Pergamon

Tetrahedron Letters, Vol. 37, No. 12, pp. 2079-2082, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00197-9

On Reaction of Enamides with Acetyl Nitrate

Jacek W. Morzycki*, Agnieszka Z. Wilczewska and Zenon Łotowski

Institute of Chemistry, University of Warsaw, Bialystok Branch, Al. Pilsudskiego 11/4, 15-443 Białystok, Poland

Abstract: The reactions of four steroidal enamides with acetyl nitrate were studied. The nitronium ion attacks the terminal carbon atom of the enamide moiety. Further transformations of the unsaturated nitro derivative consist of an allylic oxidation or a Nef-type reaction.

Acetyl nitrate is a frequently used reagent for nitration of organic compounds. The reactions of some simple alkenes[1] and enol esters[2] with this reagent have also been studied. However the reactions of enamides with acetyl nitrate have not been yet investigated.

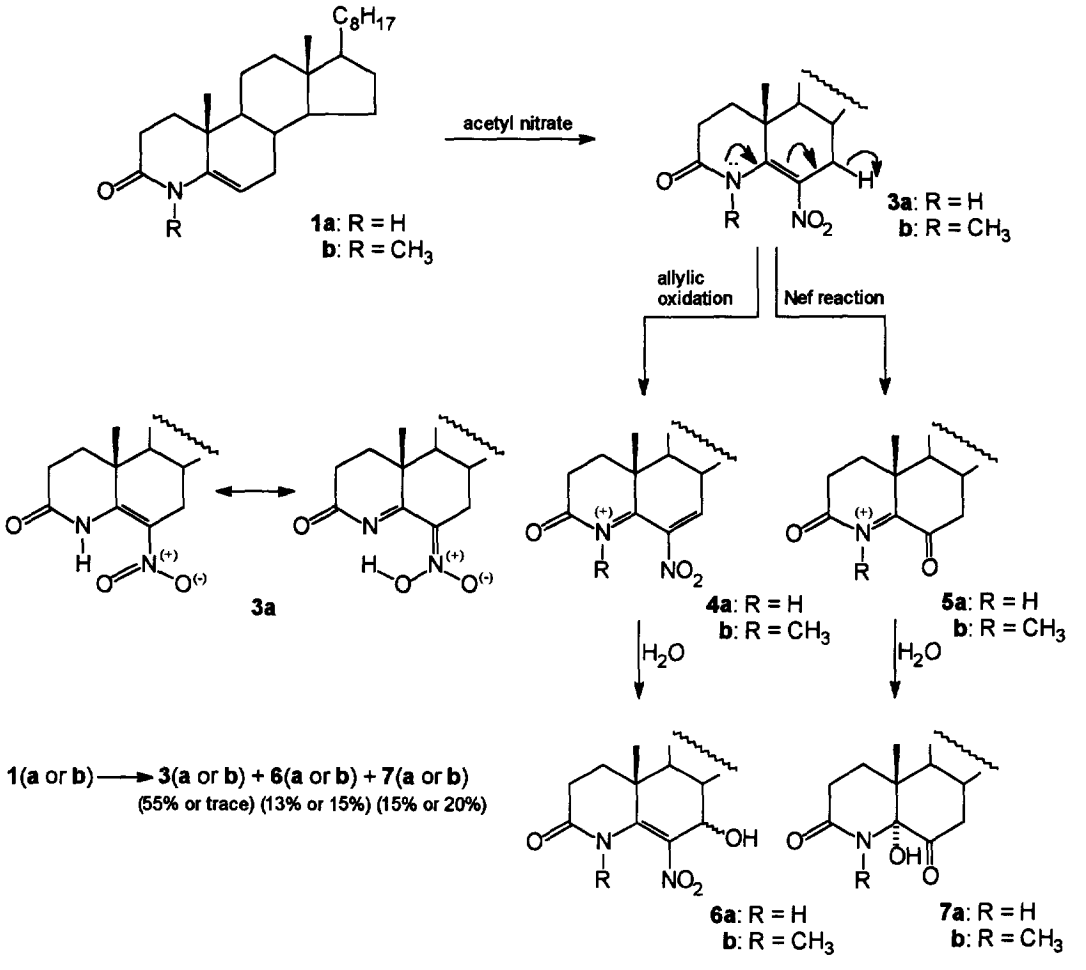
Certain azasteroids display interesting biological activity.[3,4] Among them some 4-aza[5] and 6-aza[6] cholestanes have recently been found to be effective inhibitors of enzyme steroid 5α-reductase. We therefore chose 4-azacholest-5-en-3-one (**1a**)[7] and 6-azacholest-4-en-7-one (**2a**)[8] along with their N-methyl derivatives as the subject of our investigations. Herein we report the results.

