1,1-Dideuterio-*n*-octyl Alcohol (6). To a stirred suspension of 4.2 g (0.1 mol) of lithium aluminum deuteride in dry THF (150 mL) under nitrogen was added a solution of 15.8 g (0.1 mol) of commercial methyl octanoate (**5**) in dry THF (30 mL) during 30 min. After an additional 4 h of reflux, the mixture was cooled with ice bath and treated cautiously with THF/water (1:1 v/v mixture, 50 mL) and then with water (50 mL). It was poured into chilled water (100 mL), and 10% sulfuric acid (300 mL) was added. The mixture was extracted with ether (2 × 150 mL). The combined ether layers were washed with water and evaporated after being dried (Na_2SO_4) to afford 13 g (98.5%) of 1,1-dideuterio-*n*-octyl alcohol (**6**) (deuterium content >95%, by NMR analysis). The latter when assayed by GC showed >98% purity and was used without further purification for subsequent reactions: NMR ($CDCl_3$) δ 0.9 (3 H, t), 1.1–2.0 (12 H, m), 1.7 (1H, s).

1,1-Dideuterio-*n*-octyl methanesulfonate [**7a**: bp 95–96 °C (0.05 mm); n^{20}_D 1.4403] was obtained from **6** with the previously described procedure[16] for unlabeled derivative **1a**: NMR ($CDCl_3$) δ 0.9 (3 H, t), 1.1–1.9 (12 H, m), 3.0 (3 H, s). 1,1-Dideuterio-*n*-octyl chloride [**7b**: bp 179–181 °C (760 mm); n^{20}_D 1.4298] was prepared from **6** by following a reported procedure[17] for unlabeled derivative **1b** [lit.[17] bp 181.5 °C (765 mm); n^{20}_D 1.4306]. Quaternary phosphonium salts **2a,b** were obtained from the corresponding hexadecyltributylphosphonium methanesulfonate (**2c**) by exchange with the appropriate anion.[4,5]

Commercial methanol, Me_2SO, chlorobenzene, and cyclohexane were carefully purified and dried by standard methods[4] and stored under nitrogen over molecular sieves. In all cases Karl Fishcher analyses showed a water content of ≤50 ppm.

Kinetic Measurements. At zero time a standardized solution (20 mL) of substrate [(10–40) × 10^{-2} M] was added to a standardized solution (80 mL) of quaternary salt [(2.5–5) × 10^{-2} M] in a 100-mL flask thermostated at 60 ± 0.1 °C. Samples (2–5 mL), withdrawn periodically, were quenched in ice-cold MeOH (50 mL) and analyzed by potentiometric titration with 0.01 N silver nitrate. The unreacted nucleophile was determined in the case of methanesulfonate **1a** or tosylate **1e**. When the leaving group was the halogen, the halide ion formed during the reaction was evaluated in the presence of 3 mL of 6 M HNO_3. The second-order rate constants were evaluated by using a least-squares analysis computer program, as previously described.[4]

Registry No. **1a**, 16156-52-8; **1b**, 111-85-3; **1c**, 111-83-1; **1d**, 629-27-6; **1e**, 3386-35-4; **2a**, 66997-37-3; **2b**, 67047-78-3; **2c**, 86471-19-4; **5**, 111-11-5; **6**, 78510-02-8; **7a**, 86471-18-3; **7b**, 86471-20-7; D_2, 7782-39-0.

(16) Williams, H. R.; Mosher, H. S. *J. Am. Chem. Soc.* **1954**, *76*, 2984.
(17) Vogel, A. J. *J. Chem. Soc.* **1940**, 640.

Reaction of (Acyloxy)alkyl α-Halides with Phenols: Effect of Nucleofugicity and Nucleophilicity on Product Distribution

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The product distribution obtained from the reaction of (acyloxy)alkyl α-halides (**1** or **5**) with phenols was found to depend on the nucleophilicity of the phenol, the nucleofugicity of the leaving group, and the ability of the electrophile to stabilize a carbenium ion. More nucleophilic phenols tended to give more acylation while better leaving groups and more stable incipient carbenium ions in the electrophile tended to favor the formation of alkylated products. In addition, the reaction of methanol with **1a** was found to give a mixture of acylated and alkylated products (40:60). Thus, a general trend for all the nucleophiles for which information is available suggests that better nucleophiles undergo relatively more acylation and that poorer nucleophiles undergo more alkylation. These results are suggested to be consistent with the observations of Westaway on the effect of leaving group nucleofugicity and nucleophilicity of the nucleophile on bond lengths in the S_N2 transition state. Facile rearrangements of acylated to alkylated products and of one alkylated product to another caused by the phenolate anion were also observed in the 3-phenoxy-1(3*H*)-iosbenzofuranone–phenyl 2-formylbenzoate series.

