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LETTERS

Nitration of Cyclopentenecarboxaldehyde: Studies Toward 1-Amino-2-Nitrocyclopentanecarboxylic Acid

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Abstract: The formation of 2,2-dinitrocyclopentanone oxime is described during an attempted nitroacetamidation of cyclopentenecarboxaldehyde using ceric ammonium nitrate and sodium nitrite in acetonitrile. Progress towards the total synthesis of 1-amino-2-nitrocyclopentanecarboxylic acid is also discussed. © 1998 Elsevier Science Ltd. All rights reserved.

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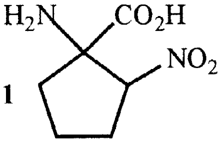
Our current research involves the synthesis of the non-protein, phytotoxic amino acid 1-amino-2-nitrocyclopentanecarboxylic acid, (ANCPA, **1**).[1] While a synthesis of this naturally occurring compound has already been published,[2] it involved the use of dinitrogen tetroxide (N_2O_4), an insidious, highly toxic gas.[3] We sought to develop a route to the production of ANCPA that avoided the use this reagent. We also wanted our synthetic route to be flexible enough to both facilitate the preparation of ANCPA analogs and to allow the separation of stereoisomers.



1

The published synthesis of **1** began with the nitration of cyclopentenecarboxylic acid using a mixture of N_2O_4 and iodine in ether to give 1-iodo-2-nitrocyclopentanecarboxylic acid.[2] The iodine was then replaced with an amino group using NH_4OH to yield the desired amino acid as a mixture of stereoisomers. In order to avoid the use of dinitrogen tetroxide, we evaluated several alternative nitrating systems.[4] The most attractive for our purposes was the use of ceric ammonium nitrate (CAN) and sodium nitrite in acetonitrile.[5] If successful, these conditions would have given direct nitroacetamidation of the unsaturated aldehyde **2**, acid **3**, or ester **4** to give amides **5**, **6**, or **7** respectively (**Scheme 1**). This reaction had previously only been demonstrated on alkenes and not α,β-unsaturated carbonyl systems. In order to work, a high energy carbocation, adjacent to a carbonyl, would be formed which would then be subsequently trapped by the acetonitrile solvent.[5] Although somewhat of an unlikely reaction, it was decided that the potential positive outcome necessitated its trial. The one-step introduction of the protected amine was also crucial for our future plans to enzymatically resolve stereoisomers. Aldehyde **2** was easily obtained from cyclohexene through an established literature procedure.[6] The aldehyde was then oxidized by silver oxide to give carboxylic acid **3** which in turn was esterified with 2,4′-dibromoacetophenone to yield **4**.[7,8]

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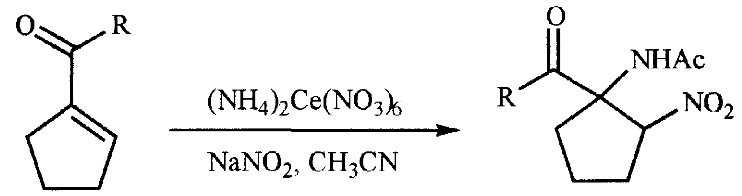
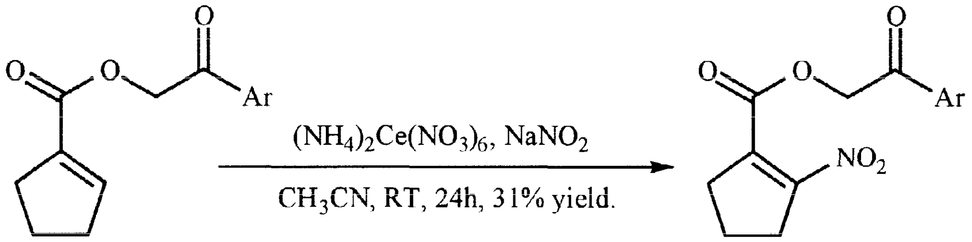


2 R = H
3 R = OH
4 R = $OCH_2C(O)Ar$ Ar= p-C_6H_4Br

5 R = H
6 R = OH
7 R = $OCH_2C(O)Ar$

Scheme 1: Proposed Nitroacetimidation of 2, 3, & 4

The unsaturated acid **3** gave no reaction with CAN and sodium nitrite, but the ester **4** did undergo nitration to give nitro-ester **8** in 31% yield under the same conditions (**Scheme 2**). The formation of the α,β-unsaturated nitro compound **8** was not without literature precedent.[4,5,9] Compound **8** does provide a possible route to ANCPA via its corresponding carboxylic acid derivative.[2] This transformation has already been demonstrated by Burrows and coworkers during their earlier work on ANCPA.[2]

