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Synthesis and Characterization of β-*O*-Tosyldehydroserine as a Precursor of Dehydroamino Acids

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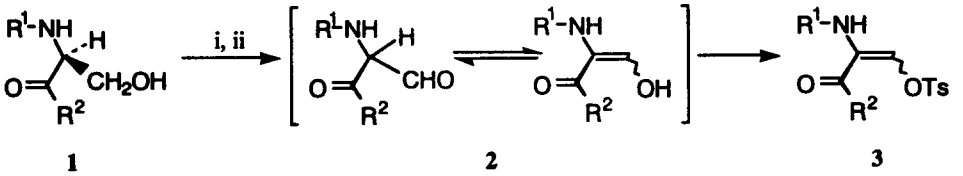
Abstract: *β-O*-Tosyldehydroserine **3** is prepared directly by the oxidation of the corresponding serine derivative **1** with dimethyl sulfoxide which is activated by *p*-toluenesulfonyl chloride. The enol tosylate **3** retains reactivities characteristic of aldehydes like those expected for the corresponding dehydroserine derivative **2**. A typical reaction of **3** includes substitution of the tosyl group with nucleophiles such as primary and secondary amines, leading to other dehydroamino acids. © 1997 Elsevier Science Ltd.

Dehydro analogues of naturally occuring amino acids have been found as components of a variety of bioactive peptides. A planar and extended configuration around the α,β-unsaturated residue induces the peptide to assume an unusual backbone structure which is often crucial for the biological activity. To elucidate the structure-function relationships of such substances, a large variety of the relevant dehydroamino acids need to be provided by chemical syntheses. The known approaches to synthesize α,β-dehydroamino acids and their peptide derivatives include the Hofmann elimination[1a] and dehydration of serine[2] or threonine.[1a-c] Although each of these procedures has had substantial success in incorporating a particular dehydroamino acid residue into a peptide chain, there remains to be established a versatile method that generates a functional group convertible to a variety of unsaturated amino acids with unique side-chain structures and functions.

Intending to exploit the aldehyde group that can potentially be derived from the primary alcohol of a serine residue, we undertook efforts to devise a new method for introduction of a dehydroamino acid into a peptide by the condensation between the carbonyl group and a nucleophile to form a carbon-carbon double bond. The requisite α-formylglycine derivative (**2**) was synthesized by aldol condensation of glycine and formate ester nearly a century ago.[3] However, all attempts to obtain **2** from the serine derivative (**1**) were unsuccessful by conventional procedures for oxidation employing dimethylsulfoxide (DMSO) in combination with a series of activators.[4-6] Because the effective and mild nature of activated DMSO seemed especially advantageous for the oxidation of such sensitive substrates as serine-containing peptides, we searched for an alternative activator among electrophiles involving acyl halides and acid anhydrides, and the best results were obtained when using *p*-toluenesulfonyl chloride (TsCl). This reagent not only activates DMSO effectively to oxidize **1**, but also serves to convert the extremely labile product **2** into the more stable enol tosylate (**3**), reducing the possibility of side reactions. In this report, we describe the remarkable features of the oxidation using DMSO activated by TsCl,

with which the primary alcohol in the side chain of the serine derivative **1** is directly converted to an enol tosylate to yield the corresponding β-*O*-tosyldehydroserine **3** (Scheme 1).



1 **2** **3**

i: *p*-toluenesulfonyl chloride (3 equiv.), DMSO/DMF (1:2), −5°C; ii: Et3N.
1a-3a: R^1 = Bz (benzoyl), R^2 = NHMe; **1b-3b**: R^1 = Z (benzyloxycarbonyl), R^2 = NH_2.