Compounds **1a**, **1b**, **2a** and **2b** (0.5 mmol) were treated with acetyl nitrate prepared by adding 1 mL of 65% nitric acid to 5 mL of acetic anhydride. The reaction mixtures were allowed to stand for 1 hour at room temperature and quenched with water followed by separation of products[9] by silica gel chromatography.

The reaction of enamide **1a** afforded, in order of increasing polarity, the 6-nitro derivative **3a**[10], the epimeric 7-hydroxy (predominantly 7α-OH) 6-nitro compounds **6a**[11,12] and the hydroxy ketone **7a**.[14] The tentative mechanism of their formation is outlined in Scheme 1. The nitration at C-6 was not surprising as it is well established that the terminal carbon atom of the enamide system is the preferred site of an electrophilic attack.[16,17] The 6-nitro compound **3a** shows in its ^{1}H-NMR spectrum an usual chemical shift for N-H proton (δ 11.31) proving the presence of a strong intramolecular hydrogen bond. Compound **3a** probably exists as a hybrid of mesomeric structures with the hydrogen atom between the amide nitrogen and the nitro group oxygen. Further reaction of **3a** with acetyl nitrate consists of an allylic oxidation to the unsaturated N-acyliminium salt **4a** followed by its 1,4 hydration on aqueous workup. This accounts for the formation of the epimeric mixture of 7-hydroxy derivatives **6a**. Alternately compound **3a** may undergo a Nef-type reaction to generate the intermediate **5a**. The hydration of its N-acylimine moiety afforded the hydroxy ketone **7a** (presumably the more stable 5α-OH epimer).

The enamide N-methyl derivative **1b** appeared to be more reactive than **1a** towards acetyl nitrate. The reaction afforded a mixture of many products. The major ones, the 7-hydroxy 6-nitro compound **6b**[13] (the 7α-OH epimer) and the hydroxy ketone **7b**[15], were isolated from the reaction mixture. The primary 6-nitro product **3b** was not found among the products. The compound **3b** is apparently less stable (lack of stabilization by intramolecular hydrogen bond) compared to **3a**, and therefore rapidly underwent further transformations under the reaction conditions.

