Stereo- and Regioselective Opening of 3-Phenylglycidates by Trifluoromethylsulfonamide under Solid–Liquid Heterogeneous Conditions

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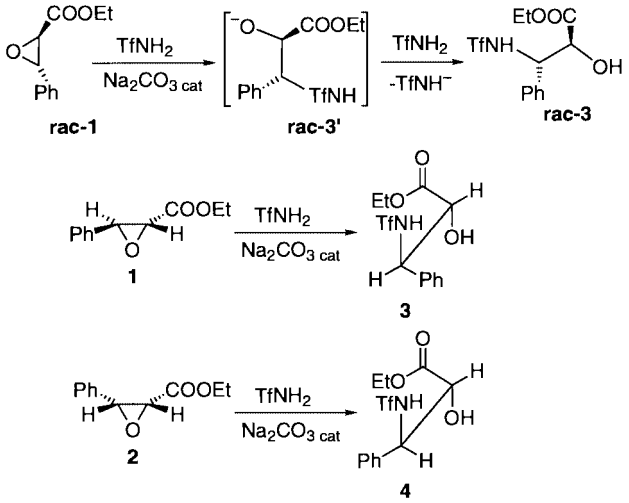
Ethyl *cis*- and *trans*-3-phenylglycidates have been opened stereo- and regioselectively with trifluoromethylsulfonamide in the presence of catalytic amounts of solid sodium carbonate. Under these conditions, (2*R*,3*R*)-3-phenylglycidate produces exclusively ethyl (2*R*,3*S*)-3-*N*(trifluoromethanesulfonyl)amino-2-hydroxy-3-phenylpropionate deriving from the attack of the nucleophile on the C-3 carbon atom.

3-Substituted glycidic acids or esters are starting materials for the preparation of a large number of polyfunctionalized compounds through oxirane ring opening with several nucleophilic reagents. In the case of nitrogen nucleophiles like ammonia,[1] amines[2] or azides,[3] β-amino-α-hydroxy or/and the regioisomeric α-amino-β-hydroxy acid derivatives are produced. Although both classes of compounds are important, in recent years the synthesis of β-amino-α-hydroxy acids has attracted the largest interest. In fact, these structural frameworks are often found in proteins, peptides and biologically active molecules precursors,[4] such as taxol and its derivatives.[1,5] The (2*R*,3*S*)-3-phenylisoserine unit, contained in the taxanes backbone, is of paramount importance for the activity of these potent anti-cancer molecules and many efforts have been done for its chemical synthesis. One of the most attractive methodologies is the transformation of ethyl (2*R*,3*R*)-3-phenylglycidate (**2**) into a precursor of the taxol side chain.[1]

In this paper we describe the efficient *trans*-stereo- and regioselective ring opening of *cis*- and *trans*-3-phenylglycidates **1** and **2** by trifluoromethylsulfonamide ($TfNH_2$)[6] to produce in high yields 3-*N*(trifluoromethanesulfonyl)amino-2-hydroxy-3-phenylpropionates **3** and **4**, respectively, as sole regioisomers (Scheme 1). Other amides, like trifluoroacetamide, *p*-toluenesulfonamide and *o*- or *p*-nitrobenzenesulfonamide, that we used with good results for the opening of terminal oxiranes,[7] resulted scarcely reactive towards glycidates. This is probably due to the increased steric hindrance (in the case of *o*-nitrobenzenesulfonamide), and to their reduced acidity. In fact, as well known,[8] the oxiranes react easily with nucleophiles in the presence of protic or Lewis acids that activate the ring by coordination to the oxiranic oxygen. An accurate screening was conducted on racemic *trans*-3-phenylglycidate (**rac-1**) as a model compound to determine the optimal ring opening conditions (Table 1).



Scheme 1.

Table 1. Yields and distributions of products **3,4** from ring opening of glycidates **1,2**

Entry	Substrate	Conditions[a]	T/°C	t/h	**rac-3**/%	**rac-4**/%
1	**rac-1**	Na_2CO_3 (L) / 2 $TfNH_2$	120	4	80	8
2	**rac-1**	Na_2CO_3 (L) / 2 $TfNH_2$	90	7	80	7
3	**rac-1**	Na_2CO_3 (L) / 2 $TfNH_2$/ 0.1 TEBA	90	7	75	7
4	**rac-1**	Na_2CO_3 (L) / 1 $TfNH_2$	90	15	78	–
5	**rac-1**	Na_2CO_3 / 2 $TfNH_2$	90	11	76	7
6	**rac-1**	Na_2CO_3 (L)/ 2 $TfNH_2$[b]	120	2	52	–
7	**rac-1**	Na_2CO_3 (L) / 2 $TfNH_2$/ dioxane	90	48	< 20	–
8	**rac-2**	Na_2CO_3 (L) / 2 $TfNH_2$	120	4	5	77
9	**rac-2**	Na_2CO_3 (L) / 2 $TfNH_2$	90	10	2	54
10	**2**[c]	Na_2CO_3 (L) / 2 $TfNH_2$	120	4	15[d]	67[e] (78)[f]
11	**2**[c] *S*	Na_2CO_3 (L) / 2 $TfNH_2$	90	10	9[d]	46[e] (53)[f]

[a]$TfNH_2$ = $CF_3SO_2NH_2$; in the presence of 0.1 mol equiv of sodium carbonate; (L) = lyophilized. [b]In the presence of 1 mol equiv of sodium carbonate. [c](86 : 14) Mixture of [*cis*-(2*R*,3*R*)- : *trans*-(2*R*,3*S*)-] ethyl 3-phenylglycidates. [d]Ethyl (2*R*,3*R*)-3-*N*(trifluoromethane-sulfonyl)amino-2-hydroxy-3-phenylpropionate (**3**). [e]Ethyl (2*R*,3*S*)-3-*N*(trifluoromethane-sulfonyl)amino-2-hydroxy-3-phenylpropionate (**4**). [f]In parentheses are reported the yields with reference to the actual amount of *cis*-epoxide **2** in the mixture.

