Transacylations between Sterically Hindered Aromatic Ketones and Various Arenes

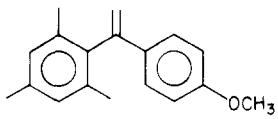
Ahmed M. El-Khawaga,† Royston M. Roberts,* and Kevin M. Sweeney

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

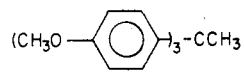
Received October 4, 1984

Transacylations between various aromatic ketones and arenes catalyzed by aluminum chloride and other Lewis and protonic acids at 100 °C are described. The presence of two substituents ortho to the acyl function in the ketone and sufficient nucleophilic character in the arene as exemplified by a benzene ring having at least two methyl groups are required for the transfer of the acyl group. The catalyst concentration and the temperature are important factors in determining the extent of transacylation vs. competing reactions that produce diarylethenes and triarylethanes from substituted acetophenones. Possible mechanisms for the reactions are proposed.

In an extension of our previous studies on the novel reactions of sterically hindered ketones with aromatic hydrocarbons,[1,2] we investigated the reaction of acetomesitylene with anisole and $AlCl_3$ at 100 °C. On the basis of the previous results, we expected 1-mesityl-1-(4-methoxyphenyl)ethene (1) as a product. However, no diaryl-

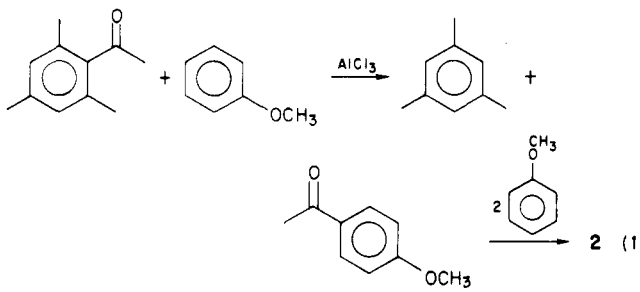


1



2

ethene was observed, but a small amount of 1,1,1-tris(4-methoxyphenyl)ethane (2) was isolated. This product was though to have arisen by a transacylation from mesitylene to anisole to yield *p*-methoxyacetophenone (3), followed by reaction of this ketone with two molecules of anisole (eq 1).



(1)

3

This finding encouraged us to examine the literature for other reports of transacylation. The only one found was that of Baddeley and Pendleton,[3] who reported that in the presence of $AlCl_3$ at 100 °C, acetyldurene (2,3,5,6-tetramethylacetophenone) was isomerized to acetylprehnitene (2,3,4,5-tetramethylacetophenone, 80%), with the concomitant formation of diacetyldurene (10%) and aromatic hydrocarbons (10%). However, Schlosberg and Woodbury[4] later criticized this work on the theoretical basis that acid-catalyzed transacylation is incompatible with NMR data on protonation of ketones. They repeated exactly the acetyldurene experiment of Baddeley and Pendleton and claimed that no transacylation occurred but that other products were formed by trans*alkyl*ations and reorientations of methyl groups. To support their theory that transacylations should not occur, they studied several possible transacylations in other aromatic ketone–arene systems and reported that in no case was transacylation detected.

†Robert A. Welch Postdoctoral Fellow, on leave from Assiut University, Assiut, Egypt.

Table I. Transacylation between Aromatic Ketones and Anisole[a]

entry	ketone	% transacylation[b]
1	acetophenone	0
2	2-methylacetophenone	0
3	4-methylacetophenone	0
4	4-methoxyacetophenone	0
5	2,4-dimethylacetophenone	6
6	2,4-dimethoxyacetophenone	0
7	acetomesitylene	85
8	acetodurene	82
9	benzophenone	0
10	benzoylmesitylene	60
11	1-acetyl-2-methylnaphthalene	80

[a] Reaction at 100 °C for 3 h; reactants (molar ratio), ketone:anisole:$AlCl_3$:H_2O = 1:3:1.2:0.24. [b] Based upon the moles of aromatic hydrocarbon produced by deacylation of the original ketone. Basing the calculation on the moles of "new" ketone formed gave approximately the same value for the extent of transacylation. The uncertainty was ca. ±5%, based on duplicate runs.

