Regioselectivity in Photochemical Chlorocarbonylation of Carbonyl Compounds

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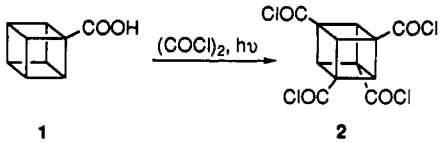
Photochemical chlorocarbonylation of a series of cyclic and acyclic carbonyl compounds shows remarkable regioselectivity and gives β- or γ-substituted products in reasonable yields. Irradiation of cyclopentanone in oxalyl chloride followed by esterification with methanol gave methyl 3-oxocyclopentanecarboxylate (**4**). Similarly, photochemical chlorocarbonylation of cyclobutanone yielded methyl 3-oxocyclobutanecarboxylate (**6**). Application of the chlorocarbonylation reaction to 3-pentanone gave methyl 4-oxohexanoate (**8**) and dimethyl 4-oxopimelate (**9**). When a mixture of 3-methylbutanoic acid and oxalyl chloride was irradiated, dimethyl 3-methylglutarate (**11**) was obtained after methanolysis. A kinetically-controlled mechanism for the photochemical process was deduced.

Introduction

The photo- or peroxide-induced homolysis of oxalyl chloride is a mild free-radical process that has been used to introduce the versatile chloroformyl group in hydrocarbons.[1] Radical chlorocarbonylation has been applied to adamantane,[1b] norbornane,[1c] and bicyclo[1,1,1]pentane.[1d] Because a number of reactive sites were present in these compounds, however, selectivities were generally low. We have recently explored the effect of electron-withdrawing groups, notably carboxy groups, on the regioselectivity of the chlorocarbonylation reaction and demonstrated its applicability in an efficient synthesis of the cage compound 1,3,5,7-tetrakis(chlorocarbonyl)cubane (**2**) from cubanecarboxylic acid (**1**).[2]



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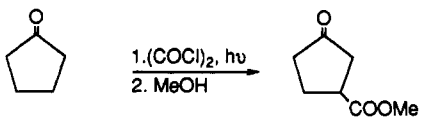
The selectivity was provisionally interpreted in terms of an electron-withdrawing field effect of the carboxyl group resulting in retarded cleavage of the α-C–H bonds, leading to predominant chlorocarbonylation at the β positions. The present work further demonstrates the synthetic potential of chlorocarbonylation by extending it to other carbonyl compounds as a means of understanding the regioselectivity of the substitution.[3]

Results and Discussion

In our study the chlorocarbonylation of cyclopentanone, cyclobutanone, 3-pentanone, and 3-methylbutanoic acid was investigated. Chlorocarbonylation of these reactants can give a number of easily identified isomeric substitution products. For example, α-chlorocarbonylation of cyclopentanone would yield, after methanolysis, commercially-available methyl 2-oxocyclopentanecarboxylate. Beta substitution would afford methyl 3-oxocyclopentanecarboxylate[4a] (**4**), an important agricultural intermediate[4b] which is difficult to prepare by other routes. Similarly, synthesis of the pharmaceutically important intermediate, methyl 3-oxocyclobutanecarboxylate[5a] (**6**), requires a multistep process.[5b]

Irradiation of cyclopentanone in oxalyl chloride for 24 h, followed by esterification with methanol, gave methyl 3-oxocyclopentanecarboxylate (**4**) in 60% yield.[6] No



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evidence for the formation of any α-substituted product

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(6) Under this reaction condition, no evidence for formation of diester or chlorinated product was obtained.

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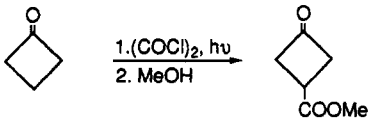
was observed,[7] suggesting that the resonance stability of the α-radical does not play a decisive role in the regioselectivity of this chlorocarbonylation.

