REACTION OF ALKYL RADICALS WITH γ-PYRON DERIVATIVES,

2-METHOXYCARBONYLCHROMONE AND DIMETHYL CHELIDONATE.

Masaru Tada* and Naruo Mori

Department of Chemistry, School of Sciene and Engineering,

Waseda University, Shinjuku, Tokyo 169, Japan


Abstract - The raction of alkyl radicals with 2-methoxycarbonylchromone (**3**) and dimethylchelidonate (**4**) gave dimeric products, 2,2'-bis(2,2'-dimethoxycarbonyl-3,3'-dialkyl)chromanone (**5** and **6**) and 2,2'-bis(2,2'6,6'-tetramethoxycarbonyl-3,3'-dialkyl)-2,3-dihydro-4-oxo-4*H*-γ-pyran (**8** and **9**). Both the dimeric products consist of two stereoisomers, *meso* and *dl* at the central bond of the dimer. The formation of the dimeric products is acccounted for by the innitial attack of alkyl radical to the α-position of the γ-pyrone derivatives having ester group at β-position. The intervention of the *capto-dative* radicals is supported by the thermal equilibrium with the dimeric products.

We have been studying the reaction of alkyl radicals with π-electron deficient *N*-heterocycles. Our findings indicate that the reaction proceeds through the nucleophilic addition of an alkyl radical to the heterocycles, followed by the oxidative aromatization of a radical intermediate as reported by Minisci.[1] These reactions provide a versatile method for alkyl or ω-aminoalkyl modification of pyridine,[2] pyrazine,[3] and lumazine derivatives.[4]

The reaction of alkyl radicals with *O*-heterocycles, however, has been rarely examined, though Engberson *et al.* reported [5] that the reaction of alkyl radical with 4-oxo-4*H*-benzpyran, chromone (**1a**, R=H), gave addition products,

2-alkylchromanones (**2**), and substitution products, 2-alkylchromones (**1b**, R=alkyl), in comparable yields.

We report here the reaction of alkyl radicals with 2-methoxycarbonyl-4-oxo-4*H*-chromene (2-methoxycarbonylchromone) (**3**) and 2,6-dimethoxycarbonyl-4-oxo-4*H*-pyran (dimethylchelidonate) (**4**). These *O*-heterocycles have poor aromaticity [6] and are expected to have electrophilic character due to the attached electron withdrawing ester groups.

| 1 | 2 | 3 | 4 |
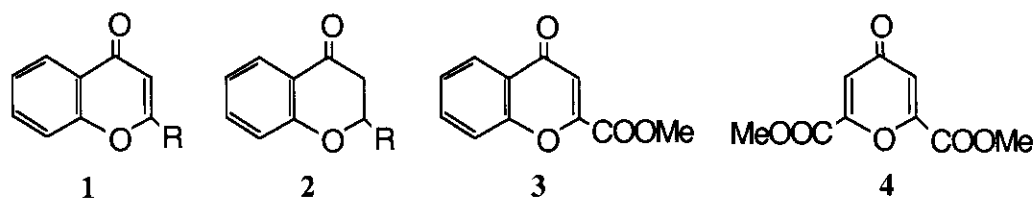
Results and Discussion

tert-Butyl, isopropyl, and ethyl radical are generated by the persulfate oxidation[7] of 2,2-dimethylpropanoic acid, 2-methylpropanoic acid, and propanoic acid, respectively (Scheme I).

$$RCOOH \xrightarrow{\ S_2O_8^{2-} / Ag^+\ } R\bullet \ + \ CO_2 \ + \ H^+$$
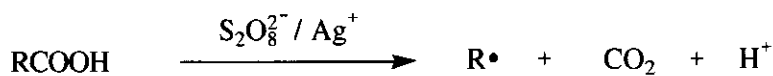
Scheme I

