4-Alkyl-2-trichloromethyloxazolidin-5-ones: Valuable Precursors to Enantiomerically Pure *C*- and *N*-Protected α-Alkyl Prolines

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Abstract: An efficient, economical and enantioselective method for preparation of various mono-and diprotected α-substituted proline derivatives is described. The lithium enolate of known 2-trichloromethyloxazolidin-5-one **3b** reacted with electrophiles to furnish the 4-alkyloxazolidinones **4a-d** with high diastereoselectivity and in good yields. The oxazolidinones **4** represented versatile synthons that could be converted in a single step into useful proline peptidomimetics. For example oxazolidinones **4a-d** reacted with sodium methoxide by a novel mechanism that involved elimination of trichloromethyl anion from an intermediate tetrahedral adduct to afford *N*-formyl α-substituted proline methyl esters **5a-d**. Alternatively acidic methanolysis of oxazolidinone **4a** afforded the amino acid methyl ester hydrochloride **6**. Hydrolysis of the *N,O*-acetal function of **4a** could be effected under acidic conditions (6 N HCl, RT) to afford the free amino acid **1a** after ion exchange chromatography. Our procedure represents a convenient and general route to a valuable class of peptidomimetics and should be welcomed by chemists preparing conformationally restricted peptides and other compounds.

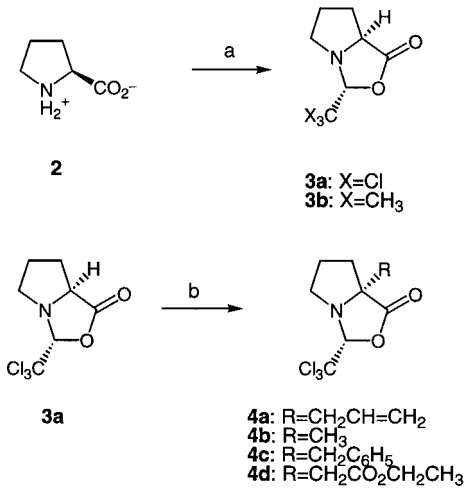
Keywords: prolines, oxazolidinones, peptidomimetics, peptides

Proline, by virtue of its cyclic structure, occupies a special place among the twenty-one naturally occurring amino acids.[1] For instance peptide linkages incorporating proline populate both *s*-cis and *s*-trans configurations, in contrast to linkages involving the other amino acids, which exist almost exclusively in the *s*-trans configuration.[2] Further, restricted rotation about the N-Cα bond of proline constrains the peptide backbone of the proline residue to the ϕ=-60° region of conformational space.

The unique structural characteristics of proline-containing peptides influence their biological properties. In many cases only one of the two configurational isomers of the peptide displays biological activity.[3] To identify the biologically active conformer of proline-containing peptides, chemists have often turned to the synthesis and evaluation of peptides which incorporate proline peptidomimetics.[4] The structures of these mimetics restrict the peptide linkage to exclusively *s*-cis[5] or *s*-trans[6] configurations.

α-Substituted proline derivatives are very popular precursors for both *s*-cis and *s*-trans classes of peptidomimetics.[5c,d,g,h,6b,c,e,g] α-Alkyl prolines have also found utility as starting materials for natural product syntheses,[7] as well as probes of polymer structure.[8] Certain α-alkyl prolines also display potent biological activity as inducers of collagen synthesis.[9] A number of methods for enantioselective preparation of α-substituted prolines have been reported.[10] Although several of these methods are quite elegant, they possess drawbacks in terms of efficiency, expense, or limited structural variety.

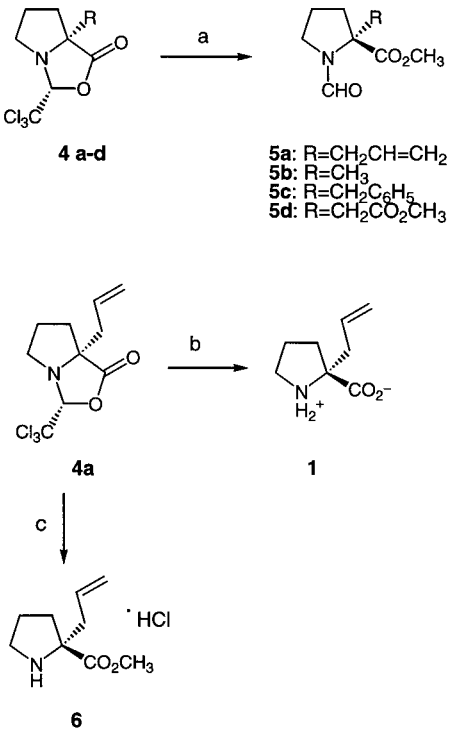
We now report a novel route to *N*-formyl α-substituted proline methyl esters **5**, which represent a *C*, *N*-diprotected version of α-alkyl prolines (Scheme 2). These compounds are obtained in a single step from 4-alkyl-2-trichloromethyloxazolidinones **4**, which are in turn readily available from the known oxazolidinone **3a** (Scheme 1). In addition the versatile oxazolidinones **4** can be converted to either the analogous free amino acids **1** or methyl ester hydrochlorides **6** under mild conditions. Together these reactions provide efficient access to various forms of enantiomerically pure α-substituted prolines, and should make these important peptidomimetics available economically for the first time.



