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Amination of Olefinic Compounds with Bis(2,2,2-trichloroethyl) Azodicarboxylate†

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Although allylic amines are important functional groups,[1] few options are offered to synthetic chemists for their preparation from olefins. Existing methods employ sulfur or selenium diimido compounds[2-4] and, more recently, *N*-sulfinylbenzenesulfonamide[1] as an aminating species for olefins. Presumably with the diimido compounds, the amination occurs via an ene reaction followed by a [2,3]-sigmatropic rearrangement.[3] With *N*-sulfinylbenzenesulfonamide[1] the ene adduct is isolated and silylation induces the rearrangement. Therefore, in all cases the aminated product is obtained with the double bond at its initial position. However, transformation of the N-SO_2R[1,3,4] and N-CO_2Me[2] (after cleavage of the RN-S-NR (R = Ts, CO_2Me), TsN-Se-NTs, or $PhSO_2$-N-S-$OSiMe_3$) to the corresponding free amines requires harsh conditions.

An interesting alternative for the synthesis of 2-alkenylamines from alkenes which would also be complementary to the other methods is where the aminating agent is an azo compound. Thus the amination of an olefin could take place via an ene reaction with the azo compound to afford the aminated product with transposition of the double bond. For this reaction, a sufficiently reactive azo reagent is required to give the ene products under mild conditions. In addition, the enophile should contain functions that could be removed under such conditions that will allow the cleavage of the N-N bond and provide the free amine without alteration of the double bond.

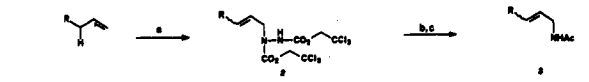
The ene reaction of diethyl azodicarboxylate (DEAD) and dienes has already been reported.[5a] Also in 1976, Stephenson and Mattern had studied the stereochemistry of an ene reaction between 1-phenyl-4-methyl-2-pentene and dimethyl azodicarboxylate (DMAD).[5b] However, since only a poor yield of the ene adduct was obtained, it became apparent that DEAD and similar azo compounds would not be suitable. Furthermore the resulting ene adducts could be converted to the corresponding allylic amines only with difficulties.

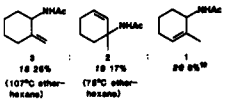
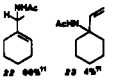
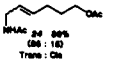
Herein is reported our results for the ene reaction of bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD) and olefinic compounds. As shown in Table I, BTCEAD undergoes an ene reaction with olefins, under mild conditions, to provide the protected 3-hydrazinoalkenes **2**. With cyclopentene (**4**) and cyclohexenes (**5**) as substrates, the reaction was complete after 12 h[6] (24 h for **5**) at 80 °C in benzene, to give the ene adducts **10** and **11** in 77% and 70% yields, respectively. In order to explore the regioselectivity of the reaction, alkenes with more than one allylic site were used as substrate. For 1-methylcyclohexane (**6**) a mixture of regioisomers of the ene products **12** was obtained (based on the deprotected products) whereas with both 3-methylcyclopentene (**7**) and ethylidenecyclohexane (**8**) as substrates, a high selectivity was observed to provide predominantly the more substituted olefinic compounds **13** and **14** in high yields. In these last two cases the reaction took place at 40 °C[7] as for the acyclic olefin **9** where the trans and cis ene adducts (85:15) were obtained in 85% yield.

The cleavage of the N-N bond of the protected 3-hydrazinoalkenes (**10-15**) and the removal of the protecting groups were achieved in a single operation under conditions developed in our laboratories[8] (Zn, HOAc, acetone). The free amines were then protected as the acetamido derivatives (**16-24**).

