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THE PRACTICAL USE OF A GLYCINE ANION EQUIVALENT FOR THE PREPARATION OF 3-CARBOXY-1,2-DIHYDRO-1-OXOISOQUINOLINE

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Abstract. Reaction of the dianion derived from N-Cbz-glycine ethyl ester with 2-carboxybenzaldehyde gave the 2-(phthalidyl)glycinate derivative **8** as the major product. Successive treatment of the latter with LiOH and CF_3CO_2H/CF_3SO_3H afforded the title compound in good overall yield.

Isoquinolines represent a fundamental structure in the medicinal chemist's arsenal. The development of novel, efficient methods of preparing functionalized derivatives of these compounds is thus of continual interest. While substituents on the "A" ring of isoquinolines are readily incorporated either by direct electrophilic substitution or by use of an appropriately substituted phenyl group for the preparation of the isoquinoline nucleus, the introduction of substituents on the "B" ring, especially those which can serve as functional groups for further transformations, is more problematic. We have recently described the use of an α-formylglycine equivalent for the synthesis of isoquinoline-3-carboxylates from

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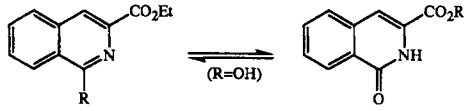


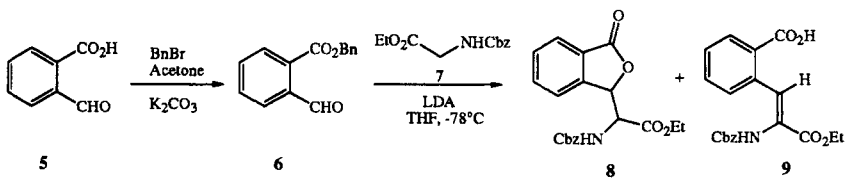
1 R=H
2 R=OH

3 R=Et
4 R=H

benzaldehydes.[1] In this communication, we wish to report a very convenient procedure for preparing the 1-hydroxy derivative of **1**, i.e. **2** (which, in its most stable form, exists mainly as the 1-oxo tautomer **3**) based on use of the dianion derived from N-Cbz-glycine ethyl ester.

Sporadic reports of the synthesis of **3** and its carboxylic acid derivative **4** have appeared in the literature over the years. These methods include reaction of isocoumarin-3-carboxylic acid with ammonia,[2] alkaline hydrolysis of 5-*o*-carbomethoxybenzylidene-2-phenyloxazol-4-one,[3] reaction of rhodanine with *o*-carboxy aromatic aldehydes,[4] and the palladium-catalyzed coupling of 2-iodobenzonitrile with ethyl 2-ethoxyacrylate.[5] Central nervous system activities of peptide derivatives of **4** have also been reported.[6]

Our methodology for the preparation of **3** and **4** depends on the use of 2-carboxybenzaldehyde **5** as starting material (Scheme 1). The latter, which favors the thermodynamically more stable phthalide form, could be efficiently esterified



