Pergamon

Tetrahedron Letters, Vol. 36, No. 19, pp. 3303-3306, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00526-9

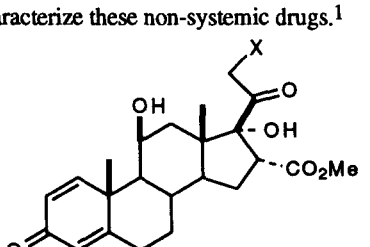
Suppression of the Mattox Rearrangement of 16α-Cyanoprednisolones in Acid: Synthesis of Methyl 16α-Prednisolonecarboxylates

Zhengqing You, Mounir A. Khalil, Dong-Hoon Ko and Henry J. Lee*

Center for Drug Discovery Research, College of Pharmacy and Pharmaceutical Sciences,
Florida A & M University, Tallahassee, FL 32307

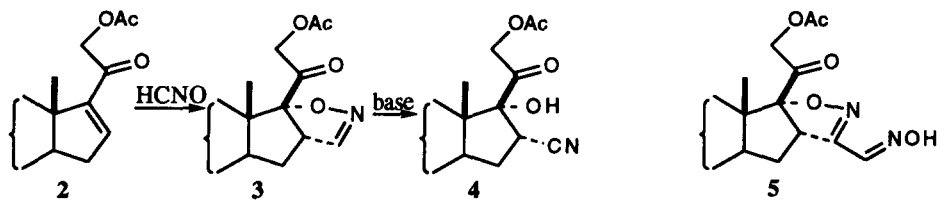
Abstract: *Prednisolone derivatives with a 16α-methyl carboxylate group were synthesized by a novel procedure of 1,3-dipole addition of fulminic acid to 21-acetyloxy-11β-hydroxy-3,20-dioxo-1,4,16-pregnatriene, followed by base-catalyzed ring opening of the resulting isoxazoline to yield a 16α-cyanoprednisolone derivative and treatment of the nitrile with methanolic HCl. Conversion of the cyanosteroids in the acid to the corresponding methyl carboxylates was achieved with or without the Mattox rearrangement by controlling reaction temperature and protective group for the 21-OH.*

In an effort to develop local anti-inflammatory steroids without systemic side effects, metabolically labile functional groups, alkyl carboxylates, at various strategic positions of potent corticosteroids were introduced.[1-4] The reduced systemic side effects of this new class of locally active steroids is ascribed to rapid hydrolysis of the ester function to an inactive acid upon entry into the circulation system. The "antedrug" concept was introduced in 1982 to characterize these non-systemic drugs.[1]



1

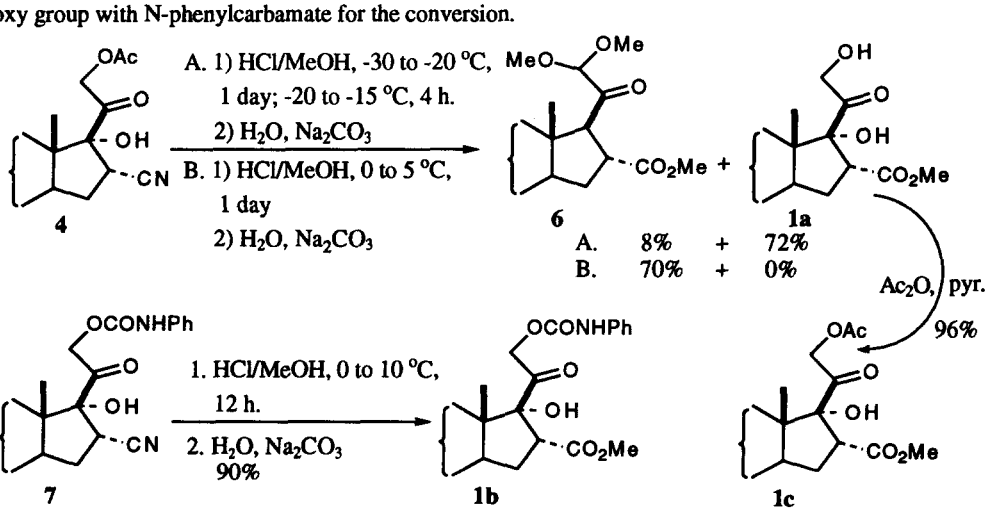
Our current investigation involves synthesis and evaluation of methyl 11β,17α,21-trihydroxy-3,20-dioxo-1,4-pregnadiene-16α-carboxylate and its 21-substituted derivatives (**1**). We initiated a study to establish a new, efficient and reliable synthetic methodology for the title compounds since the reported procedures for 17α-hydroxylation of 17-deoxy-16α-methoxycarbonylprednisolone[5,6] did not yield the desired result. In search of a regio and facial selective introduction of 17α-OH and 16α-carboxylate equivalent to enone **2**,[5] it was envisaged that 1,3-dipole addition of fulminic acid to enone **2** could yield isoxazoline **3**.[7,8] This heterocyclic ring could then be cleaved with base[9] to afford nitrile **4**, a potential immediate precursor to **1**.