In summary, BTCEAD is an efficient enophile in the ene reaction with olefins. The amination of olefins via an ene reaction make it possible to prepare, from a given

Table I



olefin	ene adduct site 1	site 2	acetamide
	10 73%[d] (132 °C, ether–hexane)		
	11 70%[e] (155 °C, ethyl acetate–hexane)		
	12 60%[f,g]		
	13 75%[a] (114–115 °C, ethyl acetate–hexane)	5%[a]	
	14 88%[a]	6%[a]	
	15 85%[a] (85:15) trans:cis		

[a] $Cl_3CCH_2O_2CN{=}NCO_2CH_2CCl_3$ 1.2 equiv, 40 °C, 18 h. [b] Zn dust, 3 equiv by weight, HOAC then acetone, room temperature, 2 h. [c] Ac_2O, py, CH_2Cl_2, room temperature, 18 h. [d] As *a* except 80 °C, 12 h. [e] As *a* except 80 °C for 6 h then 80 °C for 18 h with additional reagent (0.5 equiv). [f] As *a* except 18 h at 54 °C.

† Dedicated to Brian J. Fitzsimmons.

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(6) The progress of the reactions were initially followed by ^1H NMR in benzene-d_6.
(7) With diethyl azodicarboxylate as enophile for substrate **7** no ene adduct was detected after 18 h at 40 °C.
(8) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889-2892.
(9) The isomeric mixture was not separated at this stage. The formation of diene adducts was observed (≈10%).
(10) This isomer has not been isolated in a pure form.
(11) The two isomers **22** and **23** were separated by flash chromatography.

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alkene, allylic amines inaccessible by the tandem ene/[2,3]-sigmatropic reaction. We also believe that the conditions to transform the protected hydrazines into amines could be applied to other cases.[8]

Experimental Section

NMR spectra were recorded on a Bruker AM 250 (250 MHz) and on a Bruker 300 (300 MHz) spectrometer. Bis(2,2,2-trichloroethyl) azodicarboxylate was purchased from Aldrich Chemical Co.

Typical Procedure for the Ene Reaction of Olefins with BTCEAD. Preparation of 1-(2-Cyclopenten-1-yl)-1,2-hydrazinedicarboxylic Acid Bis(2,2,2-trichloroethyl) Ester (10). To a solution of cyclopentene (4) (250 mg, 3.57 mmol) in benzene (17 mL) (sealed tube) was added BTCEAD (1.70 g, 4.50 mmol). The resulting yellow-orange solution was heated at 80 °C for 12 h. The crude mixture was then purified by flash chromatography (10% ethyl acetate in hexane) to give after crystallization 1.20 g (73%) of the ene adduct **10** as a white solid: mp 132 °C; ^{1}H NMR (300 MHz, CD_3CN, 353 K) δ 2.10–2.50 (m, 4 H), 4.72 and 4.80 (2 s, 4 H), 5.30 (m, 1 H), 5.65 (bs, 1 H), 6.00 (m, 1 H), 7.70 (bs, 1 H). Anal. Calcd for $C_{11}H_{12}Cl_6N_2O_4$: C, 29.59; H, 2.69; Cl, 47.08; N, 6.28. Found: C, 29.48; H, 2.65; Cl, 46.93; N, 6.14.

1-(2-Cyclohexen-1-yl)-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester (11): mp 155 °C (ethyl acetate–hexane); ^{1}H NMR (300 MHz, toluene-d_8, 380 K) δ 1.30–1.85 (m, 6 H), 4.45 and 4.55 (2 s, 4 H), 4.75 (m, 1 H), 5.50 (m, 1 H), 5.65 (m, 1 H), 6.00 (bs, 1 H). Anal. Calcd for $C_{12}H_{14}Cl_6N_2O_4$: C, 31.30; H, 3.04; N, 6.08. Found: C, 31.21; H, 3.06; N, 6.04.

