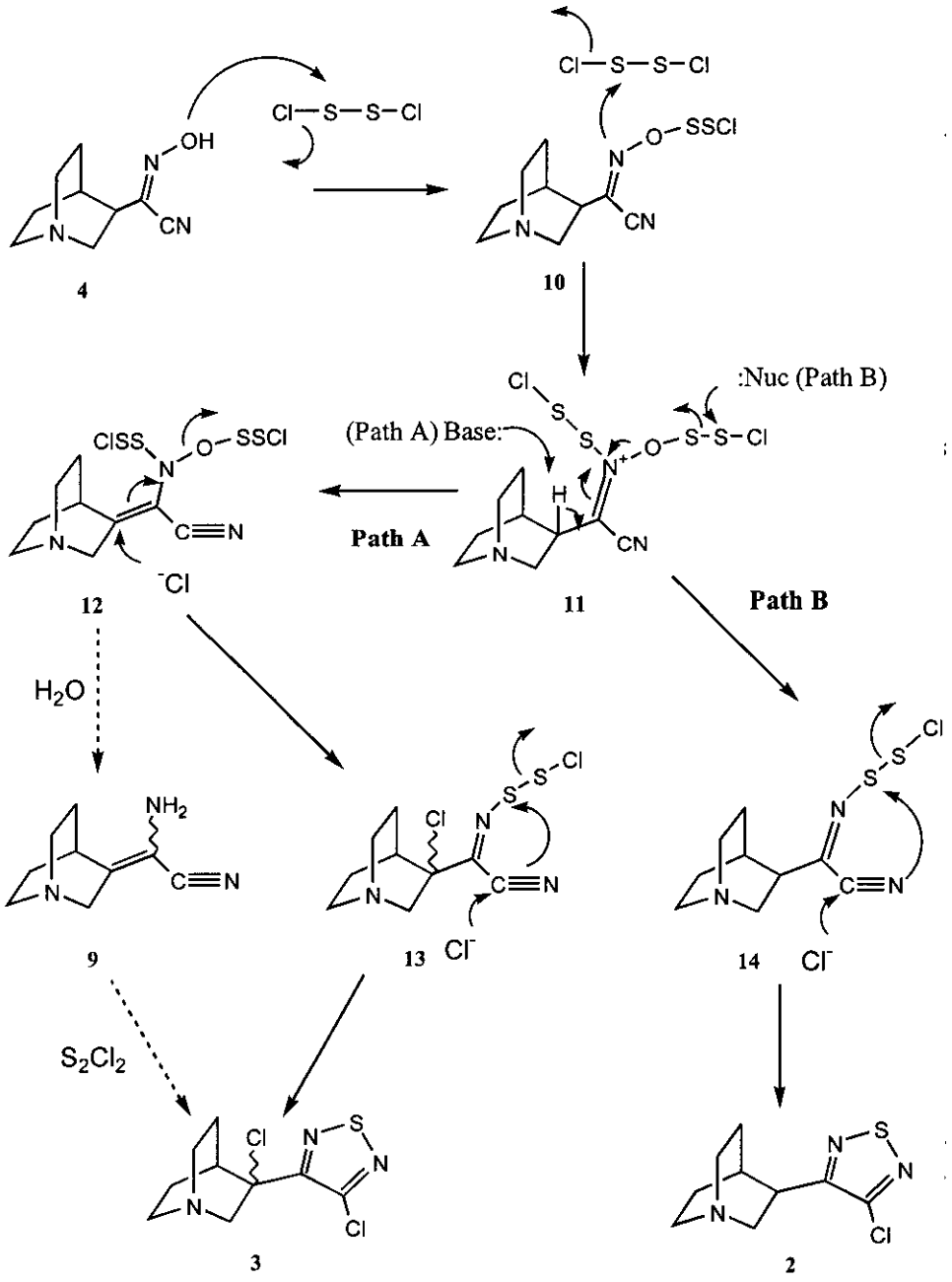


Figure 2. Proposed mechanism for the formation 3-chloro-1,2,5-thiadiazoles (**2**) and (**3**).

