Trifluoromethanesulfonates of α-Hydroxycarboxylates—Educts for the Racemization—Free Synthesis of *N*-Substituted α-Amino Acids

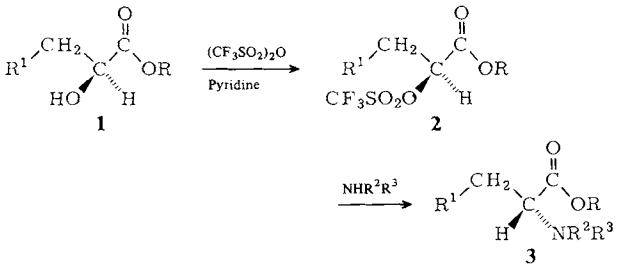
By *Franz Effenberger**, *Ulrike Burkard*, and *Joachim Willfahrt*

Many *N*-substituted α-amino acids exhibit high biological activity[1]. They can be prepared by substitution at the NH_2 group of the respective amino acid; this synthetic procedure is limited, though, by the reactivity of the alkylating or arylating agent as well as by the possibility of

[*] Prof. Dr. F. Effenberger, U. Burkard, Dr. J. Willfahrt
Institut für Organische Chemie der Universität
Pfaffenwaldring 55, D-7000 Stuttgart 80 (Germany)

  0570-0833/83/0101-0065 $ 02.50/0

either elimination or multiple reactions. Alternatively, the desired amino function can be introduced directly by nucleophilic substitution of appropriate α-substituted carboxylic acid derivatives. Especially with α-halo carboxylates, however, this reaction is accompanied by extensive racemization; with α-methanesulfonyloxy and α-toluenesulfonyloxy carboxylic acid derivatives, both racemization and elimination products are formed, *inter alia,* owing to the drastic conditions required[1a,2].



1 2 3

α-Trifluoromethanesulfonyloxy carboxylates **2** are obtained in high yield from α-hydroxy carboxylates **1** and trifluoromethanesulfonic acid anhydride/pyridine[3]. The trifluoromethanesulfonates **2** are fairly stable and can be kept for months at 0—10 °C. Even with weakly nucleophilic amines, however, they are smoothly converted, with Walden inversion, into the corresponding α-amino carboxylates **3**; the compounds **3** are isolated in excellent yield by distillation or filtration through a silica gel column (Table 1).

Comparison of the relative reactivity of various α-substituted ethyl propionates towards benzylamine in refluxing dichloromethane reveals a strong dependence on the nature of the leaving group, not quite expected for S_N2 reactions[4]. **2c** is converted quantitatively into **3f** within 20 min; for α-bromo, α-methanesulfonyloxy, α-toluenesulfonyloxy and α-chloro ethyl propionate, on the other hand, conversion to **3f** is only 40, 10, 5, and < 1%, respectively, after 22 h.

The high reactivity of the trifluoromethanesulfonates 2 proves especially advantageous for the synthesis of phenylalaninic and aspartic acid derivatives since in this case poorer leaving groups (*e.g.* $Br^{\ominus}$, $CH_3SO_3^{\ominus}$) strongly favor elimination. The unequivocal stereochemistry of the substitution reaction has been confirmed by reaction of **2** with optically active amines; the diastereomeric amino carboxylates **3** can be differentiated by capillary GLC.

Table 1. *N*-Substituted α-aminocarboxylic esters **3** from **2** and amines in dichloromethane at room temperature [5]. In the reaction scheme, *S*-configuration is given for **2**, and *R*-configuration for **3**.

Educts					Products	Yield
2	R	R^1	R^2	R^3	**3**	[%]
(*S*)-**2a**	Me	Ph	$PhCH_2$	H	(*R*)-**3a**	92
			Ph	H	(*R*)-**3b**	93
			$-(CH_2)_4-CH(Et)-$ [b]		(2*R*,2′*R*)-**3c**	83
(*S*)-**2b**	Et	$EtCO_2$	$PhCH_2$	H	(*R*)-**3d**	93 [c]
			Ph	H	(*R*)-**3e**	94
(*S*)-**2c**	Et	H	$PhCH_2$	H	(*R*)-**3f**	85
			$-(CH_2)_4-$		(*R*)-**3g**	84
			$2,6-(CH_3)_2C_6H_3$	H	(*R*)-**3h**	92
			Ph	Me	(*R*)-**3i**	75
			Ph–CH(Me)– [a]	H	(2*R*,1′*S*)-**3j**	76
			Ph–CH(Me)– [b]	H	(2*R*,1′*R*)-**3k**	78
			$EtCO_2$–CH(Me)– [a]	H	(2*R*,2′*S*)-**3l**	81
(*R*)-**2c**			$EtCO_2$–CH(Me)– [a]	H	(2*S*,2′*S*)-**3m**	93

[a] *S*-form. [b] *R*-form. [c] Addition at −65 °C.

Both *R*- and *S*-α-amino carboxylates can be prepared by the synthetic procedure described here; subsequent hydrolysis of the esters to the corresponding *N*-substituted α-amino carboxylic acids proceeds without detectable racemization.

Received: August 19, 1982 [Z 135 IE]
revised: November 16, 1982
German version: *Angew. Chem. 95* (1983) 50

[1] a) R. M. Scott, G. D. Armitage, DOS 2650434 (3. Nov. 1976), Shell Int. Res. Maatschappij B.V.; *Chem. Abstr. 87* (1977) 67990n; b) J. D. Kemp, *Biochem. Biophys. Res. Commun. 74* (1977) 862.
[2] A. J. Speziale, E. G. Jaworski, *J. Org. Chem. 25* (1960) 728.
[3] a) C. D. Beard, K. Baum, V. Grakauskas, *J. Org. Chem. 38* (1973) 3673; b) K. Shiosaki, G. Fels, H. Rapoport, *ibid. 46* (1981) 3230.
[4] R. D. Howells, J. D. McCown, *Chem. Rev. 77* (1977) 69.
[5] *Procedure:* (*R*)-**3f**: A solution of (*S*)-**2c** (1.75 g, 7 mmol) in CH_2Cl_2 (25 mL) is added dropwise within 5 min at room temperature to a stirred solution of benzylamine (1.50 g, 14 mmol) in CH_2Cl_2 (25 mL), and stirring continued for 30 min at room temperature. The reaction mixture is filtered, the solution washed with water, dried over Na_2SO_4, concentrated, and the residue (1.36 g) distilled *in vacuo*. Yield 1.24 g (85%) (*R*)-**3f**, b.p. 73 °C/5 × 10^{-3} torr.