1-(3-Methyl-2-cyclopenten-1-yl)-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester (13): mp 114–115 °C (ethyl acetate–hexane); ^{1}H NMR (300 MHz, CD_3CN, 353 K) δ 1.75 (s, 3 H), 2.10–2.45 (m, 4 H), 4.75 (m, 5 H), 5.25 (m, 1 H), 7.70 (bs, 1 H). Anal. Calcd for $C_{12}H_{14}Cl_6N_2O_4$: C, 31.30; H, 3.04; Cl, 45.45; N, 6.01. Found: C, 31.21; H, 3.04; Cl, 45.36; N, 6.02.

1-[1-(1-Cyclohexen-1-yl)ethyl]-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester (14): ^{1}H NMR (300 MHz, CD_3CN, 353 K) δ 1.30 (d, 3 H), 1.50–1.67 (m, 4 H), 1.95–2.20 (m, 4 H), 4.70 (q, 1 H), 4.80 (s, 4 H), 5.70 (m, 1 H), 7.65 (bs, 1 H). Anal. Calcd for $C_{14}H_{18}Cl_6N_2O_4$: C, 34.26; H, 3.66; N, 5.71. Found: C, 34.67; H, 3.88; N, 5.60.

1-(6-Acetoxy-2-hexen-1-yl)-1,2-hydrazinedicarboxylic acid bis(2,2,2-trichloroethyl) ester (15): ^{1}H NMR (300 MHz, CD_3CN, 348 K) δ 1.68 (quintet, 2 H), 1.95 (s, 3 H), 2.10 (q, 2 H), 4.05 (t, 2 H), 4.10 (d, 2 H), 4.79 and 4.81 (2 s, 4 H), 5.58 (m, 1 H), 5.73 (m, 1 H), 7.90 (bs, 1 H). Anal. Calcd for $C_{14}H_{18}Cl_6N_2O_6$: C, 32.30; H, 3.46; N, 5.38. Found: C, 32.13; H, 3.06; N, 5.76.

Typical Procedure for the Conversion of Ene Adducts to Acetamides. Preparation of 3-Acetamido-1-cyclopentene (16). To a solution of the hydrazide **10** (500 mg, 1.12 mmol) in glacial acetic acid (3 mL) was added zinc dust portionwise over 5 min. The resulting mixture was stirred for 15 min at room temperature, and acetone (≈250 μL) was then added. After 1 h, CH_2Cl_2 was then added, and the resulting mixture filtered through a pad of Celite. The solvents were removed on rotavapor and on high vacuum pump for 1 min. CH_2Cl_2 (5 mL) was then added to the crude mixture followed by pyridine (few drops) and an excess of acetic anhydride. After the mixture stood overnight at room temperature, the solvents were removed under reduced pressure and the mixture was purified by flash chromatography (50–80% ethyl acetate in hexane) to provide 120 mg (90%) of the title compound. The acetamide was crystallized in ether–hexane to give 115 mg (85%) of white needles: mp 73–74 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 1.54 (m, 1 H), 1.82, (s, 3 H), 2.24 (m, 2 H), 2.36 (m, 1 H), 4.87 (m, 1 H), 5.63 (m, 1 H), 5.85 (m, 1 H), 7.00 (bs, 1 H); high-resolution mass spectrum, m/z for $C_7H_{12}NO$ $(M + H)^+$ calcd 126.0919, found 126.0918.

3-Acetamido-1-cyclohexene (17): mp 85 °C (ether–hexane); ^{1}H NMR (300 MHz, acetone-d_6) δ 1.43–1.80 (m, 4 H), 1.83 (s, 3 H), 1.95 (m, 2 H), 4.35 (m, 1 H), 5.53 (m, 1 H), 5.75 (m, 1 H), 6.95 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_8H_{14}NO$ $(M + H)^+$ 140.1076, found 140.1075.