Fulminic acid addition to enone **2** according to literature procedure[7] gave isoxazoline **3** (50-60%) as expected. The reaction was highly regio and stereoselective and no isomer of **3** was detected. The major side product in the conversion was oxime **5** (20-40%), presumably through addition of fulminic acid dimer to **2**.[10] Conversion of **3** to nitrile **4** proceeded well (95%) by treatment with triethylamine in THF.[9]

Transformation of nitrile **4** to the corresponding acid or methyl ester encountered a few pitfalls. Acid (HCl) and base (NaOH)-catalyzed hydrolysis of nitrile **4** at elevated temperatures did not give the desired acid. Treatment of **4** with methanolic HCl at 0 °C followed by hydrolysis afforded an unknown compound as the predominant product and very low yield of **1a** (**1**, X=OH). While the failure under the basic conditions appeared to be related to the homoannular rearrangements,[11-14] possible side reactions under the acidic conditions included the Mattox rearrangement.[15-17]

Careful examinations of the methanolysis and hydrolysis process revealed that the major compound was indeed a product from the Mattox-rearrangement followed by acetal formation (**6**). In order to suppress the Mattox process, two routes for the methyl ester formation were designed. One approach was lower temperature treatment of **4** with methanolic HCl since the Mattox rearrangement was expected to slow down and the methanolysis is known to proceed at temperatures much below 0 °C.[18,19] The other was protection of the 21-hydroxy group with N-phenylcarbamate for the conversion.

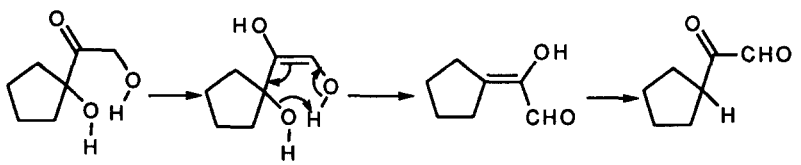


All methanolic reactions were carried out in methanol saturated with HCl. The resulting mixture was poured into water followed by neutralization with sodium carbonate powder to pH 3-4, and the methyl ester product was then extracted into ethyl acetate. At low reaction temperatures (ca. -20 °C) **4** was converted to ester **1a** in good yield. At higher temperatures (0-5 °C), the Mattox rearrangement became much more competitive and **6** was the major product. The carbamate **7** was synthesized from **4** in an overall yield of 80%

through hydrolysis of the acetate group (aqueous sodium carbonate/methanol) and treatment of the resulting alcohol with phenyl isocyanate and triethyl amine in THF. With the carbamate protection of the 21-hydroxy group, the Mattox process was totally eliminated even at room temperature, resulting in only **1b**. When nitrile **7** was heated in 10% aqueous HCl and THF to reflux for 14 hours, no reaction was observed, further demonstrating the stability of the steroid system in acid with protection of the 21-OH group.

It should be pointed out that the acetate group of **4** was cleaved during the methanolysis reaction before the hydrolysis, and thus provided little, if any protection of the hydroxy group at C-21. Reesterification of **1a** was accomplished by treatment of the alcohol with acetic anhydride in pyridine to afford **1c** in excellent yield.

Especially noteworthy is while the Mattox rearrangement was a serious contender at moderate temperatures and without protection at C-21, no dehydration between C-16 and C-17 was observed in our reactions involving **4** and **7**, which was probably due to the inaccessibility of the hydroxy group at C-17 through intermolecular contact and the resulting difficulties in protonation of this group. The Mattox process, however, could deliver a proton to the hindered hydroxy group via an intramolecular 6-membered ring mechanism shown below.



The structure of products (**1a-c, 3-7**) was confirmed by ^{1}H-NMR, ^{13}C-NMR and MS spectra, as well as elemental analysis. The stereochemistry created in the conversions was ascertained by difference NOE experiments. Irradiation on the 18-methyl of isoxazoline **3** resulted in signal enhancement of the 16-proton, vice versa. Similar NOE interactions in alcohol **1a** and carbamate **1b** were also obtained between their 18-methyl and 16-proton. The 17-proton in Mattox product **6** was determined to be on the α-side since irradiation on it caused a strong enhancement of the 14α-proton. Irradiation on the 16-H, however, gave strong enhancement of the 15β-H and no enhancement of the 14α-H, indicating its β-orientation.

