Facile Synthesis of 4-Hydroxycoumarins by Sulfur-Assisted Carbonylation of 2′-Hydroxyacetophenones with Carbon Monoxide

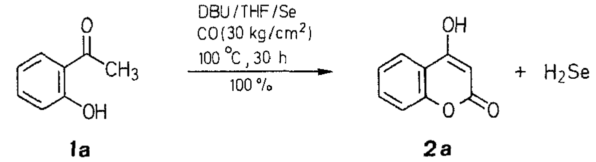
Takumi Mizuno,*[a] Ikuzo Nishiguchi,[a] Tsuneaki Hirashima,[a] Akiya Ogawa,[b] Nobuaki Kambe,[b] Noboru Sonoda[b]

[a] Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Jyoto-ku, Osaka 536, Japan
[b] Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

4-Hydroxycoumarins (4-hydroxy-2-oxo-2*H*-1-benzopyrans) were synthesized in good to excellent yields by C-carbonylation of 2′-hydroxyacetophenones with carbon monoxide in the presence of sulfur and bases. This is the first example of sulfur-assisted C-Carbonylation with carbon monoxide.

Carbon monoxide has been lately recognized to have considerable importance as a reducing agent or a source of carbon in organic syntheses. For the utilization of carbon monoxide, numerous of studies[1] have been carried out, which have provided many useful synthetic methods. However, with regard to C-C bond formation using carbon monoxide, most of the studies have been focused on carbonylation using a transition metal catalyst. Only a few types of C-carbonylation with carbon monoxide have been reported besides the transition metal-catalyzed reactions: (1) carbonylation through organic boron compounds,[2] (2) acid catalyzed C-carbonylation (Koch reaction),[3] (3) reaction of carbanion with carbon monoxide,[4] and (4) selenium-assisted carbonylation.[5]

We recently reported that selenium could assist the carbonylation of alkyl aryl ketone with carbon monoxide in the presence of base to effectively afford coumarin derivatives in excellent yields.[5]



1a **2a**

Table 1. Effects of Bases and Reaction Temperature in the Preparation of 4-Hydroxycoumarin (**2a**)[a]

Run	Base	(mmol)	Temp. (°C)	Yield[b] (%)
1	DBU[c]	30	120	88
2	DBU[d]	30	120	78
3	DBN[e]	30	120	30
4	DABCO[f]	30	120	0
5	1-$CH_3(NC_4H_8)$[g]	30	120	0
6	K_2CO_3	30	120	0
7	NaOH	30	120	0
8	none		120	0
9	DBU	30	140	32
10	DBU	30	100	93
11	DBU	30	90	89
12	DBU	30	80	95
13	DBU	30	70	69
14	DBU	30	60	71

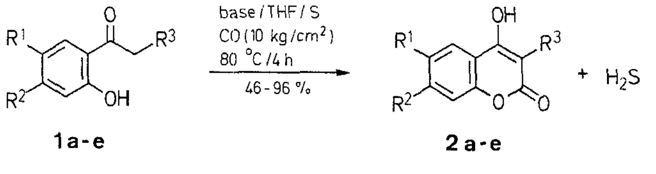
[a] **1a** (10 mmol), sulfur (30 mmol), Et_3N (30 mmol), THF (20 mL), CO (10 kg/cm^2), 4 h.
[b] Isolated yields based on **1a** used.
[c] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[d] In the absence of triethylamine.
[e] 1,5-Diazabicyclo[4.3.0]non-5-ene.
[f] 1,4-Diazabicyclo[2.2.2]octane.
[g] 1-Methylpyrrolidine.

