Rapid Synthesis of Novel and Known Coumarin-3-carboxylic Acids Using Stannous Chloride Dihydrate under Solvent-Free Conditions

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Various coumarin-3-carboxylic acid (=2-oxo-2*H*-1-benzopyran-3-carboxylic acid; CcaH) derivatives have been synthesized in good yields using catalytic amounts of $SnCl_2 \cdot 2\,H_2O$ under solvent-free conditions. This inexpensive, nontoxic, and readily available catalytic system (10 mol-%) efficiently catalyzes the *Knoevenagel* condensation and intramolecular cyclization of various 2-hydroxybenzaldehydes or acetophenones with *Meldrum*'s acid. High product yields, use of inexpensive and safe catalyst, and solvent-free conditions display both economic and environmental advantages.

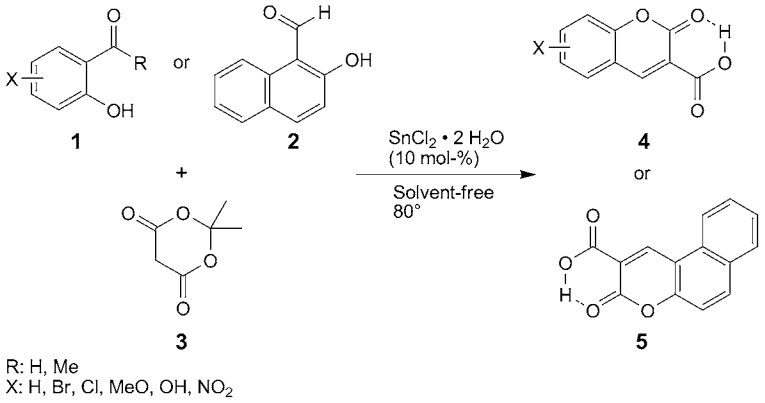
Introduction. – Regarding several reports on the effective applications of $SnCl_2$ as an inexpensive *Lewis* acid catalyst for one-step synthesis of quinolines [1], synthesis of 1,3-dithiolane [2], esterification of carboxylic acids with alcohols [3], and cyclization of nitro arenes *via* N,N bond formation [4], here, we present a simple and environment-friendly method for the synthesis of novel and known coumarin-3-carboxylic acid derivatives using $SnCl_2 \cdot 2\,H_2O$ under solvent-free conditions.

Results and Discussion. – Solid-phase organic synthesis (SPOS) has emerged as powerful tool for combinatorial drug discovery allowing the preparation of highly diverse compound libraries [5–7]. The use of solid-phase or solvent-free systems obviously reduces labor cost, eliminates hazards, and improves ventilation problems in confined spaces.

In connection with our studies on the synthesis of organic compounds under mild and environment-friendly conditions [8–10], we now found that catalytic amounts of $SnCl_2 \cdot 2\,H_2O$ can be used as an efficient, safe, and very cheap catalyst for the *Knoevenagel* condensation and intramolecular cyclization of 2-hydroxybenzaldehydes and acetophenones, **1**, or 2-hydroxynaphthalene-1-carbaldehyde (**2**) with *Meldrum*'s acid (**3**) under solvent-free conditions to afford coumarin-3-carboxylic acid (=2-oxo-2*H*-chromene-3-carboxylic acid = 2-oxo-2*H*-1-benzopyran-3-carboxylic acid) derivatives **4** or **5** in good yield (*Scheme 1*). It should be mentioned that all of the coumarin-3-carboxylic acids form intramolecular H-bonds [11].

To improve the effectiveness of this method by preventing chemical waste, it was important to investigate optimal reaction conditions. For the elucidation of simple and suitable conditions for synthesis of coumarin-3-carboxylic acid derivatives using $SnCl_2 \cdot 2\,H_2O$, the treatment of salicylaldehyde (=2-hydroxybenzaldehyde; **1** with R = H, X = H) with **3** was chosen as a model reaction (*Table*; product **4a**). First, we found that, in

Scheme 1. *Synthesis of Coumarin-3-carboxylic Acids under Solvent-Free Conditions*



the absence of the catalyst, the reaction was not completed after a long reaction time even at high temperature. After examining the various amounts of $SnCl \cdot 2\ H_2O$ and a wide range of temperatures, it was found that this reaction can be efficiently carried out by adding 10 mol-% of catalyst at 80° under solvent-free conditions in a short time span of 60 min. After optimization of the reaction, condensation of various compounds **1** or 2-hydroxynaphthalene-1-carbaldehyde (**2**) with **3** was carried out to afford coumarin derivatives **4** or **5**. The results are collected in the *Table*.

