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The cyclocondensation of *N*-(2-bromoethyl)phthalimide with the enolate of benzyl phenyl acetate afforded two possible compounds depending on the experimental conditions used.

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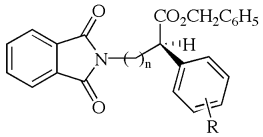
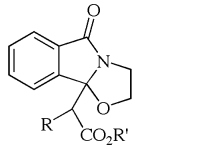
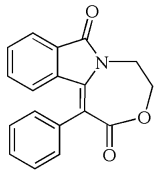
N-(haloalkyl)phthalimides have been widely used for the introduction of aminoalkyl groups in a variety of substrates. As an example, we recently developed a convenient method using *N*-bromomethyl or *N*-(3-bromopropyl)phthalimide and lithium enolate of aryl acetic acid esters, to obtain in good yield some racemic *N*-phthalyl β and δ-amino esters **1a** and **1c** [1].



1a n = 1
1b n = 2
1c n = 3



2a R = $(CH_2)_2CH_3$, R' = CH_3
2b R = $CH(CH_3)_2$, R' = CH_3
2c R = C_6H_5, R' = $CH_2C_6H_5$



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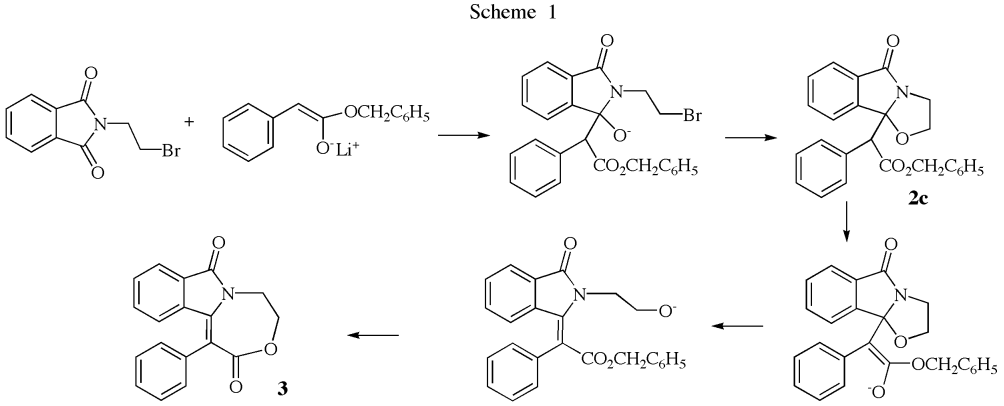
However, the preparation of γ-amino acid derivatives **1b** cannot be considered using the same procedure, since it has been shown that the imide carbonyl function of *N*-(2-bromoethyl)phthalimide rapidly reacts with nucleophiles [2]. Thus, the reaction of *N*-(2-bromoethyl)phthalimide with lithium enolates of methyl butyrate or methyl isobutyrate leads to the corresponding isoindolone **2a** and **2b** [2b,2f]. The same reaction realized with the lithium enolate of ethyl phenylacetate showed the same reactivity, but in this particular case the lactone **3** was the only reaction product [2g]. The authors assume that this result may be related to the enhanced acidity of the phenylacetate and also to the solvent mixture used.

These latter results prompt us to present our observations, which underline that the base stoichiometry is an important factor on the reaction course.

We investigated the reaction of *N*-(2-bromoethyl)phthalimide with the lithium enolate of benzyl phenylacetate using the same experimental conditions as those previously used for the preparation of *N*-phthalyl β and δ-amino esters **1a** and **1c** [1].

A THF solution of benzyl phenylacetate was added, at low temperature (-78 °C), to a mixture of 1.2 equivalents of lithium diisopropylamine (LDA) and 5 equivalents of DMPU [3] in THF. One hour later, a solution of N-(2-bromoethyl)phthalimide (1.1 equivalent) in THF was added dropwise at the same temperature. After one hour stirring at –78 °C and then one night at room temperature, a classical workup provided compound **3** (20%), which crystallized in the ether extracts. The structure of **3** was ascertained from the NMR spectral data (^1H and ^{13}C), mass spectrometry (FAB), X-ray diffraction analysis (Figure 1) [7] and from comparison with previous results [2f]. Under these conditions, 30% of vinyl phthalimide [4] was also

Scheme 1



formed *via* a dehydrobromination of the N-(2-bromoethyl)phthalimide [5,6].

