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Synthesis of 4-Carboethoxy-4-Oxazolin-2-ones from 3-Nosyloxy-2-ketoesters

Robert V. Hoffman*, M. Catherine Johnson, and John F. Okonya

Department of Chemistry and Biochemistry
New Mexico State University
Las Cruces, NM 88003-0001

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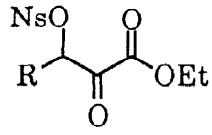
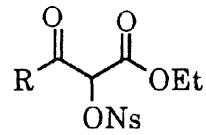
Abstract: 3-Nosyloxy-2-ketoesters, available from 2-ketoesters, react efficiently with methyl carbamate and tosic acid in refluxing toluene to provide 4-carboalkoxy-4-oxazolin-2-ones in good yields (41-84%).

We recently described the preparation of 3-nosyloxy-2-ketoesters **1** from α-ketoesters and some aspects of their use as precursors for the synthesis of 1,2,3-functionalized products.[1] In contrast to the isomeric 2-nosyloxy-3-ketoesters **2** which are extraordinarily versatile intermediates,[2] the synthetic utility of **1** is compromised by the extreme electrophilicity of the ketone carbonyl group which dominates the chemistry of **1**. For example, the carbonyl group of **1** hydrates readily to the *gem*-diol and thwarts subsequent nucleophilic manipulation of the carbonyl group, and **1** is also quite sensitive to base-promoted decomposition.[1]



1



2

Acid catalyzed additions of weakly basic nucleophiles to **1** offer a potential solution to this reactivity problem since acidic conditions would catalyze dehydration of the *gem*-diol back to the ketone, and would minimize any base-induced transformations of **1**. At the same time the carbonyl group of **1** should be sufficiently electrophilic to react with even weak nucleophiles which would be present under acidic conditions. We are pleased to report that the reaction of **1** with methyl carbamate under acidic conditions provides an efficient access to 4-carboethoxy-4-oxazolin-2-ones **3**, a little known type of oxazolinone.

Treatment of a series of 3-nosyloxy-2-ketoesters **1a-g** with methyl carbamate and TSA (10%) in refluxing toluene for 15 h gave oxazolinones **3a-g**[3] in generally good yields (eq 1). Product **3b** was also obtained by treating **1b** with either *tert*-butyl or benzyl carbamate and TSA in

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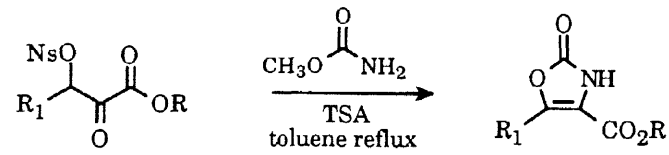


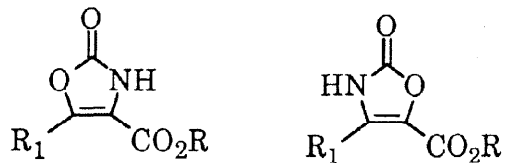
(1)

1a, R_1=H, R=Me
1b, R_1=$CH_2C_6H_5$, R=Et
1c, R_1=n-C_5H_{11}, R=Et
1d, R_1=*i*-Bu, R=Et
1e, R_1=*i*-Pr, R=Et
1f, R_1=CH_3, R=Et
1g, R_1=C_6H_5, R= Et

3a, 51%
3b, 80%
3c, 84%
3d, 70%
3e, 41%
3f, 56%
3g, 46%

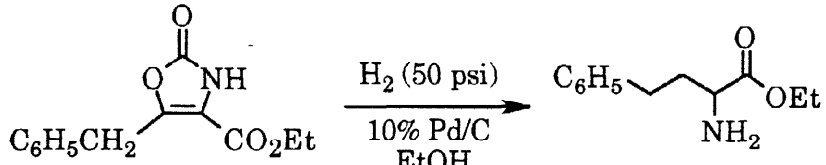
refluxing toluene but the yield was lower (60%) and the product was more difficult to purify.

