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REGIOSELECTIVE REDUCTIONS OF VINYLOGOUS IMIDES

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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](image)

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 (\(\lambda, 1650\) cm\(^{-1}\); \(\delta 2.40-1.51\), 8H's ring C-protons) in 73% yield.\(^6\)

\[ \begin{align*}
\text{R, R} & = \text{OCH}_2\text{O} \\
\text{R, R} & = \text{H, H}\n\end{align*} \]
The presence of a single OH group (i.e., reduction of the C-1 carbonyl to a methylene group) was readily demonstrated by D$_2$O exchange and acylation (Ac$_2$O/ 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 reduced or removed.

Treatment of 1a with Meerwein reagent (Et$_3$OBF$_4$) in CH$_2$Cl$_2$ resulted in the precipitation of a salt (4a), which when treated with NaBH$_4$ in CH$_3$OH, afforded the enamino-ketone 5a (C-6 reduction) in 65% yield. The desmethylenedioxy system also underwent this same reaction to afford 5b 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$_3$OBF$_4$ 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.

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
led to further preparations and reductions of vinylogous imide tosylate \( \text{12} \), bromide \( \text{13} \) and methyl ether \( \text{14} \). Like enamido-ketones \( \text{1} \) and \( \text{6} \), compounds \( \text{12, 13 and 14} \) gave a salt upon treatment with \( \text{Et}_3\text{O}^+\text{BF}_4^- \)(or \( \text{CH}_3\text{OSO}_2\text{F} \)) in \( \text{CH}_2\text{Cl}_2 \) and subsequently underwent C-6 reduction with \( \text{NaBH}_4/\text{CH}_3\text{OH} \).

Thus, enamido-ketones \( \text{1, 6, 12, 13 and 14} \) formed \( \text{5 (a or b)} \) by this two step reduction process, with interchange or loss of the \( \beta \)-ethylamino heteroatom. Observing that all the selective C-6 carbonyl reductions occur only on vinylogous imides (\( \text{1, 6, 12, 13 and 14} \)) which contain a heteroatom (oxygen or halogen) at the \( \beta \)-position on the N-ethyl units suggested that intermediate salt, \( \text{4a or 4b} \), formed via the action of Meerwein salt or methane fluorosulfonate on these imides, had the following structure:

\[
\text{Scheme II}
\]

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

This also accounts for alcohol \( \text{5} \) as being the only reduction product from these various substrates. The same salt, \( \text{4} \) (fluorosulfonate counterion), was prepared from the reaction of vinylogous imides \( \text{1 and 6 (5a or from 12, 13 and 14 (4b))} \) with methyl fluorosulfonate in \( \text{CH}_2\text{Cl}_2 \).

These salts were air stable, non-hygroscopic solids and on treatment with \( \text{NaBH}_4/\text{CH}_3\text{OH} \) afforded the enamino-ketones \( \text{5a,b} \). Bromide \( \text{13} \), upon standing overnight at room temperature in \( \text{CHCl}_3 \), also formed small amounts of \( \text{4b} \). This salt could readily be isolated from the \( \text{CHCl}_3 \) solution by filtration and reduced with \( \text{NaBH}_4 \) to give enamino-ketone \( \text{5b} \).

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Notes and References

6. Hydride reduction of enamido-ketone 3a with diisobutylaluminum hydride also afforded C-1 reduction, affording the C-1 secondary alcohol in 60% yield.
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.
10. Treatment of the N-butyl and N-benzyl enamido-ketones 7 and 8 with Et₃⁺BF₄⁻/CH₂Cl₂, then NaBH₄/CH₃OH 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 PBr₃/CHCl₃ did not afford the desired bromide but rather gave salt 4a directly.

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