Synthesis of Novel Hydroxy-Substituted Aromatic Aminoxyl Esters and their Azo Derivatives

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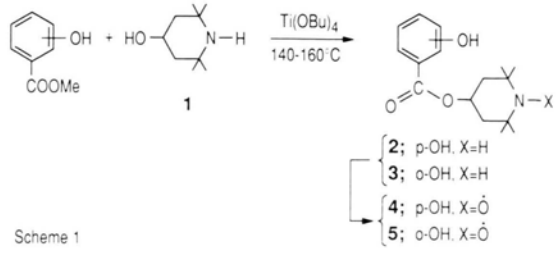
Synthesis, Hydroxy Aromatic Aminoxyl Ester, Stable Aminoxyl Radical, Spin Label, Aminoxyl Azo Compound

Transesterification or acylation method has been used for the preparation of three novel hydroxy-substituted aromatic aminoxyl esters **4, 5,** and **8** from which three new spin-labelled azo compounds **10, 13,** and **14** have been synthesized.

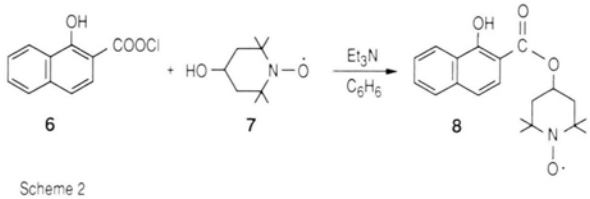
Over previous two decades, aminoxyl spin-labelled transition metal complexes have been extensively investigated for studies of radical-metal interactions [1, 2]. Although hundreds of spin-labelled ligands have been prepared, spin-labelled azo ligands are rarely reported. Azo moiety employs a good coordinative property which would be useful for the construction of spin-labelled metal complexes. We have discovered that spin-labelled azo ligands can make strong complexes with Cu(II), Ni(II) and Co(II) [3]. Therefore, synthesis of spin-labelled azo ligands is a potentially attractive research field. In our course to spin-labelled azo ligands, several hydroxy-substituted aromatic aminoxyl esters **4, 5,** and **8** were needed. After literatural searching, it was found that these compounds are not to our knowledge previously reported. We present herein the synthesis of these novel esters and some of their azo derivatives.

Some normal esterification methods are not suitable for the preparation of **4** and **5.** For example, the reaction mixture of p-HOC_6H_4COOH, 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (**7**), PCl_3 (or $SOCl_2$), and Et_3N in C_6H_6 did not produce the desired compound **4,** but instead generated tris(2,2,6,6-tetramethyl-1-oxyl-4-piperidinyl)phosphite (or bis(2,2,6,6-tetramethyl-1-oxyl-4-piperidinyl)sulfite). Aminoxyl ester **4** also was not generated by transesterification of **7** with p-HOC_6H_4COOMe in the presence of $Mg(OMe)_2$ as a catalyst in toluene. It was thought that the increase of reaction temperature and large excess of hydroxy-containing species **1** or **7** would be necessary to the achievement of the transesterification reaction. High temperature does destroy aminoxyl compound such as **7,** and therefore, 4-hydroxy-2,2,6,6-tetramethylpiperidine **1** was chosen to replace its aminoxyl analogue **7.** A two-step route as illustrated in Scheme 1 was tested and in a consequence compounds **4** and **5** were fortunately obtained in good yields.



Scheme 1

Aminoxyl ester **8** was conveniently acquired by acylation of 1-hydroxy-2-naphthoyl chloride **6** and **7** with triethylamine as the acceptor of the generated acid HCl (Scheme 2).



Scheme 2

Coupling reactions of **4** and **8** with several diazonium ions have been conducted and three novel spin-labelled aromatic azo compounds have been prepared. The coupling activity of the diazonium compound **9** is not strong. This compound reacted with ester **8** to give black-red aminoxyl **10,** but did not couple with **4** to generate the desired azo ligand **11** which probably employs an excellent coordinative property because of the existence of the HO–, –N=N–, and COOH groups in its molecule as shown in Scheme 3. Aminoxyl ester **4** reacted with equivalent of **12** to afford the azo

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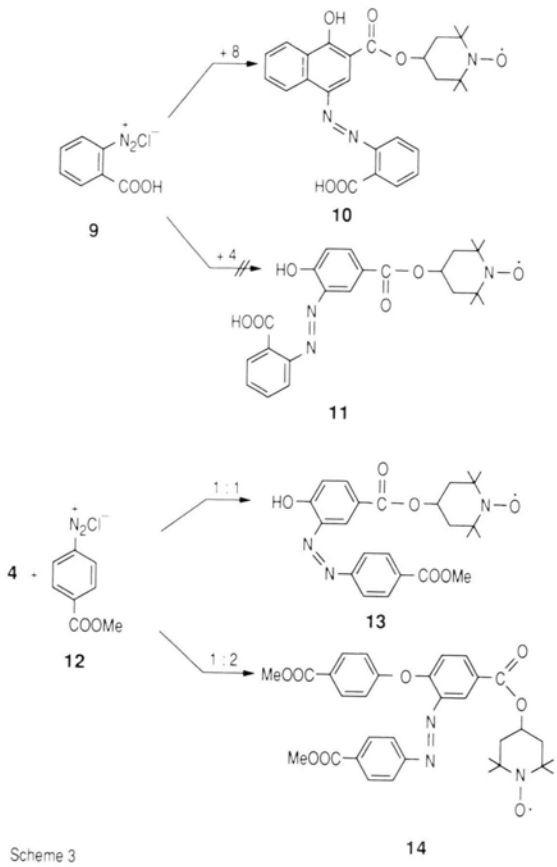

Scheme 3

compound **13** and reacted with excess **12** to result another azo compound **14** which indicates that the nucleophilic substitution reaction of the anion of **13** to **12** has taken place.

