Perfluoroalkanesulfonic Acid Catalyzed Acylations of Alkylbenzenes: Synthesis of Alkylanthraquinones[1]

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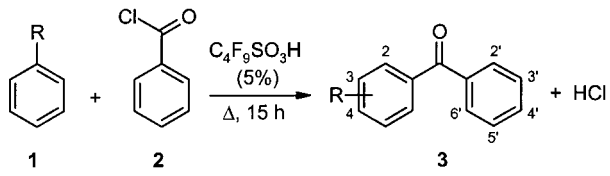
Abstract: The acylation of alkylbenzenes **1** with benzoyl chloride **2** and catalytic amounts of perfluorobutanesulfonic acid affords the corresponding 2-, 3-, and 4-alkylbenzophenones **3** with unusually high amounts of *ortho* products. Surprisingly, even *tert*-butylbenzene reacts under these reaction conditions without any acid catalyzed dealkylation. The yield of benzoylation of *p*-xylene **4** with benzoic acid in the presence of 5 mol% $C_4F_9SO_3H$ to give 2,5-dimethylbenzophenone **5** could significantly be improved from 14% to 90% by continuous removal of water formed during the acylation. Also in the preparation of alkylanthraquinones **7** by reaction of alkylbenzenes with phthalic anhydride, water removal is the decisive factor to obtain satisfactory yields for the second acylation, allowing to cyclize **6** with catalytic amounts (10 mol%) of CF_3SO_3H in organic solvents to the corresponding alkylanthraquinones **7**.

Key words: acylation, alkylbenzophenones, alkylanthraquinones, perfluoroalkanesulfonic acid catalysis

2-Alkylanthraquinones (e. g., 2-*tert*-butyl, 2-isopropyl or 2-ethylanthraquinone) are important catalysts for the production of hydrogen peroxide,[3] therefore many procedures for their preparation have been developed.[4] The acylation of alkylbenzenes with phthalic anhydride and subsequent cyclization of the primarily formed benzophenone-2-carboxylic acids is one important route to prepare 2-alkylanthraquinones.[4] Disadvantages of this procedure are the great excess of $AlCl_3$ (more than two molar) necessary for the first acylation step, and the large amounts of concentrated sulfuric acid required for the cyclization.

In previous publications we have demonstrated that aromatics can also be acylated with carboxylic acid chlorides and catalytic amounts of perfluoroalkanesulfonic acids avoiding large amounts of $AlCl_3$.[5] As expected, the perfluoroalkanesulfonic acid catalyzed acylation is especially favorable for donor-substituted aromatics (toluene, xylene, etc.).[5] Therefore, the acid catalyzed acylation of alkylbenzenes with phthalic anhydride should also be possible. However, in acid catalyzed acylations of isopropylbenzene and, even more pronounced, of *tert*-butylbenzene, undesired side-reactions of the alkylbenzenes, especially dealkylation but also isomerizations, could occur.[6] Applications of the *tert*-butyl group as a positional protective group in reactions of aromatics is based on easy debutylation.[7]

First, we have therefore investigated in general the acylation of alkylbenzenes with acid chlorides under perfluoroalkanesulfonic acid catalysis. The acylations of toluene and *p*-xylene, respectively, with benzoyl chloride previously described[5] should be extended to the alkylbenzenes **1b**–**d** (Scheme 1).



1	a	b	c	d
R	Me	Et	*i*Pr	*t*Bu

3	a',a'',a'''	b',b'',b'''
R	2-,3-,4-Me	2-,3-,4-Et
3	**c',c'',c'''**	**d',d'',d'''**
R	2-,3-,4-*i*Pr	2-,3-,4-*t*Bu

Scheme 1

Following the known procedure,[5] alkylbenzenes **1a**–**d** have been reacted with benzoyl chloride **2** in the presence of perfluorobutanesulfonic acid ($C_4F_9SO_3H$, 5 mol%) to give the alkylbenzophenones **3**. After 15 hours reaction time, the conversion was determined by isolation of the unreacted benzoyl chloride as benzoic acid. The results are listed in Table 1.