Scheme 1

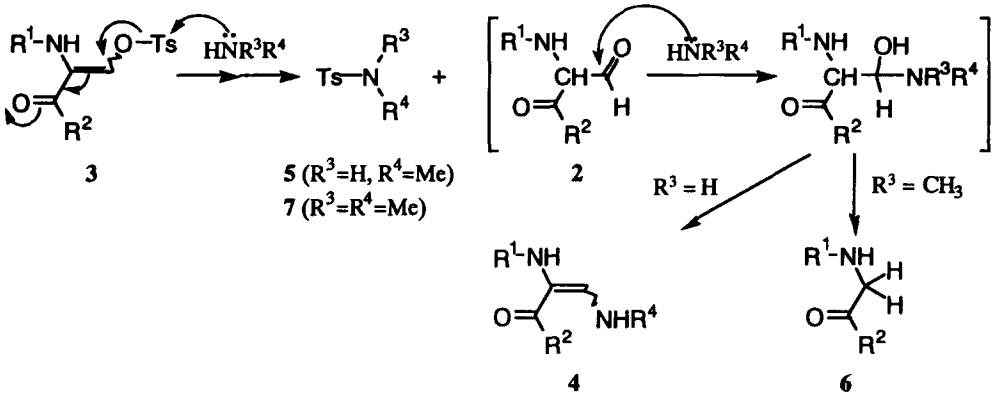
In this scheme we assume that **2** is in equilibrium with its enol tautomer which is subsequently tosylated to give **3**. For this reaction, benzoyl chloride may be employed as an activator in place of TsCl, but the resulting enol benzoate is usually less stable than the tosyl analogue and is obtained in a slightly lower yield. Neither benzoic anhydride nor methanesulfonyl chloride enabled DMSO to oxidize **1** under the present conditions.

The activation of DMSO with TsCl could be accomplished according to the standard reaction conditions of the Moffatt procedure[4,5] with some minor modifications. Generally, an amino- and carboxyl-protected derivative of serine (**1**; 1 mmol) was dissolved in DMF (5 ml), added to a freshly prepared solution of TsCl (3 mmol) in a mixture (1:1, v/v, 5 ml) of DMSO and DMF, and allowed to react for 5 minutes at −5°C. To the stirred reaction mixture was added 1.5 ml of triethylamine (or *N*-methylmorpholine), and the resulting solution was allowed to warm to room temperature for one hour. The mixture was then diluted with a sufficient amount of water so that the product could be extracted by an appropriate organic solvent from the aqueous layer. In the case starting with Bz-Ser-NHMe (**1a**), the organic layer was washed with water, dried over anhydrous Na_2SO_4, and solvent evaporated under reduced pressure. After silica-gel chromatography (toluene:AcOEt; 1:3) of the residue followed by recrystallization (twice from AcOEt-petroleum ether) of each incompletely resolved fraction, *E*- and *Z*-isomers of **3a** were isolated pure in 35% and 13% yields, respectively.[7] The ratio of the *E*- to *Z*-isomer was estimated to be 2:1 (total yield of 90%) from the intensities of the respective signals in the ^1H NMR spectrum of the products extracted in the organic phase, where neither recovery of **1a** nor formation of Bz-ΔSer-NHMe (**2a**) was detected; a side reaction to form the methylthiomethyl ether of **1a** occurred only marginally (< 8%) as judged from the TLC and ^1H NMR analyses.

As an activator of sulfoxides, TsCl has never been the best choice due to relatively lower efficiency compared to trifluoroacetic anhydride or oxalyl chloride.[5,6] The crucial advantage of TsCl in the present case is that it protects **2** *in situ* from undesirable side reactions or spontaneous degradation, making up for its deficiency in the activation of DMSO. In fact, **2a** is considered to be extremely labile to electrophiles so that its enolic functional group is readily acylated as it is formed. Furthermore, the keto form of **2** should act as an aldehyde to which nucleophiles are accessible; a typical example will be presented in the next paragraph which deals with the relevant reactions of **3**.[8] Unlike the cases with serine, the secondary alcohol of a threonine derivative was oxidized by the present method to give the corresponding ketone in a yield comparable to that achieved by

dicyclohexylcarbodiimide and DMSO.[9] No enol tosylate analogous to **3** was detected by ^{1}H NMR measurement of the reaction products. These findings suggest that the tendency to yield enol tosylate **3** is not an intrinsic feature of the present procedure but is related to the unusual nucleophilic character of **2**.

Although the esters of **3** (R^1 = Bz, R^2 = OMe, OEt) were obtained in a similar manner as above (40-60% yields), we preferred to use the amides (**3a** and **3b**) for further reactions with nucleophiles that could also be reactive to esters. When **3** was subjected to reactions with hydrazine, primary amines, and a few secondary amines, the tosyl group was readily replaced by the nucleophile. For example, reaction of **3** with methylamine yielded an enamine (**4**),[8a] thereby forming an essentially equimolar amount of *N*-methyltosylamide (**5**). Exceptionally, treatment of **3** with dimethylamine led to almost quantitative formation of the corresponding glycine derivative (**6**) and *N*,*N*-dimethyltosylamide (**7**).[8b] These findings suggest that a nucleophile attacks the sulfonyl group of **3** to afford **5** or **7** together with a dehydroserine derivative **2** and again the nucleophile attacks the carbonyl carbon of **2** to form a tetrahedral intermediate, which then undergoes either the dehydration leading to **4** or the retroaldol reaction to **6** (Scheme 2).



