

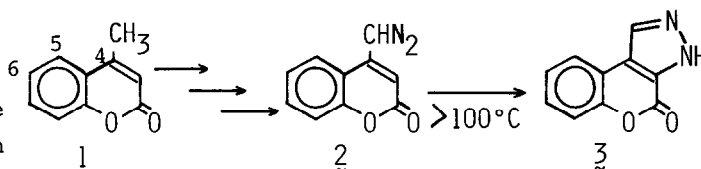
## A NOVEL AND EFFICIENT SYNTHESIS OF 5-SUBSTITUTED AND 5,6-DISUBSTITUTED 4-METHYLCOUMARINS USING ORGANOCERIUM(III) REAGENTS<sup>1,2)</sup>

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**Summary:** Addition of organocerium(III) reagent,  $Cl_2CeCH_2COOt-Bu$ , to the appropriate *ortho*-methoxymethoxyacetophenones followed by acid-treatment gives 5-substituted and 5,6-disubstituted 4-methylcoumarins in excellent yields.

During the course of our studies on diazoalkanes as a potential fluorogenic reagent for acidic substances, 4-diazomethylcoumarin derivatives (**2**) were found to unexpectedly isomerize into **3** in refluxing toluene.<sup>3)</sup> In order to verify the generality of this cyclization, therefore, we required a diversity of 4-methylcoumarins (**1**) bearing substituents in the 5-position or in both the 5- and 6-positions.

Two representatives, *i.e.*, the Pechmann<sup>4a)</sup> and Reformatsky<sup>5)</sup> reactions have appeared for the preparation of 4-methylcoumarins. How-



ever, neither can be satisfactory due to the following crucial disadvantages. [1] The Pechmann condensation of ethyl acetoacetate and phenols in conc.  $H_2SO_4$  does not always yield 4-methylcoumarins. Especially, in the case of 3,4-disubstituted and/or 3,4,5-trisubstituted phenols *isomeric* 2-methylchromones result under similar conditions.<sup>4a-c)</sup> [2] Only 7-substituted 4-methylcoumarins ensue, as well known, instead of the desired 5-substituted compounds when applied to phenols such as *meta*-cresol and resorcinol in an analogous manner.<sup>4a)</sup> [3] Conversion of unprotected *ortho*-hydroxyacetophenones with a large excess (10eq.) of lithio *tert*-butyl acetate,  $LiCH_2COOt-Bu$ <sup>6)</sup>, in the Reformatsky-type reaction to a coumarin is unsuccessful.<sup>7)</sup> [4] In contrast to the normal adducts formation on protected *ortho*-hydroxyacetophenones, the Reformatsky reaction of 6-substituted 2-methoxymethoxyacetophenones under a wide variety of reaction conditions affords only starting materials unchanged owing to just

enolization.<sup>8)</sup>

Most recently three groups successively reported the reaction of lanthanides reagents on the  $\alpha,\beta$ -unsaturated and/or readily enolizable carbonyl compounds leading to the 1,2-adducts cleanly.<sup>9)</sup> It is, in particular, interesting that a marginal yield(57%) of the 1,2-adduct was obtained from the reaction of 2,4,6-trimethylacetophenone with *n*-butylcerium(III) chloride.<sup>9a)</sup>

Thus, we now report in this letter a general, efficient and operationally convenient approach to the synthesis of 5-substituted and 5,6-disubstituted 4-methylcoumarins(7a-e) based upon addition of never known organocerium(III) reagent,  $\text{Cl}_2\text{CeCH}_2\text{COOt-Bu}$ <sup>10)</sup> (4), which can be prepared from anhyd. $\text{CeCl}_3$ <sup>11)</sup> and solid  $\text{LiCH}_2\text{COOt-Bu}$ <sup>6)</sup>, to the appropriate *ortho*-methoxymethoxyacetophenones (5a-e) and subsequent acid-hydrolysis.