(a) **3a**: Cl_3CCHO (2 equiv), dry acetonitrile, RT, 12 h; **3b**: cat CF_3CO_2H, $(CH_3)_3CHO$ (7 equiv), pentane, reflux, 7 d (b) LDA, RX, -78 °C

Scheme 1

The starting material for the syntheses was the 2-trichloromethyloxazolidinone **3a**,[12] which was obtained through condensation of *L*-proline with chloral (trichloroacetaldehyde) (Scheme 1). This crystalline, air-stable compound was produced in high yield as a single diastereomer, whose stereochemistry was established by X-ray crystallography.[12]



(a) $NaOCH_3$, dry CH_3OH, RT, 30 min (b) 6 N HCl, RT, 18 h, or reflux, 1 h; (c) cat HCl, dry CH_3OH, reflux, 1 h

Scheme 2

Alkylation of the enolate of oxazolidinone **3a** proved to be highly diastereoselective. Removal of the α proton was effected by lithium diisopropylamide (LDA) in THF at -78 °C, resulting in a darkly colored solution of the enolate. Addition of allyl bromide to the enolate gave a single alkylation product according to the crude NMR spectrum. We used difference NOE experiments to establish the stereochemical outcome of the alkylation. Irradiation of the acetal hydrogen of the product resulted in enhancement of the intensity of the pyrrolidine beta hydrogens. This finding was consistent with the angular allyl group being located *cis* to the trichloromethyl group, as in **4a**.

The generality of the alkylation reaction to prepare other substituted bicyclic oxazolidinones was investigated by using various electrophiles (Table 1). The stereoselectivity was high in each case (>95:5), with a single isomer or only a trace of a minor isomer of the product detected in the crude NMR spectrum. The stereochemistry of each alkylation product was ascertained by difference NOE experiments as for allyl derivative **4a**. The major isomer in each case had the electrophilic group located *cis* to the trichloromethyl group, as in **4b-d**. A welcome property of all of the alkylation products **4** was their crystalline nature, which simplified their purification (Table 1).[15]

The stereochemical course of the alkylation of the 2-trichloromethyloxazolidinone **3a** proceeded in an identical manner as the alkylation of the enolate of the 2-*t*-butyloxazolidinone **3b**, whose chemistry was pioneered by Seebach and co-workers.[10a] While the outcomes of the

Table 1. Yields and properties of alkylated oxazolidinones **4**

R	Isolated Yield (%)	Characteristics
$CH_2CH{=}CH_2$ (**4a**)	69	mp 20-24 °C; $[\alpha]^{25}_D$= +44.6° (c 2.0, $CHCl_3$)
CH_3 (**4b**)	58	mp 57-60 °C; $[\alpha]^{25}_D$= +6.5° (c 1.0, $CHCl_3$)
$CH_2C_6H_5$ (**4c**)	51	mp 72-77 °C; $[\alpha]^{25}_D$= +43.4° (c 1.0, $CHCl_3$)
$CH_2CO_2CH_2CH_3$ (**4d**)	30	mp 57-60 °C; $[\alpha]^{25}_D$= +42.5° (c 1.0, $CHCl_3$)

alkylation of both oxazolidinones **3a** and **3b** were essentially identical, other aspects of the chemistry of the two oxazolidinones differed. In particular the use of the 2-trichloromethyloxazolidinone **3a** may be preferable to use of the *t*-butyloxazolidinone **3b** for preparation of α-alkyl prolines due to its greater stability and its significantly lower cost of production. A summary of these features is given in Table 2.