1-Acetamido-2-methylenecyclohexane (18): mp 107 °C (ether–hexane); ^{1}H NMR (250 MHz, acetone-d_6) δ 1.20–1.35 (m, 2 H), 1.45–1.60 (m, 1 H), 1.70–1.95 (m, 3 H), 1.92 (s, 3 H), 2.00–2.10 (m, 1 H), 2.40 (td, 1 H), 4.30 (m, 1 H), 4.65 (d, 1 H), 4.73 (d, 1 H), 7.10 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_9H_{16}NO$ $(M + H)^+$ 154.1231, found 154.1196.

3-Acetamido-3-methyl-1-cyclohexene (19): mp 75 °C (ether–hexane); ^{1}H NMR (250 MHz, acetone-d_6) δ 1.40 (s, 3 H), 1.42–1.70 (m, 3 H), 1.80 (s, 3 H), 1.85–1.95 (m, 2 H), 2.05–2.20 (m, 1 H), 5.10 (td, 1 H), 5.80 (bd, 1 H), 6.70 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_9H_{16}NO$ $(M + H)^+$ 154.1231, found 154.1198.

3-Acetamido-1-methyl-1-cyclopentene (21): mp 65 °C (ether–hexane); ^{1}H NMR (250 MHz, acetone-d_6) δ 1.55 (m, 1 H), 1.70 (s, 3 H), 1.80 (s, 3 H), 2.10–2.40 (m, 3 H), 4.80 (m, 1 H), 5.25 (m, 1 H), 7.00 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_8H_{14}NO$ $(M + H)^+$ 140.1076, found 140.1074.

1-(1-Acetamidoethyl)-1-cyclohexene (22): ^{1}H NMR (250 MHz, acetone-d_6) δ 1.10 (d, 3 H), 1.50 (m, 4 H), 1.80 (s, 3 H), 1.95 (m, 4 H), 4.30 (quintet, 1 H), 5.50 (m, 1 H), 6.95 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_{10}H_{18}NO$ $(M + H)^+$ 168.1388, found 168.1388.

1-Acetamido-2-vinylcyclohexane (23): ^{1}H NMR (250 MHz, acetone-d_6) δ 1.40–1.65 (m, 8 H), 1.85 (s, 3 H), 2.15 (m, 2 H), 4.90 (dd, 1 H), 5.05 (dd, 1 H), 6.00 (dd, 1 H), 6.60 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_{10}H_{18}NO$ $(M + H)^+$ 168.1388, found 168.1388.

1-Acetamido-6-acetoxy-2(*E*)-hexene (24): ^{1}H NMR (300 MHz, acetone-d_6) δ 1.65 (quintet, 2 H), 1.85 (s, 3 H), 1.95 (s, 3 H), 2.05 (m, 2 H), 3.70 (t, 2 H), 4.00 (t, 2 H), 5.45–5.65 (m, 2 H), 7.10 (bs, 1 H); high-resolution mass spectrum, m/z calcd for $C_{10}H_{18}NO_3$ $(M + H)^+$ 200.1286, found 200.1286.

Supplementary Material Available: ^{1}H NMR spectra for **16–19** and **21–24** (8 pages). Ordering information is given on any current masthead page.

Mechanism of Phosphodiester Cleavage with β-Cyclodextrin

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Cyclodextrins are cyclic oligomers of glucose with a hydrophobic pocket that form complexes with a range of organic compounds.[1] The secondary hydroxyl groups are clustered around one rim of the cavity and have been found to act as catalysts in the hydrolysis of esters, lactams, amides, carbonates, and other compounds.[1] These hydroxyls have a pK_a of 12 and act in some instances as nucleophiles and in some instances as a general base to promote nucleophilic attack by water.

We have examined the reaction of cyclodextrin with phosphodiesters as part of an ongoing project to investigate the transition states of phosphoryl-transfer reactions using heavy-atom isotope effects.[2] Before doing the isotope effect studies on the cyclodextrin reaction, we needed to understand the overall chemical mechanism. This report covers our elucidation of the overall mechanism.

The reactions of cyclodextrins with several different types of phosphorus compounds have been previously studied. The fission of diaryl pyrophosphates in the

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