A Simple and Efficient Way to Substituted 3-Halogenopyruvamides from Substituted α-Carbamoyl-α-cyanooxiranes

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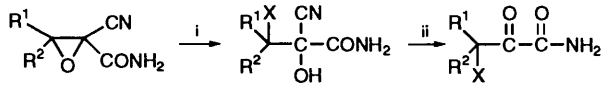
Regioselective ring opening of the readily accessible α-carbamoyl-α-cyanooxiranes with hydrogen halides gives β-halogeno-α-cyanohydrins which on being decyanated give, quantitatively, the corresponding substituted 3-halogenopyruvamides.

α-Halogeno ketones are both valuable starting materials in organic synthesis[1] and also useful as affinity labels in enzymology.[2] Of this class of compound 3-halogenopyruvamides are of special interest since they are able to bind pyruvate-dependent enzymes but not able to accept them as substrates during the catalytic process;[2] they are also of interest as activators for phototropic compositions.[3] To the best of our knowledge, only the parent compounds α-chloro- and α-bromopyruvamides have been prepared in low yield through the HX ring-opening of the corresponding glycide amide, followed by an oxidation of the chlorohydrin intermediate.[2,4] The interesting biological properties of α-halogenopyruvates and the synthetic potentialities of these polyfunctionalized derivatives prompted us to design a simple synthesis of the until now unknown substituted α-halogenopyruvamides. Previous work indicated that epoxides **1** could be valuable starting materials for such a synthesis.[5–7] We now show that substituted 3-halogenopyruvamides **3** are readily prepared from the epoxides **1** (see Scheme 1).

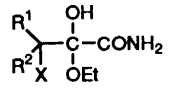


1 **2** **3**

		M.p. (*T*/°C)
3a	R^1 = Ph, R^2 = H, X = Cl	121
3b	R^1 = Ph, R^2 = H, X = Br	142
3c	R^1 = *p*-ClC_6H_4, R^2 = H, X = Cl	152
3d	R^1 = *p*-ClC_6H_4, R^2 = H, X = Br	148
3e	R^1 = *p*-MeC_6H_4, R^2 = H, X = Cl	114
3f	R^1, R^2 = $CH_2(CH_2)_3CH_2$, X = Cl	120

Scheme 1 *Reagents and conditions:* i, HX (12 mol dm^{-3}), MeCN, room temp., 12 h, yield ~80%; ii, MeCN, $Ni(OAc)_2$, room temp., 1–3 h, yield 90–100%

The starting epoxides **1** were easily obtained by treating the corresponding cyano ester epoxides with ammonia according to a described procedure.[8] The ring opening of these epoxides **1** by HX is regioselective and the halogen in **2** is always located α to the R^1 and R^2 groups. We have been able to prove that the ring opening is *trans* because the chlorohydrin formed gave back only the starting epoxide **1** when treated with sodium hydroxide. In contrast to other cyano epoxides which by ring opening give unstable and non-isolable halohydrins,[5,6] the ring opening of **1** gives the halohydrins **2** stable enough to be isolated and characterized (yield ~80%). Since compounds **2** are also α-cyanohydrins, they can be thermolysed to give **3**. However, as expected,[2] the carbonyl group of **3** is very reactive and the thermolysis of **2** is a reversible reaction. In order to shift the equilibrium towards **3** nickel acetate was added to the medium



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(in order to trap the HCN formed) and in this case the reaction **2** ⟶ **3** was almost quantitative at room temperature. Compounds **3** were too reactive to be recrystallized from alcohol and when boiled in ethanol gave immediately the hemiacetals **4** which were isolated and characterized. However, very pure samples of **3** were prepared by sublimation. Furthermore, since the chlorohydrins **2** and the hemiacetals **4** are stable they are valuable as a way to store the α-halogenopyruvates **3**.

