

REGIOSELECTIVE REDUCTIONS OF VINYLOGOUS IMIDES

Thomas A. Bryson¹ and Ronald B. Gamill

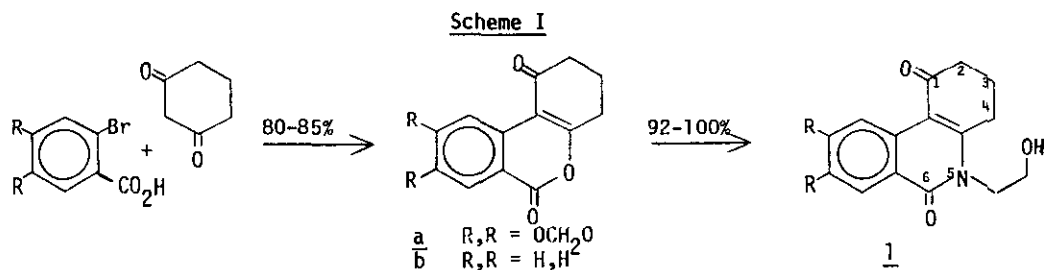
Department of Chemistry

University of South Carolina

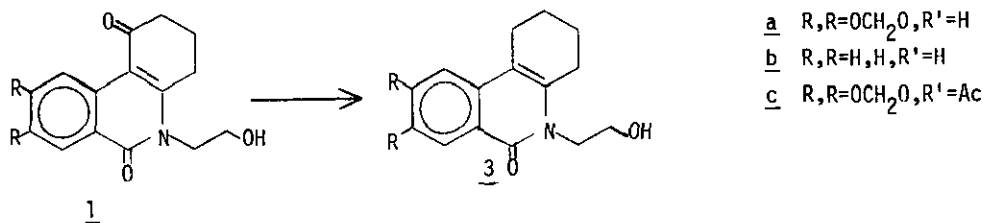
Columbia, SC 29208

Abstract - The regiospecific reduction of unsymmetrical vinylogous imides was investigated. Controlled selective reduction was realized via employing neighboring group participation to effect reduction of the less reactive carbonyl group.

Enamido-ketones have been key synthetic intermediates in natural product synthesis². The complete reduction of this functional unit (excess LiAlH_4) has been described, however, chemoselective reduction has not been reported.³ Herein, we describe such regiospecific reductions, one of which proceeds via a novel neighboring group participation reaction. The synthesis of the vinylogous imides used in this study were prepared as outlined in Scheme I.⁴

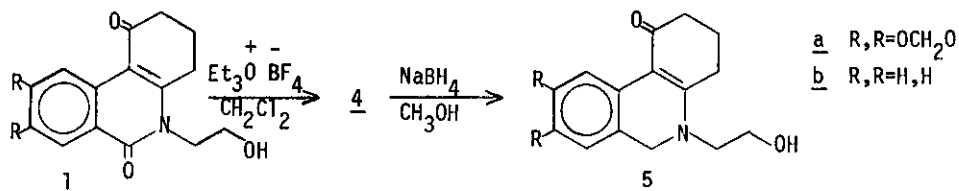


While diborane readily reduces simple amides to amines,⁵ we found that treatment of enamido-ketone **1a** with 2.6 equiv. of diborane in tetrahydrofuran at reflux resulted in reduction at C-1, thereby affording enamide **3a** (λ , 1650 cm^{-1} ; δ 2.40-1.51, 8H's ring C-protons) in 73% yield.⁶



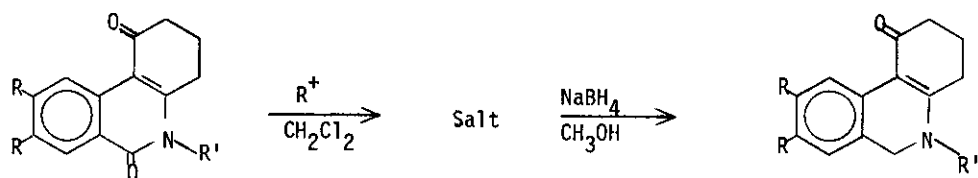
The presence of a single OH group (i.e., reduction of the C-1 carbonyl to a methylene group) was readily demonstrated by D₂O exchange and acylation (Ac₂O/ pyridine) of 3a, in the latter case forming monoacetate 3c. This reduction illustrated that the C-1 carbonyl is more reactive than the C-6 position toward electrophilic reducing agents and therefore can be selectively reduced⁶ or removed.