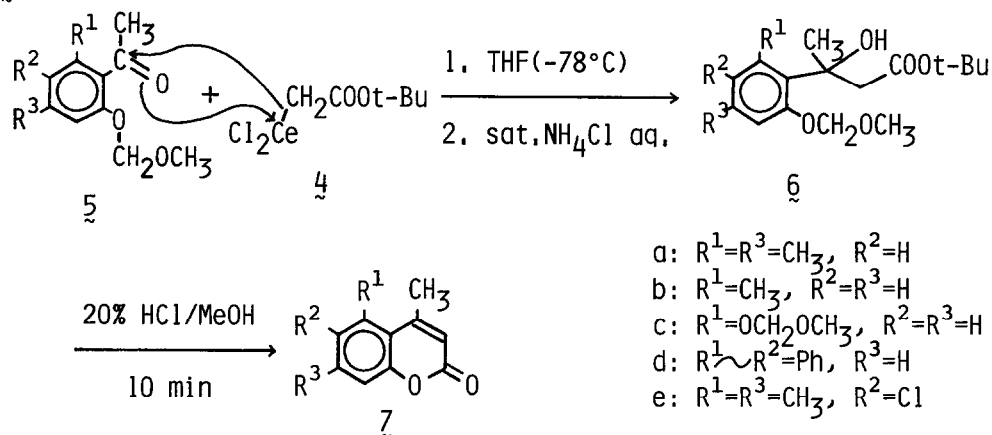


Table I. Physical Data for Adducts, 6<sub>a-e</sub>

Compound	6 <sub>a</sub>	6 <sub>b</sub>	6 <sub>c</sub>	6 <sub>d</sub>	6 <sub>e</sub>
Appearance (an oil)	colorless	colorless	colorless	pale yellow	colorless
Isolated Yield(%)	93.0	94.5	92.8	95.4	96.0
IR $\nu_{\text{cm}}^{\text{neat}}$ for -OH	3500	3500	3500	3450	3500
for -COOt-Bu	1700	1715	1720	1715	1720
PMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$ for -OH	4.4*	4.5*	5.9*	4.7*	4.6*
for -COOt-Bu	1.2	1.3	1.3	1.2	1.2
MS m/e(M <sup>+</sup> )	324	310	356	346	358/360=3

\* Disappearance on addition of D<sub>2</sub>O.

Table II. Physical Data for Coumarins, 7<sub>a-e</sub>

Coumarin	7 <sub>a</sub>	7 <sub>b</sub> <sup>a)</sup>	7 <sub>c</sub> <sup>a)</sup>	7 <sub>d</sub>	7 <sub>e</sub> <sup>a)</sup>
Appearance (colorless crystals)	plates	needles	leaflets	needles	needles
mp(°C) from 95% EtOH	182- 182.5 <sup>b)</sup>	160- 161	270- 271.5	180.5- 181 <sup>b)</sup>	196- 197
Isolated Yield(%)	97.7	100	98.0	96.7	95.0
IR $\nu_{\text{C=O}}$ for lactone $\text{cm}^{-1}$	1710	1705	1710	1700	1700
CMR $\delta_{\text{ppm}}^{\text{CDCl}_3}$ for $\text{>C=O}$	160.45	160.51	165.25	173.55 <sup>c)</sup>	162.50 <sup>c)</sup>
MS m/e(M <sup>+</sup> )	188	174	176	210	222/224=3

a) Satisfactory microanalyses were obtained (C  $\pm$ 0.05%, H  $\pm$ 0.10%).

b) No depression with an authentic specimen. c) Taken in DMSO-d<sub>6</sub>.

The following characteristics make this approach synthetically attractive. (1) The yields are virtually quantitative in every step, even after a short-path column chromatography. (2) As illustrated in Table I, addition is quite clean and is monitored simply by TLC. No side reactions, such as dimerization and self-condensation which usually complicate purification are practically observed. (3) Forming the right coumarins(7<sub>a-e</sub>) is *exclusive* as shown in Table II. Thus, the serious difficulties, *e.g.*, the formation of off-target coumarins and chromones, which are almost always encountered in its preparation by the traditional Pechmann reaction, can be completely overcome. (4) A one-step operation is employed for cleavage of *t*-butyl ester and methoxymethyl (MOM) ether, cyclization and subsequent dehydration to furnish coumarins(7<sub>a-e</sub>). (5) The completion of the coumarin formation is clearly visualized since a large amount of white solid is precipitated as soon as the reaction is done. (6) Generation of MOM ether(5<sub>a-e</sub>) is easily accomplished by KH/ClCH<sub>2</sub>OCH<sub>3</sub> in over 90% yields.

Then, we are continuing to explore further application by employing this reagent system.

