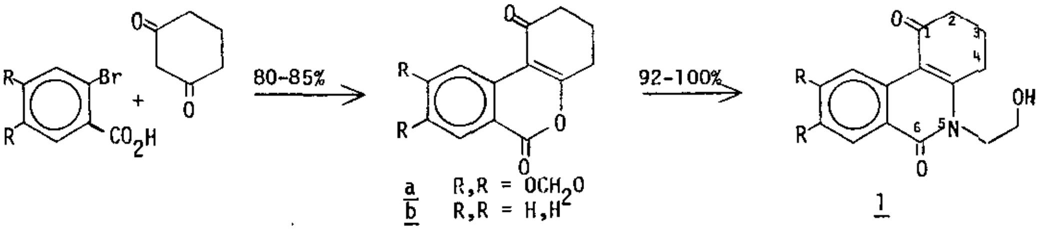
REGIOSELECTIVE REDUCTIONS OF VINYLOGOUS IMIDES

Thomas A. Bryson[1] and Ronald B. Gammill
Department of Chemistry
University of South Carolina
Columbia, SC 29208

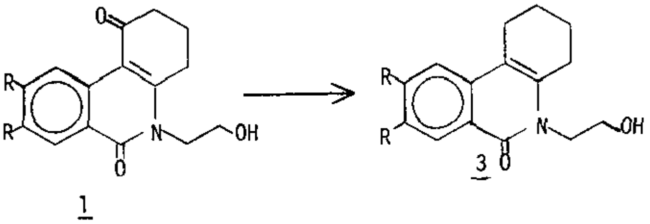
Abstract - The regiospecific reduction of unsymmetrical vinylogous imides was investigated. Controlled selective reduction was realized via employing neighboring group participation to effect reduction of the less reactive carbonyl group.

Enamido-ketones have been key synthetic intermediates in natural product synthesis[2]. 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]

Scheme I



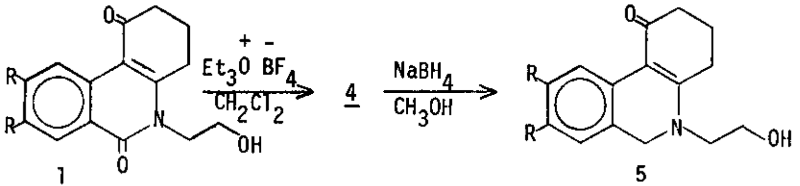
While diborane readily reduces simple amides to amines,[5] we found that treatment of enamido-ketone 1a with 2.6 equiv. of diborane in tetrahydrofuran at reflux resulted in reduction at C-1, thereby affording enamide 3a (λ, 1650 cm^{-1}; δ 2.40-1.51, 8H's ring C-protons) in 73% yield.[6]



a R,R=OCH$_2$O,R'=H
b R,R=H,H,R'=H
c R,R=OCH$_2$O,R'=Ac

The presence of a single OH group (i.e., reduction of the C-1 carbonyl to a methylene group) was readily demonstrated by D_2O exchange and acylation (Ac_2O/ 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 electrophic reducing agents and therefore can be selectively reduced[6] or removed.

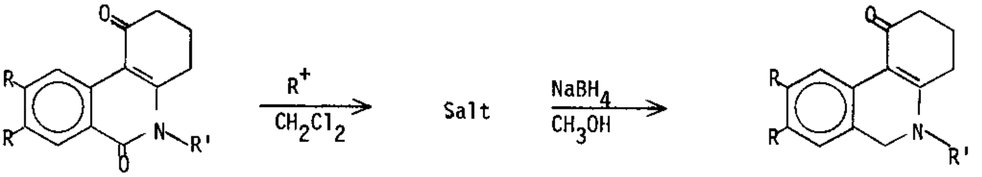
Treatment of 1a with Meerwein reagent ($Et_3O^+BF^-_4$) in CH_2Cl_2 resulted in the precipitation of a salt (4a), which when treated with $NaBH_4$ in CH_3OH, afforded the enamino-ketone 5a (C-6 reduction) in 65% yield.[7] The desmethylenedioxy system also underwent this same reaction to afford 5b (δ, 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 $Et_3O^+BF_4^-$ 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.



1 5

a R,R=OCH_2O
b R,R=H,H

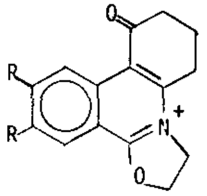
Sodium borohydride reduction of the salt generated from chloride 6 gave, unexpectedly, alcohol 5a (C-6 carbonyl reduction) rather than the envisioned chloride product 9. These results



6 R,R = OCH_2O ; R'= CH_2CH_2Cl
7 R,R = OCH_2O ; R'= $(CH_2)_3CH_3$
8 R,R = OCH_2O ; R'= $CH_2\phi$
12 R,R =H,H;R' = CH_2CH_2OTs
13 R,R =H,H;R = CH_2CH_2Br
14 R,R =H,H;R = CH_2CH_2OMe

5a R,R = OCH_2O, R'= CH_2CH_2OH
9 R,R = OCH_2O , R'= CH_2CH_2Cl
10 R,R = OCH_2O , R'= $(CH_2)_3CH_3$
11 R,R = OCH_2O , R'= $CH_2\phi$

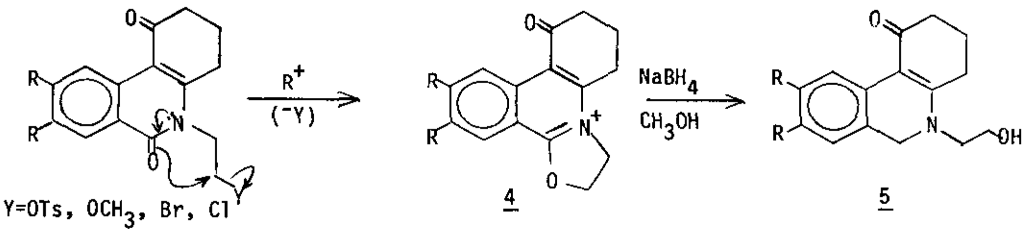
led to further preparations and reductions[10] of vinylogous imide tosylate 12, bromide 13 and methyl ether 14. Like enamido-ketones 1 and 6, compounds 12, 13 and 14 gave a salt upon treatment with $Et_3O^+BF_4^-$(or CH_3OSO_2F) in CH_2Cl_2 and subsequently underwent C-6 reduction with $NaBH_4/CH_3OH$. 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 units[10] suggested that intermediate salt, 4a or 4b, formed via the action of Meerwein salt or methane fluorosulfonate[8] on these imides, had the following structure:



4 a; R,R= OCH_2O
b; R,R= H,H
X= Br^-, BF_4^-, O_3SF^-

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 fo 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 $NaBH_4/CH_3OH$ 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. Aoyogi, 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 $Et_3\overset{+}{O}\ \overset{-}{B}F_4/CH_2Cl_2$, then $NaBH_4/CH_3OH$ 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 $PBr_3/CHCl_3$ did not afford the desired bromide but rather gave salt 4a directly.

Received, 18th November, 1981