Pergamon

Tetrahedron Letters 42 (2001) 5319–5321

TETRAHEDRON LETTERS

Cleavage of benzyloxycarbonyl-5-oxazolidinones to α-benzyloxycarbonylamino-α-alkyl esters by alcohols and sodium hydrogen carbonate

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Received 7 March 2001; accepted 1 June 2001

Abstract—The reaction of benzyloxycarbonyl-5-oxazolidinones with alcohols and sodium hydrogen carbonate to afford the corresponding benzyloxycarbonyl esters is described.

The formation of benzyloxycarbonyl-5-oxazolidinones **1** represents a simple and convenient method of achieving the simultaneous protection of α-aminoacidic functional groups.[1] 5-Oxazolidinones **1** are prepared in high yields from *N*-benzyloxycarbonyl amino acids, paraformaldehyde and catalytic amounts of *p*-toluenesulfonic acid, via azeotropic removal of water.[2] The value of this type of protection for the manipulation of the side chain of aspartic and glutamic acids without the interference of either the α-amino or α-carboxyl groups has been pioneered by Itoh,[3] and more recently illustrated by various other authors.[4a–d]

The oxazolidinone moiety is stable to acids,[3–5] but is easily cleaved via saponification with 1 M methanolic sodium hydroxide, or by catalytic hydrogenolysis to afford the corresponding free amino acid.[3,4d] In addition, it can undergo aminolysis by treatment with an amine and, therefore, allows the formation of a peptidic bond.[3] The reductive cleavage of 5-oxazolidinones **1**, performed with triethylsilane–trifluoracetic acid[6] or, less conveniently, by hydrogenolysis,[3,7] allows a facile access to *N*-methyl-α-amino acids. The best conditions for this transformation reported so far are included in the work of Aurelio et al.,[7] who also clarified some literature contradictions.[3,8] Benzyloxycarbonyl-5-oxazolidinones can also be transformed into the corresponding benzyloxycarbonylamino α-alkyl esters by treatment with an alcohol in the presence of the corresponding alkoxide, over a wide range of temperatures (from −10°C[4,5] to alcohol reflux[9,10]).

This transformation is particularly useful in the chemistry of dicarboxylic amino acids (e.g. glutamic or aspartic acids) since it allows the preparation of different esters of the two carboxylic groups. However, the strongly basic conditions reported so far in the literature present some downsides, which reduce the method's synthetic utility. In fact, under these basic conditions, the α-stereogenic center may undergo racemization, and esters can suffer concurrent transesterification. Moreover, the scope of this reaction is limited to substrates containing functional groups that are not sensitive to strong bases. Thus, in some syntheses, e.g. involving the formation of the diazoketone of glutamic acid, the opening of 5-oxazolidones before this functionalization appears an obligatory step.[9,10]

Surprisingly, no studies have so far been performed to check the possibility of carrying out this useful reaction under milder reaction conditions, and a literature survey shows that the use of alkoxides is consistently believed to be required.[4,5,9–11] These conclusions appear unjustified since the oxazolidinone ring is known to be activated towards nucleophilic attack.[3,12] Therefore, we started our search for milder conditions to achieve the cleavage of benzyloxycarbonyl-5-oxazolidinones in conjunction with our studies towards the synthesis of 5-hydroxylysines.[13] Our goal was to transform the benzyloxycarbonyl-5-oxazolidinone **1a**, derived from glutamic acid to the corresponding ester **2a**, under conditions that would avoid both racemization of the α-stereocenter and decomposition of a diazo group (Table 1 and Scheme 1).

Keywords: benzyloxycarbonyl-5-oxazolidinones; amino acid derivatives.

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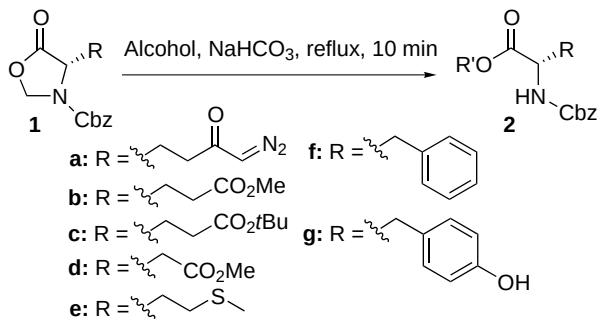
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00971-6

Table 1.