Table 1 reveals that the alkylbenzophenones **3** are obtained in good yields (referred to conversion). In the case of the benzoylation of isopropylbenzene **1c** to **3c'–c'''**, the isolated yield of **3c'–c'''** amounts to only 65% after 15 hours. Reducing the reaction time to 5 hours slightly increases the yield of **3c'–c'''** to 68% at decreased conversion of 78%. The benzoylation of *tert*-butylbenzene **1d** afforded **3d'–d'''** in 86% yield. Obviously, the acid catalyzed acylation of **1d** is faster than its dealkylation.

The isomeric ratios of products **3** were determined from the crude products by gas chromatography (Table 1). The percentage of *ortho* products is conspicuously high compared to benzoylations of alkylbenzenes with $AlCl_3$ as catalyst, giving mainly *para* products.[8] With increasing size of the alkyl group from methyl to *tert*-butyl, the amount of *ortho* products **3a'**–**d'** decreased mainly in favor of the corresponding *para* products **3a'''**–**d'''**: from 30% (**3a'**) and 68% (**3a'''**) to 5% (**3d'**) and 86% (**3d'''**). Also the percentage of *meta* products **3a''**–**d''** increases slightly: from 2% (**3a''**) to 9% (**3d''**).

Table 1 Acylation of Alkylbenzenes **1a–d** with Benzoyl Chloride **2** in the Presence of 5% $C_4F_9SO_3H$

Educt	Reaction Conditions		Conversion (%)	Products	Yield (%)	Isomeric Ratio *o*:*m*:*p*
	Temp (°C)	Time (h)				
1a	110	15	91	**3a'**, **a''**, **a'''**	85	30:2:68[a]
1b	136	15	87	**3b'**, **b''**, **b'''**	77	21:4:75
1c	153	15	89	**3c',c'',c'''**	65	
1c	153	5	78	**3c'**, **c''**, **c'''**	68	17:5:78
1d	168	15	92	**3d'**, **d''**, **d'''**	86	5:9:86

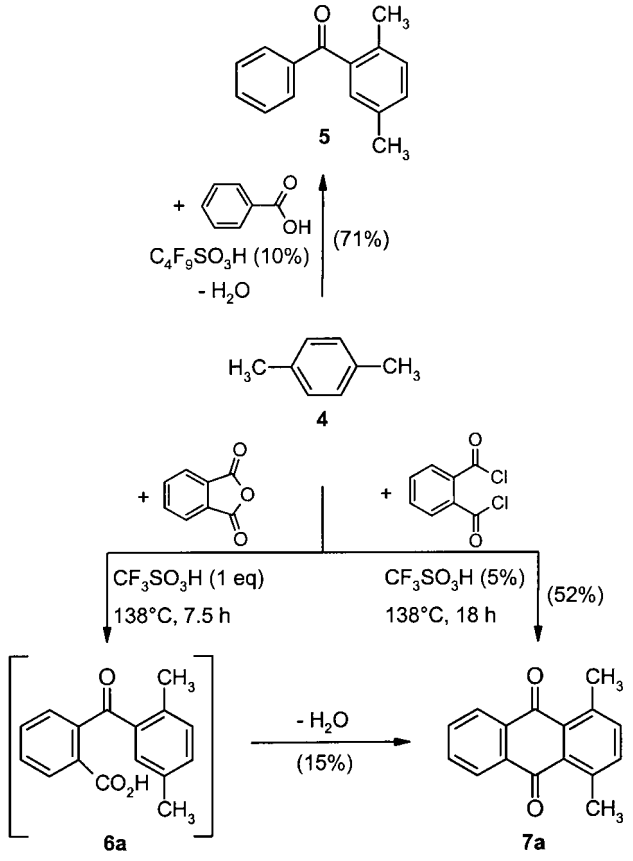
[a] Data from literature.[5]

The second step in the formation of anthraquinones from benzenes with phthalic anhydride is the cyclization of the benzophenone ortho acids with an excess of sulfuric acid. Since we were also interested in a catalytic process for this ring closure, we first investigated the acid catalyzed acylation of *p*-xylene with benzoic acid as a model reaction. Under $C_4F_9SO_3H$ catalysis (5 mol%) the acylation of *p*-xylene **4** with benzoic acid gives the acylation product **5** in only 14% yield.[5] For the acylation of aromatics with catalytic amounts of perfluoroalkanesulfonic acids, the formation of a mixed carboxylic perfluoroalkanesulfonic anhydride is essential.[9] Since the formation of water during the reaction was probably the main reason for the low yields of acylation product,[5] water was removed from the reaction mixture by azeotropic distillation and adsorption onto molecular sieves in the back flow (see experimental part). By this procedure the yield of acylation product **5** formed by reacting xylene **4** with benzoic acid in the presence of 10 mol% $C_4F_9SO_3H$ could be improved to 90% when referred to conversion. After distillation, 2,5-dimethylbenzophenone **5** was obtained in 71% yield (Scheme 2).