Treatment of 1a with Meerwein reagent (Et₃O⁺BF₄⁻) in CH₂Cl₂ resulted in the precipitation of a salt (4a), which when treated with NaBH₄ in CH₃OH, afforded the enamino-ketone 5a (C-6 reduction) in 65% yield.⁷ The desmethylenedioxy system also underwent this same reaction to afford 5b



(δ , 4.37 benzylic methylene; λ , 1600, 1540 cm⁻¹) in 50-60% yield. Even though 1a and 1b gave similar results there was a marked difference in reactivity with respect to treatment with Et₃O⁺BF₄⁻ in that 1a afforded a salt in a few (~ 3) hours, while 1b required no less than 20 hours for visible salt formation. It seems reasonable to assume that the difference in reactivity of these two systems (1a and 1b) arises from an electron donating effect of the methylenedioxy group of 1a (absent in 1b) enhancing the nucleophilicity of the C-6 carbonyl group, explaining the observed differences in salt formation and other reactions cited below.

Sodium borohydride reduction of the salt generated from chloride 6 gave, unexpectedly, alcohol 5a (C-6 carbonyl reduction) rather than the envisioned chloride product 9. These results



6 R,R = OCH₂O ; R' = CH₂CH₂Cl

7 R,R = OCH₂O ; R' = (CH₂)₃CH₃

8 R,R = OCH₂O ; R' = CH₂φ

12 R,R = H,H; R' = CH₂CH₂OTs

13 R,R = H,H; R' = CH₂CH₂Br

14 R,R = H,H; R' = CH₂CH₂OMe

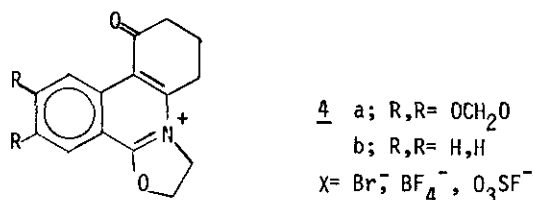
5a R,R = OCH₂O, R' = CH₂CH₂OH

9 R,R = OCH₂O, R' = CH₂CH₂Cl

10 R,R = OCH₂O, R' = (CH₂)₃CH₃

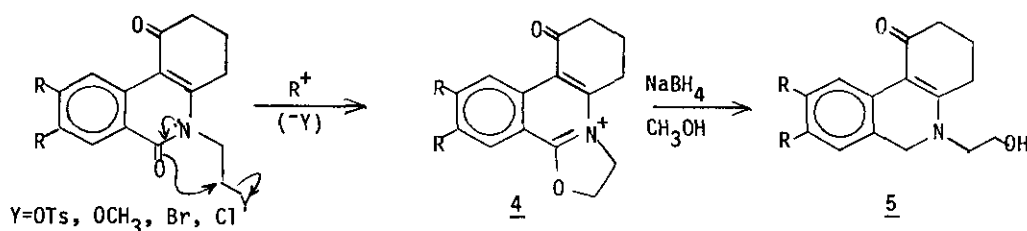
11 R,R = OCH₂O, R' = CH₂φ

led to further preparations and reductions¹⁰ of vinylogous imide tosylate 12, bromide 13 and methyl ether 14. Like enamido-ketones 1 and 6, compounds 12, 13 and 14 gave a salt upon treatment with $\text{Et}_3\text{O}^+\text{BF}_4^-$ (or $\text{CH}_3\text{OSO}_2\text{F}$) in CH_2Cl_2 and subsequently underwent C-6 reduction with $\text{NaBH}_4/\text{CH}_3\text{OH}$. Thus, enamido-ketones 1, 6, 12, 13 and 14 formed 5 (a or b) by this two step reduction process, with interchange or loss of the β -ethylamino heteroatom. Observing that all the selective C-6 carbonyl reductions occur only on vinylogous imides (1, 6, 12, 13 and 14) which contain a heteroatom (oxygen or halogen) at the β -position on the N-ethyl units¹⁰ suggested that intermediate salt, 4a or 4b, formed via the action of Meerwein salt or methane fluorosulfonate⁸ on these imides, had the following structure:



