On the Use of Hydrogen Peroxide in the Hydrolysis of Azido *N*-(Arylacetyl)-2-oxazolidinone Derivatives

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In our continuing studies directed toward the synthesis of vancomycin and related glycopeptide antibiotics, nonproteinogenic amino acids are required as the subunits. For this purpose, compounds **1a**−**d** were synthesized from commercially available materials via standard well-established asymmetric azidation chemistry.[1] Conversion of these compounds to arylglycine and arylalanine subunits for the aforementioned target molecules required hydrolytic removal of the chiral auxiliary. Compound **1a** was treated with 2 equiv of LiOH in the presence of 6 equiv of H_2O_2, which has been reported as a method of choice to minimize any racemization.[1] After TLC showed the hydrolysis was complete, Na_2SO_3 was added to quench the reaction. The usual aqueous workup gave a 9:1 mixture (91% total yield) of **2a** and **3a**, with **2a** as the major component. Fischer esterification (PTSA·H_2O/EtOH) provided **4a** and **5a**, which were separated by flash chromatography. Compound **4a** has been used in the synthesis of 16-membered cyclic peptide models for teicoplanin and ristocetin A.[2]

The minor formation of the side product **3a** was not cause for concern, but a more serious problem was encountered with **1b** as the substrate. Hydrolysis with LiOH/H_2O_2 gave a 1:1 mixture of **2b** and **3b**, in a combined yield of 87%. Esterification with PTSA·H_2O/MeOH furnished **4b** and **5b**, chromatographic separation of which, in a variety of solvent systems, failed. Similarly, a 1:1 mixture of **2c** and **3c** (89% total) was obtained when **1c** was subjected to the same hydrolysis conditions. Esterification gave **4c** and **5c**, chromatographic separation of which was achieved with 1:4 EtOAc/hexanes as solvent. The structure of **5c** was secured by comparing its IR and ^1H and ^{13}C NMR spectra with a sample prepared by standard methods.[3]

2a R = H, **4a** R = Et; **2b** R = H, **4b** R = Me; **2c** R = H, **4c** R = Me; **2d** R = H

3a R = H, **5a** R = Et; **3b** R = H, **5b** R = Me; **3c** R = H, **5c** R = Me; **3d** R = H

Evans and co-workers have reported[1c] uncharacterized minor side reactions during hydrogen peroxide-mediated hydrolysis of azido *N*-(phenylacetyl)oxazolidinones, which they hint as being free radical in nature. To check whether the side reaction leading to compound **3** is a free radical-mediated process, we ran the reaction in THF as received from Aldrich (containing 0.029% BHT), THF distilled from $LiAlH_4$, and THF distilled from Na/benzophenone. The results were comparable. This "undesired" reaction also did not depend on whether the reaction was conducted under Ar atmosphere or open to the air. On the basis of these observations, we do not believe that free radical processes account for the formation of compounds **3**.

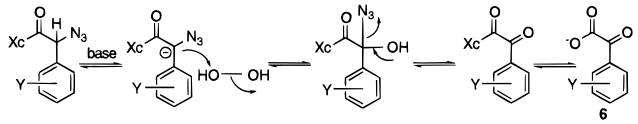
In the following proposed mechanism[4] (Scheme 1) compound **6** is believed to be the key intermediate, which leads to the formation of **3** via a known hydrogen peroxide-mediated oxidation.[5] From this mechanism, one can see that formation of **6** depends on the electronic properties of the substituents on the neighboring aromatic ring. More oxidation product is obtained when the aromatic ring is more electron deficient, which is consistent with base-catalyzed tautomerization of the azidoacyl derivative followed by addition of HOO^-. The fact that no keto acid derivative is observed during hydrolysis in the absence of hydrogen peroxide indicates that HOO^- is indeed the nucleophile in this reaction (see next paragraph). This mechanism is also supported by the fact that the oxidation products are formed only in the preparation of arylglycine derivatives, while **1d** did not give any "undesired" product **3d**. In a related kinetic study of oxidation of α-ketols by alkaline hydrogen peroxide, aromatic ketols were found to react much faster than aliphatic ketols.[6]

(1) (a) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881. (b) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (c) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

(2) (a) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1995**, *60*, 7153. (b) Pearson, A. J.; Bignan, G.; Zhang, P.; Chelliah, M. *J. Org. Chem.* **1996**, *61*, 3940.

(3) 3-Chloro-4-hydroxybenzoic acid was treated with K_2CO_3 (3 equiv)/MeI (5 equiv) to give 3-chloro-4-methoxybenzoic acid methyl ester (**5c**). **3c** was also obtained as the side product from the oxidation of 3-chloro-4-methoxybenzyl alcohol with PCC.

(4) Another plausible pathway leading to **6** is as follows:



(5) Oxidation of α-keto acids by alkaline hydrogen peroxide is a known reaction: March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1985; p 1175.