As previously proposed [2f], the reaction may first lead to **2c** by carbaniom attack at one imide carbonyl group of the phthalimide, followed by ring closure (Scheme 1). Then, enolization of compound **2c** provided formation of compound **3**. Warana [2f], who used only one equivalent of base, proposed that enolization of compound **2** results from the consumption of another equivalent of the enolate of phenylacetate. In our case, it can also be considered that the excess of LDA (1.2 equivalents used to form the enolate) was responsible of this enolization process.

To control if the reaction investigated would stop with the formation of compound **2c** when using less than one equivalent of base, the same reaction was carried out using 0.95 equivalent of LDA. Under these conditions, the formation of compound **3** as well as the formation of vinyl phthalimide was not observed. The only product obtained was compound **2c** indicating that under these conditions and in absence of an excess of base there was no enolization of compound **2c**. In fact, the reaction afforded the 2,3-dihydroxazolo[2,3-*a*]isoindole derivative **2** as previously described when using the enolates of methyl butyrate or methyl isobutyrate [2b,2f].

Compound **2c** was isolated in 55 % yield after chromatography as a mixture of two diastereoisomers in a ratio close to 83/17. The main diastereoisomer rac-(*R*,*S*)-**2c** was easily obtained after one recrystallisation. Its structure was ascertained from the spectra data (^{1}H and ^{13}C NMR) and its stereochemistry from the X-ray diffraction analysis (Figure 2) [8].

In conclusion, these results showed that it was possible to modify the reaction course of the cyclocondensation of *N*-(2-bromoethyl)phthalimide with the lithium enolate of benzyl phenyl acetate just changing the base stoichiometry. This method allowed the first preparation and characterization of the corresponding homochiral 2,3-dihydroxazolo[2,3-*a*]isoindole derivative **2c**.

EXPERIMENTAL

4,5-Dihydro-1-Phenyl[1,4]oxazepino [5,4-*a*]isoindole -2,7-dione (**3**).

A solution of *n*-butyllithium (2.5 *M*) in hexane (2.2 ml, 3.0 mmol) was added dropwise over 5 minutes to a stirred solution of diisopropylamine (0.45 ml, 3.2 mmol) in dry THF (6 ml) at –78 °C under argon atmosphere. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (1.7 ml) was added in one portion and the mixture was then stirred at –78 °C for 1 hour. A solution of benzyl 2-phenylacetate (565 mg, 2.5 mmol) in THF (7 ml) was then added over 10 minutes, keeping the temperature below –78 °C during the addition. After 1 hour stirring at –78 °C, the *N*-bromoethylphthalimide (762 mg, 3.0 mmol) was added dropwise in dry THF (5 ml) at the same temperature. The mixture was stirred for an additional 1 hour at –78 °C, and then warmed slowly to room temperature. After 16 hours stirring at room temperature the reaction mixture was

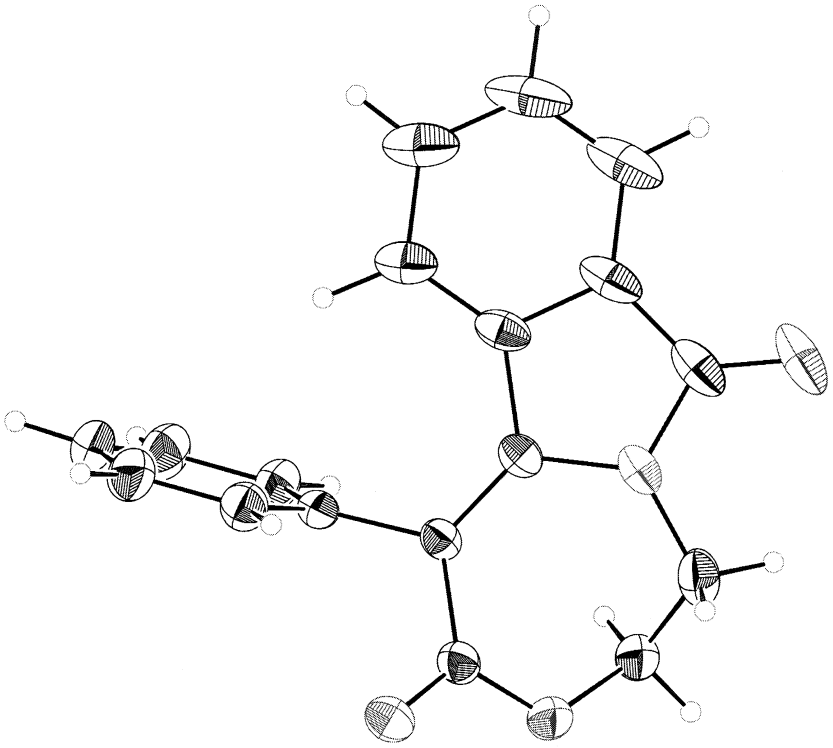


Figure 1. ORTEP drawing of compound **3**.