Scheme 2

Note that the reaction with diethylamine proceeded in favor of the enamine corresponding to **4**. In this connection, also note that an attempt to replace the tosyl group of **3a** with a hydroxyl group using 0.1M NaOH resulted only in a complex mixture of fragments including a glycine derivative. These results consistently demonstrate how effectively the tosyl group serves to stabilize **3** while restoring the potential reactivity of **2** towards nucleophiles. Enamine **4** is also convertible to other amino acids by further reactions. For example, **4**, as well as **3**, reacted with indole to give a dehydrotryptophan derivative as expected from the putative carbanionic character of indole (manuscript in preparation).[10]

In conclusion, the oxidation using DMSO activated with TsCl successfully converted the hydroxyl group of **1** to a potential carbonyl function in the form of an enol tosylate. The product **3** proved to be devoid of the inherent instability of **2** and adequately retaining the requisite reactivities for use as a precursor of other dehydroamino acids. The efficiency of the present method should now allow development of mild and effective methods for new side-chain building blocks to be incorporated in place of the enol tosylate function.

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7. **3a**: ***E* isomer**: mp. 118-119°C; Anal. Calc. for $C_{18}H_{18}N_2O_5S$: C, 57.74; H, 4.85; N, 7.48. Found: C, 57.87; H, 4.79; N, 7.35; IR (KBr) 3453, 1666, 1647, 1525, 1490, 1373 cm^{-1}; ^1H NMR (270MHz, DMSO-*d*6) δ 2.43 (3H, s,CH_3-Ph), 2.60 (3H, d, *J* =4Hz, CH_3-N), 7.40 (1H, s, β-CH), 7.50-7.88 (9H, m, aromatic H), 8.06 (1H, q, *J* =4Hz, NH-C^α), 9.80 (1H, s, $N^\alpha H$). ***Z* isomer**: mp. 90-92°C; IR (KBr) 3269, 1673, 1627, 1578, 1523, 1391 cm^{-1}; ^1H NMR (270MHz, DMSO-*d*6) δ 2.39 (3H, s, CH_3-Ph), 2.62 (3H, d, *J*=4Hz, CH_3-N), 7.27 (1H, s, β-CH), 7.50-7.88 (9H, m, aromatic H), 8.08 (1H, q, *J* =4Hz, NH-C^α), 9.63 (1H, s, $N^\alpha H$). The configuration of each isomer was unambiguously determined by ^1H-^1H NOESY experiments at 270 MHz with a mixing time of 450 ms. The crucial NOE correlations observed were between N^α amide and C^β protons (*E* isomer) and between C^α-methylamide and C^β protons (*Z* isomer).
8. (a) N^α-benzyloxycarbonyl-*O*-tosyldehydroserine amide (Z-Δ(Ts)Ser-NH_2; **3b**) (1.65g: 1 mmol) was dissolved in methanol (3 ml) containing 30% (w/v; large excess) of methylamine, diluted with additional methanol (4 ml), and allowed to react at room temperature. Within a few hours, colorless crystals separated out, yielding 0.90 g (85%) of the product **4** (N^α-benzyloxycarbonyl-β-(*N*-methylamino)-dehydroalanine amide): mp. 185°C. Anal. Calc. for $C_{12}H_{15}N_3O_3$: C, 57.62; H, 6.04; N, 16.79. Found: C, 57.66; H, 6.04; N, 16.78; IR (KBr) 3443, 3330, 1719, 1666, 1548, 1251 cm^{-1}; ^1H NMR (270MHz, DMSO-d6) δ 2.78 (3H, d, *J* =4.9Hz, CH_3-N), 5.01 (2H, s, benzyl-CH_2), 5.73 (1H, m, C^β-NH), 6.14 (2H, s, C^αO-NH2), 7.06 (1H, d, *J* =13.2Hz, β-CH), 7.3-7.5 (5H, m, aromatic H), 7.56 (1H, s, $N^\alpha H$). (b) N^α-Benzyloxycarbonylglycine amide **6** (mp. 135°C) was obtained almost quantitatively under essentially the same conditions as (a) except that dimethylamine was used in place of methylamine. All the products **5** through **7** were isolated and identified by comparison with authentic samples with respect to melting points, ^1H NMR and IR spectra, as well as TLC.
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