Entry	Alcohol	Starting compound	Yield (%)	Product
1	MeOH	**1a**	87	**2a**; R′ = Me
2	MeOH	**1b**	88	**2b**; R′ = Me
3	MeOH	**1c**	87	**2c**; R′ = Me
4	MeOH	**1d**	78	**2d**; R′ = Me
5	MeOH	**1e**	75	**2e**; R′ = Me
6	MeOH	**1f**	75	**2f**; R′ = Me
7	MeOH	**1g**	80	**2g**; R′ = Me
8	EtOH	**1a**	81	**2a**; R′ = Et
9	EtOH	**1b**	82	**2b**; R′ = Et
10	EtOH	**1c**	78	**2c**; R′ = Et
11	EtOH	**1d**	86	**2d**; R′ = Et
12	EtOH	**1e**	88	**2e**; R′ = Et
13	EtOH	**1f**	89	**2f**; R′ = Et
14	EtOH	**1g**	83	**2g**; R′ = Et
15	CH_2=$CHCH_2OH$[a]	**1a**	85	**2a**; R′ = CH_2CH=CH_2
16	CH_2=$CHCH_2OH$[a]	**1b**	85	**2b**; R′ = CH_2CH=CH_2
17	CH_2=$CHCH_2OH$[a]	**1c**	76	**2c**; R′ = CH_2CH=CH_2
18	CH_2=$CHCH_2OH$[a]	**1d**	82	**2d**; R′ = CH_2CH=CH_2
19	CH_2=$CHCH_2OH$[a]	**1e**	78	**2e**; R′ = CH_2CH=CH_2
20	CH_2=$CHCH_2OH$[a]	**1f**	70	**2f**; R′ = CH_2CH=CH_2
21	CH_2=$CHCH_2OH$[a]	**1g**	78	**2g**; R′ = CH_2CH=CH_2

[a] Freshly distilled.



Scheme 1.

We report herein a new, simple, and efficient synthetic method to open 5-oxazolidinones, performed by treatment with different alcohols under reflux in the presence of sodium hydrogen carbonate (Scheme 1). The reaction also occurs slowly at 45°C, but not at room temperature or in the absence of sodium hydrogen carbonate. This method tolerates the presence of a diazoketone moiety and does not suffer from transesterification in the presence of other ester functions.[14]

The reaction we have chosen as representative to describe the synthetic utility of the method[15] involves the diazo ketone **1a** containing a function necessary for the preparation of various amino acidic halo ketones used in collagen cross link synthesis,[16,17] and an allylic alcohol. The latter is very useful for the protection of the carboxylic group of amino acids, since it can be removed selectively using palladium(0) catalysis[18,19] under non hydrolytic conditions. Thus the new method appears particularly valuable for the preparation of amino-esters bearing base-labile groups in the molecule such as diazo ketones, and for the preparation of different esters of glutamic and aspartic acids.

The integrity of the α-stereocenters in amido-esters **2b–g** was verified by GLC of the corresponding trifluoroacetate esters [methyl, ethyl and propyl (for R′ = CH_2CH=CH_2)][20] on a chiral column The stereochemistry of the amido-ester **2a** was verified by its utilization for the synthesis of the pure (5*R*)- and (5*S*)-epimers of L-hydroxylysine.[13]

In conclusion, we report the successful implementation of 5-oxazolidinone chemistry resulting in a new general and mild route from benzyloxycarbonyl-5-oxazolidinones to benzyloxycarbonylamino esters under racemization-free conditions. This transformation is efficiently carried out by treatment of the 5-oxazolidinone with an alcohol and sodium hydrogen carbonate.

Acknowledgements

This work was financially supported by the Italian MURST (Ministero dell'Università e della Ricerca Scientifica).

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14. All new compounds show correct elemental analyses and consistent physicochemical properties.
15. The allyl (*S*)-2-benzyloxycarbonylamino-6-diazo-5-oxohexanoate **2a** ($R' = CH_2CH{=}CH_2$) was prepared by treatment of (*S*)-3-(benzyloxycarbonyl)-4-(4-diazo-3-oxobutyl)-5-oxazolidinone **1a** (2.5 g, 7.9 mmol) with $NaHCO_3$ (1.5 g) and allylic alcohol (75 mL; to obtain the methyl or ethyl esters, 200 mL of the appropriate alcohols were used) at reflux for 10 min. The solvent was then evaporated under reduced pressure and the residue oil was chromatographed (eluting with hexane:AcOEt, 60:40 v/v) to afford pure **2a** ($R^1 = CH_2CH{=}CH_2$) (2.3 g, 85%): an oil; $[\alpha]_D$ +9.6 (*c* 1, $CHCl_3$); IR (film) 2100, 1730, 1710, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36–7.28 (5H, aromatics-H), 5.87 (1H, m, $CH_2{=}CH\text{-}CH_2$), 5.52 (1H, d, $J = 5.8$ Hz, N*H*), 5.30 (1H, d, $J = 17.2$ Hz, $CHH{=}CH\text{-}CH_2$), 5.23 (1H, d, $J = 10.5$ Hz, $CHH{=}CH\text{-}CH_2$), 5.20 (1H, bs, 6-H), 5.11–5.05 (2H, AB system, OCH_2Ph), 4.60 (2H, d, $J = 4.1$, $CH_2{=}CH\text{-}CH_2$), 4.36 (1H, m, 2-H), 2.43–2.32 (2H, overlapping, 4-Ha and 4-Hb), 2.20 (1H, m, 3-Ha), 1.99 (1H, m, 3-Hb). Anal. calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 59.37; H, 5.41; N, 12.31%.
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20. Compounds **2b**–**g**, after hydrogenolysis (H_2, Pd/C, MeOH, rt, 12 h), were trifluoroacetylated [$(CF_3CO)_2$:CF_3CO_2H; 1:1, v/v, rt, 2 h)] and their behavior on chiral GLC[13,21] [octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin (Lipodex E) capillary column] was examined and compared with that of the corresponding derivatives of natural and racemic amino acids, prepared as described by us for hydroxylysine.[13]
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