Reductive Homo-Coupling of 2-Aryl-2-Oxazolinium Salts¹

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Abstract: The reductive homo-coupling of 2-aryl-2-oxazolinium salts was achieved by reduction with Zn-CTMS, electroreduction with zinc anode, or direct electroreduction. The homo-coupled products were converted to α -diketones.

Oxazolines are inert to the Grignard reagents or some reducing agents like NaBH₄ and LiAlH₄, and are therefore used to protect carboxylic groups.² On the other hand, it has been reported that the reduction of 2-aryl-2-oxazolines with DIBAL,³ diborane,⁴ sodium,⁵ or electrochemical method⁶ yields amino alcohols and the reduction of oxazolinium salts with NaBH₄⁷ or electrochemical method⁸ forms oxazolidines which can be transformed to the corresponding aldehydes upon acidic hydrolysis. So far, the reductive homo-coupling of oxazolines or oxazolinium salts has, however, been unknown.⁹ We wish to report herein a hitherto unknown reductive homo-coupling of 2-aryl-2-oxazolinium salts and its utilization as a new route for the synthesis of α diketones (eq 1).



First, the reduction of 2-phenyl-3,4,4-trimethyl-2-oxazolium iodide 1a in DMF with zinc powder was found to be very slow even at an elevated temperature. Since it has been known that chlorotrimethylsilane (CTMS) activates zinc powder,¹¹ the reduction with zinc was carried out in the presence of CTMS (method A)¹² and the homo-coupled product 2a was obtained in 84% yield. As the electroreduction using zinc as the anode is another known method to generate activated zinc,¹³ the electroreduction of 1a with zinc anode and cathode (method B)¹⁴ was also studied and found that it gave almost the same yield of 2a as the method A. When the electroreduction was carried out using platinum as the anode in stead of zinc, the yield of 2a decreased (33%) and the unchanged 1a was recovered. This result suggests that the direct electron transfer from the cathode to 1a is slow.

The results of reductive homo-coupling of other 2-aryl-2-oxazolinium salts are summarized in Table 1. The 2-aryl-2-oxazolinium salts having an electron withdrawing substituent on the p-position of the aryl group gave the corresponding homo-coupled products in good yields (runs 2 and 3). The reduction with method A was considerably disturbed by an electron donating group on the aryl group (runs 4 and 5). 2-Aryl-3-methyl-2-oxazolinium triflates also gave the homo-coupled products in moderate yields (runs 6 and 7). 2-Alkyl-2-oxazolinium salts could not be reduced due to their more negative reduction potential than 2-aryl-2-oxazolinium salts.¹⁶

		$\frac{1}{X} = \frac{1}{Ar} = \frac{1}{1}$	-	Method	I A, B			2	
Run	Oxazolinium Salts 1					% Yield of 2^a (dl/meso)^b			
		Ar	R	x		Method A		Method B	
1	1a	Ph	Me	1	2a	84	(73/27)	84	(76/24)
2	1b	p-MeO ₂ CC ₆ H ₄	Мө	1	2b	66	(93/7)	75	(93/7)
3	1c	p-ClC ₆ H₄	Me	I	2c	76	(67/33)	61	(68/32)
4	1d	p-MeC ₆ H₄	Me	I.	2d	33	(67/33)	70	(68/32)
5	1e	p-MeOC ₆ H₄	Me	T	2e	0		43	(63/37)
6	1f	Ph	н	OTf	2f	41	(80/20)	54	(72/28)
7	1g	p-CIC ₆ H ₄	Н	OTf	2g	59	(80/20)	69	(54/46)

Table 1. Reductive Coupling of 2-Aryl-3-methyl-2-oxazolinium Salts 1

a. Isolated yields. b. Determined by ¹H NMR spectra. See ref. 15.

R^R

The reduction of a chiral oxazolinium salt 1h gave the homo-coupled product $2h^{17}$ as a single stereoisomer (eq 2). Although the stereostructure could not confidently be determined, the structure shown in eq 2 seems reasonable in view of the steric hindrance of substituents on the oxazolinium ring.