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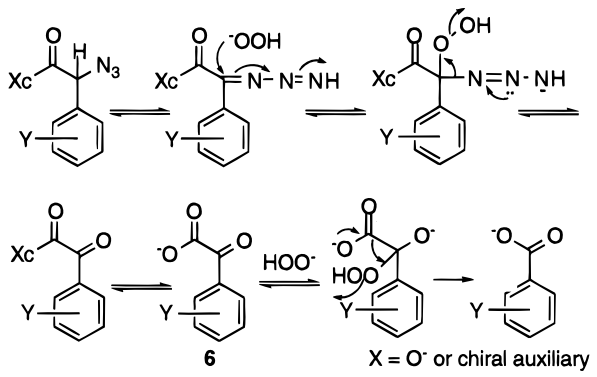
Scheme 1



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On the basis of the supposition that hydrogen peroxide-mediated scission of the azido intermediate was the major cause of the side product formation, we chose to use LiOH without H_2O_2 in the hydrolysis step. The experimental results showed clean reactions (~90% yield) with both **1b**,**c**. The observation that hydrogen peroxide is necessary for α-keto acid formation indicates that the mechanism of this reaction is different from the earlier reported hydrolysis of related compounds.[7] Now the main concern was the extent of racemization, which was checked by Mosher's method after **4b**,**c** were hydrogenated with H_2/Pd−C (10%) in the presence of 5 N HCl.[8] Mosher's amide formation was performed under standard conditions.[9] For **4c**, ^{1}H and ^{19}F NMR of the product showed a ratio of 92:8, confirming that there was little racemization, considering **1c** was also a 92:8 mixture of diastereomers. For **4b**, a 97:3 diastereomeric mixture was observed from NMR.

In conclusion, while LiOH/H_2O_2 has been recommended for the hydrolysis of racemization-prone substituted oxazolidinones, problems that arise from oxidative cleavage of azido-substituted derivatives make it less attractive for the preparation of electron deficient arylglycines. In those cases the use of standard LiOH-mediated hydrolysis provides an efficient, racemization-free alternative.

Experimental Section

General Methods. General methods used are as described elsewhere.[10]

General Preparation of 1. To a −78 °C solution of the *N*-(arylacetyl)oxazolidinone starting material in THF was added KHMDS (0.5 M in toluene, 1.1 equiv). The mixture was stirred at −78 °C for 20 min, a solution of trisyl azide (1.3 equiv) in THF was then added via cannula. After 2 min, the reaction was quenched with glacial acetic acid (3.5 equiv) and the mixture was warmed to 35 °C immediately. The slurry was stirred for an additional 3 h, diluted with CH_2Cl_2, and separated. The organic layer was washed with brine and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography with EtOAc/Hex gave the desired compound (**1a**,**d** have been reported elsewhere[2]).

1b: yield 79%; $[\alpha]^{23}_D$ +169.3 (*c* 1.0, $CHCl_3$); R_f 0.53 (1:2 EtOAc/Hex); IR ($CHCl_3$) 1796, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.45−7.15 (m, 10H), 6.75−6.60 (m, 3H), 6.05 (s, 1H), 5.01 (s, 2H), 4.55 (m, 1H), 4.09 (m, 2H), 3.76 (s, 3H), 3.37 (dd, 1H, *J* = 13.4, 2.9 Hz), 2.80 (dd, 1H, *J* = 13.4, 9.9 Hz); ^{13}C NMR ($CDCl_3$) 169.1, 161.1, 160.3, 152.4, 136.5, 134.8, 129.4, 129.0, 128.6, 128.1, 127.6, 127.5, 107.0, 106.9, 102.4, 70.2, 66.4, 63.6, 55.7, 55.5, 37.6; HRMS calcd for $C_{26}H_{24}N_4O_5$ 472.1747, found 472.1728.

1c: obtained as a mixture of 92:8 diastereomers; yield 85%; $[\alpha]^{23}_D$ −112.4 (*c* 1.1, $CHCl_3$); R_f 0.53 (1:2 EtOAc/Hex); IR ($CHCl_3$) 1782, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.60−6.90 (m, 8H), 6.16 (s, 1H), 5.61 (d, 1H, *J* = 7.2 Hz), 4.79 (dq, 1H, *J* = 7.2, 6.6 Hz), 3.97 (s, 3H), 1.00 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) 168.8, 156.0, 152.1, 132.5, 130.2, 129.0, 128.8, 128.5, 126.0, 125.6, 123.3, 112.3, 79.4, 62.9, 56.2, 55.5, 14.5; HRMS calcd for $C_{19}H_{17}ClN_2O_4$ ($M^+ - N_2$) 372.0868, found 372.0869.

