Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 3945–3947

Tetrahedron Letters

Novel nitration of estrone by metal nitrates

Ashley Bose,[†] Widyanti P. Sanjoto,[†] Samantha Villarreal,[†]
Hector Aguilar[‡] and Bimal K. Banik[*]

Department of Chemistry, The University of Texas—Pan American, 1201 West University Drive, Edinburg, TX 78541, USA

Received 16 February 2007; revised 10 April 2007; accepted 11 April 2007
Available online 14 April 2007

Abstract—Nitration of estrone has been investigated with different types of metal salts in the presence of solid surfaces under various conditions.

1. Introduction

The usefulness of clay-mediated organic synthesis has been documented in a large number of recent publications.[1] For example, commercially available montmorillonite has shown considerable promise as a solid support in carrying out different chemical reactions. Based on our research on bismuth salt-induced reactions, we became interested in exploring nitration of estrone in detail.[2] These experiments have culminated in a facile, remarkably simple and highly efficient synthetic method of the nitration of estrone by various metal salts in the presence of different solid surfaces. This study clearly establishes that the nitration of estrone with metal salts depends on the nature of the solid surfaces. Nitroestrone derivatives have demonstrated several crucial biological activities.[3]

We have been engaged in the development of aromatic compounds such as anticancer and antibacterial agents. Recently, structure–activity relationship studies from our group have identified a few lead biologically active compounds on which a polycyclic aromatic rings are bound.[4,5] The nitro compounds required for the synthesis of these derivatives were prepared by using the conventional nitric acid–sulfuric acid or nitronium tetrafluoroborate. To avoid complication and associated hazards, we set out to test the nitrating abilities of nitrate salts with the most crucial female sex hormone, estrone. Montmorillonite clay impregnated with anhydrous cupric nitrate was used for aromatic nitration reaction.[6] A large excess of acetic anhydride was required when this reagent combination was used as the nitrating agent. The actual nitrating species was believed to be acetyl nitrate. Clay with ferric nitrate was also used as the reagent for the nitration of estrone in poor yield.[7] Moreover, extreme precautions were necessary for the preparation of this reagent.[8] Sulfuric acid supported on silica gel catalyzed nonselective nitration of simple aromatic compounds was reported.[9] In contrast, our studies on metal salt-induced nitration on estrone are simple and high yielding.

2. Results and discussion

Mixing estrone **1** with bismuth nitrate, montmorillonite with tetrahydrofuran and evaporation of the solvent using a rotavapor comprised the reaction conditions for the successful nitration of estrone (Scheme 1). This method produced a mixture of mononitro **2** and dinitro derivative **3** in a ratio of 2:1 in 90% yield.

A comparison with other solid supports, such as silica gel, alumina, ground molecular sieves and egg shells was also carried out. The results by our method are shown in Table 1. Interestingly, the sites of the electrophilic attack were found to be identical to the conventional nitric acid or acetyl nitrate mediated nitration reaction. But, conventional method with corrosive reagents yielded products **2** and **3** with a very low yield (20%). Neutral alumina and molecular sieves in the presence of bismuth nitrate produced a product with high

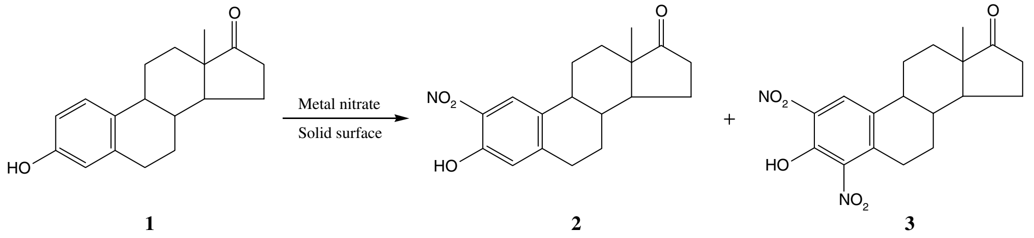
---

[*] Corresponding author. Tel.: +1 956 380 8741; fax: +1 956 384 5006; e-mail: banik@panam.edu

[†] High school research participants; contributed equally.

[‡] Undergraduate research participant.

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.04.050



Scheme 1.

