A Convenient Synthesis of Unsymmetrical Acyclic Imides

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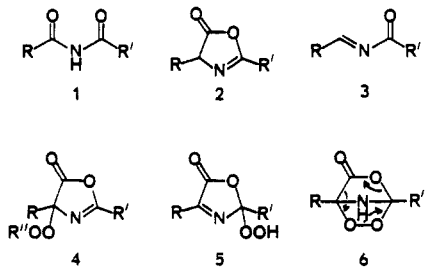
Available methods for the synthesis of unsymmetrical acyclic imides suffer from low yields, high temperatures, or scrambling of the groupings to give symmetrical imides.[1] Thus, when we found imide **1a** as a 2% byproduct during a reduction of azlactone **2a** with hydrogen over Pd/C,[2] we decided to vary the conditions to see if the yield of imides **1** could be improved. We find that imide **1b**, unaccompanied by other imides, is formed in 82% yield when oxygen is bubbled through a Me_2SO solution of azlactone **2b** in the presence of Pd/C.

Azlactones **2** are easily prepared from *N*-acylglycines and aldehydes or ketones via unsaturated azlactones, from α-amino acids $RCH(NH_2)COOH$ and anhydrides $(R'CO)_2O$, or from α-amido acids $RCH(NHCOR')COOH$ and Ac_2O.[3] We have found that the azlactone **2** need not be isolated but can be oxidized directly in the acetic anhydride–acetic acid solution in which it is prepared. Thus, in one-pot reactions, *N*-benzoylvaline was converted into imide **1a** in 50% yield, *N*-benzoylphenylalanine into **1b** in 60% yield, and phenylalanine into **1c** in 55% yield.



	R	R′
a	*i*-Pr	Ph
b	benzyl	Ph
c	benzyl	Me

In experiments designed to narrow the mechanistic possibilities, we ruled out mechanisms involving decarbonylation of **2** to imine **3** by oxidizing **2c** with $^{18}O_2$ to **1c** containing two ^{18}O's and mechanisms involving singlet O_2 by recovering 9,10-diphenylanthracene unchanged under the reaction conditions.[4] The reaction apparently involves autoxidation of **2** to **4** (R″ = H) and/or **5** by triplet oxygen, tautomerization of **4** (R″ = H), and/or **5** to **6**, and fragmentation (not necessarily concerted) of **6** to **1** and CO_2. Pd/C is involved in the first (i.e., autoxidation) step, as **2** was recovered unchanged in its absence.[5] The yield is lowered somewhat when acetic anhydride is present by the trapping of some of the hydroperoxide **4** (R″ = H) as the perester **4** (R″ = Ac), as indicated by the isolation of perester **4b** (R″ = Ac) in 22% yield during the preparation of **1b** in acetic anhydride–acetic acid. An attempted selective aminolysis of perester **4b** (R″ = Ac) to hydroperoxide **4b** (R″ = H) with morpholine gave no imide **1b**, probably because of attack on the *lactone* carbonyl group.

Because these reactions are very easy to run, occur at relatively low temperatures, and give no scrambling of groups, they should find use for the preparation of unsymmetrical imides **1**.

Experimental Section

^1H NMR spectra were run in $CDCl_3$ at 250 MHz on a Bruker WM-250 spectrometer or at 60 MHz on a Varian EM-360 instrument. Mass spectra were run on a Varian MAT 311A spectrometer. Melting points were determined in capillaries on a Thomas-Hoover apparatus and are uncorrected.

***N*-Isobutyrylbenzamide (1a).** After *N*-benzoyl-DL-valine[6] (500 mg, 2.26 mmol) in acetic anhydride (5 mL) was heated at 100 °C for 30 min and the mixture was cooled to 25 °C, 10% Pd/C[7] (50 mg) was added and the mixture was stirred overnight while oxygen was bubbled through. After the mixture was filtered through Celite, the Celite washed with 3 × 30 mL of ether, and the ether evaporated, the residual oil was subjected to LC (silica). Elution with ethyl acetate–hexane gave **1a**: 216 mg (50%); mp 149–150 °C; ^1H NMR δ 8.5 (br, NH), 7.86 (~d, 2 H, J = 7.9 Hz), 7.60 (~t, 1 H, J = 7.3 Hz), 7.50 (~t, 2 H, J = 7.4 Hz), 3.66 (heptet, 1 H, J = 6.8 Hz), 1.26 (d, 6 H, J = 6.8 Hz); MS, m/e 191 (M), 122, 105, 77, 70. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.90; H, 7.00; N, 7.31.

