Oxidative Decarboxylation of α-Amino and α-Hydroxy Acids Using Copper(II) Bromide–Lithium tert-Butoxide

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α-Monoalkyl α-amino acids were oxidized to the corresponding alkanenitriles in good yields by treatment with copper(II) bromide–lithium tert-butoxide. The oxidation of α,α-disubstituted α-amino and α-hydroxy acids also gave the corresponding ketones.

Since oxidations of α-amino acids and their derivatives are important processes in the fields of synthetic organic chemistry as well as biological chemistry, various methods and reagents have been developed for these transformations. The modes of oxidation of α-amino acids are classified into two categories: the oxidative transformation of an amino group into carbonyl or nitro group[1] and oxidative decarboxylation.[2-5]

The latter oxidation leads to the formation of various carbonyl compounds[2] or nitriles[3-5] of one less carbon atom depending on the reagent and reaction conditions employed. In connection with oxidative decarboxylation of α-amino acids, it was reported that the lead tetraacetate oxidation of their N-acyl derivatives gave N-acylimines which were hydrolyzed to the corresponding aldehydes.[6] As for the transformation into nitriles, N-bromosuccinimide[3] and alkaline bromine[4] have been employed as oxidizing agents. The isolated yields of nitriles obtained by these reactions, however, are only moderate or not described in the literature. Although the oxidation of α-amino acid with chloramine-T usually gave nitriles in good yields,[5] the method suffers a disadvantage that the corresponding aldehydes are produced as byproducts.

Recently we reported the oxidations of alcohols to aldehydes and ketones,[7] secondary amines to imines,[8] primary amines to nitriles,[8] and primary carboxamides to N-(tert-butoxycarbonyl)amines[9] using the copper(II) oxidizing agent 1 prepared by the treatment of copper(II)

bromide with lithium tert-butoxide, in which tert-butoxycopper(II) bromide 2 would serve as the active species. The advantages of these oxidations are that the reagent is less toxic and the reactions proceed in an aprotic medium under mild reaction conditions. In this paper, we describe the oxidations of α-amino acids 3 and related compounds, α-hydroxy acids 4 and their esters 5 and 6, with the copper(II) oxidizing agent 1.

Firstly the oxidation of methyl 2-amino-2-phenylacetate hydrochloride (5) was examined. The treatment of the ester with 4 equivalents of the oxidizing agent 1 preferentially gave the corresponding azine 7 which would be produced by the further oxidation of the initially formed imine (Scheme 1; table, entry 1). We assumed that the oxidative decarboxylation of the intermediate imine would take place when free α-amino acid 3 was treated with 1.
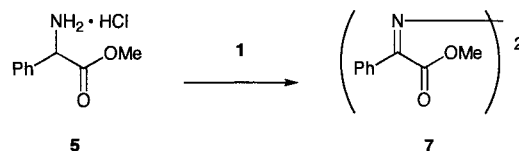
Scheme 1

As was expected, the oxidation of α-monosubstituted α-amino acids 3 ($R^2 = H$) required greater than 4 equivalents of the oxidizing agent 1 to complete the reaction, and the corresponding alkanenitriles 8 were obtained as sole products in good yield. The present oxidation is operationally simple and easily carried out in a large

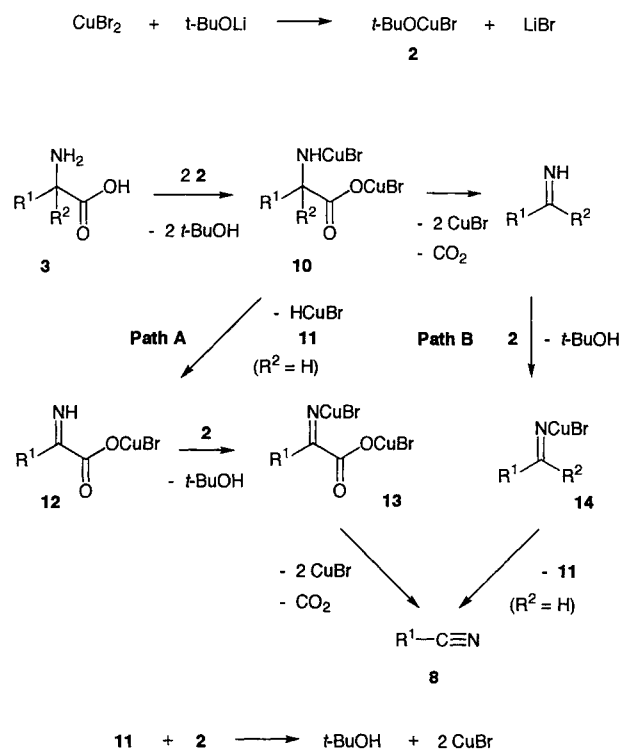Table. Oxidation of α-Amino Acids, α-Hydroxy Acids, and Their Esters[a]

