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One Step Conversion of Highly Dipolarophilic Olefins to α-Hydroxy-β-cyanoadducts with Metal Fulminate

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Abstract: *Olefins conjugated with carbonyl, carboxylic ester, and phenyl groups as well as highly strained non-conjugated olefin norbornylene were converted to their corresponding α-hydroxy-β-cyanoadducts by treatment with mercuric fulminate and lithium bromide. The transformation appears to go through a 1,3-dipolar cycloaddition of metal fulminate to the olefin followed by a spontaneous cleavage of the resulting heterocycle. Thus, the study provides the first one step cis-cyanohydroxylation of olefinic species.*

1,3-Dipolar cycloaddition of nitrile oxides (RCNO) to alkenes and alkynes provides an important tool for the construction of isoxazoline and isoxazole species which in turn can be further manipulated to give compounds of synthetic interest.[1-4] In spite of the intensive efforts in this area, however, there has been little study on the corresponding metal fulminate (MCNO) cycloaddition reactions[5] which could be followed by a spontaneous metal carbon bond cleavage, resulting in products such as β-hydroxynitriles and β-oxonitriles. We wish to report here such a process that offers one step conversion of olefinic species to *cis*-cyanohydroxylation adducts.

In our effort to synthesize anti-inflammatory steroids with metabolically labile alkyl carboxylate groups on the basis of the antedrug concept,[6-8] a new procedure was recently developed which utilized nitrile **4** as a crucial intermediate.[9] The nitrile was prepared with triethyl amine from isoxazoline **2** which in turn was obtained by 1,3-dipolar cycloaddition of fulminic acid (HCNO) to enone **1** (SCHEME I). A serious side product, oxime **3**, was also produced by fulminic acid dimer addition to **1** and it remained a significant interference despite our repeated trials with the literature procedure[10] and its modified versions.

In order to improve the yield of **2**, we decided to explore more selective methodologies. Instead of the rapid reaction of trimethylsilanecarbonitrile oxide with water to generate fulminic acid,[10] a slow formation of fulminic acid was designed by an intrinsically sluggish interaction between a certain metal fulminate and a weak acid. While treatment of enone **1** with mercuric fulminate (an explosive material !!!)[11] and acetic acid in THF for one week gave a mixture of predominantly unknown compounds, metal exchange between potassium iodide and mercuric fulminate in the presence of acetic acid and **1** resulted in the known products shown in TABLE I. The outcome was highly dependent upon the amount of acetic acid: with a large excess (200 molar equiv., entry 1), isoxazoline **2** and oxime **3** were obtained in 75% and 15% respectively, while a smaller amount (15 molar equiv., entry 2) yielded nitrile **4** as the major product (55%) together with **2** (15%) and **3** (3%) as the minor ones. The unexpected formation of the nitrile was originally interpreted by fulminic acid addition to enone **1** followed by isoxazoline ring cleavage catalyzed by some of the reagents in the mixture. However, treatment of isoxazoline **2** with the same reagents (as entry 2) gave little nitrile **4** with most of the starting material being recovered (entry 3). Another example to demonstrate the irrelevance of **2** in the conversion of **1** to **4** is shown in

entries 4 and 5. While metal exchange between potassium acetate and mercuric fulminate in the presence of enone **1** and acetic acid gave **4** (45%), subjecting **2** to the same conditions did not afford any **4**.

SCHEME I

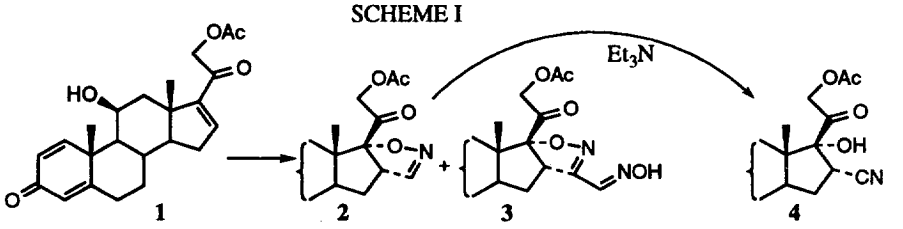
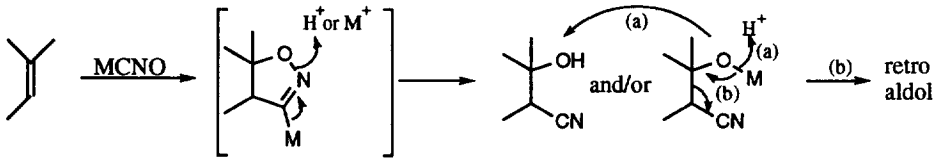