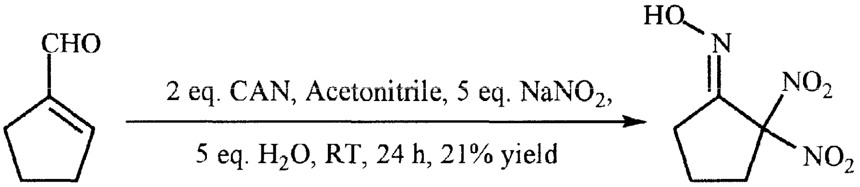


4

Scheme 2: Nitration of Ester 4

8

Attempts to nitrate aldehyde **2** however, under identical experimental conditions, produced the rare dinitrooxime product **9** instead of the desired **5** (**Scheme 3**).



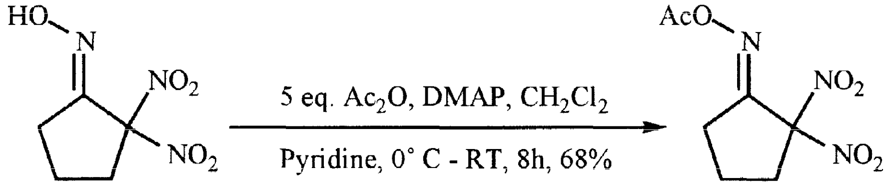
2

9

Scheme 3: Formation of 2,2-Dinitrocyclopentanone Oxime

The structure of **9** was determined by standard spectroscopic means and confirmed by its single crystal X-ray structure.[9] The yield of chromatographically purified **9** was quite low, but examination of the crude reaction mixture by 200 MHz ^1H NMR showed it to contain approximately 85% of **9**. This compound is somewhat unstable, partially decomposing on standing at room temperature over several days, although it appears to be stable to prolonged storage at -10° C. The compound also decomposed at its melting point and failed to give a molecular ion during mass spectrometry, even under conditions of soft ionization. Oxime **9** was esterified using a mixture of acetic anhydride and 4-dimethylaminopyridine (DMAP) in a pyridine/methylene chloride mixture to give the dinitrooxime ester **10** in 68% yield (**Scheme 4**).[9] Preparation of **9** using isotopically labeled sodium nitrite ($Na^{15}NO_2$) revealed that all three of the nitrogens contained in **9** originate from the nitrite and not from the CAN.

The arrangement of organic functionality in compound **9** is quite unusual. A literature survey showed few compounds with the α,α-dinitrooxime grouping have been synthesized. These earlier compounds were prepared by a) reaction of nitric acid with chloroglyoximes,[10] b) reaction of a chloroxime with a dinitro anion,[11] or c) Michael addition of hydroxylamine to an unsaturated dinitro substrate.[12,13] The formation of α-nitrooximes from alkenes has been reported previously, but in these cases only mononitration was observed.[14,15,16] The reaction that we describe (**Scheme 3**) not only produces the α,α-dinitrooxime moiety under mild conditions, but also results in decarbonylation of the aldehyde. We are currently in the process of studying the mechanism of the reaction as well as examining its application to other unsaturated aldehydes. In preliminary biological studies, the dinitrooxime **9** exhibited moderate plant growth inhibition *in vitro*. Further studies of these properties are also underway.



9 **10**

Scheme 4: Acetylation of 2,2-Dinitrocyclopentanone Oxime

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9. Compound **8**: To a 100 mL oven-dried round bottom flask under nitrogen at room temperature was added 50 mL of distilled acetonitrile into 425.0 mg (1.85 mmol) of ester **4**. Then, 712.0 mg (10.18 mmol) of sodium nitrite was added with 2.54 g (4.63 mmol) of ceric ammonium nitrate. Next, 0.167 mL (9.25 mmol) of distilled water was added dropwise. The reaction was stirred at room temperature for 24 hours. The reaction mixture was then diluted with 200 mL of water and 200 mL of diethyl ether. The solution was added to a separatory funnel and the organic layer was washed with 200 mL of saturated aqueous sodium bicarbonate. The organic layer was separated, dried with anhydrous sodium sulfate, filtered, and concentrated under vacuum to give 0.509 g of crude oil. The crude material was purified by the use of silica gel flash chromotography eluting with 20% ethyl acetate/ hexanes to give 161.0 mg of product. The product was isolated as a white solid (25% yield.): m.p. 116° - 118°; Rf 0.20 (85:15-hexane:ethyl acetate); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (pentet,

