Registry No. II, 18495-77-7; III, 58-72-0; IV, 74064-34-9; 1,1,2,2-tetraphenylethane, 632-50-8; 1,1,2,2-tetraphenylethylene, 632-51-9; 1,1,2-triphenylethane, 1520-42-9; bromine, 7726-95-6; 1,2,2-triphenylethanol, 2294-93-1; 1-bromo-1,2,2-triphenylethylene, 1607-57-4.

Exclusive Ortho α-Chloroacetylation of Phenols

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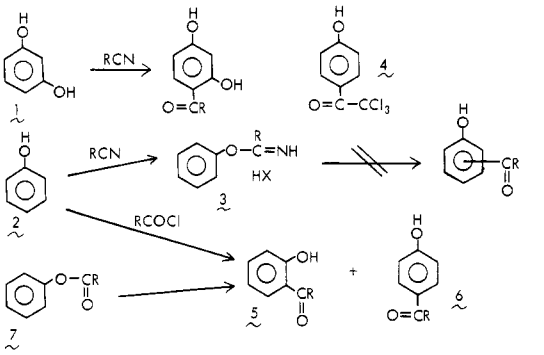
Resorcinol (1) can be easily acylated on the aromatic ring by treatment with nitriles in the presence or absence of Lewis acids such as zinc chloride or aluminum chloride in acidic medium (Houben–Hoesch reaction), while in contrast, phenol (2) itself can not be ring-acylated by a similar treatment, giving only a salt of iminomethyl phenyl ether (3) (Scheme I). Moreover, an attempt at thermal rearrangement of 3 gives no ring-acylated product by treatment with or without acidic catalyst. The only exception is that 2 reacts with trichloroacetonitrile, giving directly 4-(trichloroacetyl)phenol (4).[1a] On the other hand, Friedel–Crafts reaction of 2 or anisole with acyl chloride in the presence of various acidic catalyst gives 2- and 4-ring-acylated products (5 and 6), with a predominant amount of the latter in all cases.[1b] Further, Fries rearrangement of phenol esters (7) always gives a mixture of 5 and 6.[1c] Thus, no regioselective ortho-acylation reaction of 2 has been known to date.

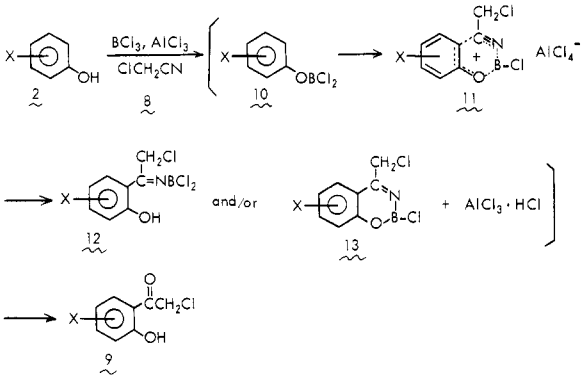
By continuing studies of our previously reported specific ortho-substitution reaction of aniline,[2] we found that using a combination of boron trichloride and aluminum trichloride could solve this problem. Namely, the reaction of 2 and chloroacetonitrile (8) in the presence of boron trichloride and aluminum trichloride in dichloromethane, dichloroethane, or benzene at room temperature or under reflux gave, after acidic workup, 2-hydroxy-α-chloroacetophenone (9) exclusively. The desired product could also be obtained by using phenyldichloroborane[3] instead of boron trichloride (Table I, run 4). The presence of from 0.1 to 1 mol equiv of aluminum trichloride was indispensable, because the reaction did not proceed with boron trichloride or phenyldichloroborane alone. Therefore, we assumed that aluminum trichloride might stabilize very unstable phenoxydichloroborane 10[4] (Scheme II) initially formed, which otherwise would have easily decomposed into triphenoxyborane and boron trichloride under disproportionation, in order to generate a stabilized intermediate such as tetrachloroaluminate (11).[5] From 11, (2-hydroxyphenyl ketimino)chloroborane (12 and/or 13) may be formed and aluminum trichloride regenerated.