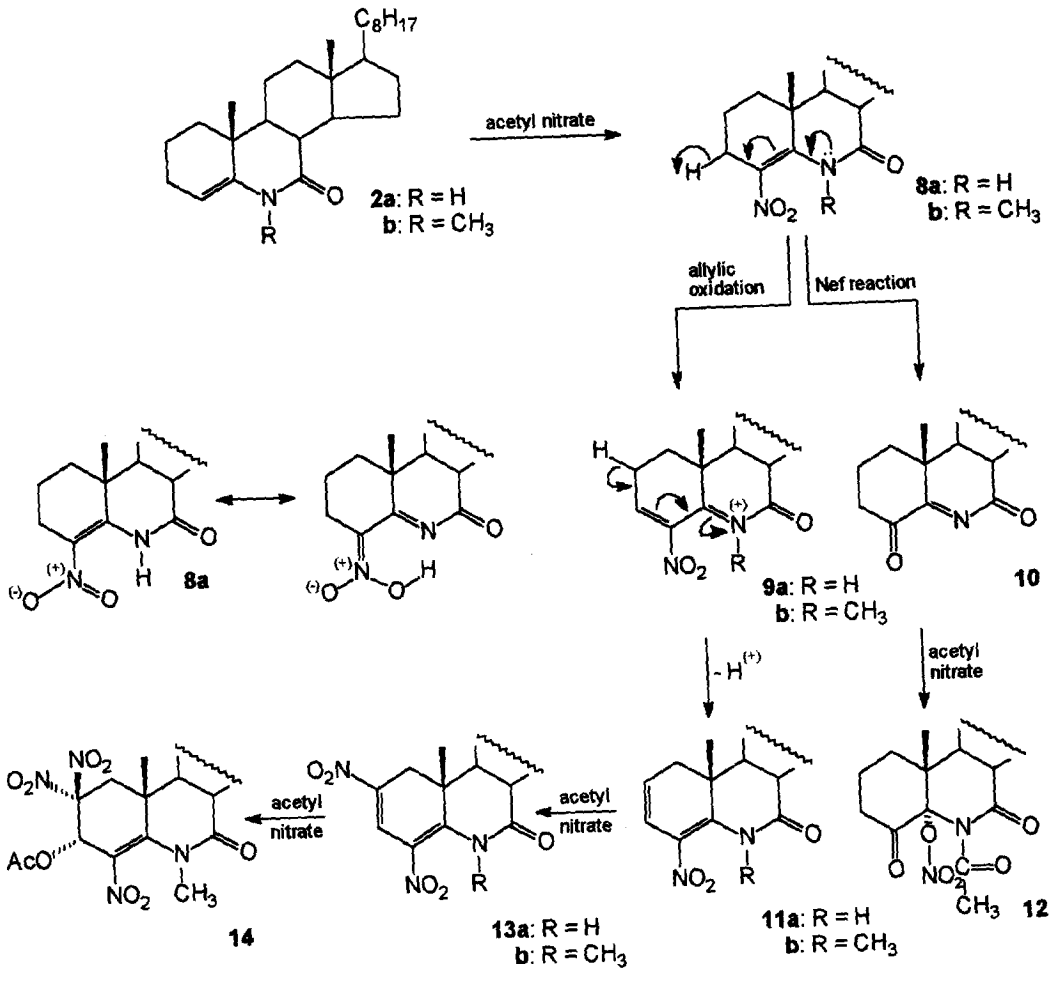
Scheme 1



The reaction of enamide **2a** with acetyl nitrate is to some extent similar to that of compound **1a** (Scheme 2) although it is considerably faster. The increased reactivity of 6-aza compared to 4-aza enamide is a result of the lack of steric hindrance in the ring A of the former compound (the approach of nitronium ion to the ring B double bond in 4-aza enamide is more difficult). The major product of the reaction appeared to be the 4-nitro derivative **8a**[18] stabilized by an intramolecular hydrogen bond (chemical shift of N-H proton - δ 11.22). Two minor products **12**[19] and **13a**[20] were also found in the reaction mixture. The former (the configuration at C-5 was ascribed arbitrarily) probably derives from the reactive N-acylimine intermediate **10** which undergoes addition of acetyl nitrate. Allylic dehydrogenation of the 4-nitro compound **8a** followed by further nitration of the diene **11a** with acetyl nitrate accounts for the formation of the dinitro derivative **13a**.

Much more complex is the nitration reaction of enamide N-methyl derivative **2b**. Compound **2b** appeared to be the most reactive of the four enamides studied. Among several products formed only the major one, the trinitro compound **14**[21], was isolated and identified. Presumably, the product was produced from the dinitro

Scheme 2



2a ⟶ **8a** (40%) + **12** (17%) + **13a** (12%)
2b ⟶ **14** (20%)

diene **13b** by addition of acetyl nitrate. The intermediate 4-nitro compounds **8b** and **13b** are much more reactive than their demethyl analogs **8a** and **13a** due to the less efficient mesomeric stabilization. The configuration of the acetoxyl group at C-3 in compound **14** could not be established by analysis of its spectra. The molecular mechanics[22] calculations (MM+ force field) show that the 3α-acetoxy compound is more stable, in its preferred conformation, than the 3β-epimer by about 1.2 kcal/mol. Since it is likely that there is the product development control in the formation of **14**, the reaction probably yields the more thermodynamically stable 3α-epimer.

Further investigations on the enamides reactions with electrophilic reagents are under way.

The Authors gratefully acknowledge financial support from the State Committee for Scientific Research, Poland. We also thank Dr. L. Siergiejczyk for assistance in recording some NMR spectra and Mrs. J. Maj for help in preparation of the manuscript.

