SHORT PAPER

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Formation of an imidosuccinimide by cyclisation of a sterically hindered β-cyanoester with the lithium salt of a primary amine†

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The reaction of β-cyanoester **1** with a two-fold excess of the lithium salt of homoveratrylamine in THF at 0 °C to room temperature affords the imidosuccinimide **3**, which undergoes derivation to the succinimide monooxime **4** by treatment with *m*-chloroperoxybenzoic acid.

Imidosuccinimides (5-imino-2-pyrrolidinones) are close functional derivatives of succinimides that have attracted only scattered attention. The parent imidosuccinimide and certain α,β-disubstituted derivatives were at first prepared by controlled hydrolysis of the corresponding succinimidines (2,5-diiminopyrrolidines).[1] Later methods of preparation were the ring closure of β-cyanoamides promoted by sodium hydroxide[2] or aluminium chloride,[3] the cyclisation of β-cyanopropionic esters with primary amines at high temperature,[4] and the three-component cyclisation of enamines, isocyanates and isonitriles.[5] Herein, the preparation of an imidosuccinimide by cyclisation of a sterically hindered β-cyanoester with the lithium salt of a primary amine under mild conditions is described.

In connection with our project on the synthesis of a family of β-cyanoamides for evaluation as modulators of tumoral resistance to chemotherapy,[6] the reaction of β-cyanoester **1** with the lithium salt of homoveratrylamine was performed with the idea of preparing a new β-cyanoamide of the family by aminolysis of the ester. Since this α,α,α-trisubstituted ester is sterically hindered, a literature procedure for the aminolysis of nonreactive esters by means of the lithium salts of secondary amines[7] was employed. However, the procedure was slightly modified to adapt it to a primary amine. Thus, the lithium salt of homoveratrylamine was used in a two-fold excess to prevent a possible lowering of yield that would result from quenching of the requisite lithium salt by transfer of the acidic *N*-proton of the emerging β-cyanoamide (Scheme 1). Working in this manner in THF at 0 °C to room temperature, the imidosuccinimide **3** was obtained as the reaction product in good yield, instead of the desired isomeric β-cyanoamide. The lithium salt of this amide (**2**) is more likely to be an unstable intermediate, that would undergo an intramolecular addition of the anionic nitrogen to the cyano group forming the imidosuccinimide ring system.[2]

The imidosuccinimide **3** was soluble and stable in aqueous hydrochloric acid at pH < 5 at room temperature; above this pH it precipitated. This basicity of the compound is consistent with the existence of an amidino group (N–C=NH) in structure **3**, but not with the isomeric β-cyanoamide structure mentioned above. Furthermore, the IR spectrum of the compound showed two strong absorptions at ν_{max}/cm^{-1} 1710 and 1610 for a carbonyl and imidoyl (C=NH) group in structure **3**, respectively,[8] while, on the other hand, the spectrum showed no absorption for a cyano group. The absence of this group in the structure was ascertained by the Raman spectrum. The ^{13}C NMR spectrum also agreed with structure **3**, showing two downfield peaks at δ_C 181.0 and 167.7 which are assigned to the carbonyl and imidoyl carbons, respectively.[9] In this spectrum, the imidoyl carbon and several other carbons displayed line broadening, which decreased at 50 °C. This effect is ascribed to the occurrence of an exchange of *E* and *Z* imidoyl configurations.

In contrast to the imidoyl group of the parent imidosuccinimide that is easily hydrolysed by boiling water with formation of succinimide,[1a] the imidoyl group of **3** was resistant to hydrolysis. Thus, **3** was quantitatively recovered from a water–dioxane solution under prolonged reflux, even in the presence of excess sodium hydroxide. In hot concentrated hydrochloric acid, decomposition of **3** was observed without evidence of formation of the corresponding succinimide. This resistance to hydrolysis of the imidoyl group is ascribed to steric hindrance at the carbon atom. A derivative of **3** could be made by treatment with *m*-chloroperoxybenzoic acid, which oxidised the imidoyl nitrogen forming the succinomonooxime **4**. The oxime was obtained in low yield as a mixture of the *E* and *Z* isomers. The ^1H NMR spectrum of the isomeric mixture showed that both the α- and isopropyl-methyl groups of the major isomer are weakly shielded with respect to corresponding groups of the minor isomer. Protons on backbone carbons of oximes are generally shielded when they become away from the hydroxyl group in going from one geometrical isomer to the other.[10,11] Thus, the *Z* configuration, in which the α- and isopropyl-methyl groups are away from the hydroxyl group in comparison with the *E* configuration, is assigned to the major isomer. This *Z* isomer, which is less sterically demanding and presumably more stable, predominated in a 1 : 4 ratio.

