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A Convenient Method for the Preparation of 4-(3-Halogenatedphenyl)- and 4-(3,5-Dihalogenatedphenyl)-4-oxobutyric Acids

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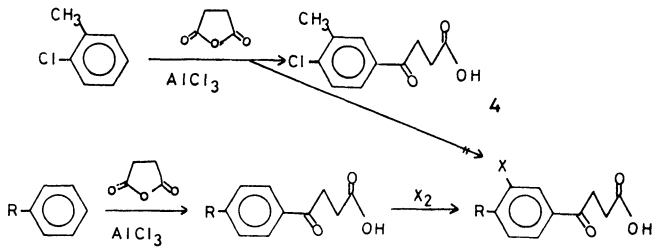
Synopsis. Various 4-(3-halogenatedphenyl)- and 4-(3,5-dihalogenatedphenyl)-4-oxobutyric acids were synthesized by the nuclear halogenation of the corresponding 4-aryl-4-oxobutyric acids in the presence of an excess of aluminum chloride. In most of these reactions, consecutive succinoylation and halogenation of the aromatic compounds were carried out in one pot operation.

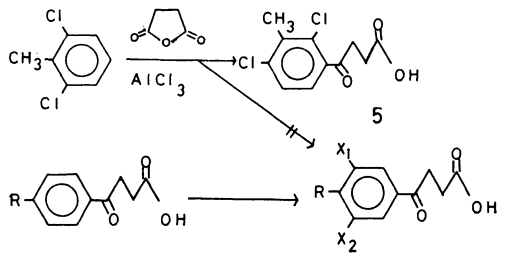
When aromatic aldehydes and ketones are halogenated in the presence of a sufficient amount of aluminum chloride to complex completely the carbonyl groups, halogenation takes place in the benzene rings rather than in the side chains[1] (swamping catalyst method). Krausz *et al.*[2] prepared 4-(3-chloro-4-isopropylphenyl)-, 4-(3-chloro-4-*t*-butylphenyl)-, and 4-(3-chloro-4-cyclohexylphenyl)-4-oxobutyric acids from the corresponding 4-aryl-4-oxobutyric acids by this method. However, halogenation of other 4-aryl-4-oxobutyric acids and the usage of halogenating agents other than chlorine have not been reported.

In connection with the synthesis of fungicidal 6-aryl-3(2*H*)pyridazinones, it became necessary for us to prepare various 4-aryl-4-oxobutyric acids bearing halogens on their 3'- and(or) 5'-positions.[3] These acids are required as starting materials for the synthesis of the heterocycles mentioned above.[4]

It is reported that the Friedel-Crafts reaction of *o*-chlorotoluene with succinic anhydride gave rise to 4-(4-chloro-3-methylphenyl)-4-oxobutyric acid (**4**) owing to a *p*-directing effect of the chlorine atom.[5] In our experiment, this result was also confirmed and the reaction of 2,6-dichlorotoluene with succinic anhydride under the same conditions produced only 4-(2,4-dichloro-3-methylphenyl)-4-oxobutyric acid (**5**). Accordingly, the swamping catalyst method would be very helpful to obtain the 3'- and(or) 5'-halogenated products.



1a: R=CH_3 **2a**: R=CH_3 **3a**: R=CH_3, X=Cl
b: R=H **b**: R=H **b**: R=CH_3, X=Br
c: R=Br **c**: R=Br **c**: R=H, X=Cl
d: R=Cl **d**: R=Cl **d**: R=H, X=Br
e: R=F **e**: R=F **e**: R=Br X=Cl
f: R=Cl, X=Br
g: R=F, X=Cl
h: R=F, X=Br



2a: R=CH_3 **6a**: R=CH_3, X_1=X_2=Cl
f: R=C_2H_5 **b**: R=CH_3, X_1=X_2=Br
g: R=*i*-C_3H_7 **c**: R=CH_3, X_1=Cl, X_2=Br
h: R=*n*-C_4H_9 **d**: R=C_2H_5, X_1=X_2=Cl
i: R=OCH_3 **e**: R=*i*-C_3H_7, X_1=X_2=Cl
f: R=*n*-C_4H_9, X_1=X_2=Cl
g: R=OH, X_1=X_2=Cl