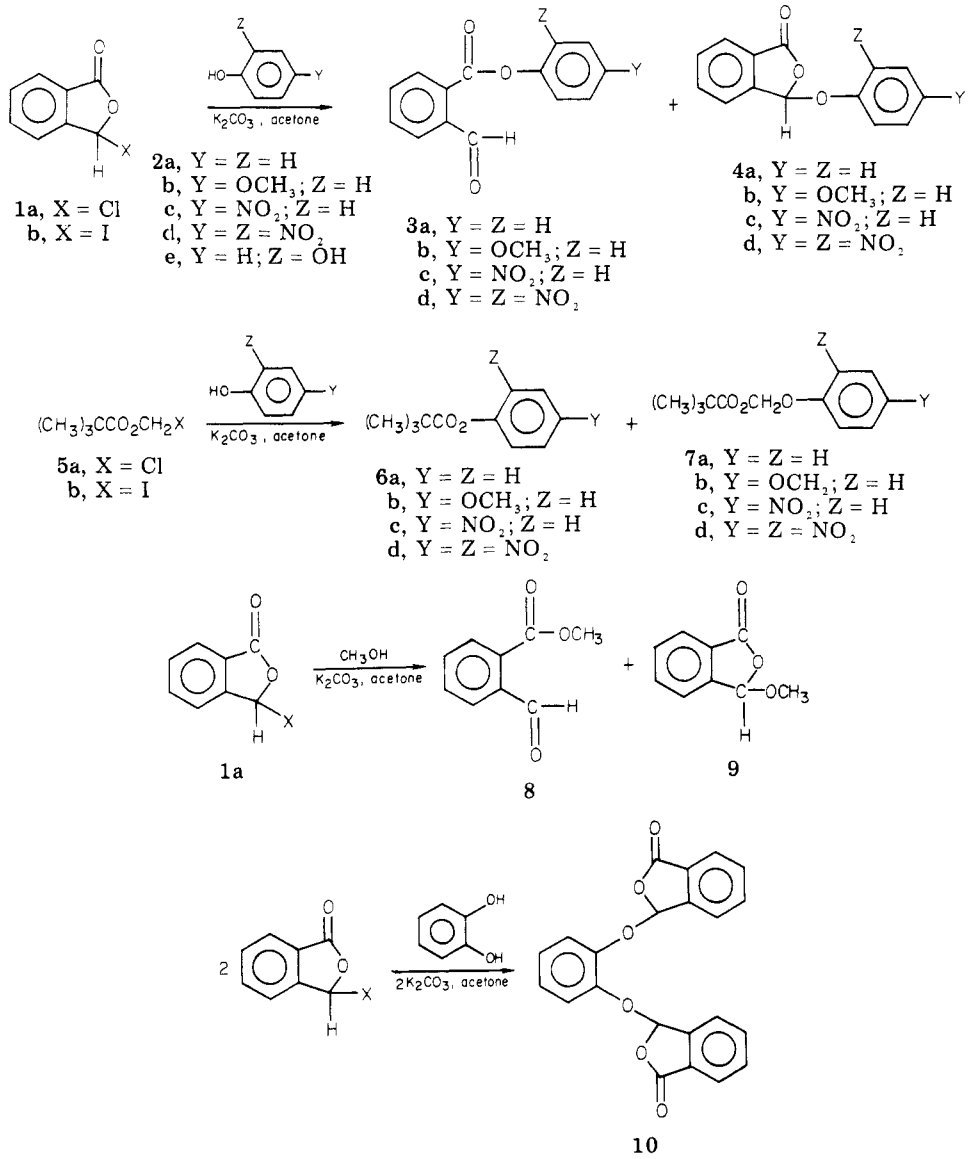
A recent study of the effect of the nucleophilicity of the amine and the nucleofugicity of the leaving group on the product distribution obtained from the alkylation reaction of amines with (acyloxy)alkyl α-halides (**1** or **5**)[1] revealed two interesting trends. First, better nucleophiles tended to undergo acylation (reaction at the acyl carbon atom) upon reaction with the α-chlorides while poorer nucleophiles tended to undergo alkylation (reaction at the alkyl α-halide carbon atom). Second, the extent of alkylation of the more nucleophilic amines was increased by using a better leaving group in the electrophile, i.e., an α-iodide. These trends were rationalized in terms of looser (good nucleophile–poor leaving group) and tighter (poorer nucleophile–better leaving group) transition states.[2] However, the fact that it was necessary to use amines with significant structural differences in order to obtain the desired range of nucleophilicites made it desirable to obtain collaborative evidence from another series of nucleophiles. Phenol nucleophiles represent an attractive series in that regard. Nucleophilicities can be varied over several orders of magnitude by changing the 4-substituent from nitro to methoxy[3] without affecting the steric requirements of the nucleophile.

In addition, the products of the alkylation reaction of phenols with (acyloxy)alkyl α-halides [(acyloxy)alkyl α-ethers (**4** and **7**)] represent an important class of derivatives of phenols because they have the potential to serve as protecting groups in synthetic reactions or as prodrug

(1) Sloan, K. B.; Koch, S. A. M. *J. Org. Chem.* **1983**, *48*, 635. (b) The key to these and all subsequent numbered compounds can be found in Scheme I.
(2) Westaway, K. C.; Ali, S. F. *Can. J. Chem.* **1979**, *57*, 1354.
(3) Hine, J. "Physical Organic Chemistry"; McGraw-Hill: New York, 1962; p 159.

0022-3263/83/1948-3777$01.50/0

Scheme I



derivatives of biologically active phenols. The first convenient synthesis of these (acyloxy)alkyl α-ethers of phenols from the reaction of phenols with (acyloxy)alkyl α-halides has been described elsewhere.[4] In this paper a study of the effects of the nucleophilicity of the phenol and the leaving group ability of the halide in the (acyloxy)alkyl α-halide on the relative formation of alkylated and acylated products in S_N2 reactions[5] will be described.

Results and Discussion

The alkylation reactions of phenols (Scheme I) were run in dry acetone by using anhydrous K_2CO_3 as the base and either the chloride or the iodide as the leaving group. An attempt to use conditions (1 equiv, of amine as an acid scavenger) more nearly identical with those used in the majority of the experiments in the previous study[1] of the reactions of amines with **1** resulted in little or no reaction at all being observed. For instance, the reaction of the triethylamine salt of **5a** with β-estradiol did not give either acylated or alkylated products,[6] while the reaction between **5a** and **2a** in the presence of triethylamine gave only 14% acylation. Fortunately, the use of K_2CO_3 as an acid scavenger had been shown to give the same qualitative results as the use of the second equivalent of amine in the reactions of amines with (acyloxy)alkyl α-halides so that these results are comparable with those obtained in the study of the reactions of amines.

In addition, the use of 1 equiv of the tertiary amine as the acid scavenger in the reactions of **1** or **5** with **2** raised the question of whether the amine salts of **1** or **5** are formed in the reaction and if so where the tertiary amine as a leaving group fits into the trend of halide leaving groups; probably it is a poorer leaving group than chloride.[7] This would explain the lack of reaction between the amine salt of **5a** and β-estradiol. On the other hand, in the reactions of 2 equiv of secondary amines with **5** or **1**,[1] the question of leaving group ability was not a problem because the formation of the quaternary salt was also the product forming process.

Phenol, 4-methoxyphenol, 4-nitrophenol, catechol, and 2,4-dinitrophenol were chosen as the phenol nucleophiles to be studied. The first three phenols listed gave the best results for comparison. In that series 4-methoxyphenol

(4) Bodor, N.; Sloan, K. B.; Kaminski, J. J.; Shih, C.; Pogany, S., submitted for publication in *J. Org. Chem.*

(5) The fact that the product distribution is dependent on the nucleophile supports the conclusion that these are S_N2 reactions.

(6) Bodor, N., unpublished results.

(7) Ingold, K. C. "Structure and Mechanism in Organic Chemistry"; Cornell University Press: Itaca, NY, 1953; p 339.

was the most and 4-nitrophenol the least nucleophilic. Although 2,4-dinitrophenol presented some steric hindrance to reaction not encountered with the other phenols, it was studied to see what effect a highly acidic phenol would have on reactivity. Similarly, the reaction of catechol with **1** was investigated to see what effect the incorporation of a second nucleophilic group would have on the relative amounts of acylation. It was also of interest to see if the incorporation of one bulky 1(3*H*)-oxoisobenzofuran-3-yl group would prevent the incorporation of a second such bulky group into the 2-position.