Table 2. 4-Hydroxycoumarins **2a**–**e** Prepared

Product	R^1	R^2	R^3	Yield[a] (%)	mp (°C)[b] (solvent)	Lit. mp (°C)	IR (KBr)[c] ν(cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[d] δ	MS (70 eV)[e] m/z (%)
2a	H	H	H	95	205.1 (AcOEt/ C_6H_6, 1 : 1)	206[8]	2400–3700, 1710, 1615	5.66 (s, 1H); 7.20–8.00 (m, 4H); 12.48 (br s, 1H)	162 (M^+, 99); 120 (100)
2b	H	H	CH_3	84	229.5 (AcOEt/ C_6H_6, 2 : 1)	230[9]	2850–3700, 1665, 1615	2.08 (s, 3H); 7.20–8.04 (m, 4H); 11.12 (br s, 1H)	176 (M^+, 100); 121 (90)
2c	CH_3	H	H	92	255.7 (MeOH)	258[10]	2500–3600, 1685, 1610	2.36 (s, 3H); 5.60 (s, 1H); 7.20–7.68 (m, 3H); 12.40 (br s, 1H)	176 (M^+, 78); 134 (100)
2d	H	CH_3O	H	96	253.5 (MeOH)	256[11]	2400–3600, 1690, 1610	3.84 (s, 3H); 5.50 (s, 1H); 6.80–7.04 (m, 2H); 7.60–7.84 (m, 1H); 12.36 (br s, 1H)	192 (M^+, 100); 150 (91)
2e	H	OH	H	46	264.0 (MeOH/ C_6H_6, 1 : 1)	265[9]	2400–3700, 1660, 1595	5.44 (s, 1H); 6.68–6.92 (m, 2H); 7.60–7.80 (m, 1H); 10.52 (br s, 1H); 12.16 (br s, 1H)	178 (M^+, 100); 136 (83)

[a] Isolated yield based on **1a**–**e** used.
[b] Uncorrected, measured with a Mettler-FP5 apparatus.
[c] Recorded on a JASCO A-3 Infrared spectrophotometer.
[d] Measured using a JEOL FX90Q spectrometer.
[e] Recorded on a JEOL HX-100 spectrometer.

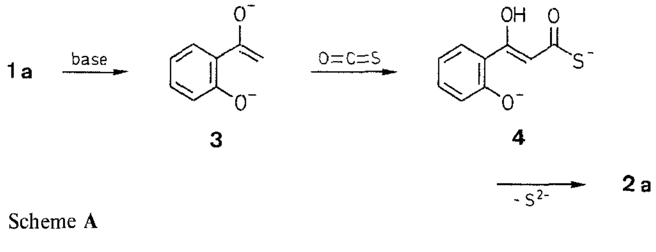
In this study, we wish to report the sulfur-assisted C-carbonylation of 2′-hydroxyacetophenones **1**, which provides a facile method for synthesis of 4-hydroxycoumarins **2**.



Sulfur-assisted carbonylation of 2′-hydroxyacetophenones proceeded under milder reaction conditions (80 °C, 10 kg/cm^2) than those for selenium-assisted carbonylation,[6] and afforded 4-hydroxycoumarins in good to excellent yields. This is the first example of C-carbonylation with carbon monoxide assisted by sulfur to our knowledge.

In a study of reaction conditions using 2′-hydroxyacetophenone (**1a**) as model, it was found that bases were indispensable and considerably influenced the yields of 4-hydroxycoumarin (**2a**). Various sorts of bases were examined (Table 1).

As seen in Table 1, a mixture of DBU (1,8-diazabyciclo[5.4.0] undec-7-ene) and triethylamine was suitable for this carbonylation (run 1).[7] Reaction temperature also affected the yield of 4-hydroxycoumarin (**2a**). For example, **2a** was obtained at 80 °C in almost quantitative yield (95 %; run 12), while considerable decrease in yield was observed at 140 °C (32 %; run 9) or 70 °C (69 %; run 13).



Scheme A

Several substituted 4-hydroxycoumarin (**2b**–**e**) were prepared by the carbonylation of 2′-hydroxyacetophenones with carbon monoxide and sulfur in the presence of DBU and triethylamine at 80 °C and 10 kg/cm^2 (Table 2).

Generally the 4-hydroxycoumarin derivatives were formed selectively in good to excellent yields, while only the reaction of **1e** resulted in low yield of **2e**.

A suggested reaction path is illustrated in Scheme **A**.