A typical procedure is as follows: 1) A suspension of anhyd.CeCl<sub>3</sub><sup>11)</sup> (1.5 g, 6mmol, 3eq. to 5<sub>a</sub>) in *dry tetrahydrofuran(THF)* (12 ml) *freshly distilled over benzophenone ketyl* (It is essential!<sup>9)</sup> was violently stirred for 1 h at room temperature under argon and then to this was added a solution of LiCH<sub>2</sub>COO*t*-Bu<sup>6)</sup> (0.61 g, 5mmol, 2.5eq. to 5<sub>a</sub>) in *dry THF* (5 ml) at -78°C. After 1.5-hr-stirring of the whole, compound(5<sub>a</sub>, 0.416 g, 2mmol) in *dry THF* (5 ml)

was added at the same temperature and the resulting mixture was stirred for an additional 4 h. The reaction was then quenched with sat.  $\text{NH}_4\text{Cl}$  aq. (25 ml). Isolation of an organic layer by a centrifuge followed by evaporation and purification using a short-path column chromatography on silica gel with n-pentane/ether(3/1) furnished a pure expected adduct ( $\underline{6d}$ , 0.60 g, 93.0%). 2) A mixture of a 1,2-adduct ( $\underline{6d}$ , 150 mg, 0.46 mmol), 20% aq. HCl (1 ml) and methanol (2 ml) was heated at 80°C (bath temp.) with stirring, during which time a large quantity of solid appeared in the reaction mixture. After 10 min, a white solid settled was filtered by suction and recrystallized from 95% aq. EtOH to provide colorless plates, 4,5,7-trimethylcoumarin ( $\underline{7d}$ , 85 mg, 97.7%), mp 182-182.5°C. Mixed mp with an authentic specimen<sup>4b)</sup> showed no depression.

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#### References and Notes

- 1) Dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
- 2) Partly presented at the 3rd IUPAC Symposium on Organometallic Chemistry directed toward Organic Synthesis, Kyoto, Japan, July, 1985. Abstracts of Papers p. 185.
- 3) K. Ito and J. Maruyama, *Heterocycles*, **22**, 1057 (1984).
- 4) a) S. Sethna and R. Phadke, *Org. React.*, **7**, 1 (1953). b) R. Adams and J.W. Mecorney, *J. Amer. Chem. Soc.*, **66**, 802 (1944). c) Attempts to duplicate the literature method<sup>4d)</sup> have been disappointing and a poor yield (5-8%) of the expected coumarin ( $\underline{7d}$ ) was given by only a hard-to-separate column chromatography. d) A. Băcovescu, *Chem. Ber.*, **43**, 1280 (1910); B.D. Patel and K.V. Bokil, *J. Univ. Bombay*, **11A**, 92 (1943) [*Chem. Abstr.*, **37**, 5969 (1943)].
- 5) a) R.L. Shriner, *Org. React.*, **1**, 1 (1942). b) M.W. Rathke, *Org. React.*, **22**, 423 (1975).
- 6) M.W. Rathke and D.F. Sullivan, *J. Amer. Chem. Soc.*, **95**, 3050 (1973). Formulation of lithium ester enolate,  $\text{CH}_2=\text{COLi}(\text{O}t\text{-Bu})$ , might be preferable.
- 7) Chromones alone formed in ca. 80% yields. Unpublished results.
- 8) Enolization was confirmed by checking the recovered acetophenones after treatment of the reaction mixture with  $\text{DCl}/\text{D}_2\text{O}$  in C-13 NMR spectra. Such enolization have been observed also in connection with the Reformatsky reaction on 2,4,6-trimethylacetophenone. [M.S. Newman, *J. Amer. Chem. Soc.*, **64**, 2131 (1942)]
- 9) a) T. Imamoto, Y. Sugiura and N. Takiyama, *Tetrahedron Lett.*, **25**, 4233 (1984); T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984); T. Imamoto and Y. Sugiura, *J. Organomet. Chem.*, **285**, C21 (1985). b) H. Schumann, J. Müller, N. Bruncks, H. Lauke, J. Pickardt, H. Schwarz and K. Eckart, *Organometallics*, **3**, 69 (1984). c) M. Suzuki, Y. Kimura and S. Terashima, *Chem. Lett.*, **1984**, 1543.
- 10) Conventionally formulated. The description of a new Aldol reaction via cerium enolates of four ketones has been reported by T. Imamoto, T. Kusumoto and M. Yokoyama [*Tetrahedron Lett.*, **24**, 5233 (1983)].
- 11) Commercially available  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  is subjected to dryness *in vacuo* (1-2 torr) first at 100°C for 10 h and then at 140°C for 3 h to produce white powdery granules.

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