J=7.6 Hz, 2H), 3.00 (triplet, J=7.6 Hz, 4H), 5.45 (singlet, 2H), 7.66 (doublet, J=8.6 Hz, 2H), 7.78 (doublet, J=8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2, 32.5, 34.4, 67.6, 130.5, 130.6, 133.6, 133.8, 137.8, 152.3, 164.6, 191.8; IR (KBr pellet) 2957, 1754, 1698, 1584, 1515, 1350, 1294, 1226, 1109, 979 cm^{-1}; Elemental Analysis, Calculated for $C_{14}H_{12}NBrO_5$: C, 47.48; H, 3.42; N, 3.96; Found: C, 47.83; H, 3.61; N, 3.96.

Compound 9: To an oven-dried 100 mL round bottom flask under nitrogen was added 500.0 mg (5.2 mmol) of 2 followed by 25 mL of acetonitrile at room temperature. To the stirred solution was added 5.72 g (10.4 mmol) of ceric ammonium nitrate and 1.79 g (25.9 mmol) of sodium nitrate. Next, 0.47 mL (25.9 mmol) of distilled water was added dropwise. The mixture was stirred at room temperature for 24 hours and then diluted with 200 mL of diethyl ether and poured into a 500 mL separatory funnel. The ethereal layer was washed three times with 200 mL portions of aqueous, saturated $NaHCO_3$. The organic layer was then separated, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 532.2 mg of a yellow solid. The material was purified by flash silica gel chromatography eluting with a 15% solution of ethyl acetate / hexanes. After purification, 215.5 mg of a white, crystalline solid was isolated (22% yield.): m.p.= 94° - 96° C; Rf 0.5 (85:15-hexane:ethyl acetate); ^1H NMR (200 MHz, $CDCl_3$) δ 2.06 (pentet, J=7.3 Hz, 2H), 2.82 (triplet, J=7.3 Hz, 2H), 3.07 (triplet, J=7.3 Hz, 2H), 8.28 (singlet, 1H, exchangeable with D_2O); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.6, 27.4, 38.4, 121.4, 155.9; ^{13}C DEPT experiment indicates that the peaks at 20.6, 27.4, and 38.4 ppm are methylene (CH_2) carbons. The peaks at 121.4 and 155.9 ppm have no hydrogens; ^{15}N NMR (40 MHz, CD_3OD) 1.60 (1N), -7.78 (2N); IR (KBr pellet) 3354, 2971, 2362, 2361, 1563, 1436, 1325 cm^{-1}; Elemental Analysis, Calculated for $C_5H_7N_3O_5$: C, 31.75; H, 3.73; N, 22.22. Found: C, 31.51; H, 3.73; N, 22.23.

Compound 10: To an oven-dried 10 mL round bottom flask under nitrogen was added 50 mg (0.26 mmol) of 9 followed by 5 mL of distilled CH_2Cl_2, 0.2 mL of pyridine and a catalytic amount of N,N-dimethyl aminopyridine. The solution was cooled to 0° C and 0.12 mL (1.32 mmol) of acetic anhydride was added. The solution was allowed to warm to room temperature and then stirred for 8 hours. The mixture was then diluted with 100 mL of ethyl acetate and poured into a 250 mL separatory funnel. The organic layer was washed with 100 mL water, twice with 100 mL portions of 10% aqueous copper sulfate, 100 mL of water, and then with 100 mL of saturated, aqueous $NaHCO_3$. The organic layer was then separated, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 60.2 mg of a yellow solid. The material was purified by flash silica gel chromatography eluting with a 20% solution of ethyl acetate / hexanes. After purification, 40.8 mg of a white, crystalline solid was isolated (68% yield.): m.p.= 80° - 82° C; Rf 0.3 (80:20-hexane:ethyl acetate); ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (pentet, J=7.3 Hz, 2H), 2.24 (singlet, 3H), 2.92 (triplet, J=7.3 Hz, 2H), 3.12 (triplet, J=7.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 20.5, 28.9, 38.3, 121.0, 162.1, 169.0; IR (KBr pellet) 2930, 1784, 1569, 1371, 1323, 1182, 1002, 945, 824 cm^{-1}; Elemental Analysis, Calculated for $C_7H_9N_3O_6$: C, 36.37; H, 3.92; N, 18.18. Found: C, 36.35; H, 3.87; N, 17.96.

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