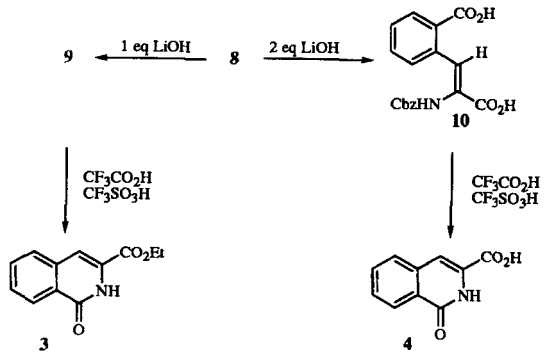
5 6 8 9

Scheme 1

by the method of Brown and Sargent.[7] Thus, treatment of **5** with potassium carbonate and benzyl bromide in acetone gave the benzyl ester **6** in 57% yield. Compound **6** reacted with the dianion of N-Cbz-glycine ethyl ester **7** (prepared by the action of 2.3 eq of LDA in THF at -78°C)[8-10] to form two products which were isolated by chromatography on silica gel. Spectral data for the major product, formed in 53% yield, indicated formation of the 2-(phthalidyl)glycinate structure **8**. The ^{1}H NMR spectrum of **8** showed, moreover an *anti/syn* ratio of 3:2 based on the H-H coupling constants at the chiral centers (2.5 and 0 Hz, respectively).[11] The second and minor product **9**, obtained in 7% yield as a single geometrical isomer, is formally the result of dehydration of the product of aldol condensation and hydrolysis of the benzyl ester moiety. However, since the ethyl ester function was not also hydrolyzed, it appears more likely that compound **9** arises from α-proton abstraction from **8** followed by furanone ring opening. This pathway is verified by the observation that compound **8** was completely transformed into the aminocinnamate **9** by treatment with 1 eq of LiOH (Scheme 2). Furthermore, treatment of **8** with 2 eq of LiOH afforded the dicarboxylic acid **10** in quantitative yield.

Finally, both **9** and **10** underwent efficient cyclization to the 1-oxo-1,2-dihydroisoquinoline 3-ester (**3**) and 3-carboxylic acid (**4**), respectively, after brief exposure to 1 eq of triflic acid in trifluoroacetic acid. The physical and spectral data of **3** and **4** were comparable to previously published values for these compounds.[4,5]

In conclusion, the present methodology for the synthesis of the title compounds represents a convenient alternative to previously described procedures and provides another example of the use of glycine derivatives for the preparation of functionalized heterocycles.[1,10,12]



Scheme 2

Experimental

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained as films (i.e., by application of a CH_2Cl_2 solution to an NaCl plate followed by evaporation of the solvent) or as a KBr pellet with a Nicolet 205 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz), Bruker WP250 (250 MHz) or Bruker Aspect 3000 (300 MHz) instrument. Chemical shifts are given as δ values with reference to Me_4Si which was used as internal standard. Electron impact (EI) and chemical ionization (CI) mass spectra were respectively recorded on an AEI MS-50 and an AEI MS-9 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm) and with a 20% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230-240 mesh) at medium pressure (200 mbar). Starting materials were purchased from Aldrich Chemical Co. and were used without

further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

Benzyl 2-Formylbenzoate (6) : To a solution of 2-carboxybenzaldehyde (**5**, 2.5 g, 16.7 mmol) in anhydrous acetone (45 mL) was added at rt solid potassium carbonate (6.55 g, 47.4 mmol) followed by benzyl bromide (1.73 mL, 14.6 mmol). The reaction mixture was stirred vigorously for 60 h, the solid was removed by filtration and the filtrate was evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel (ethyl acetate-heptane 1:9) affording compound **6** as a colorless oil (2.3 g, 57%) : EIMS m/z 240 $(M)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 2H, OCH_2), 7.30-7.50 (m, 5H, ArH), 7.60-7.70 (m, 2H, H-4, H-5), 7.90-7.95 (m, 1H, H-3), 7.98-8.04 (m, 1H, H-6), 10.60 (s, 1H, CHO) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.7, 128.5, 128.6, 128.8, 130.5, 132.0, 132.5, 133.0, 135.4, 137.2, 166.1, 192.0. Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.00 ; H, 5.00. Found : C, 74.91 ; H, 5.05.

Ethyl (2*RS*,3*RS*)-*N*-Benzyloxycarbonyl-2-(3-phthalidyl)glycinate (8) and Ethyl 2'-*N*-(Benzyloxycarbonyl)amino-2-carboxycinnamate (9) : To a solution of LDA (15.6 mmol) in anhydrous THF (48 mL) was added at -78 °C under argon a solution of ethyl N-(benzyloxycarbonyl)glycinate (**7**, 1.61 g, 6.8 mmol) in THF (16 mL). The reaction mixture was stirred for 1.5 h at -78 °C during which time a pale yellow precipitate was formed. A solution of aldehyde **6** (1.96 g, 8.14 mmol) in THF (8 mL) was then added and stirring was maintained at -78 °C for an additional 2.5 h. The reaction was quenched by addition of aqueous NH_4Cl (5 mL) and the mixture was acidified by addition of aqueous HCl (3N), diluted