Table 2. Comparison of experimental features involved in preparation of 2-trichloromethyloxazolidinone **3a** and 2-*t*-butyloxazolidinone **3b**

Characteristic	**3a** (this work)	**3b**[10a,e]
Stereoselectivity of oxazolidinone **3** formation	>95:5	>95:5
State of oxazolidinone **3**	white prisms (mp 105-108 °C)	waxy solid (mp 20-25 °C)
Stability of oxazolidinone **3**	stable to water (pH 4-8)	highly sensitive to hydrolysis, unstable in air ($t_{1/2}$ ~ 15 min)
Equivalents of aldehyde required for formation of **3**	2	7
Aldehyde expense (Sigma 1997) ($US/g)	0.07	4.27
Reaction time (days)	0.5	5-7
Yield (based on proline) (%)	57	67-74
Yield (based on aldehyde) (%)	28.5	9.6-10.6

A novel reaction of oxazolidinones **4a-d** ensued when these compounds were treated with sodium methoxide in methanol (Scheme 2). Under these conditions oxazolidinones **4a-d** were converted cleanly to the *N*-formyl-2-alkylproline methyl esters **5a-d**.[15] These products apparently arose through a sequence of eliminations, first of alkoxide, then of trichloromethyl anion, from the tetrahedral adduct formed by addition of methoxide to the carbonyl carbon of the oxazolidinone. The products **5**, which represent *N*- and *C*-protected analogs of alkylated

prolines **1**, are valuable compounds for further synthetic elaboration or biological evaluation. For example the *N*-formyl function of prolines **5** is a protecting group that can be cleaved under more mild acidic conditions than other amides.[13] In addition the products **5** may have chemotactic activity, since *N*-formyl peptides are potent chemotactic agents.[14]

Alternatively oxazolidinones **4** could be directly converted to free amino acids through hydrolysis. For instance *(R)*-2-(2-propenyl)proline (**1a**) was obtained in high yield after stirring **4a** in 6 N HCl at room temperature.[15] The optical rotation of this material was essentially identical to that for the same product obtained by Seebach's procedure.[6c] Since α-alkyl prolines[6c,g, 7, 9] particularly proline analog **1a**[5c,d,g,h,6b,c,e] are popular precursors for peptidomimetics, our procedure should find utility in preparation of compounds of medicinal interest.

The methyl ester hydrochloride **6** could be directly obtained from oxazolidinone **4a** in good yield by refluxing the oxazolidinone in acidic anhydrous methanol for one hour.[15] Importantly the latter reaction gives no characterizable products in the case of the corresponding 4-propenyl-2-*t*-butyloxazolidinone analog.[10]

In conclusion 4-alkyl-2-trichloromethyloxazolidinones **4** are readily available compounds that offer access to various α-substituted proline derivatives in enantiomerically pure form. We are currently exploring the chemistry of chloral with other amino acids and will report these results in due course.

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(15) **General Procedure for Reaction of the Enolate of 3b with Electrophiles.** An ice cold solution of LDA (1.5 equiv) in THF was added dropwise to a solution of oxazolidinone **2** (1.0 equiv) in THF at -78 °C. After 30 min, the electrophile was added, and the temperature was allowed to warm to -30 °C over a period of 2 h. The resulting mixture was partitioned between chloroform and water. The aqueous layer was extracted with another volume of chloroform. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford a crude product that was purified by crystallization.
(2*R*, 4*R*)-4-(2-Propenyl)-2-trichloromethyloxazolidin-5-one (4a) Allyl bromide (51.1 g, 422.1 mmol) and 34.4 g (140.7 mmol) of **3a** gave product **4a** (23.6 g, 69%) as a solid: mp 20-24 °C; $[\alpha]^{25}_D$= +44.6° (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 5.83 (m, 1H), 5.19 (s, 1H), 5.17 (d, *J* = 5.5 Hz, 1H), 4.96 (s, 1H), 3.16 (m, 2H), 2.54 (d, *J* = 9.6 Hz, 2H), 2.00-1.50 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 175.9, 131.9, 119.8, 102.0, 100.5, 71.1, 58.1, 41.5, 35.1, 25.1. Anal. Calcd for $C_{10}H_{12}NO_2Cl_3$: C, 42.18; H, 4.22; N, 4.92. Found: C, 42.55; H, 4.28; N, 4.72.
(2*R*, 4*R*)-4-Methyl-2-trichloromethyloxazolidin-5-one (4b) Methyl iodide (11.5 g, 81.0 mmol) and 6.6 g (27.0 mmol) of **3a** gave product **4b** (4.0 g, 58%) as yellow needles: mp 57-60 °C; $[\alpha]^{25}_D$= +6.5° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.98 (s, 1H), 3.40 (m, 1H), 3.20 (m, 1H), 2.22 (m, 1H), 1.95 (m, 1H), 1.89-1.70 (m, 2H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 176.9, 147.0, 102.5, 100.7, 58.1, 39.0, 25.7, 25.2. Anal. Calcd for $C_8H_{10}NO_2Cl_3$: C, 37.14; H, 3.87; N, 5.42. Found: C, 37.27; H, 3.86; N, 5.19.
(2*R*, 4*R*)-4-Benzyl-2-trichloromethyloxazolidin-5-one (4c) Benzyl bromide (4.2 g, 24.5 mmol) and 2.0 g (8.18 mmol) of **3a** gave product **4c** (1.4 g, 51%) as yellow crystals: mp 72-77