The reaction of 2-methoxycarbonylchromone (**3**) with the tert-butyl radical gave a pair of dimeric products, bis(2,2'-dimethoxycarbonyl-3,3'-di-*tert*-butyl)chromanone, (**5a**) and (**6a**), in the yields shown in Scheme II. Similarly the reactions with isopropyl and ethyl radicals gave products (**5b,c**) and (**6b,c**) in the yields shown in Scheme II. The dimer (**5a**) and (**6a**) showed mass peaks of M⁺/2 instead of M⁺ by EI-ionization but showed weak (M+1)⁺ peaks by CI-ionization. Other products showed weak molecular peaks by EI-ionization in addition to the strong (M⁺/2) peaks due to the formation of a
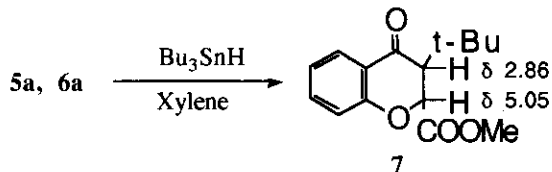
stable *capto-dative* radicals.[6] Product (**5a,b**) and (**6a,b**) gave the base peaks at m/z=205 which were formed by a McLafferty fragmentation followed by the cleavage of the central bond of the dimeric products (Scheme III). These behaviors indicate the instability of the central bond in the

| 5a, 6a | (R=t-Bu) | 35% | 35% |
| 5b, 6b | (R=i-Pr) | 41% | 39% |
| 5c, 6c | (R=Et) | 41% | 30% |
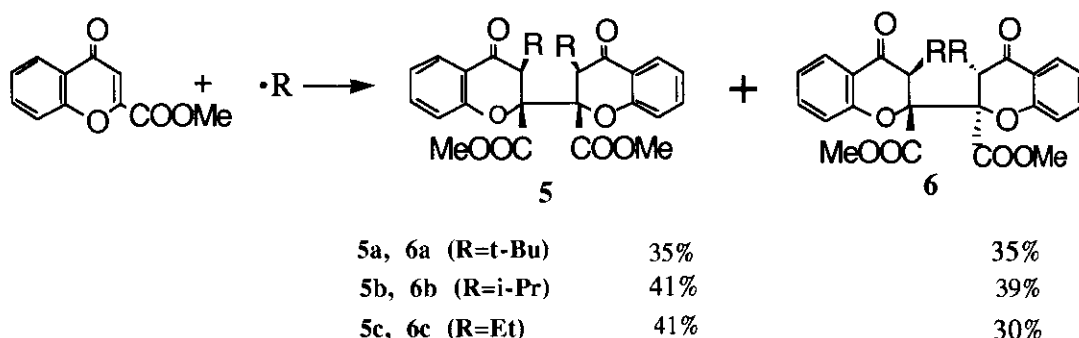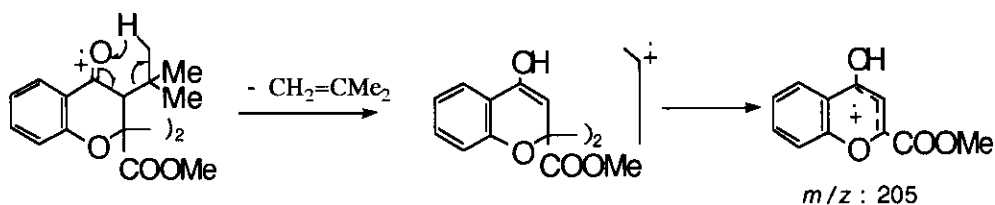
Scheme II

Scheme III

Scheme IV

dimeric products and its cleavage gives a *capto-dative* radical.[8] Indeed the treatment of **5a** and **6a** with tributyltin hydride in boiling xylene gave a reduction product (**7**), which showed a set of doublets in [1]H-nmr

spectrum at δ 2.86 and 5.05 (J=3.8 Hz) (Scheme IV). The properties of products (**5**) and (**6**) suggest that they are dimeric and are stereoisomers at the central bond. The symmetric structures for **5** and **6** are assigned since both stereo-isomers show only one set of ^{1}H-nmr signal due to the alkyl and methoxycarbonyl group respectively. The stereochemistry of alkyl group in **5** and **6** was assigned by the assumption that the radical dimerization takes place at the opposite side of the neighboring alkyl groups. The differentiation of *meso*- (**5**) and dl-isomer (**6**) were impossible from the available data, and the structures of **5** and **6** may replace each other.