Entry	Substrate	CuBr₂–t-BuOLi (eq)	Temp.	Time (h)	Product	Yield (%)	Mp (°C) or bp (°C)/Torr	
							Found	Reported[Lit]
1	5	4.4	r.t.	0.2	7	82[b]	143.5–144	
2	3a	4.4	r.t.	2.5	8a	72	82–83/20	79/17[10]
3	3b	4.4	r.t.	2.5	8b	53	109–111/13	107.1–107.3/12[11]
4	3c	4.4	r.t.	2.5	8c	78	130–132/11	127/13[12]
5	3d	4.4	r.t.	2.5	8d	83	90–95/10	100/11[13]
6	3e	5.0	r.t.	1	9d	65	103–106/9	108–110/10[14]
7	6	6.0	r.t.	14	15	86	112–113/3.5	
8	4a	6.0	reflux	1.5	16	65	84–87/10	92/10[15]
9	4b	2.2	50°C	2	9b	86[b]	47.5–48	47–48[16]
10	4c	2.2	reflux	2	9c	80	90–92/16	88.5/16[17]
11	4d	2.2	reflux	6	9d	56	106–108/10	108–110/10[14]

[a] All reactions were performed with the same procedure as described in the text on a 20 mmol scale, unless otherwise noted.
[b] The pure compound was obtained by washing the crude crystalline material with hexane.

scale. In such a case, the pure nitrile can be isolated by fractionation of the crude material. In the case of the oxidation of α,α-disubstituted amino acid **3e**, the corresponding ketone **9d** was isolated after treatment of the crude material with hydrochloric acid (table, entry 6).

On the basis of these results, the following mechanism is presumed for the oxidation of α-amino acids (Scheme 2). In the first step, the reaction of α-monosubstituted α-amino acid **3** ($R^2 = H$) with 2 equivalents of *tert*-butoxycopper(II) bromide **2** proceeds to form the carboxylate **10** which in turn eliminates copper(II) hydride **11** to afford the imine **12**. The resulting imine **12** is immediately converted to the copper salt **13** which then loses carbon dioxide and 2 equivalents of copper(I) bromide to give nitrile **8** (Path A). Another equivalent of **2** is consumed by the reaction with **11** to form copper(I) bromide and *tert*-butyl alcohol. The alternative pathway through the copper salt of aldimine **14** (Path B) should also be considered. In the case of α,α-disubstituted amino acid **3e**, **9d** would be produced by hyrolysis of the copper salt of ketimine **14**.

The most serious side reaction in the conventional transformations of α-amino acids to nitriles may be the hydrolysis of the intermediate imines to produce aldehydes. It should be noted that the selective formation of nitriles in the present oxidation is attributable to the nonaqueous medium employed.

Next the oxidation of ethyl mandelate (**6**) with a large excess of the oxidizing agent **1** was performed, and it was found that the oxidation proceeded at room temperature accompanied by transesterification to give the corresponding oxo ester **15** (Scheme 3; table, entry 7).
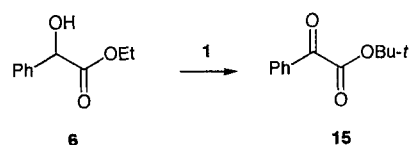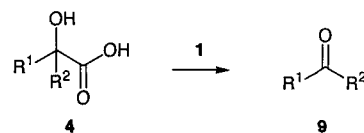
Scheme 3

This mode of oxidation is the same as that of the oxidation of common secondary alcohols.[7] On the other hand, the oxidation of the corresponding free acid **4a** required a higher reaction temperature and afforded *tert*-butyl benzoate (**16**) as the oxidation product (table, entry 8). Since it was confirmed that benzaldehyde was unreactive to **1** under similar reaction conditions, the above oxidation would proceed via the copper salt of benzoylformic acid **17** (Scheme 4). The fact that **16** was obtained in 35 % yield by the treatment of benzoylformic acid with 4 equivalents of **1** under the same reaction conditions substantiates the assumption that this reaction path is followed, at least in part, in the oxidation of mandelic acid (**4a**).