In the present investigation we demonstrate that transacylation does occur, and we examine the structural requirements of both the aromatic ketone and the arene acceptor.

Results and Discussion

The original procedure of Baddeley and Pendleton was repeated and the reaction mixture was analyzed by GC/MS. Small amounts of aromatic hydrocarbons and diacetyldurene were observed, as reported by Baddeley and Pendleton but not by Schlosberg and Woodbury.

The only example of experimental details for the other attempted transacylations described by Schlosberg and Woodbury was that of acetophenone and naphthalene, and the conditions were very different from those used on acetyldurene (e.g., lower catalyst:ketone ratio, use of CCl_4 as solvent).

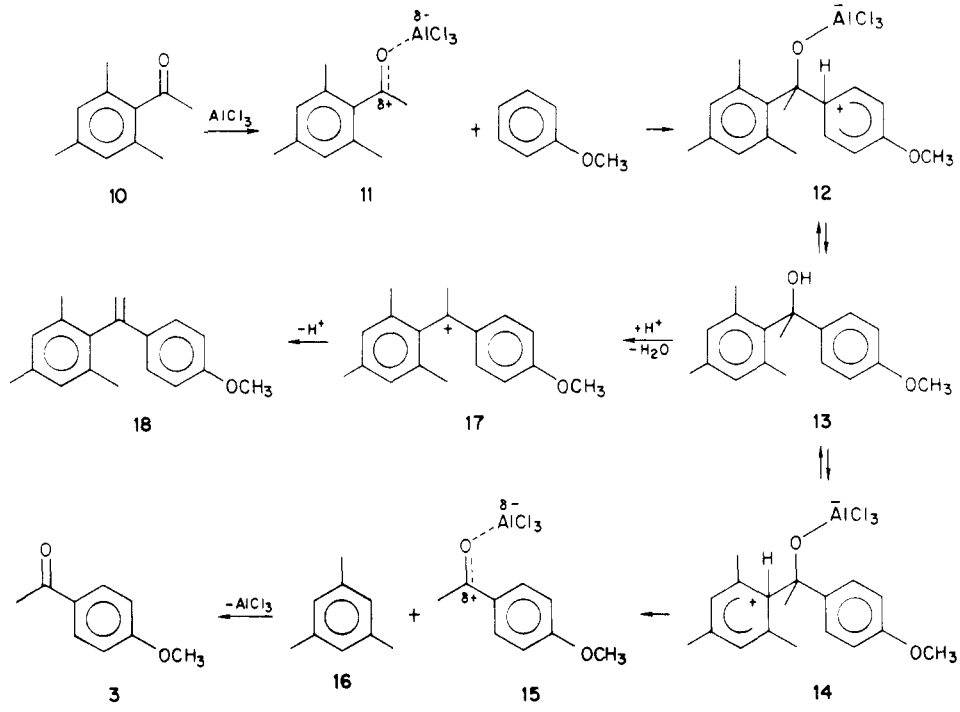
Examination of our results from reactions of various aromatic ketones with anisole and $AlCl_3$ (Table I) shows that all of the ketones with two ortho substituents gave 60–85% transacylation, 2,4-dimethylacetophenone gave a very small amount of transacylation (6%), and the other seven ketones, which contained only one or no ortho substituent, gave no transacylation.

By analogy to the mechanism proposed for decarbonylations and deacylations by Schubert and co-workers,[5,6]

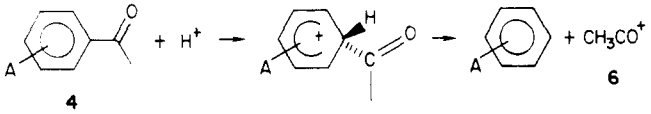
(1) Roberts, R. M.; El-Khawaga, A. M.; Roengsumran, S. *J. Org. Chem.* **1984**, *49*, 3180.
(2) El-Khawaga, A. M.; Roberts, R. M. *J. Org. Chem.* **1984**, *49*, 3832.
(3) Baddeley, G.; Pendleton, A. G. *J. Chem. Soc.* **1952**, 807.
(4) Schlosberg, R. H.; Woodbury, R. P. *J. Org. Chem.* **1972**, *37*, 2627.
(5) Schubert, W. M.; Latourette, H. K. *J. Am. Chem. Soc.* **1952**, *74*, 1829.

