A Novel Synthesis of 1,4-Dihydrobenzo[c]-1,5-naphthyridin-2(3H)-ones from Pyrrolo[1,2-b]isoquinolines[1]

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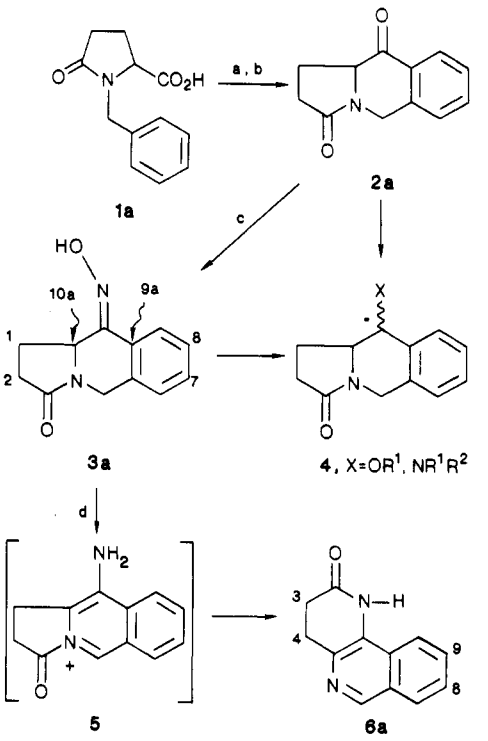
While investigating the synthesis of hydroxy- and amino-substituted pyrrolo[1,2-*b*]isoquinolines (Scheme I, **4**[2]), 1,4-dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-one (**6a**) was obtained as the exclusive product from an attempted Beckmann rearrangement of **3a**. Although partially reduced benzo[*c*]-1,5-naphthyridines (e.g., 5,6-dihydro-[3] and 5,6,6a,7,8,9,10,10a-octahydrobenzo[*c*]-1,5-naphthyridine[4]) are known, the reported syntheses do not permit the preparation of analogues such as **6a**. We wish to describe this novel synthesis of these compounds and present evidence suggesting that a Semmler–Wolff-type aromatization reaction[5] may participate in the overall transformation.

The required intermediates were prepared by Friedel–Crafts cyclization of (±)-5-oxo-1-(phenylmethyl)proline (**1a**) to give ketone **2a**,[6] which was converted to a single oxime isomer, **3a**, by standard methods. Treatment of **3a** under Beckmann conditions (polyphosphoric acid, 100 °C) gave a new compound which was neither a product of the Beckmann rearrangement nor a nitrile that would result from oxime fragmentation. On the basis of solubility properties (acid soluble), spectral data (IR, ^{1}H NMR, MS), and elemental analysis, this new compound was identified as **6a**. The formation of **6a** was rationalized as involving Semmler–Wolff-type aromatization of **3a** and rearrangement of a hypothetical acylpyridinium species such as **5** to the product.

Previous investigations have elucidated structural elements and reaction conditions which influence oximes to undergo Semmler–Wolff aromatization vs. the Beckmann rearrangement or fragmentation to nitriles. As discussed by Conley and Ghosh,[5] one of the strongest arguments for the hypothesis that the Semmler–Wolff aromatization of 1-tetralone oximes proceeds from the syn to phenyl configuration of the oxime hydroxy group is the failure of 8-substituted 1-tetralone oximes to aromatize because isomerization to the syn to phenyl configuration is sterically prohibited (e.g., 5,8-dimethyl-1-tetralone oxime affords the Beckmann product). Based on analogy to the substituted 1-tetralone oximes, we believed that the 7-chloro (**3b**) and 9-chloro (**3c**) oximes, obtained during the synthesis of nuclear substituted analogues of **4**, would provide some insight into the process which led to **6a**.