$$CuBr_2 + \text{t-BuOLi} \longrightarrow \text{t-BuOCuBr} + LiBr$$
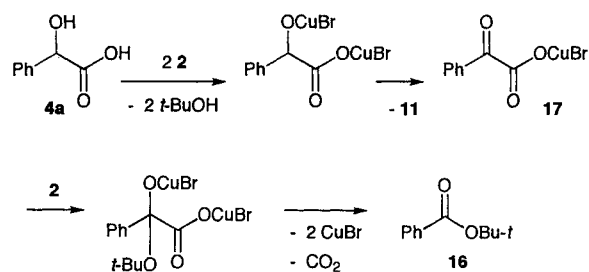
Scheme 2

Scheme 4

Scheme 5

On the basis of the above consideration, we performed the oxidation of some α,α-disubstituted α-hydroxy acids **4** using 2.2 equivalents of the oxidizing reagent **1** and found that the corresponding ketones **9** were obtained in good yields (Scheme 5; table, entries 9–11).

Although the oxidative decarboxylation of α-hydroxy acids to aldehydes or ketones can be achieved with various oxidizing agents, such as chromic acid,[18] sodium bismuthate,[19] lead tetraacetate,[6] nickel peroxide,[20] periodates,[21] N-bromosuccinimide,[22] and N-iodosuccinimide,[23] the present oxidation procedure provides a convenient method using a combination of readily available reagents.

Oxidation of 2-Amino-2-phenylacetic Acid (3a):
In a 500 mL round-bottomed flask t-BuOH (7.12 g, 96 mmol) and THF (100 mL) were placed under argon and cooled (ice bath). Then BuLi (1.69 M solution in hexane, 52.1 mL; 88 mmol) was added slowly. After the mixture was stirred for 30 min, anhyd. $CuBr_2$ (19.7 g, 88 mmol) was added in one portion. The cooling bath was then removed and stirring was continued for 40 min. Meanwhile, the color of the reaction mixture changed from deep green to deep red. Amino acid **3a** (3.02 g 20 mmol) was added and the mixture was further stirred for 2.5 h. After addition of 10% aq NH_3 (150 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with 10% aq NH_3 (100 mL) and brine (100 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by distillation under reduced pressure to give benzonitrile (**8a**); yield: 1.48 g (72%), bp 82–83°C/20 Torr.

Oxidation of Methyl 2-Amino-2-phenylacetate Hydrochloride (5):
To a THF solution of copper(II) oxidizing agent **1** prepared in a similar manner as previously described for **3a** from t-BuOH (7.12 g, 96 mmol), THF (100 mL), BuLi (1.56 M solution in hexane, 56.4 mL, 88 mmol), and $CuBr_2$ (19.7 g, 88 mmol) in a 500 mL round-bottomed flask was added **5** (4.03 g, 20 mmol) and the reaction mixture was stirred for 0.2 h. After addition of 10% aq NH_3 (200 mL), the organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with 10% aq NH_3 (100 mL) and brine (100 mL), and dried (Na_2SO_4). After evaporation of the solvent, the crude crystalline material was purified by washing with hexane (2 × 20 mL and 3 × 5 mL) to give azinodi(methyl phenylacetate) (**7**); yield: 2.67 g (82%), mp 141–143°C.

Recrystallization from hexane yielded a sample for elemental analysis (mp 143.5–144°C).

IR (neat): 1738, 1608 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.94, 3.97, 4.01 (3 s, 0.2 H, 0.2 H, and 5.6 H), 7.38–7.57 (m, 6 H), 7.74–7.83 (m, 4 H).

$C_{18}H_{16}N_2O_4$ calc.   C 66.66   H 4.97   N 8.64
                 found   66.39   5.00   8.50

Oxidation of Ethyl Mandelate (6):
To a THF solution of copper(II) oxidizing agent **1** prepared in a similar manner as previously described for **3a** from t-BuOH (9.78 g, 132 mmol), THF (130 mL), BuLi (1.64 M solution in hexane, 73.2 mL; 120 mmol), and $CuBr_2$ (26.8 g, 120 mmol) in a 1 L round-bottomed flask was added a THF (40 mL) solution of **6** (3.60 g, 20 mmol) and the mixture was stirred for 14 h. After addition of sat. aq NH_4Cl (300 mL), 1 M HCl was added to the mixture until the aqueous layer was just clarified. The organic layer was separated and the flask was rinsed with Et_2O (50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (150 mL) and brine (150 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by distillation under reduced pressure to give tert-butyl benzoylformate (**15**); yield: 3.56 g (86%), bp 112–113°C/3.5 Torr.

IR (neat): 1738, 1693 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.64 (s, 9 H), 7.45–7.77 (m, 3 H), 7.93–8.02 (m, 2 H).
$C_{12}H_{14}O_3$ calc.   C 69.89   H 6.84
                 found   70.19   6.96.