The formation of 5(a,b) is perhaps best depicted as shown in Scheme II and the role of the alkylating agent would be to assist in removal of the β -heteroatom, via alkylation, on the heteroatom of the N-ethyl group thereby allowing for participation for the C-6 carbonyl in salt formations.^{9,11}

Scheme II



This also accounts for alcohol 5 as being the only reduction product from these various substrates. The same salt, 4 (fluorosulfonate counterion), was prepared from the reaction of vinylogous imides 1 and 6 (5a) or from 12, 13 and 14 (4b) with methyl fluorosulfonate in CH_2Cl_2 . These salts were air stable, non-hygroscopic solids and on treatment with $\text{NaBH}_4/\text{CH}_3\text{OH}$ afforded the enamino-ketones 5a,b. Bromide 13, upon standing overnight at room temperature in CHCl_3 , also formed small amounts of 4b. This salt could readily be isolated from the CHCl_3 solution by filtration and reduced with NaBH_4 to give enamino-ketone 5b.

Acknowledgement: We gratefully acknowledge the National Institutes of Health (GM-28260) and the National Science Foundation (CHE 8014180) for support of this work.

Notes and References

1. A. P. Aloan Fellow 1977-1979.
2. a) H. Iida, S. Aoyagi, and C. Kibaysahi, J. Chem. Soc., Chem. Comm., 1974, 499; b) I. Ninomiya, T. Naito, and T. Kiguchi, J. Chem. Soc., Perkin I, 1973, 2257.
3. For a regioselective reduction of an imide, see J.B.P.A. Wijnberg and W. N. Speckamp, Tetrahedron Letters, 1975, 3963.
4. R. Adams, B. R. Baker, and R. B. Wearn, J. Am. Chem. Soc., 1940, ~~62~~, 2204; H. M. Fales, E. W. Warnhoff and W. C. Wildman, J. Am. Chem. Soc., 1955, ~~77~~, 5885; A. Mondon and K. Krohn, Chem. Ber., 1970, ~~103~~, 2729.
5. H. C. Brown, P. Heim and N. M. Yoon, J. Amer. Chem. Soc., 1970, ~~92~~, 1637.
6. Hydride reduction of enamido-ketone 3a with diisobutylaluminum hydride also afforded C-1 reduction, affording the C-1 secondary alcohol in 60% yield.
7. R. F. Borch, Tetrahedron Lett., 1968, 61; V. G. Granik, B. M. Pyratin, and R. G. Glushkov, Russian Chemical Reviews, 1971, ~~40~~, 747.
8. The salt formed from 12 and 13 (using methyl fluorosulfonate) was shown to be identical by ir, nmr, UV, C, H analysis and mixed melting point.
9. For the participation of the amide group in various reactions see: S. P. McManus, C. U. Pittman, Jr. and P. E. Fanta, J. Org. Chem., 1972, ~~37~~, 2353; G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, J. Am. Chem. Soc., 1966, ~~88~~, 3099; J. W. Huffman, T. Kamiya and C. B. S. Rao, J. Org. Chem., 1967, ~~32~~, 700.
10. Treatment of the N-butyl and N-benzyl enamido-ketones 7 and 8 with $\text{Et}_3\text{O}^+ \text{BF}_4^- / \text{CH}_2\text{Cl}_2$, then $\text{NaBH}_4 / \text{CH}_3\text{OH}$ did not effect C-6 carbonyl reduction (i.e. formation of 10 and 11) but afforded high recovery of starting material.
11. Interestingly, treatment of 1a with $\text{PBr}_3 / \text{CHCl}_3$ did not afford the desired bromide but rather gave salt 4a directly.

Received, 18th November, 1981