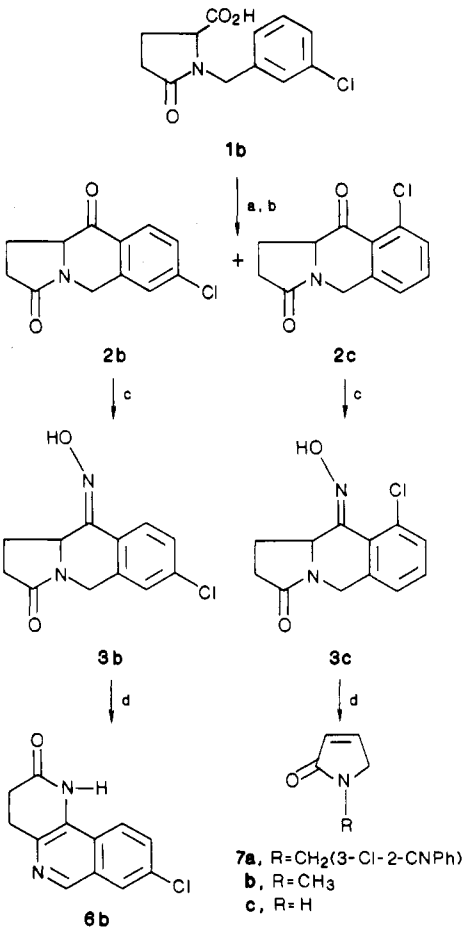
As shown in Scheme II, Friedel–Crafts cyclization of **1b** provided a mixture of chloro ketones **2b** and **2c**, which were separated by preparative HPLC and converted to oxime derivatives **3b** and **3c**, respectively. The assignment of the oxime hydroxy group of **3c** as anti to phenyl was based on steric arguments due to the presence of the 9-

Scheme I[a]



[a] (a) $SOCl_2$; (b) $AlCl_3$; (c) NH_2OH; (d) PPA/100 °C.

Scheme II[a]



[a] (a) $SOCl_2$; (b) $AlCl_3$; (c) NH_2OH; (d) PPA/100 °C.

(1) Presented in part at the 10th International Congress of Heterocyclic Chemistry, University of Waterloo, Ontario, Canada, August 11–16, 1985, papers P5–118.

(2) The synthesis of diastereoisomeric alcohol and amine analogues **4** by selective reduction of **2a** and **3a**, respectively, is the subject of a future paper.

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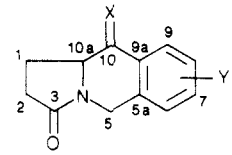
(6) During the course of this investigation, the synthesis of **2a** was reported. Rigo, B.; Kolocouris, N. *J. Heterocycl. Chem.* **1983**, *20*, 893.

0022-3263/86/1951-3697$01.50/0

Table I. ^{13}C NMR Chemical Shifts (δ) at 15.03 MHz for Ketone and Oxime Intermediates in Me_2SO-d_6



compd	X	Y	C_1	C_2	C_3	C_5	C_{5a}	C_{9a}	C_{10}	C_{10a}
2a	O	H	20.1	29.3	173.0	40.8	140.2	129.9	194.5	61.0
2b	O	7-Cl	20.0	29.4	173.1	40.5	142.3	128.8	193.8	61.0
2c	O	9-Cl	20.1	29.3	172.9	41.3	143.2	126.9	192.5	61.2
3a	NOH	H	24.5	30.0	172.4	40.3	135.2	129.4	152.9	55.0
3b	NOH	7-Cl	24.4	29.9	172.5	39.9	137.2	128.4	152.1	54.9
3c	NOH	9-Cl	23.9	30.2	172.4	40.9	140.0	127.3	152.1	54.8

chloro substituent. Mladen et al.[7] reported that α-protons of oximes which are syn to the hydroxy group appear at lower magnetic field than the α-protons of the anti isomer. Comparison of the ^1H NMR chemical shift differences for the methine (H-10a) protons of **3a** (δ 4.94), **3b** (δ 4.95), and **3c** (δ 5.18) suggested that the hydroxy groups of **3a** and **3b** are anti to the methine protons and syn to phenyl; however, these tentative assignments for **3a** and **3b** were reversed after extensive ^{13}C NMR spectral evaluation.

A number of studies employing ^{13}C NMR as an accurate tool for the assignment of oxime stereochemistry indicate that the chemical transformation of a ketone to an oxime causes both α carbons to shift upfield, but the α carbon syn to the hydroxy group of the oxime shifts an average of 5–6 ppm more than the α anti carbon. None of the compounds in the aforementioned studies contained fused aromatic ring systems, and not surprisingly our ^{13}C NMR results do not correlate precisely as described by the literature.