°C; $[\alpha]^{25}_D$= +43.4° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.35-7.11 (m, 5H), 5.03 (s, 1H), 3.33-3.28 (d, 1H, *J* = 11.8 Hz), 2.99 (m, 1H, *J* = 5.9 Hz), 2.95-2.91 (d, 1H, *J* = 11.8 Hz), 2.62 (m, 1H), 2.20-1.92 (m, 2H), 1.57-1.24 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 175.9, 134.9, 130.3, 127.6, 126.5, 101.9, 100.2, 71.7, 57.7, 55.1, 45.8, 41.1, 34.1, 24.2. Anal. Calcd for $C_{14}H_{14}NO_2Cl_3$: C, 50.22; H, 4.19; N, 4.19. Found: C, 50.57; H, 4.49; N, 3.84.

(2*R*, 4*R*)-4-Carboethoxymethyl-2-trichloromethyloxazolidin-5-one (4d). Ethyl iodoacetate (3.5 g, 16.4 mmol) and 2.0 g (8.2 mmol) of **3a** gave product **4d** (0.8 g, 30%) as white crystals: mp 57-60 °C; $[\alpha]^{25}_D$= +42.5° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.99 (s, 1H), 4.17 (m, 2H), 3.43 (m, 1H), 3.22 (m, 1H), 2.88 (m, 2H), 2.60 (m, 1H), 2.28 (m, 1H), 1.98 (m, 1H), 1.67 (m, 1H), 1.29 (t, 3H, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$): δ 175.9, 170.0, 103.3, 100.8, 70.7, 61.4, 59.2, 41.9, 36.7, 25.8, 14.8. Anal. Calcd for $C_{11}H_{14}NO_4Cl_3$: C, 39.94; H, 4.24; N, 4.24. Found: C, 40.30; H, 4.46; N, 3.89.

General Procedure for Basic Methanolysis of 2-Trichloromethyloxazolidinones. To a solution of oxazolidinone (7 mL) in dry methanol (100 mL) was added sodium metal (50 mg). The mixture was stirred for 30 min. at room temperature under a nitrogen atmosphere, then poured into saturated NH_4Cl, and concentrated under reduced pressure. After neutralization with saturated sodium bicarbonate, the mixture was extracted with diethyl ether three times. The organic layer was then dried with $MgSO_4$ and concentrated to afford the product. Chromatography on silica gel eluting with chloroform : methanol (9 : 1) afforded the methyl esters.

(*R*)-*N*-(Formyl)-2-(2-propenyl)proline methyl ester (5a). Yellow oil (69 %). $[\alpha]^{25}_D$= +14.5° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) two rotamers (2:1): δ 1.60, 1.87, 2.08, 2.76 (m, 4H), 3.03 (dd, *J* = 6.6 Hz, *J* = 7.5 Hz, 2H), 3.44, 3.50 (m, 2H), 3.73, 3.76 (2 x s, 3H), 5.12-5.22 (m, 2H), 5.56-5.70 (m, 1H), 8.26, 8.33 (2 x s, 1H). ^{13}C NMR ($CDCl_3$) two rotamers (2:1) δ 21.7, 23.4, 35.5, 35.8, 41.3, 43.2, 45.4, 48.0, 52.4, 53.0, 66.0, 67.8, 119.4, 120.3, 132.1, 133.3, 160.5, 161.8, 173.4, 173.6; HRMS *m/z* calcd for $C_{10}H_{15}NO_3$ 197.2334, found 197.2331.

(*R*)-*N*-(Formyl)-2-benzylproline methyl ester (5c). Yellow oil (53 %): $[\alpha]^{25}_D$= +16.3° (c 1.0, $CHCl_3$);^{1}H NMR ($CDCl_3$) two rotamers (1:1): δ 8.31, 8.13 (2 x s, 1H), 7.53-7.10 (m, 5H), 3.79, 3.77 (2 x s, 3H), 3.86, 3.61, 3.38, 2.92 (2 x m, 2H), 3.23 (dd, *J* = 13.7 Hz, *J* = 18.1 Hz, 1H), 3.08 (dd, *J* = 17.1 Hz, *J* = 13.9 Hz, 1H), 2.29, 2.10, 1.72, 1.61, 1.25 (m, 4 H); ^{13}C NMR ($CDCl_3$) two rotamers (1:1): δ 162.9, 161.5, 137.0, 135.5, 131.6, 131.0, 129.3, 128.8, 128.2, 128.1, 127.4, 127.1, 69.9, 53.6, 53.5, 53.3, 53.1, 53.0, 48.7, 46.2, 44.3, 38.1, 37.2, 35.8, 30.3, 23.6, 22.9, 1.65; HRMS *m/z* calcd for $C_{14}H_{17}NO_3$ 247.2932, found 247.2915.