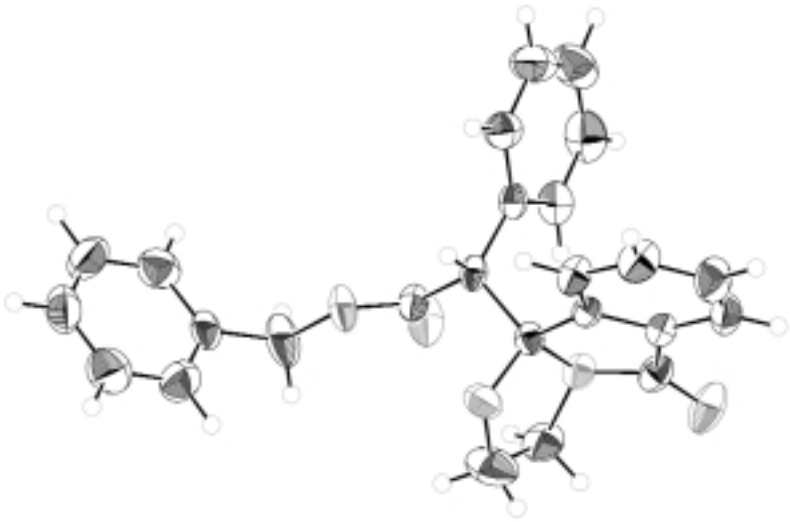


Figure 2. ORTEP drawing of the homochiral compound **2c**.

quenched with 1 *N* HCl (30 ml) and then extracted with diethylether (3 x 50 ml). The combined ether extracts were dried (sodium sulfate) and partially concentrated *in vacuo* to yield a white solid that was collected by filtration. After recrystallization from diethyl ether, compound **3** was obtained in pure form in 21 % yield (153 mg). tlc (silica gel, hexane/AcOEt/AcOH, 3/7/0.1) Rf 0.55; m.p. 191-192 °C; ms; *m/z* 292 [$(M+H)^+$]; ^{1}H nmr ($CDCl_3$): δ = 4.35 (m, 2H, CH_2-N), 4.75 (m, 2H, CH_2-O), 5.88 (d, J = 7.5 Hz, 1H, *H*-arom), 7.23 (t, $J_1 = J_2 = 7.5$ Hz, 1H, *H*-arom), 7.40 (m, 2H, *H*-arom), 7.47 (t, $J_1 = J_2 = 7.5$ Hz, 1H, *H*-arom), 7.53 (m, 3H, *H*-arom), 7.85 (d, J = 7.5 Hz, 1H, *H*-arom); ^{13}C nmr ($CDCl_3$): δ 44.09 (*C*H_2-N), 65.81 (*C*H_2-O), 112.29 (*C*), 124.09, 126.55, 129.34, 130.87, 131.12, 133.03 (*C*H-arom), 136.40, 136.74 (*C*-arom), 140.83 (*C*), 166.86, 167.92 (*C*O).

Anal Calcd. For $C_{18}H_{13}NO_3$ (291.09): C, 74.22; H, 4.50; N 4.81. Found: C, 74.00; H, 4.54; N, 4.85.

Benzyl (5-Oxo-2,3-dihydro-5*H*-oxazolo[2,3-*a*]isoindol-9b-yl)phenylacetate (**2c**).

Compound **2c** was prepared using 0.95 equivalent of lithium diisopropylamide (2.37 mmoles) and following the procedure described for compound **3**. Column chromatography on silica gel, eluting with hexane/ethyl acetate (7/3) of the crude oil obtained after evaporation of the organic extracts yielded **2c** (521 mg, 55 % yield) as a mixture of two diastereoisomers (83/17). The main diastereoisomer was isolated after recrystallization from hexane (406 mg, 45 % yield).