Similarly, photolysis of cyclobutanone in oxalyl chloride followed by esterification produced methyl 3-oxocyclobutanecarboxylate (6) as the major product (50–60%). In



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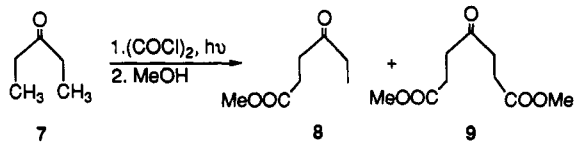
this case, the reaction was much slower than with cyclopentanone, and after 24 h of irradiation, only 50% of the cyclobutanone was consumed.[8] In addition to statistical factors (four β hydrogens in cyclopentanone compared to two in cyclobutanone), the slower reaction rate might be attributed to the increased C–H strength in the smaller four-membered ring compound compared to the five-membered cyclopentanone.[9]

Application of the chlorocarbonylation reaction was extended to two acyclic ketones, 3-pentanone (7) and 3-methylbutanoic acid (10). These compounds were



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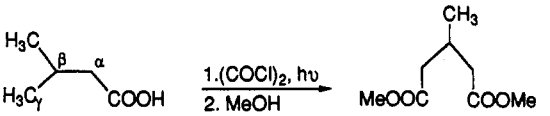
chosen due to the anticipated differences of the C–H bond reactivities within the molecules and ease of NMR characterization of the reaction products. Photochemical chlorocarbonylation of 7 with oxalyl chloride proceeded slowly at room temperature, and after 24 h of irradiation and then methanolysis, the mono- and dicarbonylated products, methyl 4-oxohexanoate (8)[10] and dimethyl 4-oxopimelate (9),[11] were obtained in 55% total yield in a ratio of 8:1, respectively.[12]

When a mixture of 10 and oxalyl chloride was irradiated at room temperature for 24 h, substitution occurred at the γ-position resulting in the formation of dimethyl 3-methylglutarate (11)[13] in 60% yield.[14] Clearly, preferential



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attack took place at the least hindered methyl site and not at the β position, which would be expected to give rise to the more stabilized tertiary radical. Moreover, statistical considerations (six γ-hydrogens to one β hydrogen) also favor substitution in the γ-position.

In free-radical substitution reactions with oxalyl chloride and related derivatives, it is commonly accepted that the overall process is initiated by the dissociation steps outlined in eq 1.[1]

$$Cl^{\bullet} + {}^{\bullet}COCOCl \overset{h\nu}{\rightleftharpoons} (COCl)_2 \overset{h\nu}{\rightleftharpoons} 2\dot{C}OCl \qquad (1)$$

$$RH + {}^{\bullet}COCl \rightarrow R^{\bullet} + CO + HCl \qquad (2)$$

$$R^{\bullet} + (COCl)_2 \rightarrow RCOCl + {}^{\bullet}COCl \qquad (3)$$

Subsequent steps would likely involve abstraction of hydrogen from the substrate molecule by either a chlorine atom or a chlorocarbonyl radical (eq 2) followed by the chain-propagation step shown in eq 3.

Our data suggest that electrophilic chlorocarbonyl (ĊOCl) or chlorine (Cl•) radicals preferentially abstract a hydrogen from the least electron-deficient carbon atom distant from the carbonyl group. In the case of 3-methylbutanoic acid, despite the familiar decrease in C–H bond strength from primary to secondary to tertiary,[15] the substitution occurring at the methyl group may also be reinforced by steric effects as well as statistical factors. Accordingly, a kinetically-controlled process for these reactions can be inferred.

Conclusion

Photochemical chlorocarbonylation of carbonyl compounds shows remarkable regioselectivity. This methodology introduces a chlorocarbonyl group at a remote site (β or γ) and makes possible the efficient synthesis of compounds which are otherwise difficult to prepare.

Experimental Section

NMR spectra were recorded on a Bruker or G.E. 300-MHz spectrometer using $CDCl_3$ as solvent. All chemical shifts are reported in ppm, downfield from internal tetramethylsilane. Mass spectra were measured on a Finnegan OWA 1020B. All the chemicals were purchased from Aldrich and used without further purification.