REFERENCES AND NOTES

1. Bordwell, F. G.; Garbish, Jr., E. W. *J. Am. Chem. Soc.* **1960**, *82*, 3588.
2. Dampawan, P.; Zajac, Jr., W. W. *Synthesis* **1983**, 545.
3. Morzycki, J. W. *Polish J. Chem.* **1995**, *69*, 321.
4. Singh, H.; Jindal, D. P.; Yadav, M. R.; Kumar, M. *Prog. Med. Chem.* **1991**, *28*, 233.
5. Bakshi, R. K.; Patel, G. F.; Rasmusson, G. H.; Baginsky, W. F.; Cimis, G.; Ellsworth, K.; Chang, B.; Bull, H.; Tolman, R. L.; Harris, G. S. *J. Med. Chem.* **1994**, *37*, 3871.
6. Haffner, C. *Tetrahedron Lett.* **1995**, *36*, 4039.
7. Shoppee, C. W.; Killick, R. W.; Kruger, G. *J. Chem. Soc.* **1962**, 2275.
8. Jacobs, T. L.; Brownfield, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 4033.
9. All new compounds exhibited spectroscopic (IR, NMR and MS) and analytical (combustion analysis or high resolution mass spectrum) data in accord with the assigned structure.
10. Compound **3a**: m.p. 81-83°C; ν_{max} 1105, 1182, 1379, 1611, 1691, 3255 cm^{-1}; ^{13}C-NMR, δ 169.5, 150.9, 123.8; m/z 430 (42%), 413 (28%), 398 (38%), 395 (100), 383 (21%).
11. The assignment of configuration at C-7 in the 7-hydroxy 6-nitro compounds **6a** is based on the coupling constants of protons at C-7 and C-8. $J_{7,8}$ is close to 0 for the 7α-hydroxy epimer ($\delta_{7\beta\text{-H}}$ 4.72 ppm) while it amounts 7.2 Hz for the opposite epimer ($\delta_{7\alpha\text{-H}}$ 4.65 ppm). These values are most consistent with axial-equatorial and diaxial coupling, respectively. This assignment is corroborated by the down-field shift of C-19 protons in the 7β-OH epimer (δ 1.36 *versus* 1.30 in the 7α-OH epimer).
12. Compound **6a** (7α-OH): m.p. 164-167°C; ν_{max} 1107, 1180, 1375, 1602, 1703, 3260, 3578 cm^{-1}; ^{13}C-NMR, δ 169.8, 154.4, 127.1; m/z 446 (21%), 428 (100), 414 (14%), 411 (21%).
13. Compound **6b** (7α-OH): m.p. 230-234°C; ν_{max} 1295, 1351, 1635, 1691 cm^{-1}; ^{13}C-NMR, δ 169.5, 149.9, 135.6; m/z 460 (28%), 443 (30%), 414 (100%).
14. Compound **7a**: m.p. 195-197°C; ν_{max} 1035, 1660, 1718, 3275 cm^{-1}; ^{13}C-NMR, δ 205.4, 173.0, 85.1; m/z 417 (1%), 399 (29%), 384 (12%), 262 (64%), 127 (100).
15. Compound **7b**: m.p. 168-171°C; ν_{max} 1645, 1712, 3499 cm^{-1}; ^{13}C-NMR, δ 208.2, 171.1, 91.5; m/z 431 (<1%), 262 (5%), 141 (100%).
16. Back, T. G.; Ibrahim, N. *Tetrahedron Lett.* **1979**, 4931.
17. Back, T. G.; Chau, J. H.-L.; Dyck, B. P.; Gladstone, P. L. *Can. J. Chem.* **1991**, *69*, 1482.
18. Compound **8a**: m.p. 149-152°C; ν_{max} 1122, 1176, 1380, 1604, 1695, 3260 cm^{-1}; ^{13}C-NMR, δ 171.9, 152.0, 123.2; m/z 430 (91%), 413 (100%), 398 (15%), 384 (46%).
19. Compound **12**: an oil; ν_{max} 1009, 1147, 1613, 1750 cm^{-1}; ^{13}C-NMR, δ 198.3, 169.5, 168.5, 97.9; m/z 461 (11%), 416 (29%), 399 (100%), 372 (99%).
20. Compound **13a**: m.p. 217-221°C; ν_{max} 1071, 1181, 1319, 1382, 1564, 1652(w), 1731, 3248 cm^{-1}; ^{13}C-NMR, δ 170.6, 157.6, 139.1, 124.2, 118.7; m/z 473 (100%), 458 (5%), 443 (7%), 427 (6%).
21. Compound **14**: m.p. 76-80°C; ν_{max} 1019, 1178, 1576, 1628, 1700, 1779 cm^{-1}; ^{13}C-NMR, δ 169.6, 166.8, 149.8, 125.9, 113.8; m/z 577 (1%), 545 (1.5%), 503 (23%), 500 (28%), 487 (100%), 458 (36%).
22. Molecular modeling was performed with HyperChem™ Release 3 from Hypercube, Inc. Minimizations employed the MM+ force field and the Polak-Ribiere (conjugate gradient) algorithm.

(*Received in UK* 8 *December* 1995; *revised* 1 *February* 1996; *accepted* 2 *February* 1996)