The clear difference between our method and the conventional "Houben–Hoesche" reaction[1a] could be seen in

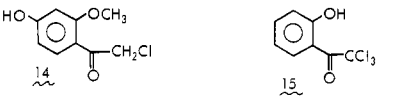
Scheme I



Scheme II



runs 11 and 14. Namely, the product in run 11 was **9g** whereas the conventional method gave the isomer **14**, in which the introduced carbon chain was situated para to the hydroxy group. In run 14, our method gave only 2-(trichloroacetyl)phenol (**15**), while in contrast, the conventional one afforded the 4-isomer (**4**) exclusively.



We tested the addition of other Lewis acids instead of aluminum trichloride and found that zinc or stannic chloride or titanium tetrachloride gave **9** only in 5–8% yield and ferric chloride gave, at best, only a 20% yield.

The compound **9** series gave reasonable analytical[10] and spectral data, namely, broad bands at about 3000 to 3100 cm^{-1} (strongly hydrogen-bonded OH) and peaks at about 1650 cm^{-1} (C=O) in the IR spectra and reasonable absorption bands in the NMR spectra (see Table I).

The limitation of this reaction was that the phenols having an electron-withdrawing group gave the desired product only in poor to modest yields. For example, chlorophenols gave the corresponding products in the yields shown in runs 6–8, indicating the effect of ortho,para orientation with deactivation due to the chloro substituent, and a similar reaction of 2- and 4-nitrophenols gave only the starting materials. As a further limitation, acetonitrile or benzonitrile did not react with 2 under these conditions. But our method is very convenient for obtaining compounds **9**, which are useful starting materials for preparing 2*H*-benzofuranones, intermediate compounds for the synthesis of natural and biologically interesting substances.[11]

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(2) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4842.
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(4) Colclough, T.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1955**, 907.
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(9) Malik, M. L.; Grover, S. K. *Chem. Abstr.* **1976**, *85*, 17707.
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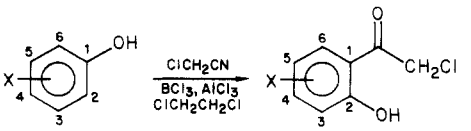
(11) Cagniant, P.; Cagniant, D. *Adv. Heterocycl. Chem.* **1975**, *18*, 414.

0022-3263/81/1946-0189$01.00/0

Table I. Synthesis of 2-Hydroxy-α-chloroacetophenones (9) from Phenols (2)



2 9

run	compd	X	reaction conditions[n]	compd	X	% yield[a]	% recovered 2	mp,[b] °C	^{1}H NMR ($CDCl_3$),[m] δ
1	2a	H	A_1	9a	H	60.7	24.2	72-73 73[6]	
2	2a	H	A_2	9a	H	85.7			
3	2a	H	B	9a	H	78.8	14.5		
4	2a	H	D	9a	H	64.6	24.9		
5	2a	H	E	9a	H	45.4	15.0		
6	2b	2-Cl	C	9b	3-Cl	10.9[c]	47.7	72-73	4.70,[g] 6.90 (1 H, t, J = 8 Hz, 5-H), 7.65 (2 H, dd, J = 8 Hz, J = 2 Hz, 4- and 6-H), 12.18[h]
7	2c	3-Cl	C	9c	4-Cl	51.4	44.3	75-76	4.62,[g] 6.92 (1 H, dd, J = 8 Hz, J = 2 Hz, 5-H), 7.05 (1 H, d, J = 2 Hz, 3-H), 7.62 (1 H, d, J = 8 Hz, 6-H), 11.80[h]
8	2d	4-Cl	C	9d	5-Cl	17.9	76.7	65-66 65[7]	4.66,[g] 6.98 (1 H, d, J = 8 Hz, 3-H), 7.47 (1 H, dd, J = 8 Hz, J = 2 Hz, 4-H), 7.68 (1 H, d, J = 2 Hz, 6-H), 11.6[h] (br)
9	2e	2-CH_3	C	9e	3-CH_3	75.0	15.0	65-66 67[8]	2.24,[i] 4.69,[g] 6.80 (1 H, t, J = 8 Hz, 5-H), 7.45 (2 H, dd, J = 8, J = 2 Hz, 4- and 6-H), 11.98[h]
10[d]	2f	2-OCH_3	C	9f	3-OCH_3	42.4	14.0	113-114	3.90,[i] 4.72,[g] 6.8-7.4 (3 H, m, aromatic H), 11.74[h]
11[e]	2g	3-OCH_3	C	9g	4-OCH_3	80.7		117-118	3.83,[i] 4.60,[g] 6.4-6.6 (2 H, m, 3- and 5-H), 7.59 (1 H, d, J = 8 Hz, 6-H), 12.17[h]
12[f]	2h	4-OCH_3	C	9h[8]	5-OCH_3	67.4	26.1	83-84	3.78,[i] 4.77,[g] 6.8-7.3 (3 H, m, aromatic H), 11.3[h]
13	2i	2,3-di-CH_3	B	9i	3,4-di-CH_3	100		95-96	2.17,[i] 2.30,[i] 4.66,[g] 6.73 (1 H, d, J = 8 Hz, 5-H), 7.43 (1 H, d, J = 8 Hz, 6-H), 12.12[h]
14[k]	2a	H	B	15[l]	H	91.9		oil	6.8-7.6 (3 H, m, aromatic H), 8.20 (1 H, dd, J = 8, J = 2 Hz, 6-H), 11.1[h]