All of the reactions were run with two (acyloxy)alkyl α-halides: a cyclic and an acyclic representative. 3-Halo-1(3*H*)-isobenzofuranone (**1**) and (pivalyloxy)methyl halide (**5**) were chosen because of the anticipated crystalline nature of the products derived from them which would facilitate their isolation and quantification. In addition, since it was known that acylation was a very favorable process with the (acyloxy)alkyl α-halide system,[8] halides that gave both acylation and alkylation (and preferably favored alkylation) were desired so that the effect of changes in nucleophilicity and leaving group ability on the product distribution (acylation vs. alkylation) could be observed. Both **1** and **5** were expected to favor alkylation based on previous experience with **1**[1,9] and chemical precedent with **5**.[10] For instance, Rasmussen and Leonard[10] observed that the reaction of (benzoyloxy)-methyl chloride with 4,6-diamino-5-formamidopyrimidine gave an acylated product while the reaction of **5a** with the amide gave an alkylated product.

The reaction of **1a** with the series of phenols (**2a–e**) in the presence of K_2CO_3 for 48 h gave only the alkylated products on the basis of examinations of the NMR spectra of the crude reaction mixtures; **2d** did not react under any conditions with **1a**. The analytically pure ethers **4a** (72%), **4b** (70%), **4c** (73%), and **10** (65%), respectively, were isolated by simple crystallization. However, when the reaction mixtures were analyzed by NMR spectroscopy after 1, 3, and 12 h, various amounts of an absorption at about δ 10.1 to 10.6 were observed which depended on which phenol was used. On the basis of literature precedent[1,11,12] this absorption was assigned to the C*H*=O absorption arising from the presence of the acylated product **3** in the reaction mixtures. It was not possible to find conditions that allowed the isolation of any of the compounds **3** that are proposed as byproducts in these reactions. Thus, after 1 h, examination of the NMR spectrum of the reaction of **1a** with **2a** showed about 8% acylation and after 3 h no acylation, while examination of the NMR spectrum of the reaction of **1a** with **2b** showed about 18% acylation after 1 h, 32% acylation after 3 h, and 14% acylation after 12 h. Similarly, if the reaction of 2 equiv of **1a** with **2e** was analyzed by NMR spectroscopy after 16 h, about 20% of what had been initially the isobenzofuranone species was present in the form of an unidentified ring-opened species (C*H*=O absorption at δ 10.46). On the other hand, examination of the NMR spectrum of the reaction of **1a** with **2c** failed to show any acylated product at any time during the course of the reaction.

The NMR spectra of the reaction between **1a** and **2a** or **2c** were too complex in the region where the OC*H*Cl and OC*H*–O–C_6H_3YZ absorptions occurred to be able to quantitate the amounts of starting material **1a** and alkylated products **4** present during the course of the reactions. However, the NMR spectrum of the reaction of **1a** with **2b** was reasonably clear of absorptions other than OC*H*Cl in that region of the spectrum. Thus, on the basis of examinations of the NMR spectra, after 1 h 82% of **1a** remained from the reaction of **1a** with **2b** and 45% of **1a** remained after 3 h, while after 12 h no detectable **1a** was observed; the reaction appears to give only **3b** initially. Although it was not possible to quantitate the amount of OC*H*Cl absorption present in the reaction of **1a** with phenol (**2a**) or 4-nitrophenol (**2c**), the absorption in each case was very small (<30%) compared to the case of **2b** after 1 h so that the reaction of **2b** with **1a** appears to be slower than that of **2a** or **2c** with **1a**; no assessment of the relative rates of the reaction of **2a** and **2c** with **1a** by NMR analyses of the reaction mixtures was possible.

In order to try to determine the relative rates of reaction of **1a** with the phenols, we ran a series of competition reactions. When **1a** was allowed to react with a fourfold excess of each of 4-nitrophenol (**2c**) and of phenol (**2a**) in the presence of K_2CO_3 in acetone, only **4a** was observed by NMR spectroscopy and subsequently isolated. Similarly, when 4-methoxyphenol (**2b**) and phenol (**2a**) were run under the same conditions, only **4b** was observed and isolated.

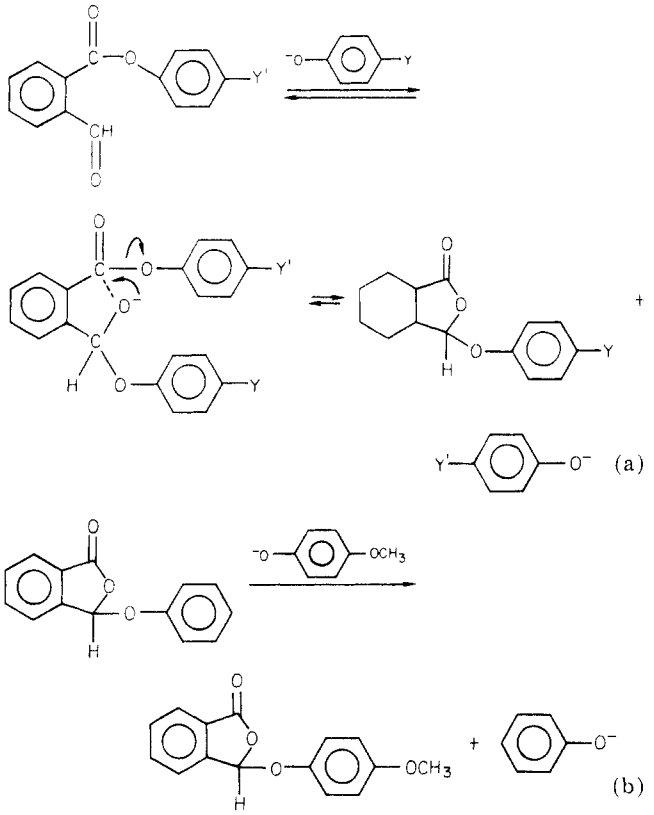
However, when **4a** was allowed to react with 2 equiv of 4-methoxyphenol (**2b**) in the presence of 2 equiv of K_2CO_3, only **4b** was observed by NMR analysis of the total reaction product, and **4b** was isolated by crystallization of the product. On the other hand, the reaction of **4a** with 4-nitrophenol under the same conditions resulted in the recovery of **4a**. The ether exchange can involve either a direct displacement of the phenoxide by a better nucleophile (Scheme IIb) or an equilibrium reaction between the alklylated and acylated product (Scheme IIa, where Y′ = OCH_3) similar to the mechanism suggested by Bender[13] for the hydrolysis of **8**. Thus, in any competitive reaction between two phenols and **1a** the only product that is obtained is the alkylated product derived from the more nucleophilic phenol, but it is not possible to determine relative rates of reaction of **2** with **1** from these experiments because of the facile ether exchange reaction which also favors the formation of the **4** derived from the more nucleophilic **2**.