0022-3263/85/1950-2055$01.50/0

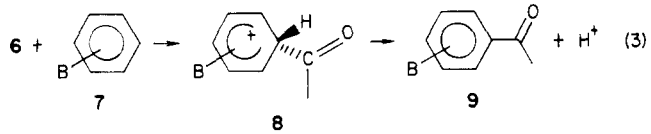
Scheme I



the transacylations observed in the present study might have as their rate-controlling step a deacylation as shown in eq 2, followed by recombination of the acylonium cation **6** with another arene (**7**) to give the other ketone (**9**), in eq 3). Schlosberg and Woodbury suggested on the basis

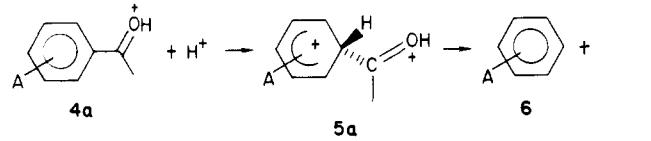


(2)



(3)

of NMR data that a ketone is O-protonated in the presence of acid and that such a deacylation would have to proceed from a diprotonated form of the ketone such as **5a** (eq 4).



$CH_3CO^+ + H^+$ (4)

The O-protonation does not change the expected electronic and steric effects of substituents on the aromatic rings, and the results from some of the ketones in Table I could be rationalized in terms of the *steric* effects of the ortho substituents in favoring the formation of the arenium ion **5** or **5a** from **4** or **4a** owing to the reduction of steric strain that occurs when the carbon to which the carbonyl group is attached changes from sp^2 to sp^3 hybridization.

However, consideration of the expected electronic effects of the substituents on the benzene ring of the ketones in Table I makes a mechanism in which the formation of **5** or **5a** is the rate-controlling step appear less reasonable. The fact that 4-methoxyacetophenone and 2,4-dimethoxyacetophenone undergo *no* transacylation is especially difficult to explain, since the arenium ion **5** should be strongly stabilized by delocalization of the positive charge on the ring by the resonance effect of the methoxy group(s).

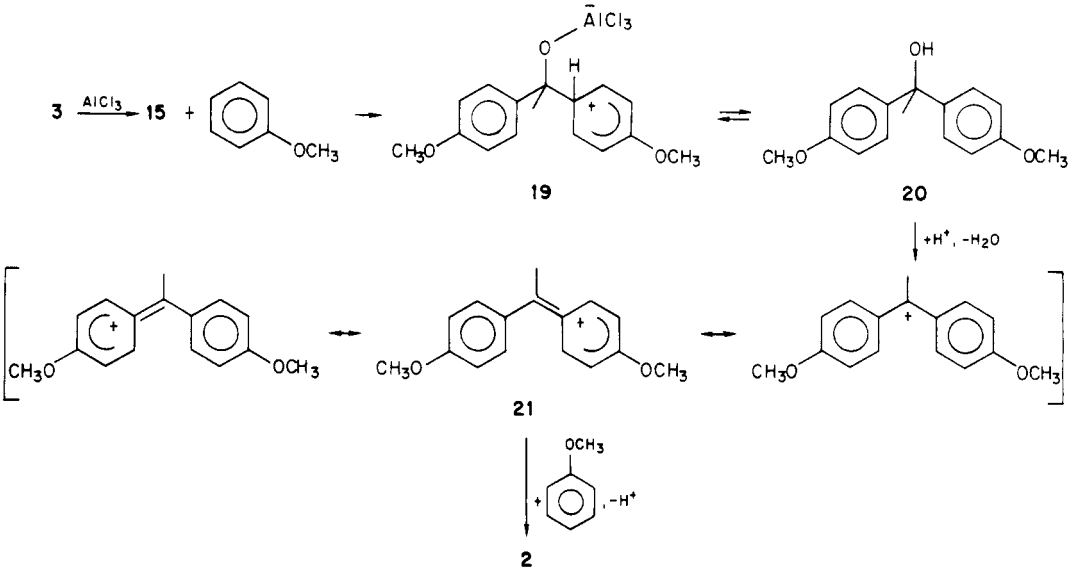
An alternative mechanism can be written (Scheme I) that rationalizes equally well the steric effect of the ortho substituents without the contradiction of the lack of electronic effect of the methoxy substituents. This mechanism also better accommodates the occurrence of the reactions observed to compete with and accompany the transacylations in the systems we have studied.