[a] Isolated yield based on the phenol used. [b] Recrystallized from ether-petroleum ether. [c] The yield was raised to 21.3% after the reaction solution had stood for 7 days under reaction conditions C. [d] 2-Hydroxyphenol (43%) was recovered. [e] The NMR spectrum of the concentrated residue of the mother liquor of **9g** showed the existence of 6-methoxy-2-hydroxy-α-chloroacetophenone (5%): NMR ($CDCl_3$) δ 3.9 (3 H, s, OCH_3), 4.9 (2 H, s, CH_2), 6.3-7.4 (3 H, m, aromatic H), 12.6 (1 H, s, OH). [f] 4-Hydroxyphenol (3.3%) was recovered. [g] 2 H, s, CH_2CO. [h] 1 H, s, OH. [i] 3 H, s, OCH_3. [i] 3 H, s, CH_3. [k] Cl_3CCN was used instead of $ClCH_2CN$. [l] *O*-Acetyl derivative (AC_2O in pyridine, room temperature, overnight): mp 72-73 °C (ether-petroleum ether); $C_{10}H_7Cl_3O_3$ (C, H, Cl); IR ($CHCl_3$) ν_{max} 1740 (OAc), 1780 (C=O); NMR ($CDCl_3$) δ 2.30 (3 H, s, OAc), 7.15-8.20 (4 H, m, aromatic H). The hydrolysis in a workup in this run required forcing conditions (refluxing for 30 min), otherwise **15** was contaminated by the corresponding imine (C=NH instead of C=O in **15**): mp 52-53 °C (ether-petroleum ether); $C_8H_6Cl_3NO$ (C, H, N, Cl); IR ($CHCl_3$) ν_{max} 3320 (OH), 1615 (C=NH). *N,O*-Diacetyl derivative: mp 79-80 °C (ether-petroleum ether); $C_{12}H_{10}Cl_3NO_3$ (C, H, N, Cl); IR ($CHCl_3$) ν_{max} 1771 (OAc), 1726 and 1676 (C=NAc); NMR ($CDCl_3$) δ 2.03 (3 H, s, $NCOCH_3$), 2.38 (3 H, s, $OCOCH_3$), 7.1-7.7 (4 H, m, aromatic H). [m] J values were obtained by measuring the intervals between signals and thus are approximate. [n] Reaction conditions: A_1, 0.1 equiv of $AlCl_3$ was used at room temperature for 20 h in CH_2Cl_2; A_2, the mixture was stirred for 4 days instead of 20 h as in A_1; B, 1.2 equiv of $AlCl_3$ was used and the mixture was refluxed for 6 h; C, see the experimental section; D, $PhBCl_2$ was used instead of BCl_3 in B; E, 0.5 equiv of $AlCl_3$ was used and the mixture was refluxed in benzene.

Experimental Section

Melting points were determined on a Yanagimoto micro melting apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ solution by a JASCO IRS spectrophotometer. NMR spectra were taken in $CDCl_3$ solution on a Varian EM-360-L spectrophotometer. Column chromatography was conducted with silica gel (E. Merck, 70–230-mesh ASTM).