Presumably, any α-oximidonitrile substrate which has a beta hydrogen would be prone to such elimination yielding α-chlorothiadiazole products. Treatment of this quenched intermediate with S_2Cl_2 results in formation of the dichlorothiadiazole product only. Attack of chloride in an S_N2' fashion on

intermediate (**12**) results in loss of an -OSSCl species and formation of the tertiary chloride intermediate (**13**) (Figure 2). Similar to the chlorothiadiazole-forming step described above, ring closure to form the dichlorothiadiazole occurs by attack of chloride on the nitrile and cyclization with loss of SCl^-, yielding chloride and elemental sulfur.

CONCLUSION

In conclusion, we have described an optimized procedure for the formation of the α-chloro-3-chloro-1,2,5-thiadiazole (**3**), which is a key intermediate in the synthesis of vedaclidine (**1**). The improvement relies upon use of a mixture of ACN and DMAC solvents and careful temperature control. Reaction intermediates found in the 3-chlorothiadiazole formation have been isolated and characterized. The intermediates were shown to be the isomeric α-cyano enamines (**9a**) and (**9b**). The presence of these reaction intermediates suggests that N-O bond reduction of the starting oxime occurs early in the formation of the chlorothiadiazole and leads to oxidation or chlorination at the carbon alpha to the thiadiazole ring. In addition, a mechanism for the formation of the 3-chloro-1,2,5-thiadiazoles (**2** and **3**) from the α-oximidonitrile (**4**) was proposed. The proposed mechanism accounts for the divergent nature of the N-O bond reduction as well as for the observed reaction intermediates. This work provides a better understanding of the cyclization of α-oximidonitriles (with beta hydrogens) in the presence of S_2Cl_2 or SCl_2 to 3-chloro-1,2,5-thiadiazoles.

EXPERIMENTAL SECTION

General Procedures. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. The ethanol used was anhydrous and denatured with 5% methanol. Melting points were obtained on a Meltemp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz; ^{13}C NMR spectra were recorded at 75 MHz. The reaction thermochemistry mesurements were performed in a Mettler RC1 Reaction Calorimeter using Version 3.3 PC Software. Reactions were monitored by HPLC analyses performed on a YMC Basic, 5μ column (25 cm x 4.6 mm i.d.) with a gradient eluent system at a flow rate of 1 mL/min, and UV detection at 250 nm. Mobile phase components: A = (5:95) ACN/ H_2O (containing 5.4 g $NH_4H_2PO_4$, diluted to 1L, pH 2.5 with H_3PO_4), B=45% ACN/55% H_2O (containing 5.4 g $NH_4H_2PO_4$, diluted to 1L, pH 2.5 with H_3PO_4). Gradient program: hold at 95% A/5% B for 8 min, linear ramp to 60% A/40% B over 17 min, hold at 60% A/40% B for 2 min, return to 95% A/5% B and equilibrate the column for 8 min. Ethyl (1-azabicyclo[2.2.2]-octan-3-ylidene)cyanoacetate hydrochloride (**6**) was prepared as described in reference 2.

(±)-*cis*-2-(1-Azabicyclo[2.2.2]octan-3-yl)-2-oximidoacetonitrile (4). A slurry of ethyl (1-azabicyclo-[2.2.2]octan-3-ylidene)cyanoacetate hydrochloride (**6**) (60.0 g, 233.7 mmol) and 5% Pd/C catalyst (3.0 g) in EtOH (240 mL) was hydrogenated between 20 and 50 psi of H_2 at ambient temperature in a Parr shaker apparatus until one equivalent (233.7 mmol) of H_2 was absorbed by the reaction. The solution was vacuum filtered through a bed of Hyflo Super Cel, and the filter cake was washed with EtOH (20 mL). The filtered solution was transferred to a 500-mL, three-neck flask equipped with a N_2 purge, an addition funnel, thermometer, and a mechanical stirrer. The solution was cooled to 0 °C, and NaOEt (21%