In order to unambiguously assign the aromatic carbons necessary for the configurational assignment of oximes **3a–c**, a combination of quaternary enhancement[11] (which permits identification of all quaternary carbons by low power noise irradiation of all protons) and long-range residual splitting[12] techniques (which permits assignment of carbons 5a and 9a by the magnitude of the residual splittings with the protons on carbon 5) were employed in conjunction with chemical shift values derived from the noise decoupled ^{13}C NMR spectra.

For oximes **3a–c**, carbons 9a did not show significant chemical shifts (δ −0.4 to +0.6) from the corresponding ketones, **2a–c**, but carbons 10a typically shifted upfield by 6 ppm upon oxime formation (Table I). On the basis of our original assumption that the oxime hydroxy group in **3c** is anti to the fused phenyl ring for steric reasons, the similarity of the chemical shifts for carbons 9a and 10a of **3a–c** indicates that the oxime hydroxy is uniformly anti to carbon 9a (phenyl) and syn to carbon 10a (methine carbon) for these compounds.

On treatment with polyphosphoric acid at 100 °C, **3b** gave **6b** as anticipated from the behavior of **3a** under similar conditions. Oxime **3c**, however, fragmented to give nitrile **7a** as the major product, which was readily identified by comparison of its ^1H NMR with published data for **7b**[13] and **7c**.[14] We believe that the formation of naphthyridine **6b** from oxime **3b** and the failure of oxime **3c** to give significant amounts of the corresponding naphthyridine product represents a close analogy to the behavior of substituted 1-tetralone oximes with respect to Semmler–Wolff aromatization as discussed by Conley and Ghosh[5] and that this analogy supports our rationalization for the participation of a Semmler–Wolff-type process in the overall transformation of **3a** to **6a**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The structures of all compounds are supported by their IR (Pye Unicam SP3-200), ^1H NMR (Varian XL 200; chemical shifts are reported in δ units relative to Me_4Si (δ 0.0) as internal standard), and MS (Finnigan 4023) spectra. Compounds **2a–c** and **3a–c** were subjected to ^{13}C NMR (JEOL FX-60; chemical shifts are reported in δ units relative to Me_2SO-d_6 (δ 39.44) as internal standard) analysis in Me_2SO-d_6. Reactions were generally conducted under a dry nitrogen atmosphere. Preparative HPLC separations were performed on silica gel with a Waters Associates Prep LC/System 500A equipped with a Gow Mac Model 80–800 UV detector. Elemental analyses were performed by MicroTech Laboratories, Skokie, IL, and results are within ±0.4% of the theoretical values unless otherwise noted.

(±)-5-Oxo-1-(phenylmethyl)proline (1a). Refluxing a solution of (±)-glutamic acid monohydrate (1.0 kg) and water (1.2 L) overnight, followed by ice–water chilling, gave 624 g (80%) of (±)-5-oxoproline as colorless crystals, mp 179–183 °C (lit.[15] mp 181.5–183 °C). As described by Campaigne and Matthews,[16] this material was converted to the methyl ester, which was benzylated and hydrolyzed to afford **1a**, mp 118–120 °C (lit.[16] mp 122–123 °C).

(±)-1-[(3-Chlorophenyl)methyl]-5-oxoproline (1b). Sodium hydride (23.4 g of a 50% mineral oil emulsion, 0.49 mol NaH) was washed with toluene and suspended in toluene (1 L). The stirred suspension was treated over 0.75 h with a solution of (±)-5-oxoproline methyl ester[16] (63 g, 0.44 mol) by using an oil bath initially as a heat sink. The resultant suspension was then held at 65 °C for 0.5 h, the bath was removed, and the mixture was treated dropwise over 10 min with a solution of 3-chlorobenzyl bromide (100 g, 0.49 mol) and toluene (50 mL). The mixture was then heated for 2 h at 100 °C, filtered through Celite, and concentrated to an oil (111 g). An aliquot (11 g) of the oil was purified by preparative HPLC (ethyl acetate) to give 8.1 g (70% by aliquot proportions) of (±)-1-[(3-chlorophenyl)methyl]-5-oxoproline methyl ester as an oil: IR ($CHCl_3$) 1745 (ester C=O), 1690 (lactam C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1–2.6 (m, 4 H, H-3, H-4), 3.7 (s, 3 H, CH_3), 4.04 (d, 1 H, NCH_2, J = 15 Hz), 4.04 (m, 1 H, H-2), 4.96 (d, 1 H, NCH_2, J = 15 Hz), 7.08–7.40 (m, 4 H, Ar H); MS

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(CI/CH_4); m/z 268 (MH^+). Anal. Calcd for $C_{13}H_{14}ClNO_3$: C, 58.33; H, 5.27; N, 5.23. Found: C, 58.13; H, 5.30; N, 5.17.