For the reactions of 4-substituted phenols with **1a** the more nucleophilic phenols initially gave more of the acylated product **3** than the less nucleophilic phenols, and the relative order of propensity to form acylated products was **2e** ≥ **2b** > **2a** > **2c**. However, it is possible that the trend observed is due to a combination of acylation and rearrangement of **3** to **4** (Scheme IIa, Y = Y′). In the reactions of amines with **1a** or **1b**,[1] the acylated products were observed to rearrange to alkylated products in the presence of excess amine, and apparently a similar sort of rearrangement has taken place here. Thus, it is possible that the observation that larger amounts of **4a** than **4b** are formed during the initial stages of the reaction of **1a** with **2a** or **2b** could be due to a faster rate of acylation of **2a** by **1a** than **2b** by **1a** coupled with a subsequent faster rate of rearrangement of **3a** to **4a** than **3b** to **4b**. Since it has not been possible to isolate compounds **3** and examine their reactions with phenols, it is not possible at this time to assess that possibility.

The alkylated products could be isolated from the reaction mixtures by trituration with ether even if consid-

(8) Zupan, J., U.S. Patent 4 275 219, June 23, 1981; 4 338 454, July 6, 1982.
(9) Sloan, K. B.; Koch, S. A. M., unpublished results.
(10) Rasmussen, M.; Leonard, N. J. *J. Am. Chem. Soc.* **1967**, *89*, 5439.
(11) Kagan, J. *J. Org. Chem.* **1967**, *32*, 4060.
(12) Henderson, G. H.; Dahlgren, G. *J. Org. Chem.* **1973**, *38*, 754.
(13) Bender, M. L.; Reinstein, J. A.; Silver, M. S.; Mikulak, R. *J. Am. Chem. Soc.* **1965**, *87*, 4545.

Scheme II



erable quantities of acylated products were present in the crude mixtures. Thus, 40–60% yields of **4b**, a 39% yield of **10**, and 50% yields of **4a** were obtained when the reactions of **1a** with **2b**, **2e**, and **2a**, respectively, were processed after 16–36 h instead of 48 h.

The reactions between **1b** and **2a–e** gave the same results after 48 h as the reactions between **1a** and the phenols except that the isolated yields were somewhat lower. On the other hand, the reaction between **1b** and **2d** gave a good yield of **4d**, in contrast to the fact that no reaction at all was observed between **1a** and **2d**. The relatively low nucleophilicity of the anion of **2d** ($pK_a = 4.11$) is probably responsible for having to use the iodide to get any reaction at all. Similar results have been reported for the reactions of carboxylic acids with (acyloxy)alkyl α-halides. In the case of indomethacin ($pK_a = 4.5$)[14] (acyloxy)alkyl α-esters were obtained by using the chloride, whereas in the case of the less nucleophilic penicillin ($pK_a = 2.5$)[15] carboxylic acid anion, the use of catalytic amounts of NaI in the reaction were necessary to obtain satisfactory yields.

It is not possible to obtain an equilibrium between alkylated and acylated products in the reactions between **5a** or **5b** and the phenols. The reactions between **5b** and the phenols (**2a–d**) with the same reaction conditions as used for **1** gave only the alkylated products **7** in good yield. As in the case of the reaction of **1** with **2d**, only the use of the iodide **5b** allowed any reaction at all between **5** and **2d** to take place.

The reactions between **5a** and the phenols **2a–c** were quite slow at room temperature. Thus, with the reaction conditions (40 h) for the reaction of **5b**, **1a**, or **1b** with phenols, only a 56% conversion of 4-nitrophenol (**2c**) and 70–78% conversions of phenol (**2a**) to products were observed. However, when the reaction mixtures were refluxed for 40 h, 86% and 100% conversions to products, respectively, were observed. Under those conditions, only acylated products **6a** and **6b** were observed and isolated from the reactions of **2a** and **2b** with **5a**, while the reaction of **2c** with **5a** gave about a 50:50 mixture of acylated and alkylated product.

Each phenol was also converted to its potassium salt, and that salt was then allowed to react with **5a** in dry acetone. The results were the same as from the reaction of the phenol with K_2CO_3 in situ. In either case, the rate at which the reaction proceeded depended on the rate of stirring, but the rate of stirring did not influence the product distribution from the reactions of **2** with **5**. Also, the reaction of phenol (**2a**) with **5a** in the presence of a phase-transfer reagent was investigated; it too gave only the acylated product.

Thus, for the reaction of 4-substituted phenols with **5a**, the less nucleophilic phenol **2c** gave more of the alkylated product **7** than the more nucleophilic phenols **2a** and **2b**, and in this case there was no complicating possibility of rearrangement of acylated to alkylated product to obfuscate the results. It is also interesting that in comparing the reactions of **1a** and **5a** with phenols that **1** always gave a higher yield of alkylated derivatives. Thus, modifications such as changing from a good to a better leaving group or a methyl to a benzyl halide, which tend to increase the development or stabilization of the alkyl carbenium ion, tended to increase the amount of alkylated product formed.

It has already been pointed out that carboxylic acids[14] undergo alkylation with (acyloxy)alkyl α-chlorides, and it has been shown here that the reaction of **1a** with phenol gave small amounts (8%) of acylated products initially, while in a previous report[1] the reaction of **1a** with piperidine was found to give 100% acylated product and with methylaniilne 100% alkylated product. On the basis of Pearson's n_{CH_3I} values,[16] carboxylic acids and aniline are less nucleophilic than phenol. In that trend methoxide lies between phenol and piperidine. It was not surprising therefore that the reaction of methanol with **1a** gave a 50:35 mixture of alkylated **9** and acylated **8** products under the same reaction conditions used for the phenols, i.e., in the presence of K_2CO_3. Thus, increasingly nucleophilic agents as defined by Pearson's n_{CH_3I} scale give increasingly greater amounts of acylated products, and most of the common oxygen-type nucleophiles as well as the amine nucleophiles that have been studied appear to fit the trend.

