Notes

A-Ring Nitration of Estrone

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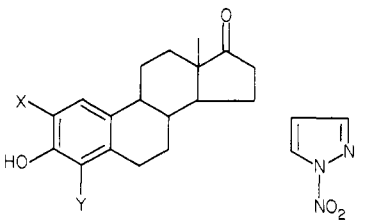
Nitroestrones (**1b–d**) are an important class of compounds that can constitute useful starting material for a number of derivatives such as fluoro,[2] iodo,[3] or [bis(2-chloroethyl)amino]estrones.[4] The only method that allows access to the above compounds still relies upon the direct nitration of estrone **1a** by means of nitric acid in acetic acid. With 65% nitric acid a mixture of 2- and 4-nitroestrones (**1b**) and (**1c**) is always obtained, along with trace amounts of 2,4-dinitroestrone **1d**. Repetition of the nitration procedure according to Werbin and Holoway[5] afforded, in our hands, a mixture of 40% of **1c** and 37% of **1b** as described. The less soluble **1c** is recovered from the mixture by crystallization, whereas isolation of the 2-isomer **1b** requires additional purification from the mother liquor of crystallization of **1c**. In connection with our work on regioselective functionalization of the A-ring of estrogens,[6] we pursued the idea of finding a regioselective preparation of either **1b** or **1c**. The procedure outlined by Olah and co-workers[7] for the nitration of simple aromatic compounds seemed attractive for our purpose. In the cited paper[7] a nitronium ion was generated from *N*-nitropyrazole (**2**)[8] in the presence of boron trifluoride etherate as catalyst, and from the described results some preference for the ortho nitration was apparent. When the same reaction was carried out on **1a** only one product of nitration was formed (40% yield after chromatography), whose ^{1}H NMR clearly indicated that the nitration had occurred regiospecifically at position 2. Yields of **1b** were 40–45% and could not be improved by variation in the amounts of **2** and of the catalyst. Also different conditions of reactions did not change the situation, and together with **1b**, unreacted estrone (30%) and more polar products were always isolated. Use of silver nitrate and BF_3·Et_2O as nitrating agents[9] gave approximately the same results, since 35% of **1b** as sole product of nitration was obtained. As previously, estrone (35%) and more polar products were isolated.



1a, X = Y = H
b, X = NO_2; Y = H
c, X = H; Y = NO_2
d, X = Y = NO_2

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With the limitation of the moderate yields, the syntheses of **1b** outlined above constitute at present the only available method for regioselective preparation of a nitroestrone. We have also further investigated the nitration of **1a** by means of nitric acid, which has been reported to give low yields of 2,4-dinitroestrone **1d**. We have found that by use of 100% nitric acid in acetic acid **1d** is formed as the sole product of reaction (90% yield of crystallized product). To our knowledge this is the first clean preparation of dinitro-**1d**, which should be a useful starting material for 2,4-disubstituted estrogens. These compounds are indeed of great interest, due to the importance of positions 2 and 4 in the metabolism of estrogens.[10]

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded for solutions in chloroform or for Nujol mulls, and absorptions are reported in reciprocal centimeters; NMR spectra were taken on a Varian HA-100 in chloroform-*d* solutions and are reported in δ units relative to Me_4Si. The mass spectra were determined on a Varian MAT 112 S spectrometer by direct inlet methods. The progress of all reactions and column chromatographies (silica 70–230 mesh) was monitored by TLC on silica gel (HF_{254}) plates. Hexane–ethyl acetate mixtures were used as developing solvents, and spots were detected by spraying with 5% ethanolic phosphomolybdic acid followed by heating (100 °C).

2-Nitroestrone (1b): (A) Via *N*-Nitropyrazole. To a solution of **1a** (0.270 g, 0.001 mol) in anhydrous dichloromethane (5 mL) was added distilled boron trifluoride etherate (0.2 mL) under nitrogen. *N*-Nitropyrazole (**2**,[8] 0.448 g, 0.004 mol) was added in portions of 1 mmol/h at room temperature. The solution was poured into water (10 mL) and extracted with ether (3 × 10 mL). The organic solution was washed with water to neutrality, and the crude mixture of products were recovered after drying (Na_2SO_4) and evaporation of solvents. Purification of the above products (0.520 g) by column chromatography allowed recovery of **1b** (0.126 g, 40%) by elution with 8:2 hexane–ethyl acetate, unreacted estrone (0.082 g, 30%), and more polar function (0.090 g), which were not further investigated. Crystallization from ethanol afforded pure **1b**: mp 176–178 °C (lit.[4] mp 176–177 °C); ^{1}H NMR δ 0.95 (s, 3 H, 18-CH_3), 6.90 (s, 1 H, C-4), 8.10 (s, 1 H, C-1). Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.57; H, 6.66, N, 4.40 Found: C, 68.42; H, 6.53; N, 4.29.