At first, several 4-aryl-4-oxobutyric acids (**2**) were monohalogenated in 1,2-dichloroethane (DCE). The halogenating agents used were chlorine, bromine, and sulfonyl chloride. The molar ratios of the reagents are

TABLE 1. NUCLEAR HALOGENATION OF 4-ARYL-4-OXOBUTYRIC ACIDS (**2**)

Starting material (Method[a])	Halogenating agent	Molar ratio: $AlCl_3$/ 1(or 2)	Molar ratio: Halogen/ 1(or 2)	Conditions: Temp °C	Conditions: Time h	Product[b] (Yield[c] %)	Mp °C
1a (B)	Cl_2	2.4	1.7	30—40	15	**3a** (72)	150—156[d]
2a (A)	SO_2Cl_2	2.4	2.2	40—50	8	**3a** (83)	
2a (A)	Br_2	2.4	2.2	20—30	24	**3b**[e] (64)	163—171[f]
1a (B)	Br_2	2.4	1.7	25—30	6	**3b** (75)	
1b (B)	Cl_2	3.0	1.7	20—30	7	**3c**[g] (48)	107—113[d]
1b (B)	Br_2	2.5	2.2	45	11.5	**3d**[h] (70)	119—122[d]
1c (B)	Cl_2	3.0	2.2	20—30	18	**3e**[i] (81)	175—178[f]
1d (B)	Br_2	3.0	2.2	20—30	24	**3f**[j] (89)	160—163[f]
1e (B)	Cl_2	3.0	10.0	20—25	49	**3g**[k] (70)	121—123[d]
1e (B)	Br_2	4.0	5.6	20—25 40	16 17	**3h**[l] (70)	121—124[m]
2a (A)	Cl_2	2.4	2.6	40—45	2	**6a**[n] (31)	183—188[f]
1a (B)	Cl_2	3.0	2.9	3—7	21.5	**6a** (52)	
2a (A)	Br_2	3.0	2.1	20—30 30—35	1 7.5	**6b**[o] (67)	188—191[d]
1a (B)	1) Cl_2 2) Br_2	3.0	1.9 1.1	5—10 30—35	24 19.5	**6c**[p] (50)	183—185[q]
2f (A)	Cl_2	3.0	7.3	0—10	18	**6d**[r] (51)	137—138[f]
2g (A)	Cl_2	3.0	2.8	0—10	16	s)	
2h (A)	Cl_2	3.0	2.8	0—10	16	**6f**[t] (16)	120—122[f]
2i (A)	Cl_2	2.4	3.0	35—40	4.5	**6g**[u] (72)	180—183[f]