General Procedure. A stirred solution of the carbonyl compound (10.0 mmol) in 50 mL of oxalyl chloride (Aldrich, 98%) in a quartz vessel was irradiated in a Rayonet photoreactor (1849–2537 Å) at 35–40 °C. After the reaction was completed, excess oxalyl chloride was removed on a rotary evaporator, and the crude reaction product was treated with methanol. The resulting methyl esters were isolated by chromatography (Chromatotron, silica gel) using EtOAc/hexane (1:3) as eluent. The

(7) For α-halogenation of cycloalkanones using *N*-bromosuccinimide see; Corey, E. J. *J. Am. Chem. Soc.* **1953**, *75*, 2301. Also see; Cooper, W. *J. Chem. Soc.* **1955**, 1386.

(8) No chlorinated product was detected. Dichlorination of 1,3-dinitrobicyclo[1.1.1]pentane under similar reaction conditions has been observed: Wiberg, K. B.; Ross, B. S.; Isbell, J. J.; McMurdie, N. *J. Org. Chem.* **1993**, *58*, 1372–1376.

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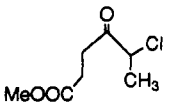
(12) Interestingly, when recycled oxalyl chloride was used, compound 12 was also obtained in <5% yield. ^1H NMR ($CDCl_3$): δ 4.41 (q, 1H), 3.70 (s, 3H), 3.00 (m, 2H), 2.65 (m, 2H), 1.63 (d, 3H).



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The formation of 12 can be explained based on the enolization of the ketone by HCl and then chlorination[7] followed by photochemical chlorocarbonylation at the carbon farthest from the electrophilic centers.

(13) Poppe, L.; Novak, L.; Kolonits, P.; Bata, A.; Szantay, C. *Tetrahedron* **1988**, *44*, 1477.

(14) At higher temperatures (50–60 °C) or prolonged reaction time, some chlorinated products were observed (GCMS).

(15) Sanderson, R. T. *J. Org. Chem.* **1982**, *47*, 3835.

identification and characterization of these compounds were achieved using a combination of NMR methods (DEPT, HETCORR, COLOC, RELAY), mass spectrometry, and where available, comparison with authentic samples and closely-related isomeric materials. The yields are based on recovered starting materials and not optimized.

Methyl 3-oxocyclopentanecarboxylate (4):[4a] ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H), 3.15 (m, 1H), 2.13–2.47 (m, 6H); ^{13}C NMR δ 216.3 (s), 174.5 (s), 51.9 (q), 40.9 (t), 40.5 (d), 37.1 (t), 26.3 (t); LRMS (NH_3, CI) calcd for $C_7H_{10}O_3$ 160 (M + 18), 143 (M + 1), found 160, 143.

Methyl 3-oxocyclobutanecarboxylate (6):[5a] ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 3.19–3.37 (m, 5H); ^{13}C NMR δ 203.7 (s), 174.4 (s), 51.8 (q), 51.5 (t), 27.1 (d); LRMS (NH_3, CI) calcd for $C_6H_8O_3$ 146 (M + 18), 129 (M + 1), found 146, 129.

Methyl 4-oxohexanoate (8):[10] ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H), 2.52 (q, 2H), 2.61 (t, 2H), 2.73 (t, 2H), 3.68 (s, 3H); ^{13}C NMR δ 204.2 (s), 173.8 (s), 51.7 (q), 36.5 (t), 35.8 (t), 33.07 (t), 26.9 (q); MS (CI) 145 (M + 1), 113, 85, 59.

Dimethyl 4-oxopimelate (9):[11] ^{1}H NMR ($CDCl_3$) δ 2.58 (t, 4H), 2.78 (t, 4H), 3.66 (s, 6H); ^{13}C NMR δ 205.3 (s), 172.9 (s), 51.7 (q), 36.8 (t), 27.6 (t); MS (CI) 203 (M + 1), 171, 143, 84, 59.

Dimethyl 3-methylglutarate (11).[13] In this case the reaction mixture was stirred at room temperature for 30 min under slight vacuum prior to the irradiation: ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 6H), 2.20–2.50 (m, 5H), 1.02 (s, 3H); ^{13}C NMR δ 172.6 (s), 51.3 (q), 40.5 (t), 27.3 (d), 19.7 (q); LRMS (NH_3, CI) calcd for $C_8H_{14}O_4$ 192 (M + 18), 175 (M + 1), found 192, 175.

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