Table 1. Nitration of estrone with various metal salts

Experiment number	Method	Nitrating agent	Surface solid	Product ratio (2:3)
1	Dean Stark[a,b,c,d,e,f]	$Bi(NO_3)_3$[a,b,c,d,e,f]	Clay[a,b,c,d,e,f]	2:1
2	Dean Stark[g]	$Ca(NO_3)_2$[g]	Clay[g]	2:1
3	Evaporation[h]	$Bi(NO_3)_3$[h]	Clay[h]	2:1
4	Evaporation[i]	$Zn(NO_3)_2$[i]	Clay[i]	2:1
5	Dean Stark[j]	$LaNO_3$[j]	Clay[j]	2:1
6	Dean Stark[k]	$NaNO_3$[k]	Clay[k]	2:1
7	Dean Stark[l]	$Bi(NO_3)_3$[l]	Silica Gel[l]	2:1
8	Dean Stark[m]	$Bi(NO_3)_3$[m]	Florisil[m]	5:1
9	Dean Stark[n]	$Bi(NO_3)_3$[n]	Molecular Sieves[n]	5:1
10	Dry[o]	$Bi(NO_3)_3$[o]	Alumina[o]	5:1
11	Dry[o]	$Zn(NO_3)_2$[o]	Alumina[o]	5:1
12	Dry[o]	$Zn(NO_3)_2$[o]	Silica gel[o]	5:1
13	Dry[o]	$Zn(NO_3)_2$[o]	Molecular Sieves[o]	5:1
14	Dry[o]	$Ca(NO_3)_2$[o]	Molecular Sieves[o]	5:1
15	Dry[o]	$Ca(NO_3)_2$[o]	Alumina[o]	5:1
16	Dry[o]	$Ca(NO_3)_2$[o]	Silica gel[o]	2:1
17	Wet[p]	$CAN/NaHCO_3$[p]	None[p]	No product
18	Evaporation[q]	CAN[q]	Clay[q]	0.8:1.2
19	Dean Stark[r]	CAN[r]	Clay[r]	9.5:0.5

For every 100 mg estrone, 5 mL solvent and 1 g solid surface was used.

[a] Estrone (100 mg) and $Bi(NO_3)_3$ (250 mg) were refluxed in a Dean Stark with benzene.

[b] Estrone (200 mg) and $Bi(NO_3)_3$ (500 mg) were refluxed in a Dean Stark with benzene.

[c] Estrone (500 mg) and $Bi(NO_3)_3$ (1.25 g) were refluxed in a Dean Stark with benzene.

[d] Estrone (100 mg) and $Bi(NO_3)_3$ (50 mg) were refluxed in a Dean Stark with benzene.

[e] Estrone (50 mg) and $Bi(NO_3)_3$ (62.5 mg) were refluxed in a Dean Stark with toluene.

[f] Estrone (50 mg) and $Bi(NO_3)_3$ (125 mg) were refluxed in a Dean Stark with toluene.

[g] Estrone (50 mg) and $Ca(NO_3)_2$ (44 mg) was refluxed in a Dean Stark with benzene.

[h] Estrone (100 mg) and $Bi(NO_3)_3$ (250 mg) were stirred with 10 mL THF, rotovapored, and left to dry overnight.

[i] Estrone (100 mg) and $Zn(NO_3)_2$ (250 mg) were stirred with 10 mL THF, rotovapored, and left to dry overnight.

[j] Estrone (100 mg) and $LaNO_3$ (250 mg) were refluxed in a Dean Stark with benzene.

[k] Estrone (100 mg) and $NaNO_3$ (250 mg) were refluxed in a Dean Stark with benzene.

[l] Estrone (50 mg) and $Bi(NO_3)_3$ (125 mg) were refluxed in a Dean Stark with benzene.

[m] Estrone (50 mg) and $Bi(NO_3)_3$ (125 mg) were refluxed in a Dean Stark with benzene.

[n] Estrone (50 mg) and $Bi(NO_3)_3$ (125 mg) were refluxed in a Dean Stark with benzene.

[o] CH_2Cl_2 (5 mL) were added to the reaction mixture and solvent was evaporated. The solid mass was kept at room temperature for 30 min.