The results here and those described previously[1] suggest that as nucleophiles approach an (acyloxy)alkyl α-halide a considerable positive charge develops on the alkyl halide carbon atom which can then redistribute to the acyl carbon atom,[1,4] and whether reaction by the nucleophile takes place at the acyl or the alkyl halide carbon atom depends qualitatively on the distance from the nucleophile to the alkyl halide carbon atom in the transition state. Thus, if the nucleophile–alkyl halide carbon atom distance in the transition state is long, the nucleophile is not closely associated with the developing positive charge (which is then free to redistribute), and the nucleophile will tend to react at the acyl carbon atom instead of the alkyl halide carbon atom, while if the nucleophile–alkyl halide carbon atom distance is short, the nucleophile will be closely associated with the developing positive charge (which will not be free to redistribute) and will tend to react with the alkyl halide carbon atom.[1] Since a better leaving group (iodide com-

(14) Sloan, K. B.; Bodor, N., unpublished results.
(15) Deehne, W. V.; Frederiksen, E.; Gundersen, E.; Lund, F.; Morch, P.; Petersen, H. J.; Roholt, K.; Tybring, L.; Godtfredsen, W. O. *J. Med. Chem.* **1970**, *13*, 607.
(16) Pearson, R. G.; Sobel, H.; Songstad, J. *J. Am. Chem. Soc.* **1968**, *90*, 319.

pared to chloride), a poorer nucleophile (4-nitrophenol compared to phenol), or a more stabilized carbenium ion substrate [1(3*H*)-oxoisobenzofuran-3-yl compared to (pivaloyloxy)methyl] in the reactions of nucleophiles with (acyloxy)alkyl α-halides all tend to favor alkylation over acylation, these conditions also appear to favor shorter nucleophile–alkyl halide carbon atom distances in the transition state. Thus, the suggestions of Westaway[2] and Pross and Shaik[17] that changes to a better leaving group or a poorer nucleophile in S_N2 reactions should cause more bond making between nucleophile and carbon and less bond breaking between leaving group and carbon in the transition state are supported.

Experimental Section

^1H NMR spectra were recorded on a Varian T-60 instrument and IR spectra on a Beckman Acculab 4 spectrophotometer. Melting points (uncorrected) were determined on a Thomas-Hoover apparatus. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Unless otherwise specified the chemicals were obtained from Aldrich except for the bulk solvents which were obtained from Fisher. TLC analyses were run on Brinkman Polygram Sil G/UV 254. The anhydrous NaI and K_2CO_3 were stored in a vacuum desiccator until immediately before use, and the acetone was stored over 4-Å 8–12-mesh molecular sieves before it was used. The silica gel used was Mallinckrodt SilicAR CC-7.

Reaction of 3-Chloro-1(3*H*)-isobenzofuranone (1a) with Phenols. The Reaction with Phenol.[4] A dry acetone (15 mL) suspension of 0.70 g (0.005 mol) of anhydrous K_2CO_3 and 0.83 g (0.005 mol) of 3-chloro-1(3*H*)-isobenzofuranone (**1a**) was allowed to react at room temperature for 52 h with 0.47 g (0.005 mol) of phenol (**2a**). The suspension was diluted with CH_2Cl_2 to 150 mL and filtered. The filtrate was concentrated to give a solid (88%; mp 112–116 °C) which was analyzed by NMR spectroscopy; no absorption in the region of δ 10–11 was observed that could be attributed to an aldehyde C*H*=O absorption due to the formation of acylated product. The solid was recrystallized from CH_2Cl_2–hexane (10:20) by concentrating the hot solution until crystals began to form to give 3-phenoxy-1(3*H*)-isobenzofuranone (**4a**): 0.81 g (72% yield); mp 117–119 °C; TLC (silica gel, ether) R_f 0.51; IR (KBr) 1770 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.07–7.45 (m, 4, aromatic H), 7.45–7.0 (m, 5, aromatic H), 6.8 (s, 1, O–CH–O); identical with an analtyical sample of **4a**.

The reaction with 4-nitrophenol (2c) gave the desired 3-(4-nitrophenoxy)-1(3*H*)-isobenzofuranone (**4c**) as a crude product (84% yield; mp 176–180 °C) which was shown by NMR spectroscopy not to contain any acylated product. The crude product was crystallized from $CHCl_3$–ether–hexane (20:30:40 mL) to give the pure product: 73% yield; mp 181–182 °C (lit.[18] mp 180–181 °C); ^1H NMR ($CDCl_3$) δ 8.0–7.6 (m, 4, aromatic H), 7.73 (AB q, 4, J = 9 Hz, $\Delta\nu_{AB}$ = 56 Hz, aromatic H), 6.87 (s, 1, O–CH–O); IR (KBr) 1790, 1780 cm^{-1} (s, CO).

The reaction with 4-methoxyphenol (2b) gave the corresponding crude product (89% yield; mp 108–112 °C); analysis of the crude product by NMR spectroscopy detected no acylated product. The crude product was recrystallized from $CHCl_3$–ether–hexane (3:10:20 mL) to give analytically pure 3-(4-methoxyphenoxy)-1(3*H*)-isobenzofuranone (**4b**): 70% yield; mp 112–114 °C; IR (KBr) 1780 (s), 1775 cm^{-1} (shoulder, C=O); ^1H NMR ($CDCl_3$) δ 8.0–7.3 (m, 4, aromatic H), 6.95 (AB q, 4, J = 9 Hz, $\Delta\nu_{AB}$ = 17 Hz, aromatic H), 6.67 (s, 1, OCH–O), 3.75 (s, 3, CH_3O). Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.09; H, 4.77.

The reaction of 3-chloro-1(3*H*)-isobenzofuranone (1a) with 2,4-dinitrophenol (2d) did not give any product in the presence of K_2CO_3 at room temperature or at the reflux temperature of acetone. Only when a trace of anhydrous NaI (about 0.04 equiv) was added did any reaction take place.

Reaction of 3-Iodo-1(3*H*)-isobenzofuranone (1b) with Phenols. Reaction with 2,4-Dinitrophenol (2d). A dry acetone (15 mL) solution containing 0.84 g (0.005 mol) of 3-chlorophthalide and 0.75 g (0.005 mol) of anhydrous NaI was allowed to stir at room temperature overnight. Then 2,4-dinitrophenol (0.922 g, 0.005 mol) and anhydrous K_2CO_3 (0.7 g, 0.005 mol) were added to the suspension that had resulted, and that mixture was stirred overnight at room temperature. The suspension was diluted to 150 mL with CH_2Cl_2 and filtered. The filtrate was concentrated to give a residue which was analyzed by NMR spectroscopy then triturated with 40 mL of ether overnight; the NMR spectrum of the crude product did not show any aldehyde C*H*=O absorption. The suspension was filtered, and the residue was dried to give the desired 3-(2,4-dinitrophenoxy)-1(3*H*)-isobenzofuranone (**4d**) as a fluffy, very pale light green solid: 1.0 g (63% yield); mp 183–185 °C; IR (KBr) 1795 cm^{-1} (s, C=O). Analytically pure, hard, greenish crystals (mp 185–187 °C, 84% recovery) were obtained by crystallizing the fluffy solid from hot CH_2Cl_2 (15 mL) layered with 50 mL of ether: IR (KBr) 1785 cm^{-1} (s, C=O); ^1H NMR (Me_2SO-d_6) δ 8.2 (AB q, 2, J = 12 Hz, $\Delta\nu_{AB}$ = 43 Hz, J_{AX} = 3 Hz, aromatic H), 7.5 (s, 1, O–CH–O). Anal. Calcd for $C_{14}H_8N_2O_2$: C, 53.16; H, 2.55; N, 8.86. Found: C, 53.09; H, 2.60; N, 8.80.

