Pergamon

Tetrahedron Letters, Vol. 36, No. 42, pp. 7761-7764, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01619-8

Reaction of Ruppert's Reagent (TMS-CF_3) with Oxazolidinones: Synthesis of Protected α-Amino Trifluoromethylketones

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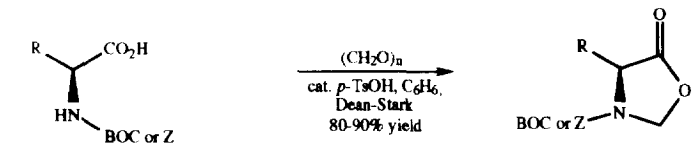
Abstract: (Trifluoromethyl)trimethylsilane adds to α-amino acid derived oxazolidin-5-ones in excellent yields. The adducts can be converted into protected α-amino trifluoromethylketones by acid hydrolysis.

The use of trifluoromethylketones as serine protease inhibitors was pioneered by Abeles and is now well established[1]. Various synthetic approaches to this class of compounds have been reported[2] including a modified Dakin-West procedure[3], reaction of trifluoroacetic anhydride with ketenes[4], and trifluoromethyl carbanions[5]. The latter approach is, however, of limited utility due to the well-documented tendency of the trifluoromethyl anion to undergo fluoride elimination[5]. Ruppert and coworkers[6] have developed a stable trifluoromethyl anion equivalent in the form of (trifluoromethyl)trimethylsilane[7] (Ruppert's Reagent/TMS-CF_3), which is an efficient nucleophilic trifluoromethylation agent for addition to certain carbonyl compounds[8]. Fluoride-catalysed addition reaction of TMS-CF_3 to ketones or aldehydes generally proceeds in good yields, but efficient reaction with carboxylic acid derivatives has only been reported in the case of five- and six-membered lactones[8].

Herein, we communicate results concerning the reaction of TMS-CF_3 with oxazolidin-5-ones, with the aim of developing a route to trifluoromethylketone derivatives of amino acids. *N*-Protected amino acids can be readily converted into oxazolidin-5-ones[9,10], which have been employed as activated amino acid derivatives in coupling reactions[9] and as chiral auxiliaries in the diastereoselective α-alkylation of amino acids[11], by reaction with paraformaldehyde and azeotropic removal of water[9] (Scheme 1).

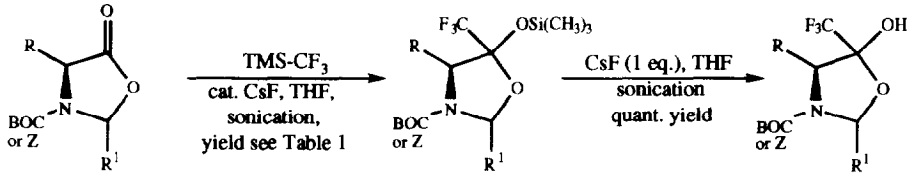


R = amino acid side chain

Scheme 1

Reaction of the *N*-benzyloxycarbonyl oxazolidin-5-one **1a** derived from phenylalanine with TMS-CF_3 using conditions developed for the reaction of Ruppert's Reagent with lactones[8] (catalytic tetrabutylammonium fluoride hydrate, THF, room temperature) gave the desired addition product **1b** in moderate yield (40%). However, use of catalytic cesium fluoride as an 'anhydrous' fluoride source with

sonication gave **1b** in excellent yield (Scheme 2) and as a single isolated diastereomer (by high field ^{1}H and ^{13}C n.m.r. analysis[12]). Desilylation of **1b** proceeded readily in quantitative yield using stoichiometric cesium fluoride, or tetrabutylammonium fluoride solution in THF, to provide **1c** (Scheme 2).



Scheme 2

The absolute stereochemistry of **1b** was established by single crystal X-ray analysis[13]. It is probable that the stereochemistry of the product is determined by the addition of the trifluoromethyl anion *anti* to the benzyl side-chain of the oxazolidin-5-one **1a**.