The synthesized compounds were characterized by IR and NMR spectroscopy, and their spectra were in good agreement with the expected structures. The NMR spectra were recorded in both $CDCl_3$ and (D_6)DMSO with TMS as internal standard. It should be mentioned that the spectrum of coumarin-3-carboxylic acid **4k** in (D_6)DMSO did not exhibit a clear resonance signal for the H-atom of COOH group (*Fig.*, *a*), whereas the signal in $CDCl_3$ appeared at 12.26 ppm (*Fig.*, *b*). This observation was also made for compounds **4a**, **4f**, **4c**, and **5**.

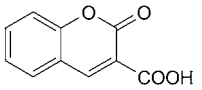
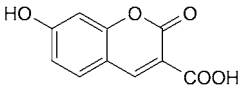
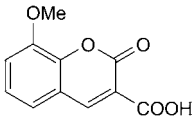
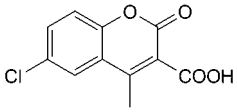
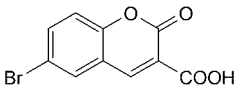
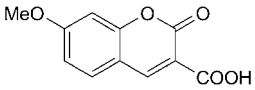
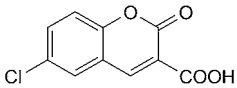
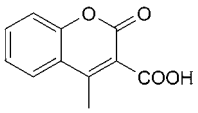
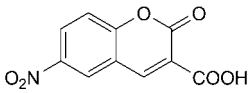
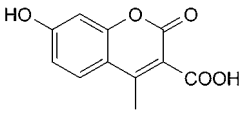
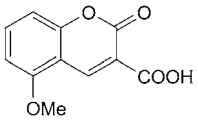
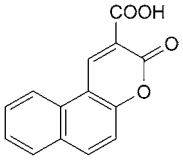
The ^{1}H-NMR spectrum of compound **4k** showed the signal for MeO–C(5) at δ(H) 4.02 (*Fig.*, *b*). The three distinct signals in the range of δ(H) 7.72 – 6.84 corresponded to H–C(6,7,8), whereas the signal for H–C(4) appeared strongly deshielded as *s* at δ(H) 9.32, in agreement with its β-position with respect to the CO group.

Encouraged by the above results, we focused on the synthesis of the novel bi(coumarin)-3,3′-dicarboxylic acid (**9**) *via* 5,5′-bi(salicylaldehyde) (**8**) under solvent-free conditions. For this, we first had to prepare also novel **8** *via* formylation of 1,1′-biphenyl-4,4′-diol (**6**) with hexamethylenetetramine (=1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]-decane; **7**) in TFA under N_2 (*Scheme 2*). The yield of **8** under these conditions amounted to 50%. The reaction of **8** with **3** in the presence of $SnCl_2 \cdot H_2O$ gave the expected 6,6′-bicoumarin-3,3′-carboxylic acid in a yield of 80% (*Scheme 2*).

A plausible mechanism for the $SnCl_2$-catalyzed syntheses of coumarin-3-carboxylic acids is proposed in *Scheme 3*.

Conclusions. – In summary, a new rapid method for the synthesis of novel and known coumarin-3-carboxylic acid derivatives with $SnCl_2 \cdot 2\ H_2O$ as inexpensive

Table. *Synthesis of Coumarin-3-carboxylic Acids Using $SnCl_2 \cdot 2\,H_2O$* (10 mol-%) *at 80° Under Solvent-Free Conditions*

	Product[a])	Time [min]	Yield [%]	M.p. [°][b])
4a		60	80	188–189 ([12]: 191–192)
4b		60	87	259–260 ([13]: 261–263)
4c		100	86	197–198 ([14]: 209–210)
4d		105	75	153–154 ([13]: 151–152)
4e		70	85	195–197 ([13]: 195–196)
4f		70	80	193–194 ([12]: 192–194)
4g		70	82	120–121 ([13]: 120–121)
4h		110	80	162–163 ([13]: 161–162)
4i		60	90	233–234 ([13]: 234–235)
4j		110	75	126–127[c])
4k		30	92	221–222[c])
5		90	85	195–196 ([12]: 216–218)

[a]) Yield of Isolated products. [b]) In parentheses, reported m.p. [c]) Novel compounds.