A stirred mixture of (±)-1-[(3-chlorophenyl)methyl]-5-oxoproline methyl ester (99 g, 0.37 mol), sodium hydroxide (16 g, 0.4 mol), and water was heated (steam bath) for 2 h. The cooled solution was washed with ether (2 × 300 mL), acidified, and extracted with dichloromethane (3 × 200 mL). The crystalline precipitate which separated from the organic phase was isolated and recrystallized from toluene (800 mL) to give 54.7 g (58%) of **1b**: mp 144–146 °C; IR (KBr) 1710 cm^{-1} (acid C=O); ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 2.04–2.68 (m, 4 H, H-3, H-4), 4.0 (d, 1 H, NCH_2, J = 14.9 Hz; m, 1 H, H-2), 5.08 (d, 1 H, NCH_2, J = 14.9 Hz), 7.12–7.44 (m, 4 H, Ar H); MS, m/z (relative intensity) 253 (10.3, M^+), 208 (33.8), 127 (30.8), 125 (100). Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.79; H, 4.77; N, 5.53. Found: C, 57.05; H, 4.80; N, 5.49.

1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione (2a). A stirred solution of **1a** (124.5 g, 0.57 mol, dried at 88 °C in vacuo) and dichloromethane (1 L) was treated rapidly with thionyl chloride (74.4 g, 0.63 mol). After refluxing overnight, the chilled (−2 °C) solution was treated in portions over 0.75 h with $AlCl_3$ (227.2 g, 1.71 mol) during which the temperature was not allowed to exceed 10 °C. The mixture was stirred with cooling for 1 h and then stirred for 1.5 h at room temperature (internal temperature reached 15 °C). The mixture was chilled with ice–water, and the reaction was quenched by cautious addition of ice chips (vigorous exothermic reaction with gas evolution). After quenching, the mixture was diluted with water and dichloromethane, and agitated thoroughly until all the solid dissolved. The phases were separated and the aqueous phase was extracted again with dichloromethane. The combined organic phase was washed with water and saturated brine, dried (Na_2SO_4), filtered, and concentrated to an oil, which crystallized to give 116.7 g of crude **2a**. Generally, the crude compound is sufficiently pure for further work. To prevent composition changes, crude **2a** was not permitted to remain in solution nor stand as an oil for prolonged periods, and the crystallized material was stored under refrigeration. In this instance, the crude material was further purified by preparative HPLC (38 g per separation, sample applied in dichloromethane, eluted with ethyl acetate) to give 93.5 g (82%) of **2a** as a yellow solid: mp 105–110 °C (lit.[6] mp 107–108 °C). Spectral data were in agreement with the literature.[6] Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.36; H, 5.43; N, 6.85.

(±)-7-Chloro-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione (2b) and (±)-9-Chloro-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione (2c). A stirred solution of **1b** (25.37 g, 0.1 mol), dichloromethane (20 mL), and thionyl chloride (13.09 g, 0.11 mol) was refluxed for 6 h. The chilled (5 °C) solution was then treated in portions with $AlCl_3$ (40 g, 0.31 mol) during which a precipitate formed and the resultant mixture was stirred with intermittent warming (steam bath) until the evolution of gas ceased. The cooled reaction mixture was cautiously treated with crushed ice and then diluted with water. The phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried (Na_2SO_4), filtered, and concentrated to give a gold solid (21.8 g), which was a mixture of **2b** and **2c** (TLC, silica gel, ethyl acetate; R_f **2b**, 0.32; R_f **2c**, 0.19). The mixture was separated by preparative HPLC (ethyl acetate) to give **2b** (12 g, 51%) as tan crystals after recrystallization from ethyl acetate: mp 150.5–154 °C; IR ($CHCl_3$) 1690 (ketone and lactam C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24–2.72 (m, 4 H, H-1, H-2), 4.36 (d, 1 H, H-5, J = 17.8 Hz; m, 1 H, H-10a), 5.26 (d, 1 H, H-5, J = 17.8 Hz), 7.38 (unresolved, 1 H, H-6), 7.42 (dd, 1 H, H-8, $J_{8,9}$ = 8.8 Hz, $J_{6,8}$ = 1.9 Hz); 8.05 (d, 1 H, H-9, $J_{8,9}$ = 8.8 Hz); MS, m/z (relative intensity) 237 (7.1, M^+ + 2), 235 (23.7, M^+), 195 (17.0), 193 (54.2), 154 (31.2), 153 (22.8), 152 (100), 151 (43.2), 89 (71.7). Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.79; H, 4.41; N, 5.89.