Experimental

Imidosuccinimide **3**: To a solution of *n*-butyllithium in dry THF (prepared from a 2.0 M hexane solution of *n*-butyllithium (1.1 mL, 2.2 mmol) and dry THF (3 mL)) at 0 °C and under nitrogen, freshly distilled homoveratrylamine (360 μL, 2.16 mmol) was added dropwise with stirring, followed by addition of a solution of β-cyanoester **1**[12] (342 mg, 1.03 mmol) in dry THF (4.5 mL). After 3 h at room temperature, the mixture was poured into water and extracted with methylene dichloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was stirred with 2 M aqueous HCl (15 mL), and the mixture was then washed with diethyl ether. The clear aqueous phase obtained was brought to *p*H 6 with 1 M aqueous KOH. The precipitated solid was filtered off, washed with water and recrystallised from methylene dichloride-diethyl ether to yield **3** (330 mg, 68%), mp 137–139 °C; ν_{max} (KBr)/cm^{-1} 3300m (NH), 1710s (C=O) and 1610s (C=N); δ_H(200 MHz; $CDCl_3$) 0.45 (3 H, s), 0.82 (3 H, d, *J* 7 Hz), 0.84 (3 H, d, *J* 7 Hz), 1.24 (3 H, s), 2.59 (1 H, sept, *J* 7 Hz), 3.00 (2 H, m), 3.84 (3 H, s), 3.86 (3 H, s), 3.89 (6 H, s), 3.90 (2 H, m), 6.8 (6 H, m) and 7.5 (1 H, br, NH); δ_C (125 MHz; $CDCl_3$) 16.3, 18.7, 18.8, 29.3, 32.6, 32.9, 39.8, 47.3, 55.8, 55.83, 55.9, 56.0, 61.5, 110.9br, 111.1br, 111.2, 112.2, 120br, 121.0, 130.4, 131.1, 147.6, 148.0br (split into 148.3br and 149.1br at 50 °C), 148.8, 167.7br (C=N) and 181.1 (C=O) (Found: C, 69.0; H, 8.0; N, 6.2. $C_{27}H_{36}N_2O_5$ requires C, 69.23; H, 7.69; N, 5.98%).

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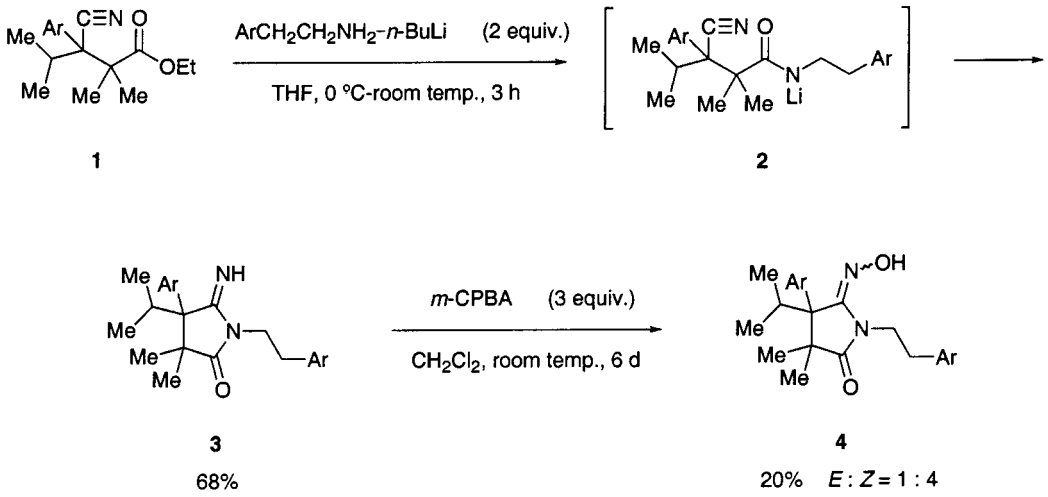
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 1 Ar = 3,4-dimethoxyphenyl

Succinimide monooxime **4**: A solution of the imidosuccinimide **3** (23 mg, 0.049 mmol) and 50–60% *m*-chloroperoxybenzoic acid (47 mg, *ca* 0.15 mmol) in methylene dichloride (250 µL) was kept at room temperature for 6 d. The resulting mixture was diluted with diethyl ether, washed with 5% Na_2CO_3 and then with water to pH 7, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. TLC on silica gel with diethyl ether-light petroleum (bp 40–60 °C) (3 : 2) as the eluent yielded **4** (5 mg, 20%), mp 165–200 °C (decomp.); t_R[reverse phase 18; 0.006 M aq. trifluoroacetic acid-acetonitrile (3 : 2)]/min 7.6 and 8.7; ν_{max}(KBr)/cm^{-1} 3280br (OH), 1700m (C=O), 1680m (C=O) and 1620s (C=N); δ_H (200 MHz; $CDCl_3$; *E : Z* = 1 : 4) 0.60 and 0.65 (*Z*- and *E*-isomer, resp.; total 3 H, 2 s, α-Me), 0.91 and 0.96 (for *Z*- and *E*-isomer, resp.; total 6 H, 2 d, *J* 7 Hz, CH_3CH), 1.30 and 1.37 (*Z*- and *E*-isomer, resp.; total 3 H, 2 s, α-Me), 2.64 (1 H, sept, *J* 7 Hz), 3.01 (2 H, t, *J* 8 Hz), 3.83, 3.87, 3.89 and 3.91 (total 12 H, 4 s), 4.20 (2 H, t, *J* 8 Hz), 6.8 (4 H, m), 7.1 (2 H, br) and 7.2 (1 H, br, OH) (Found: C, 67.3; H, 7.0; N, 5.8. $C_{27}H_{36}N_2O_6$ requires C, 66.94; H, 7.44; N, 5.78).

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