Highly Selective Formation of 2-Aminophenoxazin-3-one by Catalytic Oxygenation of *o*-Aminophenol

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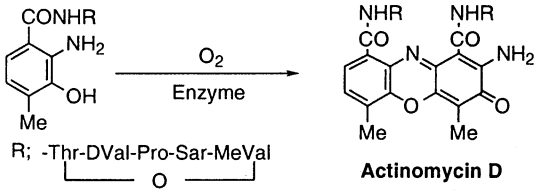
(Received June 12, 1996)

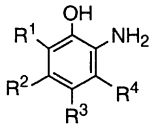
2-Aminophenol readily undergoes highly selective Co(salen) catalyzed oxygenation in methanol at room temperature resulting unexpectedly in the quantitative formation of 2-aminophenoxazin-3-one. The oxygenation of substituted 2-aminophenols provides useful information to discuss the reaction path.

The final step of the biosynthesis of actinomycins, an antineoplastic agent, is believed to be the oxidative coupling including six electron oxidation of 2-aminophenol derivatives.[1] Actually, actinomycin D has been synthesized from the appropriate 2-aminophenol precursor by catalytic oxygenation with phenoxazinone synthase.[2, 3]



Actinomycin D

Recently, the oxygenation of 2-aminophenol catalyzed with cobalt complexes has been reported in connection to the biosynthesis of actinomycins,[4 - 7] but the selectivity of these reactions is not so high. We now find that Co(salen) can catalyze the oxidation of 2-aminophenol (**1a**) with dioxygen in methanol



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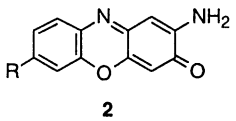
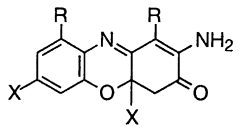


2

a; R = H **b**; R = Cl

	a	b	c	d	e	f	g	h	i	j	k	l
R^1	H	H	H	H	H	H	H	H	H	H	Me	t-Bu
R^2	H	Me	t-Bu	Cl	H	H	H	H	Me	t-Bu	H	H
R^3	H	H	H	H	Me	t-Bu	Cl	NO_2	H	H	Me	t-Bu
R^4	H	H	H	H	H	H	H	H	Me	t-Bu	H	H

at room temperature to give 2-aminophenoxazin-3-one (**2a**) unexpectedly in almost quantitative yield, although Benedini et al.[8] reported the formation of 2,2'-dihydroxyazobenzene in the Co(salen) catalyzed oxygenation of 2-aminophenol under rather drastic conditions. In order to discuss the mechanism of this interesting highly selective oxidation of **1a**, the oxidation of substituted 2-aminophenols (**1**) has also been carried out. As summarized in Table 1, compounds **2** - **7** were obtained in good yields. Analytical data of the products are in good agreement



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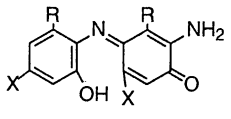
a; R = H, X = Me **b**; R =X = Me



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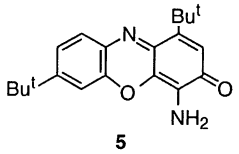
a; R = H, X = *t*-Bu



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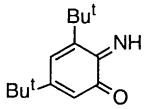

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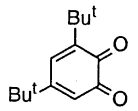

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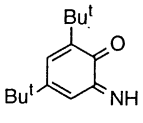

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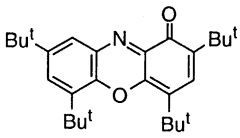

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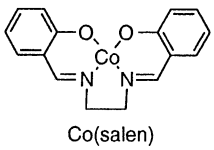


Co(salen)

Table 1. Co(salen) catalyzed oxygenation of **1**[a]

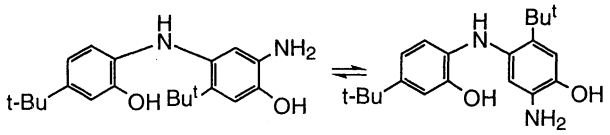
1	Time(h)	Conv.(%)	Product	(Yield/%)[b]
1a	2.5	100	**2a**	(94)
1b	2	100	**3a**	(71)
1c	1.5	100	**4a** (48)	**5** (35)
1d	50	100	**2b**	(72)
1e	4	100	complex mixture	
1f	24	100	complex mixture	
1g	40	-	complex mixture	
1h	48	0	-	
1i	20	100	**3b**	(90)
1j	15	100	**6**	(78)
1k	1	100	complex mixture	
1l	0.3	100	**7**	(64)

