Application of the Catalytic Friedel–Crafts Acylation Reaction and Regioselectivity Correlations

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Abstract: A correlation was found between electronic properties and regioselectivity in the Friedel–Crafts reaction of substituted phenylacetic and benzoic acids with anisole, utilising substoichiometric (down to 1 mol%) amounts of catalyst. Relative reactivities of selected catalysts for this reaction were also studied.

Key words: catalysis, substituent effects, regioselectivity, Friedel– Crafts reaction, acylations

Recently we became interested in the Friedel–Crafts reaction between methylsulfonylphenylacetic acid **1** and phenetole **2**. This was achieved via formation of the acid chloride, but required 1.9 equivalents of $AlCl_3$ as catalyst to achieve good rates of reaction. The yield was compromised by production of significant amounts (15–20%) of the regioisomeric *ortho*-substituted product **4** (Scheme 1).



 $Scheme \ 1 \quad \ \ AlCl_3-catalysed \ acid \ chloride \ Friedel-Crafts \ reaction.$

As our scale of production increased, we were required to dispose of correspondingly large quantities of aluminium waste. Seeking to reduce this waste, we became interested in literature reports of the Friedel–Crafts reaction of

mixed anhydrides of trifluoroacetic acid, which could potentially be catalysed by substoichiometric levels of reagent. Table 1 details representative previous examples. It should be noted that none of the corresponding *ortho*regioisomer was reported in these examples.

To investigate the utility of this catalytic Friedel–Crafts reaction of TFA anhydrides, we screened our desired substrates with a diverse range of Lewis and Brønsted acids.⁵ Good reaction rates were achieved with metal triflates, $BF_3 \cdot OEt_2$, phosphoric and triflic acids (1–2 mol%). However, whilst all substantially favored the desired para-isomer, the levels of regioselectivity were all broadly similar with the exception of $BF_3 \cdot OEt_2$, which was clearly the most selective catalyst screened. This observation was applied as shown below to give *para*-product 3 in up to 90% isolated yield (the remainder being predominantly ortho-product), with only a 10 minutes reaction time (Scheme 2). We also took the opportunity to avoid the use of a chlorinated solvent, and changed to phenetole as both reagent and solvent (7 volumes relative to 1 input weight, 12 equiv).



Scheme 2 BF₃-catalysed mixed anhydride Friedel–Crafts reaction.

Table 1 Representative Literature Results

1					
Entry	Acid	Ar	Conditions	Catalyst	Yield (%)
1	Phenyl acetic	Anisole	TFAA ^a (4 equiv), r.t., 1 min	H_3PO_4 (1.2 equiv)	80 ¹
2	Phenyl acetic	Toluene	TFAA (4 equiv), r.t., 1 min	H_3PO_4 (1.2 equiv)	40 ¹
3	Benzoic	Anisole	TFAA (1.5 equiv), 30 °C, 12 h	$Bi(OTf)_3(3.3 \text{ mol}\%)$	98 ²
4	Benzoic	Anisole	TFAA (1.5 equiv), r.t., 2.5 h	AlPW ₁₂ O ₄₀ (1.5 mol%)	96 ³
5	Benzoic	Anisole	TFAA (1.5 equiv), r.t., 10 min	Al ₂ O ₃ (1000 wt%)	80^{4}

^a TFAA = trifluoroacetic anhydride.

SYNLETT 2006, No. 7, pp 1063–1066 Advanced online publication: 24.04.2006 DOI: 10.1055/s-2006-939705; Art ID: D00506ST © Georg Thieme Verlag Stuttgart · New York Whilst this result was pleasing and met our short-term needs by vastly reducing the amount of costly metal waste that required disposal, the inferior regioselectivity exhibited by this reaction relative to the literature was still puzzling. A survey of the related previous work revealed that as in Table 1, most publications did not report the generation of the *ortho*-product at all, and there was only one report where *ortho/para*-selectivity was inferior to that we obtained.²

The major difference between our substrate and the reported literature was the electron-withdrawing property of the sulfone. To probe this we examined the Friedel–Crafts reaction of a selection of *para*-substituted phenylacetic acids possessing a range of electron-withdrawing and donating substituents. Two catalysts were examined – BF_3 ·OEt₂ as before, and Bi(OTf)₃, to make a direct comparison with the previous literature (e.g. Table 1, entry 3). Anisole was chosen as the nucleophilic partner for these reactions to again facilitate comparison with the previous reports.