with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The organic extracts were combined, washed with saturated aqueous NaCl (10 mL) and dried over sodium sulfate. Removal of the solvents under reduced pressure left an oily residue which was purified by column chromatography on silica gel. Elution of the column with dichloromethane-acetone (98:2) afforded compound **8** as an oil (1.32 g, 53%) : IR (film) 3329, 1774, 1727, 1530 cm^{-1} ; CIMS m/z 370 $(MH)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 and 1.10 (2 x t, 3H, J = 7.0 Hz, *syn* and *anti* CH_3), 3.82-4.20 (m, 2H, $C\underline{H}_2CH_3$), 4.80 (q, 0.8 H, J = 12.4 Hz, *syn* $PhC\underline{H}_2$), 4.90-5.00 (m, 0.4 H, *syn* NHC<u>H</u>), 5.00-5.10 (m, 1.8 H, *anti* NHC<u>H</u>, *anti* $PhC\underline{H}_2$), 5.36 (d, 0.4 H, J = 9.1 Hz, *syn* NH), 5.53 (d, 0.6 H, J = 8.2 Hz, *anti* NH), 5.72 (d, 0.6 H, J = 2.5 Hz, *anti* NHCHC<u>H</u>), 5.90 (s, 0.4 H, *syn* NHCHC<u>H</u>), 7.21 (m, 5H, ArH), 7.40-7.60 (m, 3H, ArH), 7.75 (d, 0.4 H, J = 7.8 Hz, *syn* ArH-6), 7.90 (d, 0.6 H, J = 7.7 Hz, *anti* ArH-6) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 14.1, 55.5, 56.8, 62.2, 62.7, 67.1, 67.5, 80.4, 80.7, 123.6, 123.9, 125.5, 125.8, 128.2, 128.5, 128.6, 129.9, 130.9, 134.2, 134.3, 135.9, 145.4, 145.7, 155.3, 156.0, 166.4, 168.4, 169.4. Anal. Calcd for $C_{20}H_{19}NO_6.0.25\ H_2O$: C, 64.25 ; H, 5.26 ; N, 3.75. Found : C, 64.11 ; H, 5.41 ; N, 3.74.

Continued elution of the chromatography column with dichloromethane-acetone (9:1) afforded compound **9** as a colorless oil (180 mg, 7%) : IR (film) 3299, 1715, 1712, 1648 cm^{-1} ; EIMS m/z 369 $(M)^+$; ^1H NMR (200 MHz, acetone-d_6) δ 3.22 (t, 3H, J = 7.2 Hz, CH_3), 4.20 (q, 2H, J = 7.2 Hz, $C\underline{H}_2CH_3$), 5.05 (s, 2H, $PhC\underline{H}_2$), 7.30 (m, 5H, ArH), 7.35-7.60 (m, 3H, H-3, H-4, H-5), 7.90 (s, 1H, C=CH), 8.00 (d, 1H, J = 7.5 Hz, H-6) ; ^{13}C NMR (50 MHz, acetone-d_6) δ 14.5, 61.9, 67.1, 127.5, 128.7, 129.2, 129.3, 130.5, 131.6, 132.9, 135.0, 136.7, 137.8, 155.5, 165.8, 168.1. Anal. Calcd for $C_{20}H_{19}NO_6.0.35\ H_2O$: C, 63.94 ; H, 5.29 ; N, 3.73. Found : C, 64.01 ; H, 5.58 ; N, 3.65.

Conversion of compound 8 into compound 9 : A solution of compound **8** (343 mg, 0.93 mmol) in dioxane (5 mL) and water (1 mL) was treated at rt with lithium hydroxide (0.3 mL of a 3 M solution ; 0.9 mmol). After 15 min, the reaction mixture was acidified by addition of concentrated HCl and extracted with ethyl acetate (3 x 5 mL). The organic extracts were combined, washed with saturated aqueous NaCl (5 mL) and dried over sodium sulfate. Removal of the solvents under reduced pressure afforded compound **9** (320 mg, 93%), identical in all respects to the minor product obtained from reaction of **6** and **7**.