Based on these results, the acylation of **4** with phthalic anhydride in presence of trifluoromethanesulfonic acid (CF_3SO_3H) to give the corresponding anthraquinone **7a** was investigated (Scheme 2). The reaction occurred in one step, but equimolar amounts of CF_3SO_3H are necessary for completion. Moreover, product **7a** obtained contains many impurities, and thus it was isolated after purification in only 15% yield. Obviously, phthalic anhydride is too stable to react with catalytic amounts of CF_3SO_3H, giving the reactive mixed anhydride.

Better results were achieved in the acylation of **4** with phthaloyl chloride (Scheme 2). Compound **4** was acylated in one step with phthaloyl chloride under CF_3SO_3H catalysis (5 mol%) to anthraquinone **7a** in 52% yield after chromatographic purification. An increased appearance of byproducts due to phthalide formation[10] was not observed.

Since the cyclization of the intermediate keto acid **6a** to anthraquinone **7a** requires large amounts of concentrated sulfuric acid, we have investigated this step separately in more detail applying the knowledge of the acid catalyzed benzoylation of *p*-xylene **4** with benzoic acid (Scheme 2). The results of the cyclization of **6a** to **7a** in various solvents and with varying CF_3SO_3H concentrations are summarized in Table 2. The use of 1,2-dichloroethane as solvent and 10 mol% of CF_3SO_3H was found to give the best results: The cyclization of **6a** afforded **7a** in 89% yield. For large batch size, effective removal of the water formed is decisive for a high conversion of **6a** to **7a** as illustrated in the Figure.

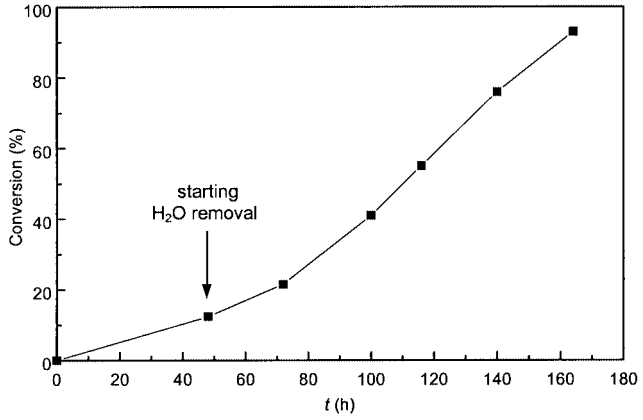


Scheme 2

Table 2 Cyclization of 2-(2,5-Dimethylbenzoyl)benzoic Acid (**6a**)[a] to Anthraquinone **7a** in Different Solvents (10 mL) under CF_3SO_3H Catalysis

		Reaction Conditions		Product **7a**
CF_3SO_3H (mol%)	Solvent	Temp (°C)	Time (h)	Yield g (%)
85	*o*-dichlorobenzene	180	7.5	0.70 (74)
85	chlorobenzene	131	18.0	0.49 (52)
85	dichloroethane	83	2.5	0.78 (82)
40	dichloroethane	83	18.0	0.65 (69)
10	dichloroethane	83	18.0	0.54 (57)
10	dichloroethane[b]	83	46.0	0.84 (89)

[a] Batch size 4.0 mmol each.
[b] Only 5 mL of solvent.