The reaction of the 3-iodo-1(3*H*)-isobenzofuranone with phenol (2a), 4-methoxyphenol (2b), and 4-nitrophenol (2c) in the presence of K_2CO_3 did not give any acylated products, i.e., aldehydes, but there was no significant advantage gained in the isolated yield of **4** obtained by using the iodide rather than the chloride.

Reaction of 3-Chloro-1(3*H*)-isobenzofuranone (1a) with Catechol (2e).[4] The reaction was run on a 0.005-mol scale under the same conditions as the reaction of **1a** with the other phenols and processed similarly to give a 95% yield of the crude product which was analyzed by NMR spectroscopy; the NMR spectrum did not contain an aldehyde absorption in the region at δ 10.6. The crude product was crystallized to give 65% yield of 1,2-bis(1(3*H*)-oxoisobenzofuran-3-yl)catechol (**10**): mp 188–190 °C; IR (KBr) 1785 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.0–7.0 (m, 12, aromatic H), 6.81 and 6.71 (2 s, 1, O–CH–O); TLC (silica gel, ether) R_f 0.02; identical with an analytical sample.

The $CHCl_3$–ether filtrate was then diluted with 20 mL of hexane and allowed to crystallize further to give 0.20 g (mp 131–136 °C) of a product which appeared to be the monoalkylated product on the basis of NMR and IR (OH at 3400 cm^{-1}) spectroscopy; TLC (silica gel, ether) R_f 0.46.

If the reaction was run for only 16 h then the NMR spectrum of the crude product contained an absorption at δ 10.6 which suggested that 20% of the crude product was an aldehyde-containing species. In that case, the desired catechol ether **10** was isolated in 39% yield by trituration with ether (20 mL).

Competitive Reactions between 3-Chloro-1(3*H*)-isobenzofuranone (1a) and Pairs of Phenols. In each case the chloride (0.21 g, 0.00125 mol) and 0.005 mol of each of the two different phenols were dissolved in 15 mL of dry acetone and allowed to react in the presence of 1.3 g (0.01 mol) of anhydrous K_2CO_3. After 24 h the suspensions were concentrated, and those residues were redissolved in 100 mL of CH_2Cl_2. The CH_2Cl_2 was extracted with 20 mL of 5% NaOH. The CH_2Cl_2 layers were separated, dried over Na_2SO_4, and concentrated. Those residues were analyzed by NMR spectroscopy and crystallized from the appropriate solvent systems to give the following products: from the competition between phenol and 4-nitrophenol only the phenol ether **4a** (100% yield) was observed by NMR spectroscopy of the crude product on the basis of the OC*H*–O absorption (OC*H*–OC_6H_5, δ 6.8, compared to OC*H*–$OC_6H_4NO_2$, δ 6.87) and isolated in 54% yield (mp 115–117 °C) from $CHCl_3$–ether–hexane (1:5:10 mL); from the competition between phenol and 4-methoxyphenol only the 4-methoxyphenol ether **4b** (94% yield) was observed by NMR spectroscopy of the crude product on the basis of the position of the OC*H*–O absorption (OC*H*–$OC_6H_4OCH_3$, δ 6.67, compared to OC*H*–OC_6H_5, δ 6.8) and isolated in 44% yield (mp 104–106 °C) from $CHCl_3$–hexane (1:15 mL).

Reaction between 4a and 2b or 2c. In each case **4a** (0.001 mol) was allowed to react with the phenol (0.002 mol) in the presence of anhydrous K_2CO_3 (0.002 mol) in 15 mL of dry acetone. After 12 or 24 h the suspensions were concentrated to give residues which were resuspended in 100 mL of CH_2Cl_2 and extracted with 20 mL of 5% NaOH. The CH_2Cl_2 layers were separated, dried

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over Na_2SO_4, and concentrated to give **4a** from the reaction of **4a** with **2c** (mp 115–117 °C; 0.13 g, 57% yield) and **4b** from the reaction of **4a** with **2b** (mp 102–106 °C; 0.14 g, 44% yield). In each case the crude product and the isolated product were identical with authentic **4a** and **4b**, respectively, by NMR spectroscopy.

Reaction of Iodomethyl Pivalate (5b) with Phenols. Reaction with 2,4-Dinitrophenol (2d). Chloromethyl pivalate (0.005 mol, 0.76 g) was allowed to react with anhydrous NaI (0.80 g, 0.0052 mol) in 15 mL of dry acetone overnight in a carefully sealed flask. The suspension was then allowed to react with 2,4-dinitrophenol (0.92 g, 0.005 mol) and anhydrous K_2CO_3 (0.70 g, 0.005 mol) overnight. The suspension that was obtained was diluted to 150 mL with CH_2Cl_2 and filtered. The filtrate was concentrated to give 1.25 g (84% yield; mp 108–110 °C) of 1-(pivalyloxy)methoxy]-2,4-dinitrobenzene (**7d**) which was recrystallized from CH_2Cl_2–hexane to give an analytical sample: 0.94 g; mp 111–112 °C; IR (KBr) 1755 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 8.66 (d, 1, J_{AX} = 3 Hz, aromatic H), 7.88 (AB q, 2, J_{AB} = 9, Hz, $\Delta\nu_{AB}$ = 5 Hz, aromatic H), 5.95 (s, 2, OCH_2O_2C), 1.23 (s, 9, $(CH_3)_3C$). Anal. Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.38; H, 4.75; N, 9.35.