Compound **2c** was isolated as the more slowly eluting material. Recrystallization from ethyl acetate gave **2c** (2.0 g, 9%) as colorless crystals: mp 198–202 °C; IR ($CHCl_3$) 1645 (ketone and lactam C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32–2.68 (m, 4 H, H-1, H-2), 4.36 (m, 1 H, H-10a), 4.42 (d, 1 H, H-5, J = 16 Hz), 5.28 (d, 1 H, H-5, J = 16 Hz), 7.24 (m, 1 H, Ar H), 7.46 (m, 2 H, Ar H); MS, m/z (relative intensity) 237 (2.7, M^+ + 2), 235 (8.5, M^+), 193 (30), 154 (26.7), 153 (17), 152 (84.4), 151 (30.1), 89 (100). Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.79; H, 4.38; N, 5.83.

(±)-(*Z*)-1,10a-Dihydropyrrolo[1,2-*b*]isoquinoline-3,10-(2*H*,5*H*)-dione 10-Oxime (3a). A stirred suspension of **2a** (15.1 g, 0.075 mol) and 95% ethanol (120 mL) was treated with a solution of hydroxylamine hydrochloride (10.3 g, 0.15 mol), sodium acetate trihydrate (22.2 g, 0.16 mol), and water (130 mL). The mixture was refluxed for 4.5 h, during which a solution formed. Ice–water cooling afforded a crystalline precipitate, which was collected, washed with 50% aqueous ethanol, and recrystallized from 95% ethanol to give **3a** (9.9 g, 61%): mp 213.5–216 °C; IR (KBr) 1665 (C=O, C=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.68–2.92 (4 m, 4 H, H-1, H-2), 4.03 (d, 1 H, H-5, J = 16 Hz), 4.93 (d, 1 H, H-5, J = 16 Hz), 4.94 (m, 1 H, H-10a), 7.36 (m, 3 H, H-6, H-7, H-8), 7.86 (m, 1 H, H-9), 11.60 (s, 1 H, OH). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.60; N, 12.95. Found: C, 66.36, H, 5.59; N, 12.93.

(±)-(*Z*)-7-Chloro-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione 10-Oxime (3b). In a similar manner as described for the synthesis of **3a**, ketone **2b** (9.0 g, 0.038 mol) was converted to the oxime derivative, which was recrystallized from *n*-propanol to give **3b** (6.45 g, 67%): mp 249–252 °C; IR (KBr) 1690 (C=O, C=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.68–2.96 (4 m, 4 H, H-1, H-2), 4.06 (d, 1 H, H-5, J = 16 Hz), 4.95 (m, 1 H, H-10a), 5.0 (d, 1 H, H-5, J = 16 Hz), 7.42 (dd, 1 H, H-8, $J_{8,9}$ = 12 Hz, $J_{6,8}$ = 2.4 Hz), 7.56 (d, 1 H, H-6, $J_{6,8}$ = 2.4 Hz), 7.86 (d, 1 H, H-9, $J_{8,9}$ = 12 Hz), 11.68 (s, 1 H, OH); MS, m/z (relative intensity) 252 (11.6, M^+ + 2), 250 (38.7, M^+), 152 (34.9), 150 (100). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.33, H, 4.51; N, 11.11.

(±)-(*Z*)-9-Chloro-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione 10-Oxime (3c). In a similar manner as described for the synthesis of **3a**, ketone **2c** (1.0 g, 0.004 mol) was converted to the oxime derivative, which was recrystallized from 95% ethanol to give **3c** (0.52 g, 52%): mp 260–265 °C; IR (KBr) 1670 (C=O, C=N) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.56–2.76 (4 m, 4 H, H-1, H-2), 3.98 (d, 1 H, H-5, J = 14.9 Hz), 4.84 (d, 1 H, H-5, J = 14.9 Hz), 5.18 (t, 1 H, H-10a), 7.28–7.52 (m, 3 H, Ar H), 11.92 (s, 1 H, OH); MS, m/z (relative intensity) 252 (3.6, M^+ + 2), 250 (11.9, M^+), 207 (12.2), 205 (36.9), 152 (37.5), 150 (100). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.55; H, 4.40; N, 11.04.