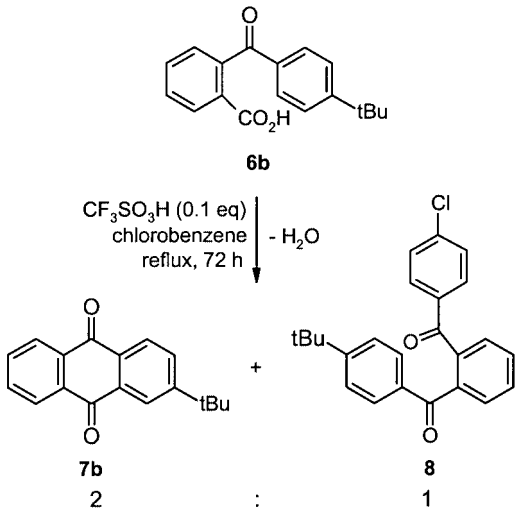


Figure

Finally, the CF_3SO_3H catalyzed cyclization of 2-(4-isopropylbenzoyl)- and 2-(4-*tert*-butylbenzoyl)benzoic acid[11] to the corresponding anthraquinones in toluene as solvent, and with removal of water was studied. In the case of 2-(4-isopropylbenzoyl)benzoic acid after 3 days at nearly complete conversion only a product mixture was isolated, which could not be separated and characterized.

2-(4-*tert*-Butylbenzoyl)benzoic acid **6b** also did not cyclize to the desired anthraquinone neither in toluene nor in dichloroethane. The diminished reactivity of 4-alkyl-substituted benzoylbenzoic acids[12] indicates that higher reaction temperatures are required. Therefore, chlorobenzene was used as solvent for the cyclization of **6b** (Scheme 3).

As shown in Scheme 3, after 72 hours reaction time in presence of 10 mol% CF_3SO_3H a product mixture was isolated, consisting of 4-*tert*-butylanthraquinone **7b** and 2-(4-chlorobenzoyl)-4-*tert*-butylbenzophenone **8** in a ratio of 2:1 (determined by NMR). The byproduct **8** is



Scheme 3

formed by acylation of the solvent chlorobenzene. The anthraquinone **7b** was obtained after crystallization from ethanol in 17% yield.

In summary, the perfluoroalkanesulfonic acid catalyzed acylation of alkylbenzenes **1** with benzoyl chloride **2** gave the corresponding alkylbenzophenones **3** in high yields without any acid catalyzed dealkylation. The application of benzoic acid as acylating agent under acid catalysis is possible, if, as shown for the acylation of *p*-xylene **4**, the water formed in the course of the reaction is continuously removed. The one-step acylation of **4** with phthalic anhydride via intermediate methylbenzoylbenzoic acid **6a** to anthraquinone **7a** requires equimolar amounts of perfluoroalkanesulfonic acid. Regarding only the second step, it could be demonstrated that cyclization of 2-(4-alkylbenzoyl)benzoic acids **6** to the corresponding anthraquinones **7** in various solvents with catalytic amounts of perfluoroalkanesulfonic acid is possible. Again, removal of the water formed is essential for obtaining satisfactory yields of anthraquinones.

Mps were determined on a Büchi SMP 20 apparatus and are uncorrected. Preparative column chromatography was performed using glass columns of different sizes packed with silica gel S, grain size 0.032−0.063 mm (Riedel-de Haen). Gas chromatography was performed with a Carlo Erba Fractovap 4160 with FID and Spectra Physics Minigrator. All solvents and starting materials were purified and dried.

Alkylbenzophenones 3; General Procedure

To nonafluorobutanesulfonic acid (300 mg, 1.0 mmol) in a flame-dried flask under Ar atm was added the respective alkylbenzene **1** (200 mmol) followed by addition of **2** (2.81 g, 20 mmol). After being stirred at reflux for 15 h (5 h for **1c**), the reaction mixture was poured into aqueous 2 N KOH (25 mL) and stirred vigorously for 6 h. After addition of Et_2O (200 mL), the phases were separated. The organic phase was washed with H_2O, and concentrated. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (6:4). The isomeric ratio of compounds **3** was determined by gas chromatography (Table 1).

In order to isolate benzoic acid, the alkaline aqueous phase was acidified with aqueous 6 N HCl and extracted with Et_2O. The combined extracts were concentrated, and the remaining benzoic acid was dried over P_2O_5 and weighed out.

Determination of Isomeric Ratio of 3 by Gas Chromatography[13]
GC was performed on a SDPE 08 capillary column (20 m) at 0.45 bar H_2; temperature programme 40−300 °C, 10° per min and 10 min at 300 °C. The correction factor (not given) was determined by weighed portion of reference substance for each reaction component.