[a] Reaction conditions: **1** (1 mmol), Co(salen) (0.1 mmol) MeOH (20 ml), 25 °C. [b] Isolated yield.

with the structures.[9] Among these products useful to discuss the mechanism of the highly selective formation of **2a**, compounds **3a** and **4a** have also been found in the enzymatic oxidation of the corresponding 2-aminophenols, although no description is given about the yields of these products or the structural feature of **4a**.[2] Nevertheless, Co(salen) obviously provides an excellent functional model for the phenoxazinone synthase.

The formation of the same type of compounds **3a** and **3b** from each of **1b** and **1i** strongly suggests that the oxidation involves a common type of intermediate **4** (R = H, Me; X = Me). This is supported by the isolation of **4a** from **1c**, where the

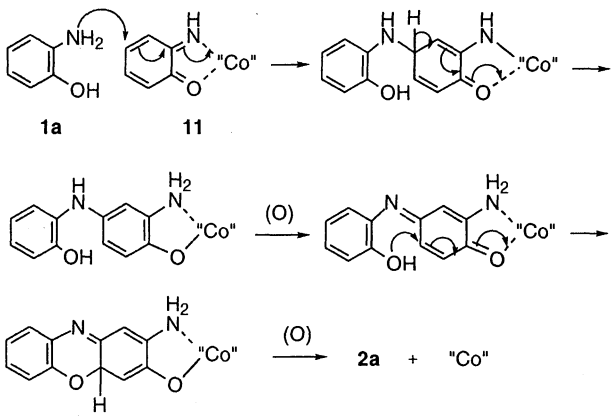
t-Bu group sterically hinders the cyclization. The formation of **2b** from **1d** may also be rationalized by assuming the reaction path involving **3** (R = H, X = Cl) via **4** (R = H, X = Cl) with elimination of HCl. Further, the results in the reaction of **1c** suggest the presence of precursor **10** and its rotamer **10'**, from which **4a** and **5** are obtained, respectively. These results seem to support the mechanism involving dimerization of substrate radical **1•** for the formation of **2**,[7, 10] but it is not likely because there are too many resonance forms of **1•** to expect a single product **2**.



10 **10'**

The specific formation of **2a** may be rationalized by assuming conjugate addition of the amino group in **1a** to an *o*-quinonimine intermediate coordinated to the Co^{III}(salen) center (**11**) (Scheme 1). The nitrogen group in **1a** is more nucleophilic and that in **11** is stronger donor than the oxygen group. It is therefore naturally

Scheme 1.



concluded that the exclusive formation of **2a** may result from the regiospecific conjugate addition of the amino group in **1a** to the 4-position of the intermediate (Scheme 1). The alternative mechanism involving the similar conjugate addition of **1a** to a free form of *o*-qiononimine seems unlikely because there is no reason why the reaction gives the sole product . In the oxidation of **1j**, the bulky *t*-butyl group at the 3-position hinders the conjugate addition reaction to result eventually in the isolation of **6** in good yield (78%), also supporting the mechanism shown in Scheme 1.

Interestingly, on the other hand, the oxidation of 4-substituted 2-aminophenols (**1e-1g, 1k**) gave a complex mixture. The results should be due to inhibition of the conjugate addition by the substituent at the 4-position to allow complicated reactions of the substrate radicals. Actually, no EPR signals are observed for the reaction where a single product is obtained, whereas the reactions of 4-substituted 2-aminophenols showed a complicated EPR signals.