a) A: Halogenation of 4-aryl-4-oxobutyric acids (**2**). B: Consecutive succinoylation and halogenation of aromatic compounds (**1**). b) Satisfactory elemental analyses were obtained for all compounds. c) Isolated yield (purity ≥95%, estimated by HPLC). d) Recrystd from benzene. e) NMR (DMSO-d_6): δ 2.41 (s, 3H), 2.60 (t, 2H), 3.23 (t, 2H), 4.90 (s, 1H), 7.47 (d, 1H), 7.89 (dd, 1H), 8.08 (d, 1H). f) Recrystd from CH_3CN. g) NMR (DMSO-d_6): δ 2.79 (t, 2H), 3.30 (t, 2H), 7.2—8.3 (m, 4H), 11.10 (s, 1H). h) NMR (DMSO-d_6): δ 2.79 (t, 2H), 3.29 (t, 2H), 7.2—8.3 (m, 4H), 10.98 (s, 1H). i) NMR (DMSO-d_6): δ 2.59 (t, 2H), 3.24 (t, 2H), 7.9—8.2 (m, 3H). j) NMR (DMSO-d_6): δ 2.57 (t, 2H), 3.28 (t, 2H), 7.78 (d, 1H), 8.03 (dd, 1H), 8.30 (d, 1H). k) NMR (DMSO-d_6): δ 2.60 (t, 2H), 3.30 (t, 2H), 7.53 (dd, 1H), 8.05 (dq, 1H), 8.17 (dd, 1H). l) NMR (DMSO-d_6): δ 2.60 (t, 2H), 3.28 (t, 2H), 7.53 (dd, 1H), 8.09 (dq, 1H), 8.29 (dd, 1H). m) Recrystd from hexane–AcOEt. n) NMR (DMSO-d_6): δ 2.48 (s, 3H), 2.65 (t, 2H), 3.27 (t, 2H), 7.59 (s, 2H), 11.68 (s, 1H). o) NMR (DMSO-d_6): δ 2.57 (s, 3H), 2.58 (t, 2H), 3.25 (t, 2H), 8.10 (s, 2H). p) NMR (DMSO-d_6): δ 2.50 (s, 3H), 2.58 (t, 2H), 3.23 (t, 2H), 7.98 (d, 1H), 8.08 (d, 1H), 11.91 (s, 1H). q) Recrystd from toluene. r) NMR (DMSO-d_6): δ 1.13 (t, 3H), 2.57 (t, 2H), 2.95 (q, 2H), 3.25 (t, 2H), 7.93 (s, 2H). s) Inseparable mixture. t) NMR (DMSO-d_6): δ 0.95 (t, 3H), 1.2—1.7 (m, 4H), 2.6—3.3 (m, 6H), 7.85 (s, 2H). u) NMR (DMSO-d_6): δ 2.57 (t, 2H), 3.24 (t, 2H), 7.99 (s, 2H), 10.33 (s, 1H).

shown along with the reaction conditions in Table 1. Mostly the starting acids (**2**) were prepared *in situ* from the corresponding aromatic compounds and succinic anhydride under the usual Friedel-Crafts conditions.[6] The reaction courses were monitored by high-pressure liquid chromatography (HPLC) in every case. The monohalogenation proceeded smoothly for every halogenating agent used, and the acids halogenated at 3′-position were obtained in good yields.

Next, certain 4-aryl-4-oxobutyric acids were dihalogenated on the 3′- and 5′-positions using more than two molar equivalents of halogenating agents. The dichlorination of the *para*-methyl analog (**2a**) at low temperatures gave higher yield of the product (**6a**) than at elevated temperatures. The nuclear dibromination of **2a** as well as its consecutive chlorination and bromination gave the desired acids (**6a** and **6b**) in good yields. In the case of 4′-isopropyl analog (**2g**), a mixture of variously chlorinated products was obtained, and the desired product (**6c**) could not be isolated.

The dichlorination of 4-(4-methoxyphenyl)-4-oxobutyric acid (**2i**) gave 4-(3,5-dichloro-4-hydroxyphenyl)-4-oxobutyric acid (**6g**) in a good yield. The HPLC indicated that the dichlorination and demethylation took place almost simultaneously in this case. The reaction of 2,6-dichloroanisole with succinic anhydride under the usual Friedel-Crafts conditions produced only tarry materials which could not be purified.

The above experiments have shown that certain 4-aryl-4-oxobutyric acids with halogens on their 3′- and(or) 5′-positions can be conveniently obtained by one pot operation starting from benzene or substituted benzenes.

Experimental

All melting points are not corrected. IR and NMR spectra were recorded on a JASCO IRA-2 spectrophotometer and Varian A-60 nuclear magnetic resonance spectrometer, respectively. HPLC apparatus used was a Hitachi Model 635-T high-pressure liquid chromatograph. Column used was 5×50 cm glass, packed with Hitachi gel 3010. Elution system was MeOH–H_2O–AcOH (94: 5: 1), and wave length was 248 nm through the experiments of monohalogenation and 236 nm through dihalogenation.