[p] Estrone (270 mg), ammonium cerium (IV) nitrate (658 mg), sodium bicarbonate (250 mg) and acetonitrile (5 mL) were added to a reaction flask and stirred at room temperature for 24 h.

[q] Estrone (100 mg) and ammonium cerium (IV) nitrate (243 mg) were stirred with 10 mL THF, rotovapored, and left to dry overnight.

[r] Estrone (100 mg) and ammonium cerium (IV) nitrate (243 mg) were refluxed in a Dean Stark using benzene for 3 h.

regioselectivity. The product was 2-nitro derivative (80% yield). The reaction with bismuth nitrate produced a mixture of 2-nitro and 2,4-dinitroestrones in a ratio of 2:1 in 90% yield in the presence of montmorillonite and silica gel at room temperature and high temperature under azeotropic distillation conditions. The nitration of estrone with freshly prepared ferric nitrate using bentonite K-10 as the solid support demonstrated the production of 2-nitroestrone in 55% yield by stirring the reaction mixture in toluene overnight. However, a mixture of 2-nitro and 2,4-dinitro estrones was obtained in 90% yield (12 h) when excess bismuth nitrate was used as the nitrating agent. Zinc nitrate and calcium nitrate also afforded a mixture of 2- and 2,4-dinitro products in 80–90% yield when montmorillonite was used as the surface. In contrast, these salts mainly afforded the 2-nitro compound in the presence of molecular sieves and alumina with 80% yield. Interestingly, egg shells failed to yield products. Sodium nitrate and lanthanum nitrate gave products **2** and **3** in low yield (20%), irrespective of the nature of the surfaces. By following a recent literature method,[10] we repeated the nitration of estrone with ammonium cerium (IV) nitrate (CAN) under various conditions (Table 1). However, the reaction also produced a mixture of **2** and **3** (entry 18). On the other hand, $CAN/NaHCO_3$ mixture failed to produce nitroestrones (entry 17). The mixture of estrone with CAN in the presence of refluxing benzene produced **2** in low yield. Unreacted estrone (approximately 30%) was recovered from the reaction mixture.

These results indicate that the nitration strongly depends on the nature of the solid support. Based on a publication,[11] we believe that the binding of metal nitrates to the free hydroxyl group of the multi-metallic montmorillonite is important and that this complex produces the nitronium ion. Clearly, the success of bismuth nitrate, calcium nitrate and zinc nitrate to produce mostly a single product with alumina and molecular sieves strengthens the importance of the composition of the solid support. It is noteworthy to observe a successful nitration of estrone with calcium nitrate and zinc nitrate using montmorillonite and other solids. These experiments have suggested that excess nitrate salts in the presence of acidic surface (at room temperature to reflux temperature) are the choices to produce 2- and 2,4-dinitroestrones. Nonacidic surfaces are necessary to direct the reaction to the mononitration side. This also suggests that the temperature of the reaction is not an important factor in this method. Concentrated nitric acid is not an effective reagent for the nitration of estrone. Because of the presence of a phenolic hydroxyl group, estrone may undergo a variety of oxidations with nitric acid. These experiments have indicated that the amount of solid supports is not crucial. For example, nitration of estrone proceeds equally well with 1 g or 5 g of montmorillonite. But, the presence of solid surfaces is important (either in dry or wet form). Nitration of estrone is not possible with these salts without a solid adsorbent. The presence of water retards nitration dramatically. A reaction without Dean Stark under an identical condition proceeds much slowly than a reaction that has been performed under azetropic distillation. It has also been found that the reaction proceeds much better if the mixture is dry enough. Keeping the solid reaction mixture in the presence of clay gives the product, but it takes 24 h to complete the reaction. Drying the same reaction mixture under a vacuum pump accelerates the speed of the reaction (30 min).

In summary, we have demonstrated a simple, rapid and convenient method for the aromatic nitration of estrone with bismuth nitrate, calcium nitrate and zinc nitrate in the presence of different solid surfaces. The superiority of this method over others includes a very rapid reaction with readily available non-corrosive reagents. Further, our method requires no strong acid for the preparation of the surface, no acetic anhydride for the reaction and it can be applied to the most important sex hormone and results in a high overall yield. Nitro estrones are excellent substrates for the preparation of advanced intermediates that can be used as steroids.