The acetophenone is initially transformed into carbanion **3** by base (DBU); then intermediate **4** is formed by electrophilic attack of carbon oxide sulfide, generated *in situ*, to the enolate anion of **3**. Subsequent condensation with elimination of hydrogen sulfide gives 4-hydroxycoumarin **2a**. This mechanism seems to be plausible from analogy with the selenium-assisted carbonylation of 2′-hydroxyacetophenone with carbon monoxide.[5]

4-Hydroxycoumarin (2a); Typical Procedure:

In a 100 mL stainless steel autoclave, 2′-hydroxyacetophenone (**1a**; 1.20 mL, 10 mmol), powdered sulfur (0.96 g, 30 mmol) (4.5 mL, 30 mmol), Et_3N (4.2 mL, 30 mmol), and THF (20 mL) are placed with a magnetic stirring bar under nitrogen atmosphere. The autoclave is then flushed several times with CO and finally charged with carbon monoxide at 10 kg/cm^2 at room temperature. The carbonylation of **1a** was carried out 80 °C for 4 h with vigorous stirring. The reaction mixture is then poured into aq. 1 N HCl (100 mL), and extracted by Et_2O (100, 2 × 50 mL). The extract is dried ($MgSO_4$) and the solvent is evaporated. The resulting solid is washed by benzene (50 mL) and dried in vacuum. Recrystallization from AcOEt/benzene (1 : 1) gives **2a**; yield: 1.54 g (95 %) (see Table 2).

We thank the Ministry of Education, Science and Culture of Japan for a Grant-in-Aid to Special Project Research (No. 62101008).

Received: 8 July 1987; revised: 19 October 1987

(1) Falbe, J. *New Syntheses with Carbon Monoxide*, Springer-Verlag, Berlin, 1980.
Ford, P.C. *Catalytic Activation of Carbon Monoxide*, ACS Symp. Ser. 152, Washington, D.C. 1981.
Keim, W. *Catalysis in C_1 Chemistry*, D. Reidel, Dordrecht, 1983.
Narayana, C., Periasamy, M. *Synthesis* **1985**, 253.
(2) Hubbard, J.L., Smith, K. *J. Organomet. Chem.* **1984**, *276*, C 41.
Kabalka, G.W., Delgado, M.C., Sastry, U., Sastry, K.A.R. *J. Chem. Soc. Chem. Commun.* **1982**, 1273.

(3) Farcasiu, D., Schlosberg, R.H. *J. Org. Chem.* **1982**, *47*, 151.
Yoneda, N., Sato, H., Fukuhara, T., Takahashi, Y., Suzuki, A. *Chem. Lett.* **1983**, 19.

(4) Seyferth, D., Weinstein, R.M., Wang, W.-L. *J. Org. Chem.* **1983**, *48*, 1144.
Seyferth, D., Weinstein, R.M., Wang, W.-L., Hui, R.C. *Tetrahedron Lett.* **1983**, *24*, 4907.
Seyferth, D., Weinstein, R.M. *J. Am. Chem. Soc.* **1982**, *104*, 5534.
Nudelman, N.S., Outumuro, P. *J. Org. Chem.* **1982**, *47*, 4347.
Seyferth, D., Hui, R.C. *Tetrahedron Lett.* **1984**, *25*, 2623.
Seyferth, D., Hui, R.C. *Organometallics* **1984**, *3*, 327.
Seyferth, D., Hui, R.C. *Tetrahedron Lett.* **1984**, *25*, 5251.
Murai, S., Ryu, I., Iriguchi, J., Sonoda, N. *J. Am. Chem. Soc.* **1984**, *106*, 2440.

(5) Ogawa, A., Kondo, K., Murai, S., Sonoda, N. *J. Chem. Soc. Chem. Commun.* **1982**, *1283*.
Ogawa, A., Kambe, N., Murai, S., Sonoda, N. *Tetrahedron* **1985**, *41*, 4813.

(6) The synthetic utility of the present sulfur-assisted carbonylation should prove to be higher than that of the similar reaction assisted by selenium: selenium is more expensive than sulfur and troublesome because of its toxicity.

(7) The use of triethylamine caused easier dissolution of elemental sulfur, which could have resulted in the higher yields observed.

(8) Anschütz, R. *Liebigs Ann. Chem.* **1909**, *367*, 196.

(9) Heilbron, I.M., Hill, D.W. *J. Chem. Soc.* **1927**, 1705.

(10) Garden, J.F., Hayes, H.F., Thomson, R.H. *J. Chem. Soc.* **1956**, 3315.

(11) Sonn, A. *Ber. Dtsch. Chem. Ges.* **1917**, *50*, 1292.