Experimental

IR spectra were recorded on a Perkin-Elmer 683 spectrometer and ^{1}H NMR spectra on a Varian EM-360L (60 MHz) spectrometer. Mass spectra were obtained on an AEI MS-50/DS-30 instrument and EPR spectra on a Varian E-109 spectrometer. Microanalysis of new compounds were performed by the Elemental Analysis Group of Institute of Chemistry, Academia Sinica.

Transesterification procedure for the preparation of **2** *and* **3**

The appropriate methyl hydroxybenzoate (10 mmol) and **1** (8 g, 50 mmol) were added to a three-necked flask. After having been stirred for 10 min at 140–160 °C, tetrabutyl titanate (0.1 g, 0.3 mmol) was quickly added. The mixture was stirred at 140 °C for additional 4–5 h. The excess **1** was removed by sublimation and the residue was recrystallized (**2** from ethyl acetate and **3** from *n*-hexane). ^{1}H NMR for **2** (CF_3COOD): δ_H 1.69 (6H, s, 2×CH_3), 1.73 (6H, s, 2×CH_3), 2.10–2.80 (4H, m, 2×CH_2), 5.67 (1H, m, COOCH) and 6.93–8.10 (4H, m, C_6H_4); δ_H for **3** (CD_3COCD_3) 1.15 (6H, s, 2×CH_3), 1.32 (6H, s, 2×CH_3), 1.87–2.13 (4H, m, 2×CH_2), 5.44 (1H, m, COOCH) and 6.80–7.84 (4H, m, C_6H_4).

Oxidation procedure for the preparation of **4** *and* **5**

Compound **2** is not soluble in normal organic solvents at room temperature and it was oxidized with hydroperoxide catalized with Na_2WO_4 in water in the presence of NaOH over 24 h at room temperature. Usual work-up gave aminoxyl **4.** Aminoxyl **5** was prepared by oxidation of **3** with excess perbenzoic acid in benzene over 12 h at room temperature. Their characterization data are presented in Table I.

(2,2,6,6-Tetramethyl-1-oxyl-4-piperidinyl)-1-hydroxy-2-naphthoate (**8**)

This ester was prepared by acylation of 1-hydroxy-2-naphthoyl chloride and 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl with triethylamine as the acceptor of HCl. The work-up crude product was purified by chromatography on silica gel eluted with chloroform and recrystallization from benzene and *n*-hexane (v/v, 1:1).

Preparation of aminoxyl **13,** *a general procedure for coupling*

To a solution of **4** (1.46 g, 5 mmol), NaOH (5 mmol) and Na_2CO_3 (1.0 g) in water (40 ml) was added dropwise at 0–5 °C the solution of the diazonium **12** freshly prepared from methyl 4-aminobenzoate (0.76 g, 5 mmol) and sodium nitrite (0.35 g, 5 mmol). The mixture was stirred for additional 2 h and then standing overnight. After filtration, the solid was dried and chromatographed on silica gel eluted with chloroform. Recrystallization from *n*-heptane/chloroform gave the pure product **13.** The data for characterization are collected in Table I.

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Table I. Characterization data for the newly synthesized compounds.

Compound	Yield (%)	M.p./°C	IR (ν, cm^{-1})	MS (m/z)	EPR (a_N/mT)	Molecular formula	Microanalysis calculated (found) (%)		
							C	H	N
2	61[a]	252	3430, 3065, 1690, 1603			$C_{16}H_{23}NO_3$	69.29 (69.16	8.36 8.36	5.05 4.97)
3	50[a]	80	3456, 3180, 1660, 1608			$C_{16}H_{23}NO_3$	69.29 (69.29	8.36 8.48	5.05 4.99)
4	21[a]	175	3370, 1700, 1610	292 (M^+)	1.59 ($CHCl_3$)	$C_{16}H_{22}NO_4$	65.73 (65.76	7.59 7.61	4.79 4.55)
5	54[b]	97–98	3130, 1660, 1610	292 (M^+)	1.55 (C_6H_6)	$C_{16}H_{22}NO_4$	65.73 (66.18	7.59 7.57	4.79 4.34)
8	35[c]	130–131	3420, 1645, 1630, 1598, 1575	342 (M^+)	1.55 (C_6H_6)	$C_{20}H_{24}NO_4$	70.15 (70.49	7.07 7.07	4.09 3.90)
10	64[c]	116–117	3400, 1734, 1653, 1629, 1596, 1577, 1500, 1450, 1396			$C_{27}H_{28}N_3O_6$	66.11 (65.71	5.75 5.92	8.56 7.60)
13	37[c]	160–161	3420, 1720, 1700, 1610, 1425	454 (M^+)	1.54 (C_6H_6)	$C_{24}H_{28}N_3O_6$	63.43 (63.22	6.21 6.30	9.24 9.22)
14	10[c]	189		425, 424		$C_{32}H_{34}N_3O_8$	65.30 (64.40	5.82 5.69	7.14 7.34)

[a] Yields were calculated from the sample after recrystallization; [b] the crude yield was 100%, twice column chromatographies on silica gel gave the product of this yield; [c] combination of chromatography on silica gel and recrystallization gave the corresponding yield of the pure aminoxyl.

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