2-Amino-4,6-di-*tert*-butylphneol (**1l**) undergoes very slow autoxidation (3 days for completion) to give 2,4,6,8-tetra-*tert*-butylphenoxazin-1-one (**9**), and a phenoxy radical coupling mechanism has been discussed.[11] Interestingly, however, when Co(salen) is applied as a catalyst in CH_2Cl_2, the oxygenation of **1l** is completed within 20 min to give **7** (64%). The results strongly suggest that the two-electron oxidation of the substrate occurs rapidly. Since **9** was obtained by just mixing of **7** and **1l**, the formation of **9** from **1l** may involve **7** as the intermediate; the mechanism suggested by Stegmann and Scheffler may not be the case.[11]

References and Notes

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9 **2a**: mp 256-258 °C. ^{1}H NMR (DMSO-d_6) δ 6.33 (s, 1H), 6.40 (s, 1H), 6.73 (bs, 2H), 7.36 - 7.46 (m, 3H), 7.68 (m, 1H). ^{13}C NMR (DMSO-d_6) δ 99.1, 103.9, 116.3, 125.6, 128.4, 129.1, 134.2, 142.4, 147.9, 148.8,149.3, 180.6. **3a**: mp 178.5 - 179.5 °C. ^{1}H NMR (DMSO-d_6) δ 1.10 (s, 3H), 2.26 (s, 3H), 2.98 (d, 1H, *J* = 15.8 Hz), 3.20 (d, 1H,*J* = 15.8 Hz), 6.05 (s, 1H), 6.38 (s, 2H), 6.72 (s, 1H), 6.81 (d, 1H, *J* = 7.9 Hz), 7.09 (d, 1H, *J* = 7.9 Hz). ^{13}CNMR (DMSO-d_6) δ 21.1, 22.2, 49.4, 77.1, 106.1, 116.7, 123.2, 125.6, 132.8, 136.7, 143.9, 146.6, 161.0, 191.7. **3b**: mp 189.0-190.5 °C. ^{1}H NMR (DMSO-d_6) δ 1.04 (s, 3H), 2.08 (s, 3H), 2.23 (3, 1H), 2.38 (s, 1H), 2.97 (d,1H, *J* = 15.9 Hz), 3.13 (d, 1H, *J* = 15.9 Hz), 5.96 (s, 2H), 6.55 (s, 1H), 6.70 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 10.5, 16.4, 20.9, 21.9, 48.8, 70.4, 113.9, 114.2, 124.3, 130.5,133.7, 135.9, 143.2, 143.8, 158.7, 190.2. Anal: C, ± 0.5%; H, ± 0.05%; N, ± 0.2%. **4**: ^{1}H NMR (DMSO-d_6) δ 1.33 (s, 9H), 1.46 (s, 9H), 4.44 (bs, 2H), 5.82 (s, 1H), 6.31 (s, 1H), 6.58 (s, 1H), 6.78 (d, 1H, *J* = 8.1 Hz), 6.93 (dd, 1H,*J* = 2.1 Hz, *J* = 8.1 Hz), 7.07 (d, 1H, *J* = 2.1 Hz). ^{13}C NMR (DMSO-d_6) δ 31.3, 31.5, 34.8, 36.5, 99.0, 112.4, 116.9, 20.5, 126.6, 133.9, 142.5, 149.9, 151.9, 159.2, 160.1, 183.7. MS; 326 (M^+). **5**: mp 184 -186 °C. ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 9H), 1.50 (s, 9H), 4.11 (s, 2H), 6.70 (s, 1H), 7.21 (d, 1H, *J* = 2.1 Hz), 7.27 (dd, 1H, *J* = 2.1 Hz, *J* = 8.1 Hz), 7.58 (d, 1H, *J* = 8.1 Hz). ^{13}C NMR (DMSO-d_6) δ 31.0, 31.1, 35.4, 36.4, 99.0, 112.2, 121.7, 123.2, 127.6, 129.6, 130.5, 143.6, 148.5, 151.98, 156.3, 180.9. Anal: C, ± 0.06%; H, ± 0.03%; N, ± 0.2%. **6**: mp 64 - 165 °C (lit.,[10] 64 °C). ^{1}H NMR ($CDCl_3$) δ 1.21 (s, 9H), 1.39 (s, 9H), 621 (d, 1H, *J* = 2.1 Hz), 6.64 (t, 1H), 12.23 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.1, 30.2, 36.1, 36.6, 120.3, 126.2, 151.6, 162.2, 166.2, 179.4. Anal: C, ± 0.01%; H, ± 0.01%; N, ± 0.02%.

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