Materials. The 4-aryl-4-oxobutyric acids, **2a**,[7] **2f**,[8] **2g**,[9] and **2i**[10] were prepared by the methods described in the literature. 4-(4-*n*-Butylphenyl)-4-oxobutyric acid (**2h**, mp 101 °C) was prepared by a similar method.

Preparation of 4-(3-Halogenatedphenyl)-4-oxobutyric Acids (3) and 4-(3,5-Dihalogenatedphenyl)-4-oxobutyric Acids (6). As a typical run, consecutive succinoylation and chlorination of **1a** are described here. To a mixture of aluminum chloride (32 g, 0.24 mol) and DCE (120 ml) was added portionwise powdered succinic anhydride (11 g, 0.11 mol) with stirring at room temperature. Stirring was continued for further 10 min. Then, toluene (9.2 g, 0.1 mol) was added dropwise in 30 min at 10 °C. After stirring for 1.5 h at 10—15 °C, the reaction mixture was warmed to 30 °C. Chlorine gas (8 ml, 0.17 mol), trapped in a Dry Ice acetone bath was introduced into the reaction mixture in 1 h at 30—40 °C. Stirring was continued thereafter, until the peak due to the monochloro derivative (**3a**) became a maximum on HPLC (relative peak height, *ca.* 95%). Then, the reaction mixture was poured into a mixture of ice (500 g) and concentrated HCl (60 ml), and the resulting oily solid was extracted with ethyl acetate (1 l). The organic solution was repeatedly washed with water, and dried over Na_2SO_4. The filtered ethyl acetate was evaporated *in vacuo*, and the crude product was recrystallized from benzene–hexane (1: 1, 200 ml) to give 16.3 g of 4-(3-chloro-4-methylphenyl)-4-oxobutyric acid (**3a**), as colorless leaflets; mp 150—156 °C. IR (Nujol): 2500—2800 (COOH) and 1700 cm^{-1} (broad, CO). NMR (DMSO-d_6): δ 2.40 (3H, s, CH_3), 2.58 (2H, t, J=6 Hz, $-CH_2-$), 3.25 (2H, t, J=6 Hz, $-CH_2-$), 7.48 (1H, d, J=8 Hz, H-5′), 7.85 (1H, dd, J=8 and 2 Hz, H-6′), and 7.92 (1H, broad s, H-2′). Found: C, 58.80; H, 4.88; Cl, 15.67%. Calcd for $C_{11}H_{11}ClO_3$: C, 58.29; H, 4.89; Cl, 15.64%.

The halogenation of other 4-aryl-4-oxobutyric acids were conducted basically as above. The conditions and results are summarized in Table 1.

Reaction of 2,6-Dichlorotoluene with Succinic Anhydride. To a mixture of aluminum chloride (40 g, 0.3 mol) and DCE (100 ml) was added portionwise powdered succinic anhydride (10 g, 0.1 mol) with stirring. The resulting deep red solution was refluxed for 1 h. The reaction mixture was treated as above to give a crude oily solid (32 g). Recrystallization of this from benzene–hexane (1: 2, 300 ml) gave 7.8 g (30%) of 4-(2,4-dichloro-3-methylphenyl)-4-oxobutyric acid (**5**) as colorless needles; mp 92—94 °C. IR (Nujol): 2500—2800 (COOH), 1700 cm^{-1} (CO); NMR (DMSO-d_6): δ 2.50 (3H, s, CH_3), 2.82 (2H, t, J=6 Hz, $-CH_2-$), 3.14 (2H, t, J=6 Hz, $-CH_2-$), 7.35 (2H, AB-d, aromatic), 9.45 (1H, broad s, OH). Found: C, 50.29; H, 3.77; Cl, 26.95%. Calcd for $C_{11}H_{10}Cl_2O_3$: C, 50.60; H, 3.86; Cl, 27.16%.

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