In the typical procedure (reaction conditions C), a solution of a phenol (5 mmol) in dichloroethane (5 mL), $ClCH_2CN$ (0.38 mL, 6 mmol), and $AlCl_3$ (334 mg, 2.5 mmol) were successively added under ice cooling to a stirred solution of BCl_3 (696 mg, 6 mmol) in dichloroethane (3 mL). The mixture was stirred at room temperature for 20 h. Next, ice and 2 N HCl (4 mL) were added and the mixture was stirred for 30 min to hydrolyze the corresponding ketimine. The mixture was extracted with CH_2Cl_2 (3 times) and the organic layer was washed with saturated aqueous NaCl, dried on $MgSO_4$, and concentrated. The extract was chromatographed on silica gel (ca. 10 g). Elution with benzene gave **9** and further elution with $CHCl_3$ gave the recovered phenol.

Registry No. 2a, 108-95-2; **2b**, 95-57-8; **2c**, 108-43-0; **2d**, 106-48-9; **2e**, 95-48-7; **2f**, 90-05-1; **2g**, 150-19-6; **2h**, 150-76-5; **2i**, 526-75-0; **9a**, 53074-73-0; **9b**, 75717-49-6; **9c**, 75717-50-9; **9d**, 24483-75-8; **9e**,

75717-51-0; **9f**, 75717-52-1; **9g**, 60965-23-3; **9h**, 75717-53-2; **9i**, 75717-54-3; **15**, 75717-55-4; **15** *O*-acetyl derivative, 75717-56-5; **15**, 75717-57-6; **15** imine *N,O*-diacetyl derivative, 75717-58-7; 2-hydroxyphenol, 120-80-9; 6-methoxy-2-hydroxy-α-chloroacetophenone, 75717-59-8; 4-hydroxyphenol, 123-31-9.

Acyclic Stereoselection. 10. A General Synthesis of *erythro*-α-Alkyl-β-hydroxy Ketones[1]

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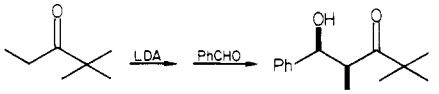
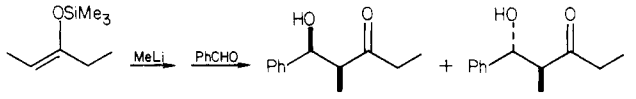
Ketones having one bulky group attached to the carbonyl usually give rise to homogeneous *Z* enolates, which condense with aldehydes to give erythro aldols.[2] Thus, ethyl *tert*-butyl ketone reacts with benzaldehyde to give aldol **1**.[2,3] However, other ketones give mixtures of *Z* and



1

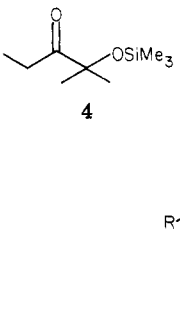
E enolates, which undergo the aldol condensation with various degrees of kinetic stereoselectivity. Even when pure *Z* enolates of such ketones are obtained by indirect means, kinetic stereoselection is not complete. For example, the *Z* enolate of diethyl ketone reacts with benzaldehyde to give the erythro and threo aldols **2** and **3** in

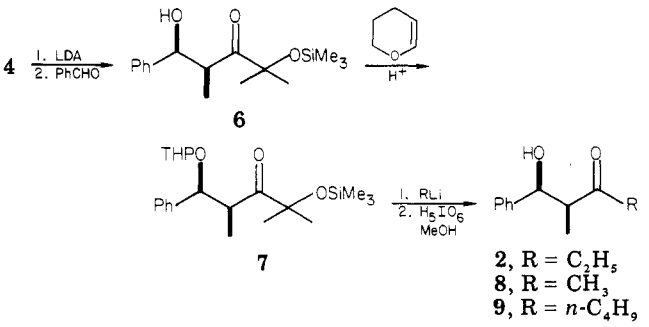


2 **3**

a ratio of only 90:10.[2,4] In this note, we put forth a general method whereby pure erythro aldols such as **2** may be obtained with high stereoselectivity (≥80:1).