In earlier papers[1,2] we showed that tri- and tetramethylphenyl ketones are more electrophilic when two methyl groups occupy the ortho positions, because of steric inhibition of the resonance that would otherwise dissipate the positive charge on the carbonyl carbon by conjugation with the aromatic ring. This same steric effect can be called upon to rationalize the order and extent of occurrence of the transacylations reported in Table I. Reaction of a ketone such as **10** with $AlCl_3$ imparts enhanced electrophilicity to the carbonyl carbon so that **11** undergoes nucleophilic attack by an arene such as anisole to produce the arenium ion intermediate **12**. A proton exchange between the two aromatic rings affords the other arenium ion **14**, and reversal of the first step gives the products of transacylation, **3** and **16**.

Further reaction of acetylanisole (**3**) with two molecules of anisole would produce 1,1,1-tris(4-methoxyphenyl)-ethane (**2**) as we initially observed, via the intermediates **19**, **20**, and **21**, as shown in Scheme II. The fact that extensive transacylation occurred in the experiments of Table I without the formation of significant amounts of the trianisylethane **2** may be attributed to the higher concentration of catalyst (1.2 mol of $AlCl_3$ per mol of ketone) used in these experiments than in the experiment in which **2** was first detected (0.2 mol of $AlCl_3$ per mol of ketone). When higher concentrations of $AlCl_3$ are present, the amount of anisole that is effective as a nucleophile is

(6) Schubert, W. M.; Zahler, R. E. *J. Am. Chem. Soc.* **1954**, *76*, 1.

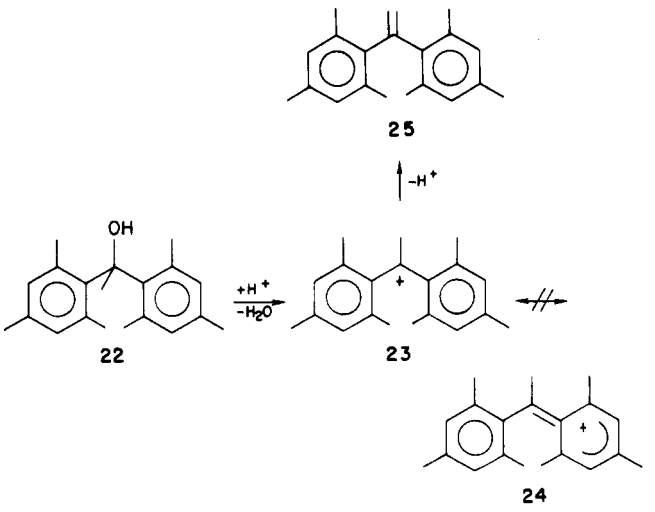
Scheme II



reduced by acid–base complexation with $AlCl_3$ so that the subsequent reaction of acetoanisole with anisole by the mechanism of Scheme II is retarded. This effect of catalyst concentration may be seen clearly in Table II, in entries 2–9. In the experiments of entries 2–4, with a low concentration of catalyst, the extent of transacylation was low and the trianisylethane **2** was detected. With increasing catalyst concentration, the extent of transacylation increased and no **2** was detected (entries 5–9).