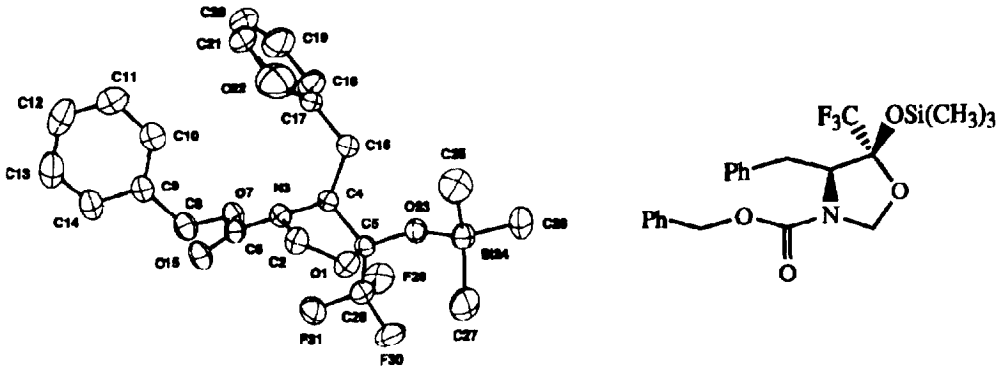


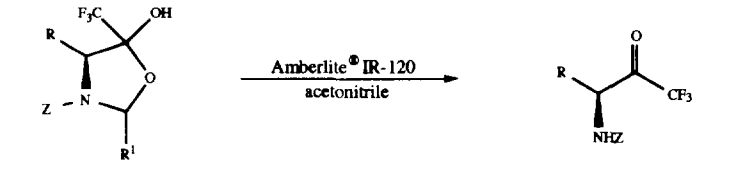
Figure 1: X-ray crystal structure of **1b**

The addition of Ruppert's Reagent to a range of *N*-urethane protected oxazolidin-5-ones was then explored. The addition proceeds efficiently with either **Z** (entries I-IV and XI-XIII in Table 1) or **BOC** (entries V-X) protecting groups. Variation of the side-chain **R** indicated that the yields are generally excellent in case of alkyl or benzyl side-chains (entries I, II, V-IX, and XI-XIII), and that even with functionalised side-chains derived from aspartic acid β-methylester, glutamic acid γ-methyl ester or *S*-benzyl-cysteine the reaction proceeds in good yield (entries III, IV, and X). The five-membered ring of **1c**, however, proved extremely resistant towards acid hydrolysis, probably due to the electron-withdrawing effect of the trifluoromethyl-moiety rendering the lone-pairs of the ring oxygen sufficiently electron-deficient such that protonation does not readily occur. Oxazolidin-5-ones having a *para*-methoxyphenyl group at the C-2 position were thus prepared using anisaldehyde[10]. Reaction of these with Ruppert's Reagent proceeds in excellent yields (entries XII and XIII in Table 1). In the case of *para*-methoxyphenyl substituted oxazolidin-5-ones, it was found that the yields were superior using tetrabutylammonium fluoride solution in THF.

Entry	Substrate	R	P. G.	R^1	Product: Yield
I	1a	$PhCH_2$	Z	H	1b: 95 %
II	2a	H_3C	Z	H	2b: 85 %
III	3a	$H_3CO_2CH_2C$	Z	H	3b: 50 %
IV	4a	$H_3CO_2C(CH_2)_2$	Z	H	4b: 70 %
V	5a	$PhCH_2$	BOC	H	5b: 80 %
VI	6a	H_3C	BOC	H	6b: 85 %
VII	7a	H	BOC	H	7b: 60 %
VIII	8a	$(H_3C)_2CH$	BOC	H	8b: 85 %
IX	9a	$(H_3C)_2CHCH_2$	BOC	H	9b: 95 %
X	10a	$PhCH_2$-S-CH_2	BOC	H	10b: 65 %
XI	11a	$PhCH_2$	Z	Ph	11b: 60 %
XII	12a	$PhCH_2$	Z	*p*-$H_3COC_6H_4$	12b: 95 %
XIII	13a	CH_3	Z	*p*-$H_3COC_6H_4$	13b: 95 %

Table 1: Addition of Ruppert's Reagent to urethane protected oxazolidin-5-ones (yields are unoptimised and refer to isolated products, P.G. = *N*-protecting group)

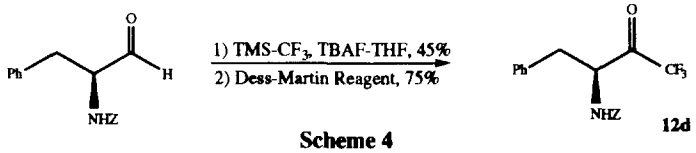
The *para*-methoxyphenyl derived oxazolidin-5-one adducts **12b** and **13b** were desilylated as previously and the five membered ring cleaved by stirring in acetonitrile in the presence of strongly acidic ion exchange resin (Amberlite® IR-120) for 36 to 48 hours. The product *N*-substituted α-amino-trifluoromethylketones were obtained in excellent yields (Scheme 3).