TABLE I. 1,3-Dipolar Cycloadditions to Enone **1** with Mercuric Fulminate at Room Temperature

Entry	Substrate	Reagents(molar ratios)	Time	Products(%yields)
1	1	$Hg(CNO)_2$(4), KI(8), HOAc(200)	2h	2(75), 3(15)
2	1	$Hg(CNO)_2$(4), KI(8), HOAc(15), THF	7d	4(55), 2(15), 1(15), 3(3)
3	2	$Hg(CNO)_2$(4), KI(8), HOAc(15), THF	7d	4(<5), 2(rec.)
4	1	$Hg(CNO)_2$(4), KOAc(10), HOAc(100), H_2O	9d	4(45), unknowns
5	2	$Hg(CNO)_2$(4), KOAc(10), HOAc(100), H_2O	9d	4(0), 2(rec.)
6	1	$Hg(CNO)_2$(4), KI(8), DMF	7d	4(30), 1(20), unknowns
7	1	$Hg(CNO)_2$(4), LiI(8), DMF	7d	4(40), 1(40), unknowns

With the exclusion of isoxazoline **2** as an intermediate, it was conceivable that the addition reaction should proceed without acetic acid. Indeed, metal exchange between potassium iodide or lithium iodide and mercuric fulminate in the presence of enone **1** also yielded nitrile **4** (entries 6 and 7). Here DMF was chosen as the solvent since it afforded less decomposition of the steroids than THF. In addition to the starting material recovered in the two reactions, some unknown compounds were also produced which could be explained by a retro aldol reaction as shown in SCHEME II which provides a proposed mechanism for the cyanohydroxylation reaction.

SCHEME II. (M=Li, K or Mercuric cation)



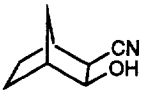
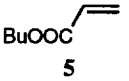
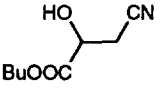
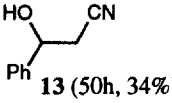
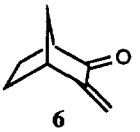
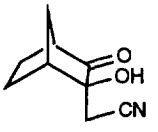
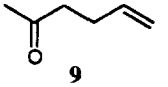
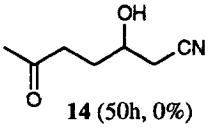
Thus a new process offering one-step *cis*-cyanohydroxylation of olefinic species has been identified. To the best of our knowledge, it is the first one step conversion of this kind. Literature procedures involving isoxazolines that effect the cyanohydroxylation of olefins include fulminic acid addition and ring cleavage with triethylamine,[10,12] sulfonylcarbonitrile oxide addition and reductive cleavage with sodium amalgam,[13] trimethylsilanecarbonitrile oxide addition and treatment with water,[5a] and carbethoxyformonitrile oxide addition followed by ester hydrolysis and heated decarboxylation.[14]

Based on the above understandings, efforts were made to improve the reaction conditions. Among the solvents studied, DMF offered the best solubility and maintained a homogeneous solution throughout the

transformations. Between the two conversions (entries 6 & 7, TABLE I) with DMF as the solvent, entry 7 yielded much less side products than entry 6 and was used as the starting point to improve both the reaction rate and chemoselectivity. We found that the reaction was greatly accelerated by a moderate elevation of temperature to 50°C, and addition of a combination of acetic acid and triethyl amine significantly decreased the side products. The acid apparently provided the proton source to stabilize the cyanohydroxylation adduct, while the amine prevented formation of fulminic acid and its resulting complications. Since DMF dissolves mercuric fulminate without the addition of a metal halide, which is in contrast to the poor solubility of mercuric fulminate in THF, water or acetic acid, the reactivity of mercuric fulminate as a 1,3-dipole in DMF was also examined. The results showed that although mercuric fulminate also gave the cyanohydroxylation adduct **4** with or without the addition of acetic acid and triethyl amine, attempts to increase the yield by heating the reaction mixture resulted in serious decomposition of the steroids. Thus, a procedure utilizing mercuric fulminate, lithium iodide, acetic acid, triethyl amine and DMF was established. As expected, LiBr, a reagent less expensive than LiI, gave results similar to LiI and was chosen to replace LiI. After these adjustments, the nitrile **4** was obtained in good yield (72%) after column purification as shown in TABLE II. The prior to purification yield was much better (~ 90%) based on TLC and NMR analyses. Given below is the detailed procedure for the conversion to **4**.