Acylation of *p*-Xylene (4) with Azeotropic Removal of H_2O; General Procedure
To a solution of the acylation agent in **4** in a flask with dropping funnel, which was filled with molecular sieves 4 Å and equipped with reflux condenser, was added the respective perfluoroalkanesulfonic acid, and the reaction mixture was heated to reflux. H_2O formed during the reaction was removed by adsorption onto molecular sieves in the back flow. In order to complete the reaction, the reaction mixture was cooled to r.t., and diluted with Et_2O or CH_2Cl_2 to double volume. The mixture was washed twice with aqueous KOH and H_2O. The organic phase was dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by distillation or recrystallization.

2,5-Dimethylbenzophenone (5)
From benzoic acid (10 g, 82 mmol) in **4** (40 mL, 324 mmol), and $C_4F_9SO_3H$ (2.4 g, 8 mmol) in 48 h was obtained 12.3 g (71%) of **5**; bp: 173 °C/10 torr (Lit.[5] bp: 171−174 °C/11 torr).

From the alkaline aqueous phase benzoic acid was re-isolated as described above.

1,4-Dimethylanthraquinone (7a)
From phthalic anhydride (1.18 g, 8 mmol) in **4** (9.8 mL, 80 mmol), and CF_3SO_3H (1.19 g, 8 mmol) in 7.5 h; followed by chromatography on silica gel with petroleum ether/CH_2Cl_2 (7:3) and recrystallization was obtained 0.28 g (15%) of **7a**; mp: 136 °C (Lit.[4] mp: 141 °C).

CF_3SO_3H Catalyzed Acylation of 4 with Phthaloyl Chloride to Anthraquinone 7a
To a solution of phthaloyl chloride (1.16 mL, 8.0 mmol) in **4** (9.8 mL, 80 mmol) was added CF_3SO_3H (5 mol% referred to phthaloyl chloride), and the stirred reaction mixture was heated to 138 °C for 18 h. After being cooled to r.t., the reaction mixture was poured on ice and stirred for a further 3 h. Et_2O (50 mL) was added, and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with H_2O (3 x 10 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (6:4) to yield 0.99 g (52%) of **7a**, mp: 140 °C.

Cyclization of 2-(2,5-Dimethylbenzoyl)benzoic Acid (6a) to Anthraquinone 7a
To **6a**[14] (1.02 g, 4.0 mmol) in 10 mL of solvent (Table 2) was added CF_3SO_3H (Table 2), and the reaction mixture was heated to reflux for the times given in Table 2. (Due to the small batch size, molecular sieves for H_2O removal were not necessary.) After being cooled to r.t., CH_2Cl_2 was added, the reaction mixture was poured into aqueous 2 N KOH (10 mL) and stirred for a further 6 h. Et_2O (50 mL) was added, and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were washed with H_2O (3 x 10 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was recrystallized from EtOH.

Following of the Cyclization of 6a to 7a
A solution of **6a** (284 g, 1.12 mol) and CF_3SO_3H (16.81 g, 0.11 mol) in DCE (1.25 L) was heated to reflux. After 48 h, a dropping funnel filled with molecular sieve 4 Å and equipped with reflux condenser was used for H_2O removal. At given time intervals samples of the reaction mixture (1 mL) were taken, worked up as described above, and the amount of **7a** and unreacted **6a** were determined.

Cyclization of 2-(4-*tert*-Butylbenzoyl)benzoic Acid (6b) to 2-*tert*-Butylanthraquinone (7b)
To **6b** (10.53 g, 37.3 mmol) in chlorobenzene (35 mL) (in an apparatus described above with molecular sieve 4 Å for H_2O removal) was added CF_3SO_3H (0.55 g, 3.65 mmol), and the reaction mixture was heated under reflux for 72 h. Workup was performed as described above for acylation of **4**. The crude product was chromatographed on silica gel with petroleum ether/CH_2Cl_2 (7:3) to yield a mixture of **7b** and 2-(4-chlorobenzoyl)-4-*tert*-butylbenzophenone (**8**) in a ratio 2:1. Crystallization from EtOH gave 1.67 g (17%) of **7b** with 99% GC purity; mp: 103 °C (Lit.[11] mp: 104 °C).

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