| 8a, 9a | (R=t-Bu) | 42% | 30% |
| 8b, 9b | (R=i-Pr) | 27% | 10% |
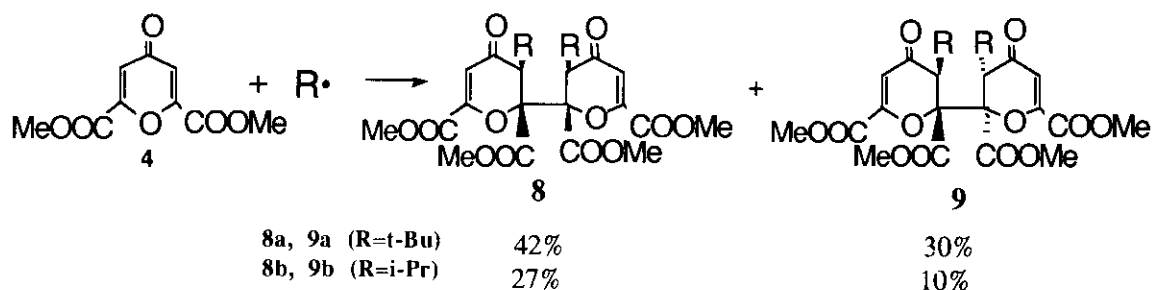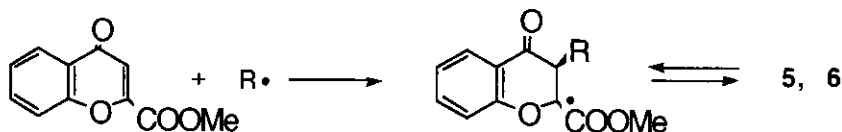
Scheme V

Scheme VI

Similarly the reaction of *tert*-butyl and isopropyl radicals with dimethylchelidonate (**4**) gave the dimeric products (**8**) and (**9**), 2,2'-bis(2,2',6,6'-tetramethoxycarbonyl-3,3'-dialkyl)-2,3-dihydro-4-oxo-4*H*-pyran (Scheme V). Mass spectra of **8** and **9** have essentially the same feature as those of **5** and **6**; M$^+$/2 peaks and the peaks due to the ion generated by a McLafferty degradation followed by the central bond cleavage (see Scheme III). The alkyl and ester groups in the product (**8**) and (**9**) showed again one set of ^{1}H-nmr signals. Differentiation of *meso*- (**8**) and dl-

isomer (**9**) is impossible from the available data, but the major product (**8**) was tentatively assigned to be the *meso*-isomer since an *anti*-periplanar conformation around the central bond is possible through out the radical coupling process and in the products.

Engbersen *et al.* reported that chromone (**1**, R=H) reacts with an alkyl radical at β-position of the γ-pyron portion.[5] The reactions of **3** and **4**, however, take place exclusively at the α-position. The structures of **3** and **4** are characterized by the ester group at the β-position, and the radical attack at α-position generates a stable capto-dative radical (Scheme IV).[8] In addition alkyl radicals behave as electrophiles in the reaction with electron poor heterocycles [9] and the ester groups in **3** and **4** are expected to enhance the α-attack of the alkyl radical.

Thus the γ-pyrone derivatives having an ester group at β-position are strong radicophiles and the resulting *capto-dative* radicals preferentially dimerize. The dimers thus formed equilibrate with *capto-dative* radicals in a solution state (see Scheme VI). These classes of γ-pyrone derivatives react with alkyl radicals at α-position, and it is in a strong contrast with the chromone without an ester group which reacts with alkyl radicals exclusively at β-position.

EXPERIMENTAL

Mass spectra were measured by a JEOL JMS-DX306 mass spectrometer by electron impact ionization (EI) at 17 eV or by chemical ionization (CI) using methane as ionizing gas, unless otherwise mentioned. Infrared spectra were made by a Shimadzu IR-400 infrared spectrophotometer in chloroform solution. Nmr spectra were made by a Hitachi R-24 (60 MHz) or a Hitachi R-90 (90 MHz) spectrometer in deuteriochloroform. Chemical shifts and coupling constants are recorded in δ-value and Hz respectively.