To a stirred mixture of enone **1** (1.0 g, 2.6 mmol), mercuric fulminate (2.3 g, 8.0 mmol), acetic acid (0.48 mL, 8.0 mmol) and triethylamine (1.0 mL, 7.1 mmol) in DMF (9 mL) was added lithium bromide powder (1.4 g, 16 mmol) over a period of 10 min. The resulting mixture was stirred under a reflux condenser at 50°C for 12 h and then poured into ethyl acetate (150 mL). Hexanes (50 mL) and water (120 mL) were added and after a thorough mixing, the aqueous layer was extracted with ethyl acetate:hexanes (1:1, 2x100 mL). The combined organic solution was washed with water (3x40 mL) and condensed. The residue was re-dissolved in acetone (20 mL) and insoluble material discarded. The acetone solution was condensed and the residue chromatographed through silica gel flash column with benzene:acetone (5/1 to 4/1) to yield **4** as a white powder (0.80 g, 72%).

TABLE II. One-step Cyanohydroxylation of Olefins at 50-55°C with Reagents(molar ratios): $Hg(CNO)_2$ (3), LiBr (6), HOAc (3), Et_3N (2.6), DMF.

Olefin	Product (time, yield)	Olefin	Product (time, yield)
1	**4** (12h, 72%)	 **7**	 **12** (60h, 35%)
 **5**	 **10** (10h, 74%)	 **8**	 **13** (50h, 34%)
 **6**	 **11** (12h, 60%)	 **9**	 **14** (50h, 0%)

The new procedure was applied to several other highly dipolarophilic olefins **5**-**8**[15] as well as a less active substrate **9** which has neither strain nor conjugation activation, and the results are summarized in Table II. These outcomes demonstrate that highly dipolarophilic olefins which are activated by conjugation and/or ring strain can be converted to the cyanohydroxylation products (**4**, **10**-**13**)[16] while the olefin lacking such activations does not participate in the reaction. It appears that conjugation with a carbonyl or carboxylic ester offers more favorable structural features for the conversion, although at this point the transformation for most of the substrates has not

been optimized. The non-reactivity of enone moieties in ring A of steroid **1** is due to a lack of dipolarophilicity as evidenced by their failure to react with fulminic acid in both the current study (entry 1 of TABLE I) and our previous investigation.[9]

In conclusion, a new process for one step conversion of highly dipolarophilic olefins to *cis*-cyanohydroxylation adducts has been developed. The transformation appears to go through metal fulminate cycloaddition to olefin followed by a spontaneous ring cleavage. This conversion provides us with a very facile method to prepare nitrile **4**, an important intermediate in our synthesis of non-systemic anti-inflammatory steroids, and it reveals another dimension in nitrile oxide cycloaddition chemistry.