(*R*)-*N*-(Formyl)-2-methylproline methyl ester (5b). Clear oil (81 %): $[\alpha]^{25}_D$= +22.5° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) two rotamers (2:1): δ 8.28, 8.20 (2 x s, 1H), 3.75, 3.73 (2 x s, 3H), 3.60 (m, 2H), 2.46, 2.21, 1.87 (m, 4H), 1.65, 1.56 (2 x s, 1H); ^{13}C NMR ($CDCl_3$) two rotamers (2:1): δ 161.5, 160.4, 101.8, 91.5, 65.5, 53.2, 52.7, 47.6, 45.2, 39.5, 39.1, 28.4, 25.2, 23.7, 21.9, 21.8; HRMS *m/z* calcd for $C_8H_{13}NO_3$ 171.1956, found 171.1962.

(*R*)-*N*-(Formyl)-2-(carboethoxymethyl)proline methyl ester (5d). Clear oil (47 %): $[\alpha]^{25}_D$= +18.8° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) two rotamers (2:1): δ 8.37, 8.21 (2 x s, 1H), 3.79, 3.71, 3.69, 3.67 (2 x s, 8H), 3.53 (m, 2H), 3.18 (dd, *J* = 20.5 Hz, *J* = 16.3 Hz, 1H), 3.01 (dd, *J* = 8.7 Hz, *J* = 16.3 Hz, 1H), 2.49, 2.21, 1.92 (m, 4H); ^{13}C NMR ($CDCl_3$) two rotamers (2:1): δ 160.7, 112.1, 101.8, 101.6, 96.9, 54.6, 53.4, 53.0, 52.3, 51.8, 51.1, 50.6, 50.3, 48.0, 45.7, 42.7, 37.7, 37.3, 36.4, 23.7, 22.1, 18.2; HRMS *m/z* calcd for $C_{10}H_{15}NO_5$ 227.2322, found 227.2313.

(*R*)-(-)-2-(2-Propenyl)proline (1a).[6c] A solution of bicyclic oxazolidinone **4a** (0.50 g, 1.8 mmol) in 6 N HCl (5 ml) was refluxed for an hour or stirred at room temperature for 12 h under a nitrogen atmosphere. The reaction mixture was filtered and washed with dichloromethane three times. The aqueous layer was concentrated under reduced pressure to give a dark brown solid. Ion-exchange chromatography (Dowex 50 W x 8 (Na^+)) furnished 0.33 g of **1a** as a yellow solid (90 %). $[\alpha]^{25}_D$= +22.8° (c 2.0, $CHCl_3$) (of *N*-Cbz derivative), [lit. $[\alpha]^{20}_D$= +20.1° (c 0.9, $CHCl_3$)[6c]]; ^{1}H NMR (D_2O) δ 1.84-2.20 (m, 4 H), 2.17-2.19 (t), 2.43-2.58 (q), 2.77-2.83 (q), 3.26-3.35 (t, 1 H), 5.15-5.20 (m, 2 H), 5.50-5.70 (m, 1 H).

(*R*)-(-)-2-(2-Propenyl)proline methyl ester hydrochloride (6). To a solution of bicyclic oxazolidinone **4a** (0.40 g, 1.4 mmol) in dry methanol (5 ml) was added 1 N methanoic HCl (from acetyl chloride and methanol). The mixture was refluxed for an hour under a nitrogen atmosphere. The solvent was removed under reduced pressure to give 0.23 g of ester **6** as a brown oil (81 % yield). ^{1}H NMR (D_2O) δ 1.98-2.20 (m, 4 H), 2.45-2.52 (t), 2.61-2.69 (q), 2.91-2.98 (q), 3.32(s), 3.41-3.46 (t, 1 H), 3.85 (s, 3H), 5.25-5.32 (t, 2 H), 5.60-5.80 (m, 1 H).^{13}C NMR (D_2O) δ 24.7, 37.4, 41.3, 43.2, 46.1, 52.3, 69.3, 118.2, 134.2, 176.0.