Main diastereoisomer : tlc (silica gel, hexane/AcOEt/, 7/3) Rf 0.50; m.p. 119-121°C; ms; *m/z* 400 [$(M+H)^+$]; ^{1}H nmr ($CDCl_3$): δ = 3.10 (ddd, J = 7.1, 9.0, 11.0 Hz, 1H, *H*CH-N), 3.75 (m, 1H, *H*CH-N), 3.92 (m, 2H, CH_2-O), 4.23 (s, 1H, C*H*COO), 4.98 (d, J = 12.3 Hz, 1H, *H*CHC_6H_5), 5.18 (d, J = 12.3 Hz, 1H, *H*CHC_6H_5), 7.05-7.40 (m, 14H, *H*-arom); ^{13}C nmr ($CDCl_3$): δ 44.65 (*C*H_2-N), 58.68 (*C*H-CO_2), 67.40 (*C*$H_2C_6H_5$), 70.70 (*C*H_2-O), 101.41 (*C*), 123.66, 124.45, 128.65, 128.83, 128.88, 129.02, 130.34, 130.65 (*C*H-arom), 133.23, 133.34 (*C*-arom), 133.49 (*C*H-arom), 135.85, 146.88 (*C*-arom), 170.63, 174.49 (*C*O).

Anal. Calcd. for $C_{25}H_{21}NO_4$ (399.15): C, 75.17; H, 5.30; N, 3.51. Found: C, 74.81; H, 5.36; N, 3.47.

Minor diastereoisomer: nmr data were deduced from comparison of the data of the diastereoisomeric mixture and pure homochiral diastereoisomer obtained after recrystallization; ^{1}H nmr ($CDCl_3$): δ = 2.72 (ddd, J = 7.5, 8.7, 11.2 Hz, 1H, *H*CH-N), 3.80 (m, 1H, *H*CH-N), 3.92 (m, 2H, CH_2-O), 4.36 (s, 1H, C*H*COO), 4.82 (d, J = 12.2 Hz, 1H, *H*CHC_6H_5), 4.94 (d, J = 12.2 Hz, 1H, *H*CHC_6H_5), 7.05-7.40 (m, 14H, *H*-arom); ^{13}C nmr ($CDCl_3$): δ 44.37 (*C*H_2-N), 57.96 (*C*H-CO_2), 67.17 (*C*$H_2C_6H_5$), 70.18 (*C*H_2-O), 101.34 (*C*), 123.93, 124.35, 127.85, 128.07, 128.88, 129.02, 130.34, 130.65 (*C*H-arom), 133.13, 133.23 (*C*-arom), 133.32 (*C*H-arom), 135.64, 146.05, (*C*-arom), 169.98, 174.42(*C*O).

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[4] The vinyl phthalimide was isolated in 30% yield from the ether extracts after column chromatography eluting with hexane / ethyl acetate (8/2).

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[7] Crystallization of an aliquot of **3** from a mixture of diethyl

ether yielded colourless crystals suitable for X-ray analysis. The diffraction data were collected on a Enraf-Nonius KappaCCD diffractometer using graphite-monochromate Mo Kα radiation and the ϕ-scan technique up to θ = 26.38. Crystal data of **3**: Molecular formula $C_{18}H_{11}NO_3$, molecular weight = 289.29, monoclinic**,** Space group P1/c, Cell constants: a = 9.6133(6) Å, b = 15.810(1) Å, c = 9.5210(4) Å, V = 1413.0(8) $Å^3$, Z = 4, Dc = 1.360 mg m^{-3}, T = 298 K, Final R = 0.051, Final Rw = 0.068.

[8] Crystallization of an aliquot of **2c** from a mixture of diethyl ether/hexane yielded colourless crystals suitable for X-ray analysis. The diffraction data were collected on a Enraf-Nonius KappaCCD diffractometer using graphite-monochromate Mo Kα radiation and the ϕ-scan technique up to θ = 26.35. Crystal data of **2c**: Molecular formula $C_{25}H_{21}NO_4$, molecular weight = 399.44, monoclinic**,** Space group P1/c, Cell constants: a = 18.583(1) Å, b = 14.994(1) Å, c = 21.333(2) Å, V = 2051.2(2) $Å^3$, Z = 4, Dc = 1.294 mg m^{-3}, T = 298 K, Final R = 0.047, Final Rw = 0.060. Details of the crystal structure determination have been deposited at the Cambridge Cristallographic Data Centre (deposition number CCDC-173136).