Ketone **4** has previously been used to convert a variety of aldehydes into erythro β-hydroxy carboxylic acids[2] and aldehydes. For preparation of an acid, the initial aldol **5** is oxidized by periodic acid.[2] For preparation of an aldehyde, the aldol is reduced with lithium aluminum hydride and then cleaved with sodium periodate.[1] In principle, ketones are obtainable by addition of an organometallic reagent, followed by periodic acid oxidation. In practice, the process is more successful if the initial aldol is protected as its tetrahydropyranyl ether prior to addition of the organometallic reagent. Alkyllithium reagents add to the resulting protected aldols, and the products are then cleaved to obtain the pure erythro β-hydroxy ketones. Grignard reagents are not suitable, as complex mixtures are obtained. The process has been demonstrated with the preparation of aldols **2**, **8**, and **9** in overall yields of





52–70%. A separate deprotection step is not necessary; the tetrahydropyranyl group is conveniently removed in the course of the vicinal diol cleavage. Note that the process not only accomplishes stereospecific synthesis of aldols derived from a wide range of simple ketones but also allows the preparation of *regiospecified* aldols. Thus, **9** is the aldol resulting from condensation of 3-heptanone specifically at C_2.

Experimental Section

For general experimental details, see ref 2.

2,4-Dimethyl-1-phenyl-1-(tetrahydropyranyloxy)-4-(trimethylsiloxy)-3-pentanone (7). To a solution of 0.46 mL (3.3 mmol) of diisopropylamine in 10 mL of dry THF at 0 °C was added 2.2 mL (3.3 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 10 min the solution was cooled to −70 °C and 0.56 g (3.0 mmol) of 2-methyl-2-(trimethylsilyloxy)-3-pentanone (**4**)[2] was added over a 3-min period. After the mixture was stirred at −70 °C for 30 min, 0.31 mL (3.0 mmol) of benzaldehyde was added, and the mixture was stirred for 2 min and quenched with 10 mL of saturated $NaHCO_3$. After warming to room temperature, the reaction mixture was extracted two times with ether. The ether layers were combined, dried (Na_2SO_4), and evaporated to give 0.89 g (100%) of **6** as a colorless oil. The crude product was dissolved in 18 mL of methylene chloride and treated with 1.0 mL (10 mmol) of dihydropyran. *p*-Toluenesulfonic acid was added in 1-mg portions every 15 min until TLC indicated some formation of product (TLC: 15% ether in hexanes; **6**, R_f 0.19; **7**, R_f 0.36). The reaction was allowed to stand for 1 h, the solvent was removed in vacuo, and the residue was purified by chromatography on 40 g of silica gel (15% ether/hexanes) to yield 0.88 g (78%) of **7** (colorless oil) as a 1:1 mixture of diastereomers: IR (thin film) 1710, 1450, 1250, 1200, 1040, 1010, 840 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (9 H, s), 0.61 (s) and 0.67 (3 H, s), 1.13 (3 H, s), 1.3 (3 H, 2 d), 4.7 (1 H, 2 d), 7.1 (5 H, br s).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 66.63; H, 9.05. Found: C, 67.01; H, 9.26.

4-Hydroxy-3-methyl-4-phenyl-2-butanone (8). To a solution of 0.27 g (0.71 mmol) of protected ketol **7** in 5 mL of dry THF was added 1.1 mL (1.5 mmol) of 1.4 M methyllithum in ether. After being stirred for 4 h at room temperature the mixture was treated with 5 mL of saturated $NaHCO_3$. The reaction mixture was extracted two times with ether. The ether layers were combined, dried ($MgSO_4$), and evaporated to give 0.25 g of crude product as a pale yellow oil which was used without further purification. This material was dissolved in a mixture of 5 mL of dioxane and 10 mL of 2:1 methanol–water and 1.1 g (4.8 mmol) of H_5IO_6 was added. After being stirred for 16 h at room temperature the reaction mixture was diluted with water and extracted three times with 25 mL of CH_2Cl_2. The CH_2Cl_2 layers were

(1) For part 9, see C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. VanDerveer, *J. Org. Chem.*, **45**, 3846 (1980).
(2) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.* **45**, 1066 (1980).
(3) J.-F. Dubois and P. Fellman, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **274**, 1307 (1972).
(4) See also J.-E. Dubois and P. Fellman, *Tetrahedron Lett.*, 1225 (1975).

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