12c: R^1 = *p*-$H_3COC_6H_4$, R = $PhCH_2$
13c: R^1 = *p*-$H_3COC_6H_4$, R = H_3C

Scheme 3

12d: R = $PhCH_2$ (92%)
13d: R = H_3C (87%)



12d

Scheme 4

Analytical data of **12d** obtained *via* addition of Ruppert's Reagent to the oxazolidin-5-one **12a** were the same as those obtained for the synthesis of **12d** *via* an alternative route (Scheme 4) starting from *N*-benzyloxycarbonyl-(L)-phenylalaninal, ($[\alpha]_D^{20}$= +23.2° (c = 0.5, $CHCl_3$) for **12d** prepared as in Scheme 3,

and $[\alpha]_D^{20}$= +22.9° (c = 0.5, $CHCl_3$) for **12d** prepared as in Scheme 4).

This is the first report of the reaction of Ruppert's Reagent with amino acid derived oxazolidin-5-ones. The addition to a wide variety of *N*-substituted oxazolidin-5-ones is a very convenient reaction and usually occurs in excellent yield. The adducts derived from addition to C-2 *para*-methoxyphenyl substituted oxazolidin-5-ones can be readily hydrolysed and the *N*-substituted α-amino-trifluoromethyl ketones are recovered in high yields.

Acknowledgements:

This work was financially supported by the European Community *via* a Human Capital and Mobility Research Network (M.W.W.). We would like to thank Dr. M. P. Rudolph and Mr J. Thirkettle for helpful discussions.

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12. Physical data for **1b**: R_f: 0.55 [$CHCl_3$-pet. ether (3:1; v/v)], m.p. 98-101°C (from ether); ν_{max} (KBr): 3040w, 1715s, 1455m, 1415m, 1235s; δ_H (200 MHz, $CDCl_3$): 0.26 (9H, s, $Si(C\underline{H}_3)_3$), 2.6-2.9 (1H, br, $PhC\underline{H}_2$), 3.05 (1H, d, J 6 Hz, $PhC\underline{H}_2$), 4.6 (1H, br, 4-H), 4.95-5.0 (3H, m, br, $PhC\underline{H}_2O$ and 2-H), 5.4 (1H, br, 2-H), 7.1-7.5 (10H, m, Ar); δ_C (125.7 MHz): 1.6 ($Si(\underline{C}H_3)_3$), 35.0 ($Ph\underline{C}H_2$), 61.6 (C-4), 68.0 ($Ph\underline{C}H_2O$), 78.0 (C-2), 102.7 (q, J_{C-F} 32 Hz, C-5), 122.1 (q, J_{C-F} 283 Hz, $\underline{C}F_3$), 126.9, 128.2, 128.6, 128.7, 128.8, 129.8 (6xAryl CH), 136.1, 137.7, (2xAr *ipso*), 154.7 (urethane C=O); δ_F (235.19 MHz, $CDCl_3$, referenced externally to $CFCl_3$ at 0.00 ppm): -85.5 ($C\underline{F}_3$); m/z: 471 (MNH_4^+, 15%), 454 (MH^+, 30%), 410 (5%), 320 (15%), 108 (50%), 91 (100%); Found: C: 58.59, H: 5.77, N: 3.06%, required for $C_{22}H_{26}F_3NO_4Si$: C: 58.29, H: 5.73, N: 3.09%.
13. Crystal data: $C_{22}H_{26}F_3NO_4Si$, M_r = 453.533, monoclinic, P $2_1/a$, a = 8.590, b = 21.466, c = 13.060 Å, α = 90, β = 105.303, γ = 90°, V = 2322.8 $Å^3$, Z = 4, D_x = 1.297 Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 0.146 mm^{-1}, F(000) = 953, T = 293 K, R = 0.0481, wR = 0.0640 for 4467 observed reflections with $I>3\sigma(I)$; 5540 independent reflections resulted of which 4476 met the criterion $I>3\sigma(I)$. The structure was solved by direct methods (SIR92). Lists of fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, UK, as supplementary material.

(*Received in UK* 30 *June* 1995; *revised* 23 *August* 1995; *accepted* 25 *August* 1995)