1,4-Dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-one (6a). Finely powdered **3a** (30 g, 0.14 mol) was added quickly to hot (100 °C), stirred polyphosphoric acid (600 g). The mixture was vigorously stirred for 10 min during which the internal temperature reached 128 °C. The hot mixture was decanted over crushed ice (2.5 L) and diluted with water to give a solution, which was basified to pH 8–9 with 50% sodium hydroxide solution. Further dilution with water to keep the inorganic salts in solution was necessary. The yellow precipitate was collected by vacuum filtration, and the filter cake was washed thoroughly with water and dried in vacuo at 40 °C over NaOH pellets to give 21.6 g (78%) of crude **6a**. Further purification by preparative HPLC (10.8-g samples applied to one silica gel column in CH_2Cl_2, eluted with ethyl acetate) gave after trituration with diisopropyl ether 17.4 g (63%) of **6a** as colorless needles, mp 227–228.5 °C. In subsequent syntheses the crude product was recrystallized from 95% ethanol to give **6a** as yellow crystals: mp 227–228 °C; IR ($CHCl_3$) 1685 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.70 (t, 2 H, H-3, $J_{3,4}$ = 8 Hz), 3.22 (t, 2 H, H-4, $J_{3,4}$ = 8 Hz), 7.62–7.88 (m, 2 H, H-8, H-9), 8.10 (d, 1 H, H-7, J = 8 Hz), 8.38 (d, 1 H, H-10, J = 8 Hz), 8.93 (s, 1 H, H-6), 10.45 (s, 1 H, NH); MS m/z (relative intensity) 198 (88.7, M^+), 197 (18.7), 170 (46.6), 169 (100). Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.69; H, 5.08; N, 14.13. Found: C, 72.53; H, 5.26; N, 14.14.

8-Chloro-1,4-dihydrobenzo[*c*]-1,5-naphthyridin-2(3*H*)-one (6b). In a similar manner as described for the synthesis of **6a**, oxime **3b** (10.2 g, 0.041 mol) was added to hot polyphosphoric acid (110 g) to give the crude naphthyridine derivative which was recrystallized from *n*-propanol to afford **6b** (6.1 g, 64%) as orange crystals: mp 281–284 °C; IR (KBr) 1660 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.64 (t, 2 H, H-3, $J_{3,4}$ = 8 Hz), 3.2 (t, 2 H, H-4, $J_{3,4}$ = 8 Hz), 7.72 (dd, 1 H, H-9, $J_{9,10}$ = 9.1 Hz, $J_{7,9}$ = 1.6 Hz), 8.16

(d, 1 H, H-7, $J_{7,9}$ = 1.6 Hz), 8.36 (d, 1 H, H-10, $J_{9,10}$ = 9.1 Hz), 8.82 (s, 1 H, H-6), 10.2-10.8 (br, 1 H, NH); MS, *m/z* (relative intensity) 234 (27.4, $M^+ + 2$), 232 (83.3, M^+), 205 (37.8), 203 (100). Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.89; H, 3.90; N, 12.04. Found: C, 62.00; H, 3.97; N, 12.00.

1-[(3-Chloro-2-cyanophenyl)methyl]-1,5-dihydro-2*H*-pyrrol-2-one (7a). In a similar manner as described for the synthesis of **6a**, oxime **3c** (1.67 g, 6.67 mmol) was added to hot polyphosphoric acid (31 g) to afford a product mixture (TLC, silica gel, ethyl acetate; R_f **7a**, 0.28). Separation of the mixture by preparative HPLC (ethyl acetate) gave **7a** (0.68 g, 44%) as the major product (slightly yellow crystals). Recrystallization from absolute ethanol provided the analytical sample: mp 106.5-108.5 °C; IR ($CHCl_3$) 2240 (C≡N), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.07 (m, 2 H, H-5), 4.86 (s, 2 H, NCH_2), 6.22-6.26 (dt, 1 H, H-3, $J_{3,4}$ = 6 Hz, $J_{3,5}$ = 1.9 Hz), 7.15-7.20 (dt, 1 H, H-4, $J_{3,4}$ = 6 Hz, $J_{4,5}$ = 1.8 Hz), 7.31-7.57 (m, 3 H, Ar H); MS, *m/z* (relative intensity) 234 (10.3, $M^+ + 2$), 232 (36.4, M^+), 206 (29.7), 205 (39.9), 204 (97.6), 203 (100), 191 (18.4), 168 (19.1), 167 (24.6), 165 (76.2), 152 (29.8), 150 (96.3). Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.76; H, 4.06; N, 12.04.