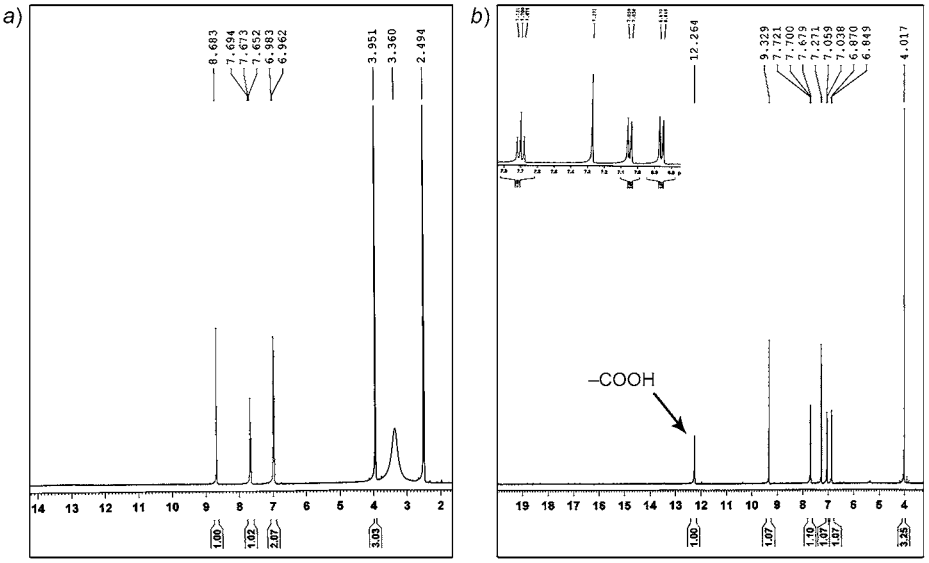
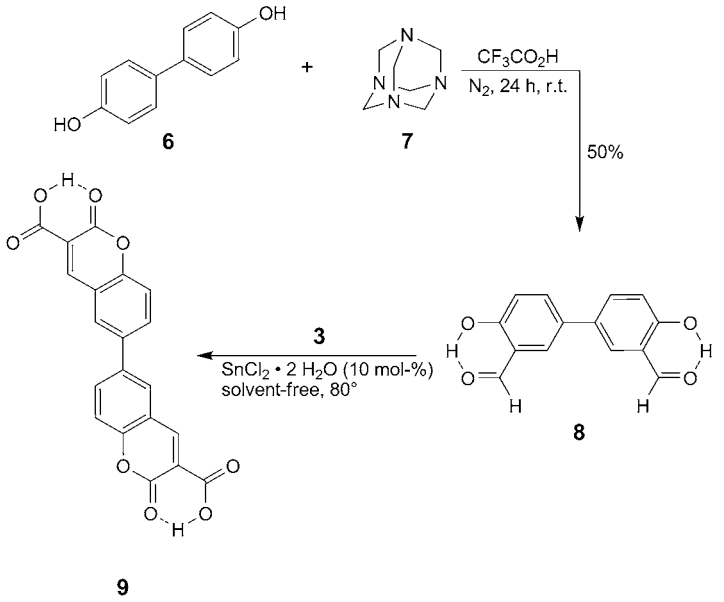


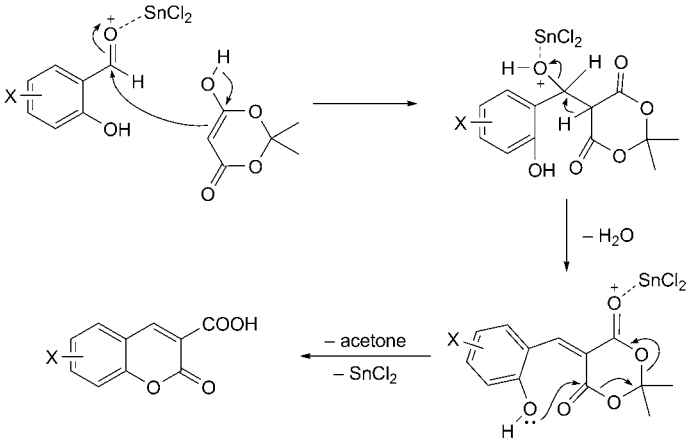
Figure. *[1]H-NMR Spectra* (400 MHz) *of compound* **4k** a) *in (D6)DMSO and* b) *in CDCl3*

Scheme 2. *Synthesis of 5,5′-Bi(salicylaldehyde)* (**8**) *and 6,6′-Bi(coumarin)-3,3′-dicarboxylic Acid* (**9**)



catalyst under solvent-free conditions has been described. This simple catalytic system is remarkably tolerant to a variety of functional groups on the hydroxybenzaldehydes or acetophenones, and offers significant advantages such as low catalyst loading, high

Scheme 3. *Proposed Mechanism for the Synthesis of Coumarin-3-carboxylic Acid Derivatives Using $SnCl_2 \cdot 2\,H_2O$ as Catalyst*



yields, avoidance of organic solvents, short reaction times, and operational simplicity. Therefore, in employing a small amount of safe and inexpensive catalyst under solvent-free conditions, this protocol is economic and environment-friendly. Further investigations toward the synthesis of biologically active substances by using the present method are currently in progress.