(B) Via Silver Nitrate. To a solution under nitrogen of **1a** (0.270 g, 0.001 mol) in dry acetonitrile (10 mL) containing silver nitrate (0.169 g, 0.001 mol), was added BF_3·Et_2O (0.2 mL) and the resulting solution kept at room temperature (2 h). After the solution was poured into water (20 mL), extractions with diethyl ether (3 × 10 mL) and usual workup were performed. The crude mixture (0.280 g) was purified by column chromatography as above. 2-Nitroestrone (**1b**) was obtained in 35% yield (0.110 g) along with unreacted estrone (0.095 g, 35%) and more polar products (0.065 g).

(1) Research Fellow from Istituto di Endocrinologia, Facoltà di Farmacia, Università di Milano.
(2) Utne, T.; Jobson, R. B.; Babson, R. D. *J. Org. Chem.* **1968**, *33*, 2469.
(3) Sweet, F.; Patrick, T. B.; Mudd, J. M. *J. Org. Chem.* **1979**, *44*, 2296.
(4) Hamacher, H. *Arzneim.-Forsch.* **1979**, *29*, 463.
(5) Werbin, H.; Holoway, C. *J. Biol. Chem.* **1956**, *223*, 651.
(6) Santaniello, E.; Ferraboschi, P. *J. Chem. Soc., Chem. Commun.*, **1981**, 217.
(7) Olah, G. A.; Narang, S. C.; Fung, A. P. *J. Org. Chem.* **1981**, *46*, 2706.
(8) Huttel, R.; Buchele, F. *Chem. Ber.* **1955**, *88*, 1586.
(9) Olah, G. A.; Fung, A. P.; Narang, S. C.; Olah, J. A. *J. Org. Chem.* **1981**, *46*, 3533.
(10) Ball, P.; Knuppen, R. *Acta Endocrinol. (Copenhagen), Suppl.* **1980**, *93*, 1.

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2,4-Dinitroestrone (1d). To a hot solution of **1a** (0.270 g, 0.001 mol) in acetic acid (10 mL) was added 100% nitric acid (0.135 mL, 0.003 mol). After cooling at room temperature (3 h), the solution was poured into ice and the yellow precipitate filtered off and rinsed with water. Practically pure **1d** was obtained in 90% yields (0.324 g). One crystallization from ethanol afforded an analytically pure sample: mp 175–177 °C; ^{1}H NMR δ 0.95 (s, 3 H, 18-CH_3), 8.30 (s, 1 H, C-1). Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 60.00; H, 5.55 N, 7.77 Found: C, 59.73; H, 5.65; N, 7.68.

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Registry No. **1a**, 53-16-7; **1b**, 5976-73-8; **1d**, 42979-83-9.

Synthesis of (±)-Umbelactone[1]

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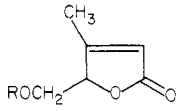
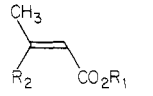
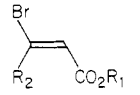
Numerous physiologically active compounds contain an α,β-butenolide system.[2] Umbelactone (**1a**) is an example



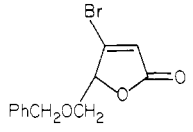
1a, R = H
b, R = CH_2Ph



2a, $R_1 = R_2$ = Li
b, R_1 = H; R_2 = Br



3a, $R_1 = R_2$ = Li
b, $R_1 = R_2$ = H



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of a naturally occurring γ-(hydroxymethyl)-α,β-butenolide which was isolated recently from *Memycelon Umbelatum* Burm.[3,4] The crude extract of this plant has been shown to exhibit activity against Ranikhe disease virus and also to have spasmolytic and antiamphetamine activity.[5]

We report the first synthesis of (±)-**1a** via preparation of its benzyl derivative **1b** followed by removal of the hydroxyl protecting group by catalytic hydrogenation. Two routes were employed for the synthesis of **1b**. The first and shorter of these involved preparation of lithium (*E*)-3-lithio-2-butenoate (**2a**) by treatment of the corresponding bromo acid **2b** with 2 equiv of *n*-butyllithium in ether at −78 °C[6] and reaction of this organolithium reagent with (benzyloxy)acetaldehyde followed by acidification. The approach allowed the preparation of **1b** in 61% yield and in a single operation but it suffers from the disadvantage that the starting bromo acid **2b** is not readily available. In fact, the best procedure that we have found for the preparation of **2b** allowed its isolation in less than 10% yield. This involved the Favorskii rearrangement of a mixture of tribromobutanones to a mixture of **2b** and the isomeric (*Z*)- and (*E*)-3-bromo-2-methylpropenoic acids and isolation of the desired product by crystallization.[6-8]

Recently, we found that β-bromo-α,β-butenolides may be prepared by reaction of lithium (*E*)-3-bromo-3-lithiopropenoates, e.g., **3a**, with carbonyl compounds in tetrahydrofuran (THF) or diethyl ether at −78 °C followed by acidification.[9] It appeared that if the bromobutenolide **4** could be synthesized by this method that it should be possible to replace the halogen atom by a methyl group by using an appropiate cuprate reagent.[10] This approach to butenolide **1b** was also successful, but we were able to accomplish the last step only in low yield.