Transacylations of acetyldurene to anisole with a variety of catalysts and under different conditions (Table II) showed that transacylation occurred with both Lewis and Brønsted acids and to an optimum extent when the ratio of catalyst to ketone was 1.2:1.

When a tri- or tetramethylphenyl ketone reacts with a tri- or tetramethylbenzene, transacylation may occur by a mechanism analogous to that of Scheme I, but a different subsequent reaction is observed. The intermediate analogous to **13** formed in the reaction of acetomesitylene with mesitylene would be **22**. A carbocation derived from



this tertiary alcohol cannot be stabilized by resonance with the aromatic rings as well as the analogous ion **21** produced in the reaction of acetomesitylene with anisole, because of steric inhibition to coplanarity in **24**, and thus its deprotonation to give the diarylethene **25** is favored over its reaction with another molecule of mesitylene to give a triarylethane. Undoubtedly steric hindrance to attachment

Table II. Transacylation between Aromatic Ketones and Anisole Using Various Catalysts[a]

entry	ketone	catalyst (mol/mol of ketone)	% transacylation[b]
1	acetophenone	$AlCl_3/H_2O$[c] (0.2)	0[d]
2	acetomesitylene	$AlCl_3/H_2O$[c] (0.2)	33[e]
3	acetyldurene	$AlCl_3/H_2O$[c] (0.2)	29[e]
4	acetyldurene	$AlCl_3$ (0.2)	28[e]
5	acetyldurene	$AlCl_3/H_2O$[c] (0.5)	63
6	acetyldurene	$AlCl_3/H_2O$[c] (1.0)	70
7	acetyldurene	$AlCl_3/H_2O$[c] (1.2)	81
8	acetyldurene	$AlCl_3$ (1.2)	87
9	acetyldurene	$AlBr_3/H_2O$[c] (1.2)	82
10	acetyldurene	$ZnCl_2$ (1.2)	71
11	acetyldurene	CF_3SO_3H (1.2)	83

[a] Reaction at 100 °C for 3 h; reactants (molar ratio), ketone:arene = 1:3. [b] Based upon the moles of aromatic hydrocarbon produced by deacylation of the original ketone. The uncertainty was ca ±5%, based on duplicate runs. [c] Molar ratio of $AlX_3:H_2O$ = 1:0.2 in all experiments. [d] $(p\text{-}CH_3OC_6H_4)_2C(CH_3)C_6H_5$ was detected in small amount. [e] $(p\text{-}CH_3OC_6H_4)_3CCH_3$ (**2**) was detected in small amount.

of a third mesityl group to the tertiary carbon in **25** also plays an important role in the failure of 1,1,1-trimesitylethane to be formed.[1]

An explanation for the failure to detect **18** from the reaction of acetomesitylene with anisole is less apparent but probably is related to both kinetic and thermodynamic factors. The formation of **3** by transacylation is fast, and then the resonance-stabilized cation **21** formed by further reaction with anisole represents a thermodynamic sink, compared to the cation **17**.

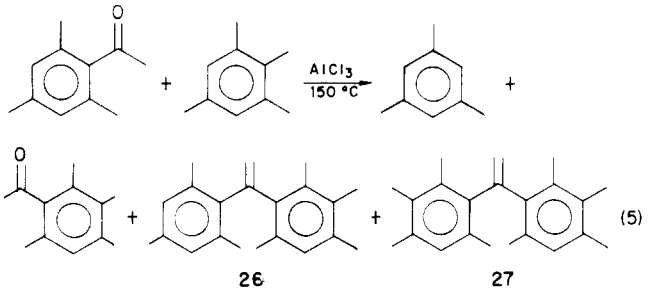
Table III shows the effect of varying the nature of the aromatic acyl acceptor in reactions with acetomesitylene. The occurrence and extent of transacylation appear to be determined by the nucleophilicity of the arene acyl acceptor. There was no transacylation to benzene or toluene. *m*-Xylene gave 20% transacylation, and presumably mesitylene gives extensive transacylation at 100 °C, but this cannot be observed unless isotopically labeled molecules are employed. However, under the same conditions used with the other arenes in Table III, that is, with an $AlCl_3$:ketone molar ratio of 1.2:1 and at a temperature of 100 °C, transacylation to isodurene occurred to the extent of 67%. Under the conditions that produced diarylethenes from the tri- and tetramethylphenyl ketones in reaction with the corresponding tri- and tetramethylbenzenes, that