Compound **2**: mp 178–180 °C;[12] IR (CH_2Cl_2): 3320, 1740, 1525, 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 10.40 (s, 1H), 7.95 (s, 1H), 6.82 (s, 1H), 3.0–1.4 (m, 15H), 0.95 (s, 3H) ^{13}C NMR ($CDCl_3$) δ: 220, 153, 149, 133, 131, 122, 119, 50, 48, 42, 37, 36, 31, 29, 26, 21, 14; MS: *m*/*e* 315 (M^+).

Compound **3**: mp 185–188 °C;[12] IR (CH_2Cl_2): 3622, 2255, 1917, 1817, 1793, 1635, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 10.65 (s, 1H), 8.20 (s, 1H), 2.98–1.45 (m, 15H), 0.97 (s, 3H) ^{13}C NMR ($CDCl_3$) δ: 220, 145, 140, 134, 132, 122, 50, 47, 42, 36, 35, 32, 27, 26, 25, 22, 13; MS: *m*/*e* 360 (M^+).[13]

Acknowledgements

We are grateful to the Welch Foundation departmental grant (BG0017). We also thank NIH-SCORE (2S06GM008038-36) for the support to B.K.B.

References and notes

1. (a) Cornelis, A.; Delaude, L.; Gertmans, A.; Laszlo, P. *Tetrahedron Lett.* **1988**, *29*, 5657; (b) Laszlo, P.; Cornelis, A. *Aldrichim. Acta* **1988**, *21*, 97; (c) Laszlo, P.; Vandormael, J. *Chem. Lett.* **1988**, 1843; (d) Laszlo, P.; Cornelis, A.; Gerstmans, A.; Laszlo, P. *Chem. Lett.* **1988**, 1839.
2. (a) Banik, B. K.; Samajdar, S.; Banik, I. *Tetrahedron Lett.* **2003**, *44*, 1699; (b) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109.
3. (a) Kraychy, S. *J. Am. Chem. Soc.* **1959**, *81*, 1702; (b) Patton, T. L. *J. Org. Chem.* **1959**, *24*, 1795; (c) Rozhin, J.; Ludwig, E. H.; Corombos, J.; Odden, D.; Horwitz, J. P.; Hughes, R.; Hughes, D. E.; Wilson, E.; Brooks, S. C. *Can. Res.* **1983**, *43*, 2611; (d) Jordan, V. C.; Koch, R. *Endocrinology* **1989**, *124*, 1717; (e) Palomino, E.; Heeg, M. J.; Pilat, M. J.; Hafner, M.; Polin, L.; Brooks, S. C. *Steroids* **1996**, *61*, 670.
4. Banik, I.; Becker, F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12.
5. Banik, B. K.; Becker, F. F. *Bioorg. Med. Chem.* **2001**, *9*, 5936.
6. Gigantee, B.; Prazeres, A. O.; Marcelo-Curto, M. J.; Cornelis, A.; Laszlo, P. *J. Org. Chem.* **1995**, *60*, 3445.
7. Cornelis, A.; Laszlo, P.; Pennetreau, P. *J. Org. Chem.* **1983**, *48*, 4771.
8. Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909.
9. Riego, J.; Sedin, Z. M.; Zaldivar, J. M.; Marziano, N. C.; Tortato, C. *Tetrahedron Lett.* **1996**, *37*, 513.
10. Sathunuru, R.; Biehl, E. *Arkivoc* **2004**, *89*.
11. Kropp, J. P.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000**, *122*, 4280.
12. Werbin, H.; Holoway, C. *J. Bio. Chem.* **1956**, 651, The melting point of 2-nitroestrone as reported in this paper is 184 °C. The melting point of 2,4-dinitroestrone as reported in this paper is 185–187 °C.
13. A representative experimental procedure is as follows: Estrone (1 mmol) and montmorillonite KSF (500 mg, Aldrich) were added to a suspension of bismuth nitrate pentahydrate (1 mmol) in THF (10 mL). The solvent was then evaporated under reduced pressure and dried in a vacuum pump for 5 min. The mixture was then repeatedly washed with dichloromethane (25 mL) and concentrated to afford the crude product. The pure product was isolated by crystallization (ethyl acetate/hexanes = 20:80). A number of conditions were examined as can be seen in Table 1.