General Procedure for Hydrolysis. 1. With H_2O_2. To a solution of starting material **1** in THF−H_2O (3:1) at 0 °C were added 30% H_2O_2 (6 equiv) and LiOH (0.5 N, 2 equiv). After TLC showed the reaction was complete (0.5−1 h), aqueous Na_2SO_3 (1.5 N, 10 equiv) was added and the solution was stirred for an additional 15 min. After removing the volatiles, the aqueous residue was extracted with CH_2Cl_2, then acidified with 1 N HCl to pH 1−2, and extracted again with CH_2Cl_2. This second CH_2Cl_2 extract was dried over Na_2SO_4 and concentrated.

2. Without H_2O_2. To a solution of starting material **1** in THF−H_2O (3:1) at 0 °C was added LiOH (0.5 N, 2 equiv). After TLC showed the reaction was complete (0.5−1 h), THF was removed, and the aqueous residue was extracted with CH_2Cl_2, acidified with 1 N HCl to pH 1−2, and extracted again with CH_2Cl_2. The second CH_2Cl_2 layer was dried over Na_2SO_4 and concentrated.

2b: yield 90% (without H_2O_2); ^{1}H NMR ($CDCl_3$) 8.92 (b, 1H), 7.40−7.20 (m, 5H), 6.62 (s, 1H), 6.54 (s, 2H), 5.00 (s, 2H), 4.93 (s, 1H), 3.75 (s, 3H).

2c: yield 89% (without H_2O_2); ^{1}H NMR ($CDCl_3$) 7.40 (d, 1H, *J* = 3.1 Hz), 7.24 (dd, 1H, *J* = 8.5, 3.1 Hz), 6.91 (d, 1H, *J* = 8.5 Hz), 4.95 (s, 1H), 3.87 (s, 3H).

General Procedure for Esterification. A solution of starting material **2** and PTSA·H_2O (2 equiv) in dry CH_3OH was refluxed overnight. After cooling to rt, CH_3OH was removed and the residue was dissolved in CH_2Cl_2. The solution was washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography with EtOAc/Hex gave the pure ester.

4b: yield 97%; $[\alpha]^{23}_D$ +95.2 (*c* 3.5, $CHCl_3$); R_f 0.50 (1:2 EtOAc/Hex); IR ($CHCl_3$) 1753 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.40−7.20 (m, 5H), 6.60−6.40 (m, 3H), 5.01 (s, 2H), 4.87 (s, 1H), 3.75 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) 169.3, 161.1, 160.3, 136.4, 135.7, 128.5, 128.0, 127.5, 106.3, 106.0, 101.9, 70.1, 65.2, 55.4, 52.9; HRMS calcd for $C_{17}H_{17}N_3O_4$ 327.1219, found 327.1224.

4c: yield 95%; $[\alpha]^{23}_D$ −99.4 (*c* 1.3, $CHCl_3$); R_f 0.51 (1:2 EtOAc/Hex); IR ($CHCl_3$) 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.41 (d, 1H, *J* = 2.2 Hz), 7.25 (dd, 1H, *J* = 8.4, 2.2 Hz), 6.94 (d, 1H, *J* = 8.4 Hz), 4.92 (s, 1H), 3.91 (s, 3H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) 169.2, 155.7, 129.5, 127.0, 126.7, 123.0, 112.2, 64.2, 56.1, 53.0; HRMS calcd for $C_{10}H_{10}ClN_3O_3$ 255.0411, found 255.0401.

General Procedure for Mosher's Amide Formation. A suspension of ~10 mg of Pd−C (10%) in 3 mL of THF was purged with H_2 for 30 min. To the suspension were added compound **4** (0.05 mmol) and 5 N HCl (3 equiv). After stirring under H_2 atmosphere at rt for 3 h, the mixture was filtered through Celite and the filtrate was evaporated to give a white solid, to which were added 4 mL of CH_2Cl_2 and pyridine (150 μL). The solution was cooled to 0 °C, and then (*S*)-(+)-MTPACl (1.4 equiv) was added. After the mixture stirred at 0 °C for 30 min and at rt overnight, CH_2Cl_2 was evaporated and the residue was dissolved in 15 mL of EtOAc. The organic layer was washed with 1 N $NaHCO_3$, 1 N HCl, and brine and dried over $MgSO_4$. The crude product was obtained as an oil.

From 4b: yield 79%; ^{19}F NMR ($CDCl_3$) −69.2, −69.4 (3:97).
From 4c: yield 96%; ^{19}F NMR ($CDCl_3$) −69.3, −69.5 (92:8).

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Supporting Information Available: ^{1}H and ^{19}F NMR spectra for compound series **b** and **c** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(6) Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061.
(7) (a) Raap, R. *Tetrahedron Lett.* **1969**, *40*, 3493. (b) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952.
(8) Acidic conditions were found to be essential to suppress dechlorination of the aromatic ring in the hydrogenation step; see also: Pearson, A. J.; Zhang, P.; Lee, K. *J. Org. Chem.* **1996**, *61*, 6581.
(9) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(10) Pearson, A. J.; Lee, K. *J. Org. Chem.* **1994**, *59*, 225.