The reaction with 4-nitrophenyl (3c) was carried out on the same approximate scale (0.0069 mol) and processed as above to give 1.52 g (89% yield; mp 41–51 °C of crude 1-[(pivalyloxy)-methoxy]-4-nitrobenzene (**7c**), which was identical with the analytical sample by NMR spectroscopy. The crude product was redissolved in CH_2Cl_2 (150 mL) and extracted with 20 mL of 5% NaOH. The CH_2Cl_2 layer was separated, dried over Na_2SO_4, and concentrated to give an oil. The oil was diluted with 15 mL of hexane, and crystals formed. The light yellow crystals were filtered and dried to give analytically pure product: 1.15 g (70% yield); mp 55–57 °C; IR (KBr) 1760 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 7.63 (AB q, 4, J = 9 Hz, $\Delta\nu_{AB}$ = 55 Hz, aromatic H), 5.81 (s, 2, OCH_2C), 1.21 (s, 9, $(CH_3)_3C$). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.07; H, 6.00; N, 5.52.

The reaction with phenol (2a)[19] was carried out on the same approximate scale (0.0068 mol) and processed as above to give an 82% yield of [(pivalyloxy)methoxy]benzene (**7a**) as a colorless oil which was identical with an analytical sample of **7a** by NMR spectroscopy and TLC: ^1H NMR ($CDCl_3$) δ 7.4–6.6 (m, 5, aromatic H), 5.73 (s, 2, OCH_2O_2C), 1.20 (s, 9, $(CH_3)_3C$).

The reaction with 4-methoxyphenol (2b) was carried out on a 0.005-mol scale but with the phenol present in 20% excess to simplify the above purification process which gave, after extraction with aqueous base to remove the excess phenol from a CH_2Cl_2 soln. of the reaction mixture, a 78% yield of pure 1-[(pivalyloxy)methoxy]-4-methoxybenzene (**7b**) by evaporation of the CH_2Cl_2: TLC (silica gel; ether–hexane, 2:10) R_f 0.3; IR (neat) 1730 (shoulder), 1740 cm^{-1} (s, C=O); ^1H NMR ($CDCl_3$) δ 7.0–6.55 (m, 4, aromatic H), 5.61 (s, 2, CO_2CH_2O), 3.71 (s, 3, CH_3O), 1.2 (s, 9, $(CH_3)_3CCO_2$). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.30; H, 7.61.

Reaction of Chloromethyl Pivalate (5a) with Phenols. Reaction with 4-Nitrophenol (2c). Several different procedures were used. The procedure that gave the most complete conversion of phenol to products is given first.

(A) Chloromethyl pivalate (0.82 g, 0.0054 mol) in 30 mL of dry acetone was alloed to react with 0.70 g (0.005 mol) of nitrophenol (**2c**) and 0.70 g (0.005 mol) of anhydrous K_2CO_3 at reflux for 40 h and was protected from atmospheric moisture with a $CaCl_2$ drying tube. The crude reaction mixture was diluted to 150 mL with CH_2CL_2 and filtered. The filtrate was concentrated to give 1.0 g of residue which was completely dissolved in $CDCl_3$ and analyzed by NMR spectroscopy. The NMR spectrum of the product exhibited absorptions corresponding to absorptions exhibited by authentic 1-[(pivalyloxy)methoxy]-4-nitrobenzene, 1-(pivalyloxy)-4-nitrobenzene, and chloromethyl pivalate in the ratio of 1:1:0.33. On the basis of that ratio of products, this method gives an 86% conversion of the phenol to products.

(B) The phenol was converted to its potassium salt by using 85% KOH in CH_3OH. The salt was isolated by evaporating the CH_3OH, suspending the residue in THF–ether (20–80 mL), and filtering the triturate. The solid was dried to give a 100% yield of the desired salt (0.88 g, 0.005 mol) which was then allowed to react with 0.82 g (0.005 mol) of chloromethyl pivalylate in 15 mL of dry acetone at room temperature for 40 h. The reaction mixture was processed as in method A. Analysis of the NMR spectrum of the residue as in method A showed that it contained the same compounds as obtained in method A plus 4-nitrophenol in the ratio of 3:5:42:3, respectively. On the basis of that ratio of products and the weight of the crude product (0.88 g), this method gives an 18% conversion of the phenol to products, with slightly more acylated product being formed than in method A. The products were separated by chromatography by using SilicAR CC-7 and hexane–ether (9:1) to ether as the eluent to give the following in order of elution: 1-(pivalyloxy)-4-nitrobenzene [**6c**: 55 mg (6% yield); mp 92–94 °C (lit.[20] mp 92–95 °C); ^1H NMR ($CDCl_3$) δ 7.67 (AB q, J = 9 Hz, $\Delta\nu_{AB}$ = 51 Hz, 4, aromatic H), 1.38 (s, 9, $(CH_3)_3C$), identical with Sadtler spectrum no. 4378];[20] 1-[(pivalyloxy)-methoxy]-4-nitrobenzene [**7c**: 31 mg (2.5% yield); mp 55–59 °C; ^1H NMR and melting point identical with those of an authentic sample from this work]; 4-nitrophenol [22 mg (3.2% yield); mp 111–114 °C (lit.[21] mp 112–114 °C); ^1H NMR identical with that of an authentic sample].

(C) Chloromethyl pivalylate (0.78 g, 0.005 mol), 4-nitrophenol (0.72 g, 0.0052 mol), and 0.72 g (0.0052 mol) of anhydrous K_2CO_3 were allowed to react at room temperature in 10 mL of dry acetone. The reaction was allowed to proceed for 72 h and was then processed as in method A to give 0.7 g of solid. The NMR spectrum of the solid analyzed as in method A showed that it contained the same products as in method B in the ratio of 14:17:1:12, respectively, with a 56% conversion of the phenol to products and again with slightly more acylated than alkylated product being formed.

The reaction with 4-methoxyphenol (2b) by method A gave 100% conversion of 4-methoxyphenol (**2b**) to 1-(pivalyloxy)-4-methoxybenzene (**6b**) contaminated with (pivalyloxy)methyl chloride but uncontaminated with 4-methoxyphenol: ^1H NMR ($CDCl_3$) δ 6.83 (sharp m, 4, aromatic H), 3.7 (s, 3, OCH_3), 1.33 (s, 9, $(CH_3)_3C$).

The other methods gave lower conversions of the phenol to products, but in every case the only product observed in the crude reaction products was the acylated 4-methoxyphenol, albeit in lower (65–69%, method B) conversion.

The reaction with 2,4-dinitrophenol (2d) gave no reaction with any of the above methods, and, in addition, phase-transfer catalysis was not at all effective.