Although the salts (3) of 2-aryl-4,4-dimethyl-2-oxazolines with trifluoroacetic acid could not be reduced by the methods A and B, the electroreduction (method C)¹⁸ of 3 with the usual electrode gave the corresponding homo-coupled products 4 in moderate yields (Table 2).

Despite the fact that oxazilidines are easily hydrolyzed to the corresponding ketones by treatment with aqueous oxalic acid,²⁰ the homo-coupled products 2a-2e could not be hydrolyzed under any acidic condition. On the other hand, the products 2f, 2g, and 4a-4d were easily converted with high yields to the corresponding α diketones by treatment with 1N HCl. (eq 3).

$$\begin{pmatrix} R^{1} & R^{2} \\ R^{3} - N & O \\ Ar & 2 \end{pmatrix} \xrightarrow{1 \text{ IN HCl}} & O \\ reflux 1^{2} hr & Ar \\ 80^{-90\%} \end{pmatrix} (3)$$

С	HN 0 -	+e		-
Run	Ar		% Yield ^a	Ds ^b
1	Ph	4a	51	(79/21)
2	p-MeO ₂ CC ₆ H ₄	4b	57	(76/24)
3	p-CIC ₆ H ₄	4c	55	(>95/5)
4	p-MeC ₆ H ₄	4d	34	(65/35)

Table 2. Electroreductive Coupling of 2-Aryl-2-oxazolinium Salts 3

a. Isolated vields. b. Diastereomeric ratios determined by ¹H NMR spectra. See ref. 19.

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- We have already reported the electroreductive cross-coupling of 2-alkyl-2-oxazolinium salts with benzyl bromide⁸ or α,β-unsaturated compounds.¹⁰
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- 12. Typical procedure is as follows: To a solution of 1a (612 mg, 1.93 mmol) in DMF (20 mL) was added CTMS (1.3 ml, 10 mmol) and zinc powder (689 mg, 10.5 mmol) at room temperature under an atmosphere of nitrogen and the reaction mixture was stirred for 6 hr. Saturated aqueous sodium bicarbonate (50 mL) was added and the insoluble solid was filtered off. The filtrate was extracted with dichloromethane and the organic layer was washed with brine, dried over magnesium sulfate and concentrated. After removal of the solvent *in vacuo*, column chromatography (basic Al₂O₃, hexane/ethyl acetate = 20/1) of the residue gave 2a as a 73:27 mixture of two diastereomers. dl-2a: ¹H NMR (CDCl₃, 200 MHz) δ 0.95 (s, 6 H), 1.22 (s, 6 H), 2.28 (s, 6 H), 3.98 (d, 2 H, J = 6.0 Hz), 4.22 (d, 2 H, J = 6.0 Hz), 6.90-7.03(m, 6 H), 7.52-7.57(m, 4 H); ¹³C NMR (CDCl₃, 50 MHz) δ 20.92 (q), 24.80 (q), 30.89 (q), 59.97 (s), 79.69 (t), 103.50(s), 125.99 (d), 126.35 (d), 128.54 (d), 129.16 (s). meso-2a: ¹H NMR (CDCl₃, 200 MHz) δ 0.66 (s, 6 H), 0.69 (s, 6 H), 2.79(s, 6 H), 3.11 (d, 2 H, J = 6.0 Hz), 3.52 (d, 2 H, J = 6.0 Hz), 7.20-7.32 (m, 6 H), 7.72-7.80 (m, 4 H).