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Registry No. (±)-**1a**, 78964-11-1; (±)-**1a** (methyl ester), 103301-78-6; (±)-**1b**, 103201-07-6; (±)-**1b** (methyl ester), 103201-06-5; (±)-**2a**, 103201-08-7; (±)-**2b**, 103201-09-8; (±)-**2c**, 103201-10-1; (±)-(*Z*)-**3a**, 103201-11-2; (±)-(*Z*)-**3b**, 103201-12-3; (±)-(*Z*)-**3c**, 103201-13-4; **6a**, 103201-14-5; **6b**, 103201-15-6; **7a**, 103201-16-7; (DL)-$HO_2C(CH_2)_2CH(NH_2)CO_2H \cdot H_2O$, 617-65-2; $3\text{-}ClC_6H_4CH_2Br$, 766-80-3; $H_2NOH \cdot HCl$, 5470-11-1; (±)-5-oxoproline, 149-87-1.

Oxidation of Enolates by Dibenzyl Peroxydicarbonate to Carbonates of α-Hydroxy Carbonyl Compounds

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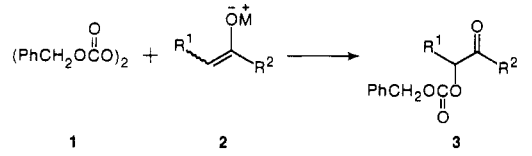
The importance of α-hydroxy carbonyl compounds has encouraged development of a variety of methods for their production,[1] including introduction of oxygen functionality adjacent to the carbonyl either directly[2,3] or via an intermediate derivative of an enol.[4,5] Studies on asymmetric oxidation of enolates bearing chiral ester[3a,b,e] or amide groups[3c,d] have achieved good to excellent diastereoselectivity by using MoOPH[2c] or 2-(phenylsulfonyl)-3-phenyloxaziridine[2e] as an oxidant. In related work, asymmetric lead tetraacetate oxidation of silyl ketene acetals derived from chiral esters gave α-acetoxy esters with 88-96% diastereoselection.[5a] Our interest in oxygen-18 labeling studies[6] led us to search for reagents that would accomplish such selective oxidations of chiral enolates and could also be readily prepared from isotopically enriched oxygen gas or hydrogen peroxide.[7] Preparation of the labeled oxaziridine reagent[8] would require several steps while the more accessible MoOPH[2c] often gives lower yields.[3c] Direct oxygenation using O_2 gas is less likely to allow stereochemical control[3a] and is often problematic if the product still bears a hydrogen at the α-carbon.[2b] This study describes the use of dibenzyl peroxydicarbonate (1) for oxidation of both chiral and achiral enolates **2** to form carbonates of α-hydroxy carbonyl compounds **3** (Scheme I).

Scheme I



Dibenzyl peroxydicarbonate (1) is easily prepared in one step from aqueous hydrogen peroxide and benzyl chloroformate under basic conditions.[9] It is an unexpectedly stable nonhygroscopic material that can be stored indefinitely without decomposition under normal conditions.[10] Although attack of carbon nucleophiles on the peroxy oxygen of benzoyl peroxide is well precedented,[2a,11] this type of reaction with dialkyl peroxydicarbonates has been examined primarily with enamine derivatives of β-di-

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(10) Although many dialkyl peroxydicarbonates explode readily,[9] small quantities of solid dibenzyl peroxydicarbonate (1) from various preparations could not be detonated by heating, grinding, or striking with a hammer. Nevertheless, all preparations of 1 were done on modest scale (≤0.1 mol) behind a safety shield, and the usual precautions for dealing with peroxides were observed (avoidance of metals, heat, intense light, etc.).

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