solution in EtOH, 218 mL, 584.3 mmol) was slowly added to maintain the reaction temperature <5 °C. Isopentyl nitrite (32.9 g, 280.4 mmol) was added over 10 min. The resulting mixture was warmed to ambient temperature and stirred 2 h. At the completion of the reaction, 1 M HCl solution was slowly added until the pH was 8.5 (The pH was measured by inserting a pH probe directly into the reaction mixture). The resulting slurry was cooled to 0 °C and stirred for 2 h. The slurry was filtered, washed with cold H_2O (25 mL) and cold EtOH (25 mL). The product was dried in vacuo at 40 °C to afford **4** (8.15 g, 72%) as a white solid, which was >99% pure by HPLC analysis. HPLC analysis was conducted on a YMC Basic, 5μ column (25 cm x 4.6 mm i.d.) with an isocratic eluent system of ACN/H_2O (10:90) containing 0.05% TFA at a flow rate of 1 mL/min, and UV detection at 220 nm. An analytical sample was obtained by recystallization from EtOH/water: mp = 212-215 °C (decomp); ^{1}H NMR (CD_3OD): δ 3.28 (m, 1H), 3.04 (m, 1H), 2.75-2.95 (m, 5H), 2.11 (sextet, J = 3.1 Hz, 1H), 1.72-1.82 (m, 2H), 1.44-1.72 (m, 2H); ^{13}C NMR (CD_3OD): δ 134.9, 111.7, 49.5, 47.7, 47.7, 40.0, 27.4, 26.2, 21.7; IR (KBr) 2955, 2922, 2889, 2216, 1454, 990, 794, 754, 702 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found C, 60.05; H, 7.45; N, 23.80.

(±)-*trans*-2-(1-Azabicyclo[2.2.2]octan-3-yl)-2-oximidoacetonitrile (8) was isolated from the above filtrate solution (50 mL) by continuous extraction with hot ethyl acetate (500 mL) for 18 h. The ethyl acetate layer was separated, dried with Na_2SO_4, and concentrated in vacuo to give a crude mixture of oximes **4** and **8** (~1:3). The oxime (**8**) was separated from the crude residue by flash chromatography on silica gel eluting with 1:1 MeOH/EtOAc (R_f of **4** = 0.1; R_f of **8** = 0.2). Concentration of the homogeneous fractions afforded the *trans* oxime (**8**) (400 mg, 1%) as semi-solid residue: ^{1}H NMR (CD_3OD): δ 3.21-3.38 (m, 2H), 2.78-3.05 (m, 5H), 2.09 (sextet, J = 3.0 Hz, 1H), 1.82-1.95 (m, 1H), 1.53-1.78 (m, 3H); ^{13}C NMR (CD_3OD): δ 142.6, 116.3, 51.7, 47.8, 47.5, 35.0, 27.5, 25.2, 22.7; IR (CCl_4) 2975, 2930, 2890, 2215, 1450, 990, 794, 764 cm^{-1}. Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found C, 60.14; H, 7.18; N, 23.69.

(±)-3-Chloro-3-(3-chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane hydrochloride monohydrate (3). A mixture of S_2Cl_2 (26.4 g, 195.5 mmol), ACN (22.5 mL), DMAC (7.5 mL) and Hyflo Super Cel (5 g) was placed in a 250-mL, three-neck flask equipped with a N_2 purge, condenser, thermometer, and a mechanical stirrer. The yellow solution was cooled to -10 °C with an acetone/ice bath. To this solution was added a slurry of the oximidonitrile (**4**) (10 g, 55.9 mmol) in ACN (22.5 mL) and DMAC (7.5 mL) over approximately 10 min, keeping the reactor temperature below 0 °C. The ice bath was removed, and the slurry was allowed to warm, controlling the temperature below 30 °C with a cool water bath. When the exotherm was complete, a heating mantle was applied to maintain the reaction temperature at 30 °C. The mixture was stirred at 30 °C for 15 h. The reaction was quenched by addition of H_2O (7 mL), followed by acetone (60 mL). The resulting mixture was cooled to -10 °C with an acetone/ice bath. After stirring 1 h at -10 °C, the slurry was filtered and the wetcake was washed with cold acetone (2 x 10 mL). The filtrate was discarded. In a clean 250-mL, three-neck flask equipped with a N_2 purge, condenser, thermometer, and a mechanical stirrer were combined the filtered solids and H_2O (50 mL). The slurry was heated to 75 °C and stirred for 1 h. The mixture was filtered at 75 °C, and the wetcake was washed with 100 mL of hot (65 °C) acetone: H_2O (1:4) (100 mL). To the filtrate was added