A General Procedure for the Alkylation of 2-Methoxycarbonylchromone and Dimethylchelidonate with Alkyl Radical.

To a 30 ml two necked flask, which was fitted with a rubber septum and a cooling condenser, were placed 2-methoxycabonylchromone (408 mg, 2.0 mmol) or dimethylchelidonate (424 mg, 2.0 mmol) with silver nitrate (28 mg, 0.2 mmol). After flushing with argon the mixture was dissolved in the mixed solvent of acetonitrile-water (7:3) and further treated with appropriate carboxylic acid (10 mmol). The reaction mixture was heated to 70°C and then treated with ammonium dithionite (1.36 g, 60 mmol) dissolved in 6 ml of the mixed solvent of acetonitrile-water (7:3) by a syringe during the period of 5 min, and the temperature of the reaction mixture was raised to 90°C. After the disappearance of 2-methoxycarbonylchromone or dimethylchelidonate (25 - 30 min) - checked by tlc analyses of the aliquotes - the reaction mixture was cooled to the ambient temperature and treated with 1N-aqueous sodium hydroxide until pH 9. The cooled mixture was extracted with chloroform (15 ml X 3) and the extract was condensed after drying over anhydrous sodium sulfate to give viscous oily products. The products mixture was placed on 5 sheets of silica gel plates (2mm X 20 X 20 cm) and developed with chloroform (product **5** and **6**) or 3 times with chloroform-acetonitrile (10 : 1) (product **8** and **9**). The chromatographic separation of the product from **3** or **4** gave two sets of products (**5** and **6**, or **8** and **9**) beside unidentified minor products. Products **5a-c, 6a-c, 8a,b,** and **9a,b** are all viscous oil and elemental analyses were not tried, but each of the products is essentially pure from analytical tlc and nmr spectra.

5a, pale yellow viscous oil. CIms m/z(%):523(M+ + 1, 0.1%), 467(M^+ - C_4H_8, 0,8%), 261($M^+/2$, 1.2%), 205($M^+/2$-C_4H_8, 100%), 204($M^+/2$ - C_4H_9, 74%), 145($M^+/2$ - C_4H_9 - CO_2CH_3, 12%). High CIms Found: m/z: 523.2355; Calcd for $C_{30}H_{35}O_8$ (M^+ + 1), m/z:523.2322. ^{1}H-Nmr 0.85(s, 18H), 2.81(s, 2H), 3.97(s, 6H), 5.91 - 6.05(m, 2H), 6.59 - 7.12(m, 4H), 7.51 - 7.74(m, 2H). Ir 3020, 1750, 1685, 1600 cm^{-1}.

6a, pale yellow viscous oil. CIms m/z(%):523($M^+ + 1$, 0.1%), 467($M^+ - C_4H_8$, 0.1%), 261(M+/2, 5.0%), 205($M^+/2 - C_4H_8$, 100%), 204($M^+/2 - C_4H_9$, 88%), 145($M^+/2 - C_4H_9 - CO_2CH_3$, 71%). High CIms Found: m/z: 261.1129; Calcd for $C_{15}H_{17}O_4$($M^+/2$) m/z: 261.1127. ^{1}H-Nmr 0.79(s, 18H), 3.30(s, 2H), 3.90(s, 6H), 6.59(d, J=8.0, 2H), 6.78 - 7.20(m, 4H), 7.28 - 7.75(m, 2H). Ir 3015, 1735, 1680, 1600 cm^{-1}.

5b, pale yellow viscous oil. EIms m/z(%): 494(M^+, 0.1%), 451($M^+ - C_3H_7$, 0.2%), 435($M^+ - CO_2CH_3$, 1.2%), 393($M^+ - C_3H_6 - CO_2CH_3$, 1.0%), 247($M^+/2$, 100%), 205($M^+/2 - C_3H_6$, 100%). High CIms Found: m/z: 495.2068; Calcd for $C_{28}H_{31}O_8$($M^+ + 1$) m/z: 495.2018. ^{1}H-Nmr 0.85(d, J=6.9, 6H), 1.15(d, J=6.9, 6H), 1.84 - 2.54(m, 2H), 3.41(d, J=3.8, 2H), 3.74(s, 6H), 6.60 - 7.48(m, 6H), 7.67(dd, J=7.8 and 1.7, 2H). Ir 3015, 1748, 1695 cm^{-1}.