Table III. Transacylations between Acetomesitylene and Various Arenes[a]

entry	arene	% transacylation[b]
1	benzene	0
2	toluene	0
3	*m*-xylene	20
4	anisole	85
5	phenetole	82
6	2-methylnaphthalene	40
7	2-methoxynaphthalene	87
8	isodurene	67,[c] 55[d]

[a] Reaction at 100 °C for 3 h. Reactants (molar ratio), acetomesitylene:arene:$AlCl_3$:H_2O = 1:3:1.2:0.24. [b] Based upon the moles of mesitylene produced by deacylation of acetomesitylene. Basing the calculation on the moles of "new" ketone formed gave approximately the same value for the extent of transacylation. The uncertainty was ca. ±5%, based on duplicate runs. [c] The catalyst:ketone ratio and temperature were the same as with the other arenes. [d] The catalyst:ketone ratio was 0.2:1, and the temperature was 150 °C. 1-Mesityl-1-isodurylethene (**28**) and 1,1-iisodurylethene (**29**) were detected in an estimated overall yield of 10–15% and in a ratio of about 10:1, respectively.

is, with an $AlCl_3$:ketone molar ratio of 0.2:1 and at a temperature of 150 °C,[1,2] the reaction of acetomesitylene with isodurene gave a smaller amount of transacylation, and two of the possible diarylethenes were detected, 1-mesityl-1-isodurylethene (**26**) and 1,1-diisodurylethene (**27**), in about a 10:1 ratio (eq 5).



26 **27** (5)

To our knowledge, this is the first report of transacylation occurring in significant amounts and the first mechanistic explanation of this reaction. Further work is being undertaken to explore more fully the potential of this reaction.

Experimental Section

The GC/MS data were obtained on a Finnigan MAT 4023 spectrometer with an INCOS data system and a J & W Scientific Inc. 50-m DB1 bonded-phase capillary column (0.25-μm film thickness). Acetomesitylene, acetyldurene, acetylisodurene, 1-acetyl-2-methylnaphthalene, and aluminum bromide were synthesized by literature procedures.[4,7] All other materials were commercially available. All organic reagents were checked for purity prior to use.

Reaction of Acetyldurene with Aluminum Chloride. (The procedure as described by Baddeley and Pendleton[3] and repeated by Schlosberg and Woodbury[4] was followed.) Acetyldurene (7.5 g, 0.043 mol), $AlCl_3$ (15 g, 0.11 mol), water (0.09 g, 0.005 mol), and NaCl (1.0 g, 0.02 mol) were stirred and heated together at 100 °C for 2 h. The reaction mixture was cooled, poured over ice, and extracted with chloroform. The chloroform extract was washed sequentially with water, saturated $NaHCO_3$, and water and then dried over $CaCl_2$. Quantitative GC/MS analysis was performed on the chloroform solution. Identification of acetylprehnitene as the major product (ca. 74%) was based upon analysis of samples spiked with authentic acetylprehnitene, acetyldurene, and acetylisodurene. Tetramethylbenzenes (ca. 10%), mainly durene, were also identified, as well as smaller amounts of tri- and pentamethylbenzenes and diacetyldurene (ca. 10%).