acetone (120 mL), and the mixture was heated to 60 °C to dissolve all the solids. The solution was slowly cooled to 0 °C and stirred for 1 h. The slurry was filtered and washed with cold acetone (2 x 10 mL). The product was dried in vacuo at 40 °C to afford 12.4 g of **3** hydrochloride (70%) as a white solid. An analytical sample was obtained by recystallization from acetone/water: mp 162-166 °C; ^{1}H NMR (DMSO-d_6): δ 4.45 (d, J = 14.5 Hz, 1H), 4.07 (d, J = 14.5 Hz, 1H), 3.3-3.6 (m, 2H), 3.10-3.30 (m, 2H), 2.90-3.10 (m, 1H), 2.36 (m, 1H), 1.98-2.18 (m, 2H), 1.77 (m, 1H); ^{13}C NMR(DMSO-d_6): δ 157.4, 143.2, 64.2, 57.5, 44.4, 44.0, 30.5, 20.2, 19.2; IR (KBr) 3367 (H_2O), 2903, 2575, 1364, 1129 cm^{-1}. The sample was >99% pure by HPLC analysis. HPLC analysis was conducted on a YMC Basic, 5μ column (25 cm x 4.6 mm i.d.) with an isocratic eluent system of ACN/H_2O (containing 2 mL TEA, 1 mL Acetic Acid, diluted to 1 L, pH 4.75) (25:75) at a flow rate of 1 mL/min, and UV detection at 270 nm. Titration of the product with NaOH showed it contained 11.5% HCl. Karl Fisher analysis showed the product contained 5.64% water.[8]

(±)-3-(3-Chloro-1,2,5-thiadiazol-4-yl)-1-azabicyclo[2.2.2]octane hydrochloride monohydrate (2). In a 500-mL, three-neck flask equipped with an mechanical stirrer, a thermometer and a condenser were combined dichlorothiadiazole hydrochloride (**3**) (20 g, 62.9 mmol), Carbon SN (3.33 g) and H_2O (200 mL). Concentrated HCl was added to achieve a pH of 1.5. The slurry was heated to 65 °C and stirred at 65 °C for 15 min. The very thin slurry was filtered over a bed of Hyflo Super Cel at 65 °C and washed with hot H_2O (35 mL). The aqueous solution was combined with *n*-pentanol (85 mL) in a 500 mL, three-neck flask equipped with a mechanical stirrer and a pH probe, and 5 N NaOH was added until the pH was 6.8. The layers were separated and the pentanol layer was combined with 5% Pd/C (2.5 g) in a Parr bomb. The mixture was hydrogenated under 100 psi H_2 at 45 °C for 19 h. The reaction mixture was heated to 70 °C in the Parr bomb, filtered over a bed of Hyflo Super Cel and washed with hot pentanol (15 mL). Heptane (95 mL) was added to the filtrate, and the solution was heated to 75 °C. The reaction was cooled to ambient temperature over about 2 h causing precipitation of the product. The mixture was cooled to 0 °C using an ice bath and stirred for 1 h. The slurry was filtered, washed with cold acetone (2 x 10 mL) and dried in vacuo at 40 °C to afford 12.3 g of **2** hydrochloride (65%) as a white solid. An analytical sample was obtained by recystallization from acetone/water: mp 149-152 °C; ^{1}H NMR (DMSO-d_6): δ 3.77 (m, 1H), 3.50-3.70 (m, 2H), 3.18-3.36 (m, 4H), 2.30 (sextet, J = 3.0 Hz, 1H), 1.83-2.12 (m, 2H), 1.54-1.78 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 159.9, 143.6, 48.8, 45.4, 44.9, 33.9, 23.9, 22.9, 18.0; IR (KBr) 3450 (H_2O), 2964, 2930, 2658, 2595, 1463, 1258 cm^{-1}. The sample was >98% pure by HPLC analysisanalysis. Analytical HPLC analysis was conducted on a YMC Basic, 5μ column (25 cm x 4.6 mm i.d.) with an isocratic eluent system of ACN/H_2O (containing 2 mL TEA, 1 mL acetic acid, diluted to 1 L, pH 5.5) (25:75) at a flow rate of 1 mL/min, and UV detection at 270 nm. Titration of the product with NaOH showed it contained 12.9% HCl. Karl Fisher analysis showed the product contained 5.8 % water.[9]