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The best results were reached by operating at 120 °C in an anhydrous heterogeneous system composed of 1 mol equiv of **rac-1**, 2 mol equiv of $TfNH_2$, in the presence of 0.1 mol equiv of anhydrous, lyophilized sodium carbonate[9] as a base, without solvent (Table 1, entry 1).[10]

A mixture (88%) of the diastereomeric β-amido-α-hydroxy esters **rac-3:rac-4** (91:9 by ^{1}H NMR analysis)[11] was thus recovered and the pure diastereoisomer **rac-3**[12] was then isolated by a single recrystallization from $CHCl_3$–hexane. A catalytic amount of sodium carbonate is sufficient to produce sodium trifluorosulfonamidate, that is regenerated during the reaction (Scheme 1). A stoichiometric amount of sodium carbonate (entry 6) gave **rac-3** in 52% only.[13] The use of commercial (entry 5) instead of lyophilized sodium carbonate increased the reaction time, probably due to the reduced contact surface. The presence of a phase transfer agent like triethylbenzylammonium chloride (TEBA) was uneffective (entry 3), whereas 15 h were necessary for the opening completion by using 1 mol equiv of $TfNH_2$ (entry 4), affording **rac-3** as a sole diastereoisomer. Finally, the use of a solvent, like anhydrous dioxane (entry 7), resulted in a very slow reaction.

The best reaction conditions found were applied to the *cis*-3-phenylglycidate **rac-2** (Table 1, entry 8) and the hydroxyamide **rac-4**[14] was obtained as the main diastereomer.

In order to verify the stereoselectivity of the reaction, a mixture of enantiopure *cis*-(2*R*,3*R*)-3-phenylglycidate (**2**) and *trans*-(2*R*,3*S*)-3-phenylglycidate (**1**) (**2**:**1** = 86:14),[15] was reacted at both 90 and 120 °C (Table 1, entries 10 and 11). After chromatographic purification the enantiopure (Mosher's ester ^{19}F NMR analyses) diastereoisomers **3** and **4** were isolated[16] thus confirming that the stereogenic carbon atom C-2 remains unchanged during the nucleophilic antiperiplanar opening.

In conclusion we showed that β-amido-α-hydroxy esters **3**, **4** can be efficiently generated by stereo/regioselective opening of glycidates **1, 2**. This reaction is promoted by small amounts of a cheap, inorganic base such as sodium carbonate and is carried out without solvent, thus providing an environmentally friendly reaction medium. To the best of our knowledge, this protocol represents the first example of glycidic esters opening using an amide as a source of nucleophilic nitrogen.

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References and Notes

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9 An aqueous solution of sodium carbonate (7.1 g/100 mL of water, i.e. a saturated solution at 0 °C) is cooled rapidly to ca. –150 °C (liquid nitrogen) under vacuum (10^{-4} mbar), and then the frozen material was left to reach room temperature. The ice cristals sublime and are collected on a trap cooled at –150 °C, leaving the lyophilized salt as a powder having an increased surface area.
10 General method for the preparation of β-amido-α-hydroxy esters **3, 4**: in a dried flask a mixture of the epoxide **1** (1 mmol, 192 mg), Na_2CO_3 lyophilized (0.1 mmol, 11 mg), and trifluoromethylsulfonamide (2 mmol, 298 mg) was stirred at 90 or 120 °C until the starting material was no detectable (TLC analysis). After cooling, the crude was diluted with CH_2Cl_2, filtered on a celite pad and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (250–400 mesh, AcOEt:hexane = 1:3).
11 Diastereomers distribution was determined by measuring the relative intensities of the H_α signals: **rac-3**, 4.63 ppm, $^3J_{anti}$= 3.5 Hz; **rac-4**, 4.43 ppm, $^3\mathbf{J}_{syn}$ = 1.9 Hz.
12 **rac-3**: white solid; mp 91–92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (m, 5H); 6.21 (d, *J* = 9.6 Hz, 1H); 4.99 (dd, *J* = 3.5, 9.6 Hz, 1H); 4.63 (dd, *J* = 3.5, 5.6 Hz, 1H); 4.13 (q, *J* = 7.1 Hz, 2H); 3.15 (d, *J* = 5.6 Hz, 1H); 1.24 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ –78.15.
13 The large amount of the base adsorbs the reagents and a higher temperature (120 °C) is necessary for a better stirring of the reaction mixture. Under these conditions there is complete formation of TfNHNa, but this transformation results detrimental for the outcome of the reaction that, on the contrary, needs the electrophilic catalysis of $TfNH_2$ as such.
14 **rac-4**: white solid; mp 85–86 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37 (m, 5H); 5.91 (d, *J* = 9.8 Hz, 1H); 5.07 (dd, *J* = 1.9, 9.8 Hz, 1H); 4.43 (dd, *J* = 1.9, 2.9 Hz, 1H); 4.36 (q, *J* = 7.1 Hz, 2H); 3.28 (d, *J* = 2.9 Hz, 1H); 1.37 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 282 MHz): δ –78.06.
15 a) For the mixture of diastereomers **1** and **2**: $[\alpha]_D^{20}$ +4.8 (*c* = 1.0, $CHCl_3$). b) W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, **56**, 2296 (1991). c) E. N. Jacobsen, L. Deng, Y. Furukawa, and L. E. Martínez, *Tetrahedron*, **50**, 4323 (1994).
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