(1) For examples: García-Raso, A.; Deyá, P.M.; Saá, J.M. *J. Org. Chem.* **1986**, *51*, 4285.
 Ochiai, M.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**, *29*, 6917.
 Rozen, S.; Bar-Haim, A.; Mishani, E. *J. Org. Chem.* **1994**, *59*, 1208.
(2) Schönberg, A.; Moubacher, R. *Chem. Rev.* **1952**, *50*, 261.
 Bacon, R.G.R.; Hanna, W.J.W.; Stewart, D. *J. Chem. Soc. (C)* **1966**, 1388.
 Clarke, T.G.; Hampson, N.A.; Lee, J.B.; Morley, J.R.; Scanlon, B. *Tetrahedron Lett.* **1968**, 5685.
 Clarke, T.G.; Hampson, N.A.; Lee, J.B.; Morley, J.R.; Scanlon, B. *J. Chem. Soc. (C)* **1970**, 815.
 Schönberg, A.; Moubacher, R.; Barakat, M.Z. *J. Chem. Soc.* **1951**, 2504.
 Chappelle, E.W.; Luck, J.M. *J. Biol. Chem.* **1957**, *229*, 171.
 Königsberg, N.; Stevenson, G.; Luck, J.M. *J. Biol. Chem.* **1960**, *235*, 1341.
 Hoyer, H.L. *Chem. Ber.* **1950**, *83*, 491.
(3) Stevenson, G.W.; Luck, J.M. *J. Biol. Chem.* **1961**, *236*, 715.
(4) Friedman, A.H.; Morgulis, S. *J. Am. Chem. Soc.* **1936**, *58*, 909.
 McGregor, W.H.; Carpenter, F.H. *Biochemistry* **1962**, *1*, 53.
(5) Dakin, H.D. *Biochem. J.* **1916**, *10*, 319.
 Dakin, H.D. *Biochem. J.* **1917**, *11*, 79.
 Kumar, A.; Bose, A.K.; Mushran, S.P. *Monatsh. Chem.* **1975**, *106*, 13.
(6) Sheldon, R.A.; Kochi, J.K. *Org. React.* **1972**, *19*, 279.
(7) Yamaguchi, J.; Yamamoto, S.; Takeda, T. *Chem. Lett.* **1992**, 1185.
(8) Yamaguchi, J.; Takeda, T. *Chem. Lett.* **1992**, 1933.
(9) Yamaguchi, J.; Hoshi, K.; Takeda, T. *Chem. Lett.* **1993**, 1273.
(10) Houben, J.; Fischer, W. *Chem. Ber.* **1933**, *66*, 339.
(11) Reitz, A.W.; Stockmair, W. *Monatsh. Chem.* **1936**, *67*, 92.
(12) Ramart-Lucas, M.; Hoch, M.J. *Ann. Chim. (Paris) Sér. 10* **1932**, *17*, 207.
(13) Vogel, A.I.; Cresswell, W.T.; Jeffery, G.H.; Leicester, J. *J. Chem. Soc.* **1952**, 514.
(14) Nivière, M.J. *Bull. Soc. Chim. Fr. Sér. 4* **1921**, *29*, 217.
(15) Kharasch, M.S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 606.
(16) Marvel, C.S.; Sperry, W.M. *Organic Syntheses*; Wiley: New York, 1956; Collect. Vol. I, p 95.
(17) Noller, C.R.; Adams, R. *J. Am. Chem. Soc.* **1924**, *46*, 1889.
(18) Westheimer, F.H. *Chem. Rev.* **1949**, *45*, 419.
(19) Rigby, W. *J. Chem. Soc.* **1950**, 1907.
(20) Nakagawa, K.; Igano, K.; Sugita, J. *Chem. Pharm. Bull.* **1964**, *12*, 403.
(21) Yanuka, Y.; Katz, R.; Sarel, S. *Tetrahedron Lett.* **1968**, 1725.
 Santaniello, E.; Manzocchi, A.; Farachi, C. *Synthesis* **1980**, 563.
 Ferraboschi, P.; Azadani, M.N.; Santaniello, E.; Trave, S. *Synth. Commun.* **1986**, *16*, 43.
(22) Barakat, M.Z.; El-Wahab, M.F.A. *J. Am. Chem. Soc.* **1953**, *75*, 5731.
(23) Beebe, T.R.; Adkins, R.L.; Belcher, A.I.; Choy, T.; Fuller, A.E.; Morgan, V.L.; Sencherey, B.B.; Russell, L.J.; Yates, S.W. *J. Org. Chem.* **1982**, *47*, 3006.