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5. Among the published nitrile oxides involved in 1,3-dipolar cycloadditions, the closest to metal fulminate is probably trimethylsilanecarbonitrile oxide: (a) Brandi, A.; De Sarlo, F.; Guarna, A. and Speroni, G. *Synthesis*, **1982**, 719. (b) Kurth, M. J.; Rodriguez, M. J. and Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 283.
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11. Mercuric fulminate is a dangerous explosive sensitive to heat, impact and friction when dry. It should be kept away from flame, sulfuric acid or strong radiation and should be stored wet until used. See Lewis, R. J., Sr. in *'Hazardous Chemicals Desk Reference'* (3rd ed.), Van Nostrand Reinhold, New York, **1993**; p. 631&811.
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15. Alkyl acrylate, styrene and norbornylene are known to be very active dipolarophiles toward benzonitrile oxide and fulminic acid (references 1 and 10) and enone **1** and **6** should also be quite active dipolarophiles due to the ring strain and activation by the carbonyl group.
16. NMR and MS data for the cyanohydroxylation adducts:
4: ^{1}H NMR (270 MHz, DMSO-d6): 7.30 (1H, 1-H, d, J = 9.8 Hz), 6.40 (1H, 17-OH, s), 6.16 (1H, 2-H, dd, J = 9.8, 1.9 Hz), 5.92 (1H, 4-H, br s), 5.10 (1H, 21-H, d, J = 17.6 Hz), 4.86 (1H, 11-OH, d, J = 3.9 Hz), 4.78 (1H, 21-H, d, J = 17.6 Hz), 4.29 (1H, 11-H, m), 3.98-3.92 (1H, 16-H, m), 2.10 (3H, Ac, s), 1.36 (3H, 10-Me, s), 0.80 (3H, 13-Me, s). ^{13}C NMR (68 MHz, $CDCl_3$/DMSO-d6) 202.20, 186.13, 170.18, 169.42, 155.98, 127.47, 122.22, 120.08, 90.20, 69.03, 67.31, 54.79, 50.45, 47.70, 43.82, 39.02, 34.01, 33.49, 31.60, 30.87, 30.04, 20.88, 20.26, 16.23. MS (PCI, 1350V): 428.5 (100, M+1).
10: ^{1}H NMR (270 MHz, $CDCl_3$): 4.41 (1H, CHOH, t, J = 5.4 Hz), 4.26 (2H, OCH_2, AB_qt, Δ_{AB} = 12.0 Hz, J_{AB} = 10.7 Hz, J_t = 6.8 Hz), 3.34 (1H, OH, br. s), 2.81 (2H, CH_2CN, AB_qd, Δ_{AB} = 18.9 Hz, J_{AB} = 16.6 Hz, $J_{d(A)}$ = 5.2 Hz, $J_{d(B)}$ = 5.9 Hz), 1.66 (2H, m), 1.39 (2H, m), 0.94 (3H, Me, t, J = 7.3 Hz). ^{13}C NMR (68 MHz, $CDCl_3$): 171.59 (C=O), 115.80 (CN), 66.83, 66.61, 30.50, 23.47, 18.95, 13.51. MS (PCI, 1350V): 172.3 (100, M+1).
11: ^{1}H NMR (270 MHz, DMSO-d6): 5.99 (1H, OH, s), 2.70 (2H, CH_2CN, AB_q, Δ_{AB} = 22.6 Hz, J_{AB} = 17.1 Hz), 2.53 (1H, m), 2.43 (1H, m), 2.17 (1H, dm, J_d = 10.2 Hz), 1.82 (1H, m), 1.66 (1H, m), 1.51 (1H, m), 1.49 (1H, br. d, J = 10.2 Hz), 1.38 (1H, m).^{13}C NMR (68 MHz, DMSO-d6): 213.03 (C=O), 117.80 (CN), 75.31 (C-OH), 47.44, 44.88, 33.02, 24.13, 22.02, 21.69. MS (PCI, 1350V): 166.0 (100, M+1).
12: ^{1}H NMR (270 MHz, $CDCl_3$): 3.92 (1H, CHOH, br. d, J = 6.3 Hz), 2.70 (1H, CHCN, dd, J = 6.3, 1.7 Hz), 2.62 (1H, m), 2.45 (1H, OH, br. s), 2.31 (1H, m), 1.95 (1H, dm, J_d = 10.8 Hz), 1.56 (2H, m), 1.32 (1H, dm, J_d = 10.8 Hz), 1.13 (2H, m). ^{13}C NMR (68 MHz, $CDCl_3$): 118.73 (CN), 73.73 (C-OH), 43.76, 42.02, 41.68, 33.95, 27.84, 23.96. MS (PCI, 1350V): 138.2 (100, M+1).
13: ^{1}H NMR (270 MHz, $CDCl_3$): 7.38 (5H, phenyl, m), 5.01 (1H, CH-O, t, J = 6.3 Hz), 2.74 (2H, CH_2, d, J = 6.3 Hz). 2.72 (1H, OH, br. s). ^{13}C NMR (68 MHz, $CDCl_3$): 141.07 (phenyl), 128.88 (phenyl), 128.75 (phenyl), 125.52 (phenyl), 117.18 (CN), 70.13 (C-OH), 27.90 (CH_2). MS (PCI, 1350V): 148.1 (100, M+1).

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