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- 14. Typical procedure is as follows: A solution of 1a (632 mg, 1.99 mmol) in DMF (20 mL) was put into an undivided cell (50 mL beaker) equipped with a zinc cathode (2 X 2 cm²) and a zinc anode (2 X 2 cm²). After 2 F /mol of electricity was passed at constant current of 0.2 A at room temperature under an atmosphere of nitrogen (32 min), the reaction mixture was poured into saturated aqueous sodium bicarbonate (50 mL). The product 2a was isolated by the same method as described above.
- 15. The diastereomeric ratios of 2 were determined by ¹H NMR spectra (200 MHz, CDCl₃). The assignment of dl and meso isomers of 2b and 2g was based on their ¹H NMR spectra in the presence of Eu(hfc)₃. That is, the signal of *N*-methyl protons of dl-isomers split, whereas that of meso-isomers did not split. The stereoconfigurations of the other 2 were assigned by the correlation of their ¹H NMR spectra with those of 2b and 2g. The chemical shifts of methylene protons adjacent to oxygen atom in 2 were as follows: dl-2a 3.98 and 4.22 (d, J = 6.0 Hz); meso-2a 3.11 and 3.52 (d, J = 6.0 Hz); dl-2b 4.02 and 4.21 (d, J = 6.0 Hz); meso-2b 3.14 and 3.54 (d, J = 7.4 Hz); dl-2c 3.95 and 4.17 (d, J = 7.6 Hz); meso-2c 3.12 and 3.51 (d, J = 6.0 Hz); dl-2d 3.95 and 4.19 (d, J = 6.4 Hz); meso-2d 3.12 and 3.51 (d, J = 7.3 Hz); dl-2e 3.93 and 4.18 (d, J = 6.5 Hz); meso-2e 3.10 and 3.50 (d, J = 7.8 Hz); dl-2f 4.24-4.45 (m); meso-2f 3.61-3.74 and 3.85-3.96 (m); dl-2g 4.18-4.34 (m); meso-2g 3.53-3.71 and 3.82-3.93 (m).
- 16. The reduction peak potential of 1a was -1.16 V vs. SCE (1 mM in DMF, 0.1 V/s), while that of 2-phenylethyl-3,4,4-trimethyl-2-oxazolinium iodide was -1.51 V vs. SCE.
- 17. **2h**: mp 197-199 °C; $[\alpha]^{25}_{D}$ +150 (c 1.1, CDCl₃);¹³C NMR (CDCl₃, 50 MHz) δ 10.76 (q), 34.78 (q), 61.64 (d), 81.67 (d), 101.35 (s), 126.07 (d), 126.27 (d), 126.68 (d), 126.99 (d), 128.21 (d), 128.46 (d), 140.11 (s), 141.20 (s).
- 18. Typical procedure is as follows: A solution of Et₄NOTs (3.5 g), 4,4-dimethyl-2-phenyl-2-oxazoline (365 mg, 2.09 mmol) and trifluoroacetic acid (1.39 mg, 12.2 mmol) in DMF (25 mL) was put into the cathodic chamber of a divided cell (50 mL beaker) equipped with a lead cathode (5 X 10 cm²), a carbon rod anode, and a ceramic diaphragm. The anodic solution was a DMF solution (10 mL) containing Et₄NOTs (1.5 g). Electricity was passed at constant current of 0.2 A at room temperature until almost all of the oxazoline was consumed (ca. 4 F/mol). The product 4a was isolated by the same method as described above.
- 19. The diastereometric ratios of 4 were determined by ¹H NMR spectra (200 MHz, CDCl₃). The stereoconfigurations were not assignable. The chemical shifts of methylene protons adjacent to oxygen atom in 4 were as follows: 4a(major) 3.30 and 3.54 (d, J = 7.1 Hz); 4a(minor) 3.24 and 3.43 (d, j = 9.0 Hz); 4b(major) 3.39 and 3.57 (d, J = 7.0 Hz); 4b(minor) 3.36 and 3.45 (d, J = 7.7 Hz); 4c(major) 3.37 and 3.55 (d, J = 7.1 Hz); 4d(major) 3.28 and 3.52 (d, J = 7.3 Hz); 4d(minor) 3.25 and 3.42 (d, J = 7.5 Hz).
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