Experimental

General Procedure for the Formation of Cyanohydrins **2**: *Preparation of* 3-*Chloro*-2-*cyano*-2-*hydroxy*-3-*phenylpropanamide* **2a** (R^1 = Ph, R^2 = H, X = Cl).—Hydrochloric acid (12 mol dm^{-3}; 10 cm^3) was added to a solution of the epoxide **1** (R^1 = Ph, R^2 = H) (1 g, 5.3 mmol) dissolved in MeCN (20 cm^3). After 12 h at room temp., the mixture was diluted with water (100 cm^3) and extracted with ether (100 cm^3 × 3). The combined extracts were dried (Na_2SO_4) and evaporated to give **2a** as a solid (0.96 g, 80%), m.p. 203 °C (MeCN). The product was characterized from its spectroscopic data and appeared as a single diastereoisomer, ν_{max}(Nujol)/cm^{-1} 3460 and 3340br (NH), 2240s (CN), and 1680s (CO); δ_H(CD_3CN; relative to TMS) 5.47 (s, 1 H, CHCl), 7.12 (br, 1H) and 6.82 (br, 1 H) (NH_2), 6.2 (br, 1 H, OH) and 7.5 (5 H, C_6H_5); δ_C(CD_3CN) 65.8 (CHCl), 77.5 (*C*$CONH_2$), 118.5 (CN), 129.8, 130.3, 130.6 and 135 (C_6H_5) and 167.4 ($CONH_2$); the molecular ion is not observed but only the signal $M^{\cdot+}$ − HCN (*ca.* 197.0243; found 197.024), furthermore all the other signals of the corresponding pyruvamide **3a** are observed.

General Procedure for the Formation of the Pyruvamides **3**: *Preparation of* 3-*Chloro*-3-*phenyl*-2-*oxopropanamide* **3a** (R^1 = Ph, R^2 = H, X = Cl).—Nickel acetate (1.25 g, 7 mmol) was added to a solution of the chlorohydrin **2a** (2.2 mmol) dissolved in MeCN (12.5 cm^3). After 1 h at room temperature the mixture was diluted with water (20 cm^3) and extracted with ether (20 cm^3 × 3). The combined extracts were dried (Na_2SO_4) and evaporated to give **3a** as a solid (0.40 g, 90%); this was purified by sublimation (m.p. 121 °C) and characterized from its spectroscopic data; ν_{max}(Nujol)/cm^{-1} 3380 and 3180br (NH) and 1655br (CO); δ_H(CD_3CN relative to TMS) 6.75 (1 H, s, CHCl) 6.6 (br, 1 H) and 7.3 (br, 1 H) ($CONH_2$) and 7.6 (br, 5 H,

C_6H_5); δ_C(CD_3CN) 62 (CHCl), 130.1, 130.2, 130.4 and 130.6 (C_6H_5), 162 ($CONH_2$) and 190 (CO) [Found: *m/z* (HRMS), 197.023. Calc. for $C_9H_8ClNO_2$: M^+, 197.0243].

General Procedure for the Preparation of the Hemiacetals **4**: *Preparation of* 3-*Chloro*-2-*ethoxy*-2-*hydroxy*-3-*phenylpropanamide* **4a** (R^1 = Ph, R^2 = H, X = Cl).—Recrystallization of the pyruvamide **3a** in ethanol gave the corresponding hemiacetal **4a**, m.p. 142 °C (EtOH) (Found: C, 54.3; H, 5.8; Cl, 14.7; N, 5.56%; M^+, 197.023. Calc. for $C_{11}H_{14}ClNO_3$: C, 54.21; H, 5.75; Cl, 14.58; N, 5.75; *M*, 197.024); ν_{max}(Nujol)/cm^{-1} 3430 and 3310br and 1650s; δ_H(DMSO, relative to DMSO) 6.62 (s, 1 H, CHCl) 8.20 (br, 1 H) and 7.85 (br, 1 H) ($CONH_2$) 3.50 (q, 2 H, OCH_2CH_3), 1.12 (t, 3 H, OCH_2CH_3) and 7.40 (br, 5 H, C_6H_5).

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