***Cis*- and *trans*-2-Amino-2-(1-azabicyclo[2.2.2]octan-3-ylidene)acetonitriles (9a and 9b).** A mixture of oximidonitrile (**4**) (20.0 g, 0.112 mol), ACN (90 mL), and DMAC (30 mL) was placed in a 250-mL, three-neck flask equipped with a N_2 purge, condenser, thermometer, and a mechanical stirrer. The off-white slurry was cooled to -10 °C (acetone/ice bath) and S_2Cl_2 (52.8 g, 0.391 mol) was added in one portion. Upon addition the reaction mixture heated itself from -10 °C to 10 °C. The cooling bath was

removed and the reaction mixture was allowed to warm to ambient temperature maintaining the reaction temperature below 30 °C with an ice bath. At the completion of the second exothermic event (approximately 50 min after the S_2Cl_2 addition) the reaction mixture was poured into water (100 mL) at 0-5 °C. After warming to ambient temperature, EtOAc (250 mL) was added and the pH was adjusted to 10 with 50% NaOH. The layers were separated and the aqueous layer was re-extracted with EtOAc (100 mL). The combined EtOAc layers were concentrated in vacuo to a crude oil (34 g) which showed 28% intermediate A (**9a**), 5% intermediate B (**9b**), 10% monochlorothiadiazole (**2**) and 19% dichlorothiadiazole (**3**) by HPLC analysis.

A portion of the crude oil (0.9 g) was purified by flash chromatography on silica gel with elution by 2:1 methanol:$CHCl_3$. Combination and concentration of fractions afforded 400 mg of **9a** as a pale oil (>90% by HPLC area %): R_f 0.12 (2:1 methanol:$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.44 (s, 2H), 2.93 (m, 2H), 2.82 (m, 3H), 1.77 (m, 2H), 1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.0, 116.0, 106.9, 52.8, 47.4, 28.5, 26.9; IR (neat) 3316, 3184, 2947, 2868, 2223, 1650 cm^{-1}; MS (EI+) **m/z** 163 (70), 94 (25), 53 (50), 42 (100).

A portion of the crude oil (3.0 g) was purified by flash chromatography on silica gel with elution by 1:1 methanol:CHCl3, then 2:1 methanol:$CHCl_3$. Combination and concentration of fractions afforded 10 mg **9b** (~90% pure by HPLC): R_f 0.09 (2:1 methanol:$CHCl_3$); MS (EI+) **m/z** 163 (65), 94 (25), 53 (55), 42 (100).

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Mr. Ross A. Johnson for NMR analysis and Mr. Stephen Gregg for mass spectral analysis. The heat of reaction data was provided by Ms. Stacey Pearce and Mr. Jason Cronin. We would also like to thank Dr. David Wirth and Dr. Charles Bunnell for the helpful discussions on thiadiazole chemistry.

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9. The theoretical potency of **2** in the hydrochloride monohydrate is 80.8% (monohydrate = 6.3% water).

Received, 26th June, 1998