6b, pale yellow viscous oil. EIms m/z(%): 494(M^+, 0.15), 451($M^+ - C_3H_7$, 0.2%), 435($M^+ - CO_2CH_3$, 1.1%), 393($M^+ - C_3H_6 - CO_2CH_3$, 1.9%), 247($M^+/2$, 100%), 205($M^+/2 - C_3H_6$, 100%). High EIms Found: m/z: 494.1988; Calcd for $C_{28}H_{30}O_4$(M^+) m/z: 494.1940. ^{1}H-Nmr 0.62(d, J=6.9, 2H), 0.92(d, J=6.9, 6H), 1.62 - 2.33(m, 2H), 3.24(d, J=3.8, 2H), 3.91(s, 6H), 6.54(d, J=8, 2H), 6.70 - 7.52(m, 4H), 7.65(dd, J=7.8 and 1.7, 2H). Ir 3015, 1768, 1700 cm^{-1}.

5c, pale yellow viscous oil. EIms m/z(%): 466(M^+, 0.3%), 407($M^+-CO_2CH_3$, 2.0%), 261(9.2%), 233($M^+/2$, 100%), 205($M^+/2 - C_2H_4$, 12%). High EIms Found : m/z: 466.1629; Calcd for $C_{26}H_{26}O_8$(M^+) m/z: 466.1628. ^{1}H-Nmr 1.07(t, J=6.9, 6H), 2.08(q, J=6.9, 4H), 3.06 3.40(m, 2H), 3.72(s, 6H), 6.77 - 7.66(m, 6H), 7.78(dd, J=7.8 and 1.7, 2H). Ir 3015, 1750, 1700 cm^{-1}.

6c, pale yellow viscous oil. EIms m/z(%): 466(M^+, 0.2%), 407($M^+-CO_2CH_3$, 5.1%), 261(5.1%), 233($M^+/2$, 100%), 205($M^+/2 - C_2H_4$, 18%). High EIms Found: m/z: 466.1677; Calcd for $C_{26}H_{26}O_8$(M^+) m/z: 466.1628. ^{1}H-Nmr 0.80(t, J=6.9, 6H), 1.69(q, J=6.9, 4H), 2.93 - 3.32(m, 2H), 3.77(s, 6H), 6.38 - 7.55(m, 6H), 7.69(dd, J=7.8 and 1.7, 2H). Ir 3010, 1728, 1685 cm^{-1}.

8a, viscous oil. CIms m/z(%): 539($M^+ + 1$, 0.7%), 523($M^+ - CH_3$, 0.3%), 269($M^+/2$, 10%), 227(17%), 213($M^+/2 - C_4H_8$, 100%), 212($M^+/2 - C_4H_9$, 35%), 152(56%). High EIms Found: m/z: 269.1043; Calcd for $C_{13}H_{17}O_6$($M^+/2$): m/z: 269.1025. ^1H-Nmr 0.93(s, 18H), 3.08(s, 2H), 3.90(s, 12H), 6.26(s, 2H). Ir 3010, 1740, 1670 cm^{-1}.

9a, viscous oil. CIms m/z(%): 539($M^+ + 1$, 1.1%), 523($M^+ - CH_3$, 1.5%), 2.69($M^+/2$, 7.3%), 227(7.9%), 213($M^+/2 - C_4H_8$, 100%). High EIms Found: m/z: 269.1062; Calcd for $C_{13}H_{17}O_6$($M^+/2$) m/z: 269.1025. ^1H-Nmr 0.92(s, 18H), 2.83(s, 2H), 3.86(s, 12H), 6.23(s, 2H). Ir 3010, 1735, 1673 cm^{-1}.