The reaction with phenol (2a) by method A gave a 100% conversion of phenol to (pivalyloxy)benzene contaminated with unreacted (pivalyloxy)methyl chloride: ^1H NMR ($CDCl_3$) δ 7.6–6.9 (m, 5, aromatic H), 1.33 (s, 9, $(CH_3)_3C$), identical with Sadtler spectrum no. 21867.[20]

The use of 1 equiv of a phase-transfer reagent (tetrabutylammonium sulfate) in the reaction between (pivalyloxy)methyl chloride (0.005 mol) and phenol (0.005 mol) in 50 mL of CH_2Cl_2/15 mL of water (0.012 mol of NaOH) also gave only the acylated product. Similarly, methods B and C also gave only the acylated product, albeit in lower (70–80%, method C) conversion.

Reaction of 3-Chloro-1(3*H*)-isobenzofuranone with Methanol. To a suspension of anhydrous K_2CO_3 (1.25 g, 0.009 mol) in 15 mL of dry acetone were added 1.45 g (0.0086 mol) of 3-chlorophthalide (**1a**) and 0.275 g (0.0086 mol) of methanol. The reaction was stirred vigorously at room temperature for 3 days in a tightly sealed flask. The reaction mixture was diluted to 150 mL with CH_2Cl_2 and filtered. The filtrate was concentrated to give an oil (89% yield) which was triturated with hexane for 2 days. The hexane suspension was then filtered and concentrated to give 0.95 g (68% yield) of a colorless oil containing 3-chlorophthalide, 3-methoxy-1(3*H*)-isobenzofuranone (**9**), and methyl 2-formylbenzoate (**8**) in the ratio of approximately 15:50:35, based on the NMR spectrum of the oil: ^1H NMR ($CDCl_3$) δ 10.46 (s, 0.35, CH=O), 7.01 (s, 0.15, OCHCl), 6.25 (s, 0.50, O*C*HOCH$_3$),

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3.97 (s, 0.35, CO_2CH_3), 3.61 (s, 0.50, $CHOCH_3$), 8.0–7.3 (m, 4, aromatic H) [lit. NMR ($CDCl_3$): 3-chlorophthalide, δ 7.07 (OCHCl);[1] 3-methoxy-1(3*H*)-isobenzofuranone, δ 6.3 ($OCHOCH_3$), 3.6 ($OCHOCH_3$); methyl 2-formylbenzoate, δ 10.4 (CH=O), 3.9 (CO_2CH_3)].[12] If the reaction was run in methanol as a solvent, only the alkylated product was obtained.

Registry No. **1a**, 6295-21-2; **1b**, 61296-43-3; **2a**, 108-95-2; **2b**, 150-76-5; **2c**, 100-02-7; **2d**, 51-28-5; **2e**, 120-80-9; **4a**, 61133-42-4; **4b**, 87116-18-5; **4c**, 53912-16-6; **4d**, 87116-19-6; **5a**, 18997-19-8; **5b**, 53064-79-2; **6b**, 19820-47-4; **6c**, 4195-17-9; **7a**, 82212-47-3; **7b**, 87116-20-9; **7c**, 87116-21-0; **7d**, 87116-22-1; **1D**, 87116-23-2; CH_3OH, 67-56-1.

o-Quinone Methide Intermediates and Their Role in Coordinated Reactions of Magnesium Phenoxides with α-Branched Aliphatic Aldehydes

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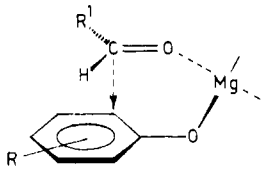
The reactions of (aryloxy)magnesium bromides with α-branched aliphatic aldehydes in apolar solvents have been investigated in order to obtain information on the role of *o*-quinone methide intermediates **8** or **9** in controlling the selectivity of the reactions of phenolic substrates and carbonyl compounds, which usually give a complex mixture of products. These reactions are characterized by high ortho regioselectivity, giving 2,2′-alkylidenebis(phenols) (**3**), 2-alkenylphenols (**4**), and 2,2-dialkyldihydrobenzofurans (**5**), according to the nature of the substituents on the aldehyde and the phenolic substrate. *o*-Quinone methides have been proved to be intermediates in these coordinated reactions by trapping experiments. The observed reaction pathways have been explained with the assumption that the steric bulkiness of the substituents leads the *o*-quinone methides to assume a geometry (**8** or **9**) that determines the subsequent reaction course.

The reactions between phenols and carbonyl compounds or their derivatives in the presence of catalysts usually give a very complex product mixture due to the occurrence of numerous competing pathways.

Recently it has been found that the use of magnesium phenolates in low-polarity media is an efficient control element for these reactions, since it leads to products of high ortho regioselectivity.[1-7] This is achieved through the formation of oriented substrate–reagent complexes (**6**), which have been isolated and studied[8] and which collapse to give ortho attack products.



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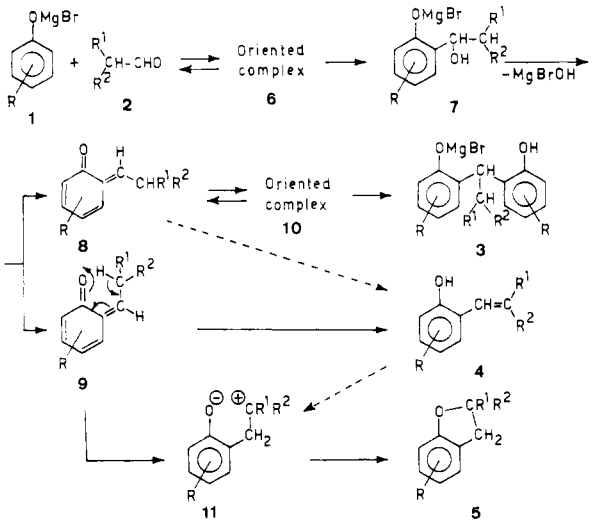
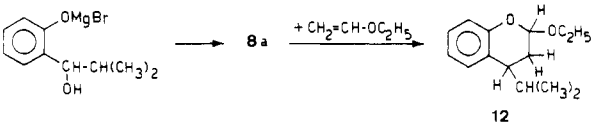
However, several competing processes leading to different products can occur, depending on the particular reagents or reaction conditions employed. Thus, 2,2′-alkylidenebis(phenols) are produced from linear aliphatic aldehydes or their acetals,[1] 2,2′-benzylidenebis(phenols) from aromatic aldehydes,[2] flavenes from certain magnesium phenoxides and cinnamaldehyde,[3] and 2-alkenylphenols from ketals;[4] in the presence of specific magnesium complexing agents, aromatic aldehydes give 2-hydroxybenzophenones,[5] cinnamaldehydes produce 2-hydroxycalchones,[6] and formaldehyde gives salicyl aldehydes[7] in good yields.

All of these competing reactions take place after the first ortho regioselective step has occurred to form salicyl al-

Scheme I



Scheme II



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