In conclusion, we have established a new procedure to prepare the title compounds through an isoxazoline intermediate and its ring-cleavage products 16α-cyanoprednisolones. Our studies showed that under acidic conditions (HCl), the 16α-cyanoprednisolones are quite stable with protection of the hydroxy group at C-21. Without such protection, the Mattox rearrangement proceeds predominantly in methanolic HCl at moderate temperatures (0-5 °C). The rearrangement, however, can be largely eliminated with low temperatures (< -20 °C). In all of our experiments, dehydration between C-16 and C-17 was not a competing process, a phenomenon that could be explained by the difficulty of an intermolecular protonation of the hydroxy group at C-17. On the other hand, the Mattox rearrangement could be attributed to a six-membered ring transition state, causing an intramolecular delivery of the proton on the 21-OH to the 17-hydroxy group. We took advantage of these selectivities and successfully converted nitriles **4** and **7** to esters **1a** and **1b**, respectively, through HCl-methanolysis and hydrolysis.

Acknowledgment. This work was supported by NIH 21627, RR 08111 and RCMI 0330. We would like to thank Dr. Taesoo Kwon for his contributions to the isoxazoline chemistry. Special thanks are also extended to Dr. Thomas E. Gedris at the Florida State University for the NMR instrumentation.

REFERENCES

1. Lee, H. J. and Soliman, M. R. I. *Science* **1982**, *215*, 989.
2. Lee, H. J.; Heiman, A. S.; Taraporewala, I. B. In *New Developments in Anti-Rheumatic Therapy*; Rainsford, K. D. and Velo, G. P. (eds); MPT Press: Lancaster, **1989**; *Vol. III*, 153-186.
3. Khalil, M. A.; Kwon, T.; Lee, H. J. *Current Topics in Med. Chem.* **1993**, *1*, 173.
4. Hong, D.; Heiman, A. S.; Kwon, T.; Lee, H. J. *J. Pharm. Sci.* **1994**, *83*, 357.
5. Taraporewala, I. B.; Kim, H. P.; Heiman, A. S.; Lee, H. J. *Arzneimittel-Forschung/Drug Research* **1989**, *39*, 21.
6. Oliveto, E. P. and Hershberg, E. B. *J. Am. Chem. Soc.* **1954**, *76*, 5167.
7. De Sarlo, F.; Brandi, A.; Guarna, A.; Goti, A.; Corezzi, S. *Tetrahedron Lett.* **1983**, *24*, 1815.
8. Brandi, A.; De Sarlo, F.; Guarna, A.; Speroni, G. *Synthesis* **1982**, 719.
9. Huisgen, R. and Christl, M. *Angew. Chem. Internat. Edit.* **1967**, *6*, 456.
10. De Sarlo, F.; Guarna, A.; Brandi, A.; Goti, A. *Tetrahedron* **1985**, *41*, 5181.
11. For reviews, see: (a) Wendler, N. L. In *Molecular Rearrangements*; de Mayo, P. (ed); Interscience: New York, **1964**; *Vol. 2*, 1114-1121. (b) Kirk, D. N.; Hartshorn, M. P. *Steroid Reaction Mechanisms*; Elsevier: Amsterdam, **1968**; 294-313. (c) Boswell, G. A., Jr. In *Organic Reactions in Steroid Chemistry*; Fried, J.; Edwards, J. A. (eds); Van Nostrand Reinhold: New York, **1972**;*Vol. II*, 382-386.
12. Moersch, G. W.; Wittle, E. L.; Neuklis, W. A. *J. Am. Chem. Soc.* **1965**, *30*, 1272.
13. Bischofberger, N. and Walker, K. A. M. *J. Org. Chem.* **1985**, *50*, 3604.
14. Delaney, E. J.; Sherrill, R. G.; Palaniswamy, V.; Sedergran, T. C.; Taylor, S. P. *Steroids* **1994**, *59*, 196.
15. Mattox, V. R. *J. Am. Chem. Soc.* **1952**, *74*, 4340.
16. Herzog, H. L.; Gentles, M. J.; Marshall, H.; Hershberg, E. B. *J. Am. Chem. Soc.* **1961**, *83*, 4073.
17. Caspi, E. and Zajac, H. *J. Chem. Soc.* **1964**, 586.
18. Schwartz, A. and Madan, P. *J. Org. Chem.* **1986**, *51*, 5463.
19. Cushman, M. and Wong, W. C. *Tetrahedron Lett.* **1986**, *27*, 2103.

(*Received in USA* 9 *February* 1995; *revised* 3 *March* 1995; *accepted* 16 *March* 1995)