The organolithium reagent **3a**, which was required for the synthesis of **4**, was prepared by treatment of the corresponding (*E*)-bromo acid **3b** with 2 equiv of *n*-butyllithium in THF at −78 °C. ((*E*)-Bromo acid **3b** was easily prepared by heating a neat sample the corresponding *Z* isomer,[11a] which is readily available from Favorskii rearrangement of tribromoacetone,[11b] at 120 °C for 3 h.) Reaction of **3a** with (benzyloxy)acetaldehyde in THF −78 °C followed by acidification gave the β-bromobutenolide **4** in 65% yield. Treatment of this compound with the lithium dimethylcuprate–dimethyl sulfide complex[12] at −78 °C for 4 h followed by warming of the mixture to −30 °C, workup under acidic conditions, and separation of the product from the unreacted β-bromobutenolide by preparative thin-layer chromatography allowed the isolation of the desired β-methylbutenolide **1b** in 28% yield (the yield was 55% based upon unrecovered starting material). Several attempts, using the lithium dimethylcuprate reagent, were made to improve the yield in the conversion of **4** into **1b**. When the reaction was run at −30 °C rather than −78 °C, a significant amount of what appeared to be the β,γ-double bond isomer of **4** was recovered. This suggested that at the higher temperature partial deprotonation of the butenolide by the cuprate reagent had occurred. When a longer reaction time or a larger excess of the cuprate reagent was employed, a smaller quantity of starting material was recovered, but the isolated yield of **1b** was not improved. Lithium methyl(thiophenyl)cuprate has been used successfully for the conversion of cyclic β-halo enones into the corresponding β-methyl enones.[13] However, attempts to use this reagent for the conversion of **4** into **1b** were unsuccessful.

Hydrogenolysis of the benzyl group in **1b** in ethyl alcohol containing 10% palladium–carbon at atmospheric pressure gave crude (±)-umbelactone (**1a**) in ~90% yield. Subjection of the material to preparative TLC gave pure (±)-**1a**, mp 60–62 °C. The synthetic material showed IR

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(2) (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (b) Avetisysan, A. A.; Dangyan, M. T. *Russ. Chem. Rev.* **1977**, *46*, 643. (c) Larock, R. C.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131.

(3) Agarwal, S. K.; Rastogi, R. P. *Phytochemistry* **1978**, *17*, 1663.

(4) Recently, there has been a considerable amount of interest in the synthesis of optically active γ-(hydroxymethyl)-α,β-butenolides, which are useful starting materials for the synthesis of antileukemic lignan lactones. See: (a) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652. (b) Tomioka, K.; Ishiguro, T.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2973. (c) Estopa, C.; Font, J.; Moreno-Manas, M.; Sanchez-Ferrando, F.; Valle, S.; Vilamojo, L. *Ibid*, **1981**, *22*, 1467. (d) Camps, D.; Font, J.; Ponsati, O. *Ibid* **1981**, *22*, 1471.

(5) Dhar, M. L; Dhar, M. M.; Dhawan, B. N.; Mehrotra, B. N.; Ray, C. *Indian J. Exp. Biol.* **1968**, *6*, 241.

(6) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 5167.

(7) Rappe, C.; Nilson, T.; Carlson, G.; Andersson, K. *Arkiv. Kemi* **1965**, *24*, 95.

(8) Frobese, A. S. Ph.D. Dissertation, Georgia Institute for Technology, 1979.

(9) Caine, D.; Samuels, W. D. *Tetrahedron Lett.* **1980**, *21*, 4057.

(10) Larock and co-workers[2c] have reported that certain organocuprates react readily with β-chloro-α,β-butenolides to give the corresponding β-alkyl derivatives. However, no specific examples were provided.

(11) (a) It has been shown previously (see: Crout, D. H. G.; Corkill, J. A. *Tetrahedron Lett.* **1977**, 4355) that the (*E*)-bromo acid is thermodynamically favored over the *Z* isomer at higher temperatures. Note that in footnote 6 of this paper the designations of the configurations of the *E* and *Z* acids have been transposed. (b) Rappe, C. *Acta Chem. Scand.* **1965**, *19*, 31.

(12) House, H. O.; Chu, C. Y.; Wilkens, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

(13) Piers, E.; Nagakura, I. *Ibid.* **1975**, *40*, 2694.

0022-3263/83/1948-0740$01.50/0