Two possible regioisomers, **3** or **4**, could be formed from the reaction of **1** with methyl carbamate, depending on whether the carbonyl group or the nosylate carbon is the initial site of nucleophilic attack and whether the nitrogen or oxygen of methyl carbamate acts as the nucleophile. Since carboalkoxy substituted oxazolinones are not well known[4] and the characterizations reported in the literature[4b,c] are incomplete, it was deemed important to establish the correct structure assignment of **3**.



3 **4**

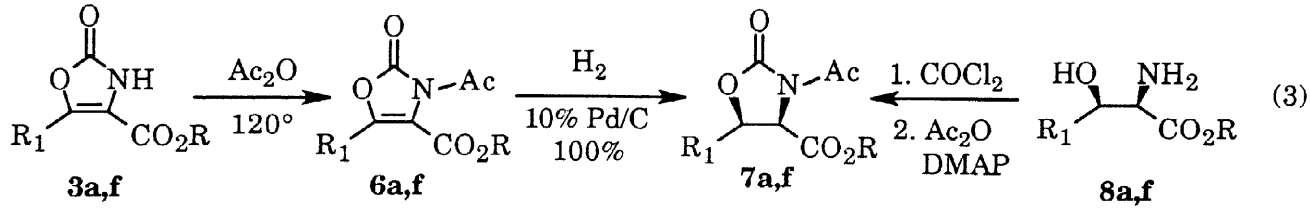
Attempts to reduce **3b** to the corresponding oxazolidinone gave ethyl homophenylalinate **5** (>90% nmr yield, 60% isolated) instead (eq 2). This result establishes the nitrogen connectivity at C-2 and, by inference, oxygen connectivity at C-3.



(2)

3b **5**

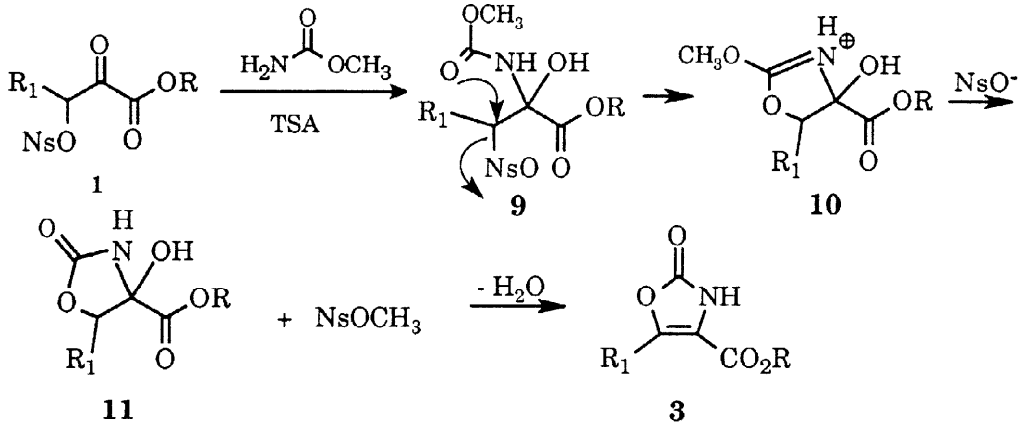
The hydrogenation of **3b** was unexpectedly sluggish, requiring 48h for completion. This was attributed to aromatic character in the oxazolinone ring.[5] Acylation of nitrogen would reduce the aromaticity and facilitate double bond reduction. Heating **3a, f** with neat acetic anhydride gave N-acetylated derivatives **6a,f** [3] in quantitative yield. Consistent with expectations, these underwent smooth catalytic hydrogenation (1 h, 100%) to oxazolidinones **7a,f** [3](eq 3). The structures of **7a,f** as well as the *cis*-stereochemistry of **7f** were proven by synthesis from serine **8a** and *allo*-threonine **8f**, respectively. With the structures of **3a,f** secure, it is reasonable to assume that the other oxazolinones **3b-e,g** also have the C-2 nitrogen , C-3 oxygen regiochemistry.