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Experimental Part

General. The chemicals were purchased from *Merck*, *Fluka*, and *Aldrich*. The reactions were monitored by TLC (silica gel *60 F_{254}* (SiO_2); hexane/AcOEt). IR Spectra (KBr disc): *FT-IR Shimadzu-470* spectrometer. NMR Spectra: *Bruker-Instrument DPX-400 Avance 2* model. All of the products (except novel compounds) were characterized by comparison of their spectra and physical data with those reported in the literature [12–14].

Preparation of Coumarin-3-carboxylic Acid Derivatives **4** *and* **5**. A mixture of **1** or **2** (1 mmol), **3** (2 mmol), and $SnCl_2 \cdot 2\,H_2O$ (10 mol-%) was stirred and heated at 80° in a preheated oil bath for an appropriate time (*Table*). After completion of the reaction as indicated by TLC (hexane/AcOEt 4 : 1), the mixture was dissolved in hot AcOEt, and the catalyst was separated by simple filtration. The solvent was evaporated, and the crude products **4** and **5** were purified by recrystallization from AcOEt.

Selected Spectral Data. Coumarin-3-carboxylic Acid (=*2-Oxo-2*H-*1-benzopyran-3-carboxylic Acid*; **4a**). IR: 3500–2600*w*, 1702v*s*, 1436v*s*, 1217v*s*, 1173v*s*. ^{1}H-NMR ((D_6)DMSO): 8.53 (*s*, 1 H); 7.7 (*d*, *J* = 7.6, 1 H); 7.51 (*t*, *J* = 7.2, 1 H); 7.23–7.17 (2*d*, *J* = 8.6, 2 H). ^{13}C-NMR ((D_6)DMSO): 164.5; 157.2; 154.9; 148.9; 134.8; 130.6; 125.3; 118.8; 118.4; 116.6.

8-Methoxycoumarin-3-carboxylic Acid (=*8-Methoxy-2-oxo-2*H-*1-benzopyran-3-carboxylic Acid*; **4c**). IR: 3500–2600*w*, 1760v*s*, 1695v*s*, 1620v*s*, 1590v*s*, 1200v*s*, 1110v*s*. ^{1}H-NMR ((D_6)DMSO): 8.55 (*s*, 1 H); 7.26–7.18 (*m*, 3 H); 7.14 (*t*, *J* = 8, 1 H); 3.74 (*s*, 1 H). ^{13}C-NMR ((D_6)DMSO): 149.3; 140.7; 144.3; 125.2; 121.6; 119.0; 116.7; 56.6.

7-Methoxycoumarin-3-carboxylic Acid (=*7-Methoxy-2-oxo-2*H-*1-benzopyran-3-carboxylic Acid*; **4f**). IR: 3434, 3045, 2955, 1732, 1691, 1618, 1217. ^{1}H-NMR ((D_6)DMSO): 8.71 (*s*, 1 H); 7.82 (*d*, *J* = 8.4, 1 H); 7.00 (*dd*, *J* = 5.6, 2.4, 2 H); 13.0 (*s*, 1 H); 3.88 (*s*, 3 H). ^{13}C-NMR ((D_6)DMSO): 169.9; 169.5; 162.4; 162.1; 154.2; 136.7; 119.0; 118.5; 116.8; 105.5; 61.4.

7-Hydroxy-4-methylcoumarin-3-carboxylic Acid (= *7-Hydroxy-4-methyl-2-oxo-2*H-*1-benzopyran-3-carboxylic Acid*; **4j**). IR: 3400–2600*w*, 1726v*s*, 1630v*s*, 1600v*s*, 1500v*s*, 1160v*s*, 1060v*s*. ^{1}H-NMR ((D$_6$)DMSO): 12.40 (*s*, 1 H); 10.43 (*s*, 1 H); 7.54 (*d*, *J* = 8.8, 1 H); 6.16 (*dd*, *J* = 6.8, 2.0, 1 H); 6.03 (*d*, *J* = 2.0, 1 H); 2.30 (*s*, 3 H). ^{13}C-NMR ((D$_6$)DMSO): 169.5; 165.5; 164.3; 134.1; 113.3; 108.6; 102.8; 26.8.