General Procedure for the Reaction of Ketones with Anisole. To a 50-mL, three-necked, round-bottomed flask fitted with a magnetic stirrer and a reflux condenser protected by a drying tube were added 0.025 mol of aromatic ketone, 8.0 g (0.075 mol) of anisole, 4.0 g (0.030 mol) of $AlCl_3$, and 0.10 g (0.006 mol) of water. The reaction mixture was stirred at 100 °C for 4 h, allowed to cool to room temperature, and poured over 50 g of ice. The mixture was extracted with two 40-mL portions of chloroform, and the chloroform extract was washed sequentially with 40 mL of water, 40 mL of saturated $NaHCO_3$, and 40 mL of water and dried over $CaCl_2$. The dry chloroform extract was then subjected to quantitative GC/MS analysis. The results are presented in Table I.

General Procedure for the Reaction of Ketones with Anisole Using Various Catalysts in Various Concentrations. In an apparatus of the type described previously were mixed 4.3 g (0.025 mol) of acetophenone, acetomesitylene, or acetyldurene, 8.0 g (0.075 mol) of anisole, 0.005–0.030 mol of catalyst, and 0.001–0.006 mol of water. Reaction conditions and workup were as described previously. The chloroform extract was subjected to quantitative GC/MS analysis. The catalysts tested were $AlCl_3$, $AlBr_3$, $ZnCl_2$, and CF_3SO_3H. Reactions using $AlCl_3$ and $AlBr_3$ were performed both with and without added water. The reaction with $ZnCl_2$ was performed with added water. The reaction with CF_3SO_3H was performed without added water. The results are presented in Table II. The extents of transacylation in Table II are all based on the moles of aromatic hydrocarbon produced by deacylation of the original ketone. In the experiments employing 1.0 or 1.2 mol of catalyst per mol of ketone, the yield of "new" ketone was approximately equal to the yield of "new" aromatic hydrocarbon, but in the experiments employing lower catalyst concentrations, the yield of the "new" ketone was lower, presumably owing to side reactions removing the "new" ketone.

General Procedure for the Reaction of Acetomesitylene with Various Arenes. In an apparatus of the type described previously were mixed 4.0 g (0.025 mol) of acetomesitylene, 0.075 mol of arene, 4.0 g (0.030 mol) of $AlCl_3$, and 0.010 g (0.006 mol) of water. The reaction conditions and workup were as described previously. The dry chloroform extract was subjected to quantitative GC/MS analysis. The results are presented in Table III.

GC/MS Quantitation Procedure. This procedure was based upon standard curves constructed for anisole, mesitylene, phenetole, phenol, acetophenone, durene, acetomesitylene, 4-methoxyacetophenone, acetyldurene, and 1,1,1-tris(4-methoxyphenyl)ethane; on-column injection techniques were used. Samples of knowns and reaction products were further standardized by use of naphthalene-d_8 as internal standard to adjust all injection volumes to a 1.0-μL basis. Typical sample preparation consisted of diluting the chloroform extract to 500 mL with chloroform, taking a 2-mL aliquot of this solution, and diluting it further to 100 mL. One milliliter of the dilute solution was taken and spiked with 10 μL of a solution of 2.0 g/L naphthalene-d_8 prior to injection. To minimize any instrument instability, standards were analyzed both before and after the reaction samples were analyzed.

Acknowledgment. Support for this work by the Robert A. Welch Foundation is gratefully acknowledged.

Registry No. **3**, 100-06-1; **10**, 1667-01-2; $AlCl_3$, 7446-70-0; $ZnCl_2$, 7646-85-7; CF_3SO_3H, 1493-13-6; anisole, 100-66-3; 2,4-dimethylacetophenone, 89-74-7; acetodurene, 2142-79-2; benzoylmesitylene, 954-16-5; 1-acetyl-2-methylnaphthalene, 50878-45-0; *m*-xylene, 108-38-3; phenetole, 103-73-1; 2-methylnaphthalene, 91-57-6; 2-methoxynaphthalene, 93-04-9; isodurene, 527-53-7; acetophenone, 98-86-2; 2-methylacetophenone, 577-16-2; 4-methylacetophenone, 122-00-9; 2,4-dimethoxyacetophenone, 829-20-9; benzene, 71-43-2; toluene, 108-88-3.

(7) Roger, A.; Binder, L. O. *J. Am. Chem. Soc.* **1941**, *63*, 2773.