8b, viscous oil. EIms Mass m/z(%): 510 (M^+, 0.2%), 495($M^+ - CH_3$, 0.7%), 468($M^+ - C_3H_6$, 1%), 467($M^+ - C_3H_7$, 3.5%, 451($M^+ - CO_2CH_3$, 0.8%), 255($M^+/2$, 90%), 213($M^+/2 - C_3H_6$, 100%). High EIms Found: m/z: 510.1711; Calcd for $C_{24}H_{30}O_{12}$ m/z: 510.1738. ^1H-Nmr 0.86(d, J=6.8, 6H), 0.95(d, J=6.8, 6H), 1.60 - 2.31(m, 2H), 3.15(d, J=3.9, 2H), 3.89(s, 12H), 6.19(s, 12H). Ir 3010, 1743, 1682 cm^{-1}.

9b, viscous oil. EIms m/z(%): 510(M^+, 0.2%), 495($M^+ - CH_3$, 0.2%), 468($M^+ - C_3H_6$, 0.3%), 467($M^+ - C_3H_8$, 1.2%), 451($M^+ - CO_2CH_3$, 0.5%), 255($M^+/2$, 54%), 212($M^+ - C_3H_6$, 100%). High EIms Found: m/z: 510.1740; Calcd for $C_{24}H_{30}O_{12}$ m/z: 510.1738. ^1H-Nmr 0.81(d, J=6.8, 6H), 0.92(d, J=6.8, 6H), 1.66 - 2.41(m, 2H), 3.12(d, J=3.9, 2H), 3.91(s, 12H), 6.18(s, 2H). Ir 3015, 1730, 1670 cm^{-1}.

Reduction of the Dimer (**5a**) and (**6a**) with Tributyltin Hydride.

In a 5 ml two necked flask, which was fitted with a cooling condenser and a rubber septum, were placed the mixture of **5a** and **6a** (240 mg, 0.46 mmol) and 3 ml of dry o-xylene. The mixture was treated, under stirring, with 1 ml of tributyltin hydride (3.7 mmol) by using a syringe and then refluxed for 3 h under nitrogen. The cooled reaction mixture was condensed under reduced pressure and the residue was chromatographed with hexane on a short column of silica gel to remove excess tributyltin hydride and other nonpolar materials.

The polar materials which were eluted by ethyl acetate were placed on three sheets of silica gel plates (2mm X 20 X 20cm) and developed by chloroform to give the monomeric product(7)in 68 % yield (164 mg).

7, pale yellow oil. EIms m/z(%): 262(M^+, 4.5%), 206(M^+ - C_4H_8, 2.3%), 205((M^+ - C_4H_9, 1.9%), 203((M^+ - CO_2CH_3, 2.0%), 147(M^+ - C_4H_8 - CO_2CH_3, 100%), 120(M^+ - $C_4H_9CH=CHCO_2CH_3$, 48%). ^1H-Nmr 1.02(s, 9H), 2.86(d, J=3.8, 1H), 3.82(s, 3H), 5.05(d, J=3.8, 1H), 6.86 - 7.69(m, 3H), 7.87(d, J=7.8, 1H). Ir 3020, 1750, 1680 cm^{-1}.

REFERENCES

1. (a) F. Minisci, _Synthesis_, 1973, 1; (b) F. Minisci and O. Porta, "Advances in Heterocyclic Chemistry", Vol. 16, ed. by A. R. Katritzky, Academic Press, London, 1974, p. 123.

2. M. Tada anf Y. Yokoi, _J. Hetrocycl. Chem._, 1989, **26**, 45.

3. M. Tada and S. Totoki, _J. Heterocycl. Chem._, 1988, **25**, 1295.

4. M. Tada, T. Ito, and K. Ohshima, _J. Heterocycl. Chem._, 1986, **23**, 1893.

5. J. F. J. Engbersen, A. Kaudijs, and H. C. van der Plas, _J. Hetrocycl. Chem._, 1982, **19**, 1281.

6. J. Staunton, "Comprehansive Organic Chemistry", Vol. 4, ed. by P. G. Sammes, Pergamon Press, Oxford, p. 661.

7. F. Minisci and A. Gitterio, _Acc. Chem. Res._, 1983, **16**, 27.

8. H. G. Viehe, R. Merenyi, L. Stella, and J. Janousek, _Angew. Chem., Int. Ed. Engl._, 1979, **18**, 917.

9. B. Giese, "Radicals in Organic Synthesis: Formation of Carbon-Carbon Bond", Pergamon Press, Oxford, 1986, p. 16 and 222.