***N*-(Phenylacetyl)benzamide (1b). A. From *N*-Benzoyl-DL-phenylalanine.**[6] An analogous procedure gave **1b**: 60%; mp 132–133 °C; ^1H NMR δ 9.06 (br, NH), 7.84 (dd, 2 H, J = 7.0, 1.5 Hz), 7.58 (tt, 1 H, J = 7.4, 1.2 Hz), 7.45 (dd, 2 H, J = 6.5, 1.3 Hz), 7.34 (m, 5 H), 4.34 (s, 2 H). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.31; H, 5.44; N, 5.86. Found: C, 75.13; H, 5.47; N, 5.97. From the preceding LC fractions was obtained perester **4b** (R″ = Ac) as a viscous oil with an NMR spectrum similar to that of azlactone **2b**: δ 7.88 (dd, 2 H, J = 6.7, 1.4 Hz), 7.55 (tt, 1 H, J = 7.4, 1.4 Hz), 7.42 (~t, 2 H, J = 7.7 Hz), 7.20 (m, 5 H), 3.48 (d, 1 H, J = 13.2 Hz), 3.28 (d, 1 H, J = 13.2 Hz), 2.14 (s, 3 H). Anal. Calcd for $C_{18}H_{15}NO_5$: C, 66.46; H, 4.62; N, 4.31. Found: C, 66.02; H, 4.31; N, 4.35.

B. From Azlactone 2b. 2b[8] (200 mg) in 12 mL of Me_2SO containing 30 mg of 10% Pd/C was stirred overnight while O_2 was bubbled through. In the workup the ether solution was washed with 10 × 40 mL of H_2O to remove Me_2SO. The crude product (176 mg) crystallized; NMR indicated 149 mg (82%) of **1b** to be present.

***N*-(Phenylacetyl)acetamide (1c).** After DL-phenylalanine (5 g, 30.3 mmol) with 50 mL of Ac_2O was heated at 100 °C for 10 min with stirring, the solution was oxidized directly as above, yielding **1c**: 2.93 g (55%); mp 124–126 °C; IR (CH_2Cl_2) 1711, 1735 cm^{-1}; ^1H NMR δ 8.4 (br, NH), 7.22 (~s, 5 H), 3.76 (s, 2 H), 2.32 (s, 3 H); MS, m/e 177 (M), 118, 91. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.91. Found: C, 67.49; H, 6.17; N, 8.18.

Using Schlenk line techniques, a reaction on 1/10 the above scale was carried out with oxidation by stirring for 4 days under 100 mL at 99% $^{18}O_2$ at 0.5 atm. The imide **1c** obtained (0.134 g, 25%) had an NMR spectrum identical with that above but had MS values of m/e 181 (M), 120, and 91.

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Registry No. **1a**, 1738-54-1; **1b**, 14072-62-9; **1c**, 10543-56-3; (±)-**2b**, 51127-19-6; (±)-**4b** (R″ = Ac), 90624-73-0; *N*-benzoyl-DL-valine, 2901-80-6; *N*-benzoyl-DL-phenylalanine, 2901-76-0; DL-phenylalanine, 150-30-1.

(1) The acylation of amides with anhydrides (Davidson, D.; Skovronek, H. *J. Am. Chem. Soc.* **1958**, *80*, 376) and the reaction of nitriles with carboxylic acids (Zil'berman, E. N. *Russ. Chem. Rev.* (*Engl. Transl.*) **1960**, *29*, 331. Durrell, W. S.; Young, J. A.; Dresdner, R. D. *J. Org. Chem.* **1963**, *28*, 831) give unsymmetrical imides **1** in 20–80% yield at 150–290 °C; pressure equipment is needed with volatile reactants. *Symmetrical* imides have recently been made in 50–60% yield from silylamines (Bowser, J. R.; Williams, P. J.; Kurz, K. *J. Org. Chem.* **1983**, *48*, 4111).

(2) Bates, R. B.; Janda, K. D. *Synthesis*, in press. Our X-ray structure determination on **1a** will be reported elsewhere.

(3) Carter, H. E. *Org. React.* **1946**, *3*, 198.

(4) Denny, R. W.; Nickon, A. *Org. React.* **1973**, *20*, 133.

(5) The Pd/C is probably serving as a radical initiator.

(6) Pfaltz & Bauer, Inc., Stamford, CT 06902.

(7) Aldrich Chemical Co., Milwaukee, WI 53201.

(8) Reference 3, p 205.

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