2'-*N*-(Benzyloxycarbonyl)amino-2-carboxycinnamic acid (10) : Following the same procedure as for the preparation of **9** from **8**, a mixture of the latter (550 mg, 1.5 mmol) in dioxane (11 mL) and water (3 mL) was treated at rt with lithium hydroxide (1.04 mL of a 3M solution, 3.12 mmol). After 30 min, the reaction mixture was worked up as before to afford compound **10** as a viscous oil (500 mg, 99%) : IR (film) 3249, 1708, 1694 cm^{-1} ; EIMS m/z 341 $(M)^+$; ^1H NMR (250 MHz, acetone-d_6) δ 5.17 (s, 2H, PhC$\underline{H}_2$), 7.32 (m, 5H, ArH), 7.45 (ddd, 1H, *J* = 7.5, 7.4 and 1.6 Hz, H-4), 7.53 (ddd, 1H, *J* = 7.6, 7.5 and 1.4 Hz, H-5), 7.60 (dd, 1H, *J* = 7.6 and 1.6 Hz, H-6), 7.80 (br s, 1H, exchangeable with D_2O, NH), 8.20 (s, 1H, C=C$\underline{H}$), 8.60 (dd, 1H, *J* = 7.4 and 1.4 Hz, H-3) ; ^{13}C NMR (75 MHz, acetone-d_6) δ 67.1, 127.4, 128.6, 128.7, 129.3, 130.6, 131.7, 133.0, 133.6, 137.0, 138.0, 155.5, 166.7, 168.0. Anal. Calcd for $C_{18}H_{15}NO_6.0.7\ H_2O$: C, 61.09 ; H, 4.67 ; N ; 3.96. Found : C, 61.11 ; H, 4.51 ; N, 3.94.

Ethyl 1,2-Dihydro-1-oxoisoquinoline-3-carboxylate (3) : A solution of compound **9** (180 mg, 0.48 mmol) in trifluoroacetic acid (1.6 mL) was treated

with trifluoromethanesulfonic acid (0.043 mL, 0.48 mmol). The reaction mixture was stirred for 15 min at rt and then evaporated to dryness under reduced pressure. The residue was taken up in water (5 mL) and extracted with chloroform (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (dichloromethane-acetone 98:2), affording compound **3** as a white solid (52 mg, 50%) : mp 139 °C (lit.[5] mp 142 °C (hexane)); IR (KBr) 3163, 3092, 1768, 1730, 1642 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, 3H, J = 7.2 Hz, CH_3), 4.42 (q, 2H, J = 7.2 Hz, CH_2), 7.40 (s, 1H, H-4), 7.50-7.80 (m, 3H, H-5, H-6, H-7), 8.40 (d, 1H, J = 7.9 Hz, H-8), 9.40 (br s, 1H, exchangeable with D_2O, NH) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 63.5, 112.8, 128.3, 128.7, 129.0, 130.4, 134.2, 137.0, 162.2, 162.8.

1,2-Dihydro-1-oxoisoquinoline-3-carboxylic acid (4). A mixture of compound **10** (157 mg, 0.46 mmol) and trifluoroacetic acid (1.5 mL) was treated with trifluoromethanesulfonic acid (0.041 mL, 0.46 mmol). The reaction mixture was stirred for 15 min at rt and then evaporated to dryness under reduced pressure. The residual solid was suspended in a mixture of ethyl acetate (1 mL) and water (1 mL) and collected by filtration, affording compound **4** as an off-white powder (50 mg, 57%) : mp 325 °C (decomp) (lit.[4] mp 326-328 °C). IR (KBr) 3442, 3114, 1702, 1642, 1602 cm^{-1} ; ^1H NMR (200 MHz, DMSO-d_6) δ 7.50 (s, 1H, H-4), 7.75 (dd, 1H, J = 7.2 and 7.4 Hz, H-7), 7.90 (dd, 1H, J = 7.2 and 7.8 Hz, H-6), 8.00 (d, 1H, J = 7.8 Hz, H-5), 8.47 (d, 1H, J = 7.4 Hz, H-8), 11.00 (s, 1H, exchangeable with D_2O, NH) ; ^{13}C NMR (75 MHz, DMSO-d_6) δ 110.5, 127.6,

128.5, 129.0, 129.6, 130.6, 136.7, 162.0, 163.6. Anal. Calcd for $C_{10}H_7NO_3.0.3$ H_2O : C, 61.73 ; H, 3.94 ; N, 7.20. Found : C, 61.72 ; H, 4.24 ; N, 6.89.

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