(3)

A reasonable scenario for the formation of **3** from **1** involves acid-catalyzed addition of the nitrogen of methyl carbamate to the carbonyl group of **1** to produce a tetrahedral intermediate **9**. Intramolecular displacement of nosylate produces **10** (Scheme 1). Demethylation of **10** followed by

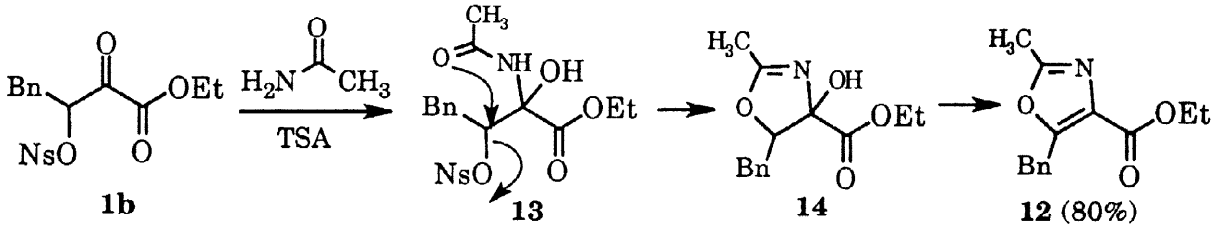
Scheme 1



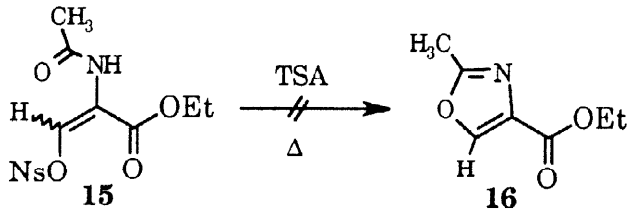
dehydration yields **3**. The involvement of the nosylate group in the demethylation of **10** is suggested by the isolation of methyl p-nitrobenzenesulfonate from the reaction mixture in yields identical to those of the oxazolinone **3**.

Based on the mechanistic synopsis shown in Scheme 1, it appeared that the reaction of primary amides with ketonosylates **1** might follow an analogous course. In the event, refluxing **1b** with acetamide and tosic acid in toluene for 4 h led to the formation of oxazole **12**[3] in 80% yield by a pathway presumed to be similar to that of the methyl carbamate reaction (Scheme 2). Careful examination of a reaction which was stopped prior to completion revealed the presence of small amounts of intermediate **14**.[3] This finding is mechanistically significant since it suggests that displacement of the nosylate group occurs in the tetrahedral intermediate **13** prior to dehydration.

Scheme 2



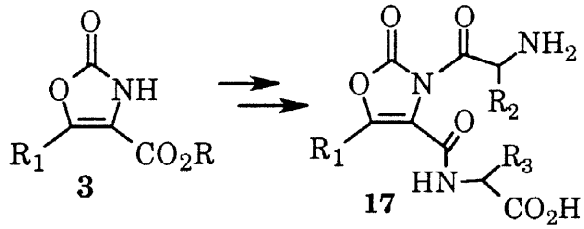
This conclusion is bolstered by the observation that nosyloxy enamide **15**, prepared by a different route,[6] fails to undergo cyclization to an oxazole **16** upon heating with TSA (eq 4). The importance of the nosylate group in orchestrating this chemistry is clear. Attempts to achieve the same transformations using 3-bromo-2-ketoesters and methyl carbamate return mostly starting



(4)

material - even after prolonged reaction times. Thus the electron withdrawing properties of the nosylate group increase the electrophilicity of the ketone group to facilitate attack by the carbamate[7] and its excellent leaving ability insures rapid cyclization of the tetrahedral intermediate **9** (Scheme 1). Consequently **3** can be prepared easily in good yields.

These results demonstrate that 3-nosyloxy-2-ketoesters **1** are useful new precursors for the preparation of 4-carboalkoxy-4-oxazolin-2-ones **3**. These compounds have received little attention in the literature[4] but could be very useful intermediates for the synthesis of β-turn mimics **17** by acylation of nitrogen followed by saponification and coupling of the carboxyl group. Moreover hydrogenation of the double bond of **3** would provide a simple stereoselective synthesis of 3-hydroxy-2-amino acid derivatives which are also of current interest(eq 3).[8]



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