5-Methoxycoumarin-3-carboxylic Acid (= *5-Methoxy-2-oxo-2*H-*1-benzopyran-3-carboxylic Acid*; **4k**). IR: 3350–2400*w*, 1760v*s*, 1690v*s*, 1620v*s*, 1220v*s*. ^{1}H-NMR (CDCl$_3$): 12.26 (*s*, 1 H); 9.32 (*s*, 1 H); 7.70 (*t*, *J* = 8.4, 1 H); 7.04 (*d*, *J* = 8.4, 1 H); 6.85 (*d*, *J* = 8.4, 1 H); 4.01 (*s*, 3 H). ^{13}C-NMR ((D$_6$)DMSO): 164.2; 157.3; 156.6; 155.9; 143.2; 136.1; 116.2; 108.3; 106.3; 56.9.

*Benzo[*f*]coumarin-2-carboxylic Acid* (= *3-Oxo-3*H-*benzo[*f*]-1-benzopyran-2-carboxylic Acid*; **5**). IR: 3046*w*, 1748v*s*, 1683v*s*, 1571v*s*, 1217v*s*. ^{1}H-NMR ((D$_6$)DMSO): 13.12 (*s*, 1 H); 9.37 (*s*, 1 H); 8.59 (*d*, *J* = 8.4, 1 H); 8.31 (*d*, *J* = 9.2, 1 H); 8.08 (*d*, *J* = 7.6, 1 H); 7.77 (*t*, *J* = 7.2, 1 H); 7.65 (*t*, *J* = 7.6, 1 H); 7.59 (*d*, *J* = 9.2, 1 H). ^{13}C-NMR ((D$_6$)DMSO): 164.8; 157.3; 155.5; 144.1; 136.3; 129.5; 126.9; 122.7; 117.8; 116.9; 112.6.

Preparation of 5,5′-Bi[salicylaldehyde] (= *4,4′-Dihydroxy-1,1′-biphenyl-3,3′-dicarbaldehyde*; **8**). A soln. of *1,1′-biphenyl-4,4′-diol* (**6**; 10 mmol), *hexamethylenetetramine* (= *1,3,5,7-tetraazatricyclo-[3.3.1.1^{3,7}]decane*; **7**; 15 mmol), and CF$_3$COOH (TFA; 30 ml) was stirred for 24 h under N$_2$. Then, 4M aq. HCl (100 ml) was added to the mixture and stirred for 20 min. Finally, the mixture was poured into CH$_2$Cl$_2$, and the org. phase containing **8** was extracted. After evaporation of the solvent, pure **8** was obtained by column chromatography (CC; hexane/AcOEt 3 : 7) in 50% yield. M.p. 106–108°. IR: 3428–3085*w*, 2850*m*, 2738*w*, 1654v*s*, 1469*s*, 1176*s*, 767*s*. ^{1}H-NMR (250 MHz, (D$_6$)DMSO): 10.75 (*s*, 1 H); 10.28 (*s*, 1 H); 7.90–6.76 (*m*, 3 H).

Preparation of 6,6′-Bi[coumarin]-3,3′-dicarboxylic Acid (= *2,2′-Dioxo-2*H,*2′*H-*6,6′-bichromene-3,3′-dicarboxylic Acid*; **9**). A mixture of **8** (1 mmol), **3** (2 mmol), and SnCl$_2$ · 2 H$_2$O (10 mol-%) was stirred and heated at 80° in a preheated oil bath for 220 min. After completion of the reaction as indicated by TLC (hexane/AcOEt 4 : 1), the mixture was dissolved in hot AcOEt, and the catalyst was separated by simple filtration. The solvent was evaporated and crude **9** was purified by recrystallization from AcOEt. Yield: 80%. M.p. 220–222°. IR: 3500–3000*w*, 1738v*s*, 1680v*s*, 1610*s*, 1564*s*, 1202*m*. ^{1}H-NMR (CDCl$_3$): 12.29 (*s*, 2 H); 9.02 (*s*, 2 H); 8.02–7.44 (*m*, 6 H). ^{13}C-NMR ((D$_6$)DMSO): 164.4; 157.1; 154.3; 148.9; 137.8; 137.1; 133.0; 129.5; 129.4; 128.3; 127.1; 126.5; 119.0; 118.8; 117.1.

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