The selectivity was determined by ¹H NMR analysis of samples of crude reaction mixtures, and results were sorted in order of the Hammett σ value for the substituent, to probe a potential correlation with electronic properties. The results are reported in Table 2 (Scheme 3).

It can be seen that the results from our previous screening were borne out, with $BF_3 \cdot OEt_2$ being in general more selective than $Bi(OTf)_3$. A higher catalyst loading was

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Scheme 3 Screen of substituted phenylacetic acids.

required with Bi(OTf)₃ to achieve a comparable reaction rate. There is also a clear trend that selectivity increased with the electron-donating ability of the substituent. For example under BF₃ catalysis, $R = NO_2$ gave 8:1 *para* to *ortho* ratio (89% *para*), whereas R = OMe returned a ratio of 31:1 (97% *para*).

We next studied substituted benzoic acids, where the electronic properties of the substituent may be expected to exhibit a greater influence on the reacting carbonyl. These reactions were attempted under two reaction conditions – $Bi(OTf)_3$ in solely anisole, to make a direct comparison with our previous results, and reactions in an anisole–toluene mixture under BF₃ catalysis, which from the result in Table 2, entry 3 may be expected to exhibit increased selectivity (Scheme 4).

The trend of selectivity increasing with electron-donating ability was repeated in this series but in a more pronounced sense, as could be expected with the more direct mesomeric interactions possible in the benzoic series. Again BF_3 was in general the more selective catalyst.

 Table 2
 Selectivity Correlation for Reactions of Phenylacetic Acids

Entry	5	R =	$\sigma_p^{\ 6}$	$BF_3 \cdot OEt_2(1.7)$	$BF_3 \cdot OEt_2 (1.7 \text{ mol}\%)^a$		Bi(OTf) ₃ (3.3 mol%) ^a	
				<i>para</i> (%) ^b	Conversion (%) ^c (yield, %) ^d	para (%) ^b	Conversion (%) ^c	
1	а	NO ₂	0.78	89	61 (54)	83	91	
2	b	SO ₂ Me	0.73	89	96 (82)	86	95	
3	b ^e	SO ₂ Me	0.73	92	(71)	_	_	
4	c	CF ₃	0.54	97	84	80	26	
5	d	OCF ₃	0.35	96	84	94	70	
6	e	Cl	0.23	95	58 (55)	90	49	
7	f	Br	0.23	96	49	98	70	
8	g	F	0.06	95	84	99	64	
9	h	SMe	0.00	95	45	91	23	
10	i	<i>i</i> -Pr	-0.15	97	58	96	49	
11	j	Me	-0.17	96	88	96	48	
12	k	OMe	-0.27	97	63	93	45	

^a Reaction performed in anisole (7 volumes relative to 1 input weight, 14 equiv) at 80 °C, except where noted.

^b Determined by ¹H NMR ratio of *ortho/para*-products.

^c Conversion of **5a-k** to *ortho-* and *para-*products by HPLC.

^d Isolated yield of analytically pure material.

^e Reaction performed in 2 volumes anisole, 5 volumes toluene at 80 °C.



Scheme 4 Screen of substituted benzoic acids.

Next we sought relative rate data from across a range of available catalysts. This proved challenging with anisole as the nucleophile. At 80 °C the reactions were complete in approximately 10 minutes, making accurate profiling difficult. Reducing the temperature resulted in the product crystallizing from solution, preventing representative sampling from a homogeneous solution. Thus for the relative rate study we chose toluene as the reagent and solvent. This less electron-rich nucleophile allowed the reaction to proceed over 1–2 hours, and more reliable data to be acquired. The results are shown in Figure 1 for the five catalysts screened – $BF_3 \cdot OEt_2$, $Bi(OTf)_3$, TMSOTf, Yb(OTf)_3, and TfOH (see also Scheme 5).

It appears that for the reaction with toluene, $Bi(OTf)_3$ gave faster reactions than $BF_3 \cdot OEt_2$, and was in general the most active catalyst. However, analysis of the HPLC profiles of these reactions revealed a significant difference in their progression compared to the reaction profile with anisole. A new species was generated under all conditions in varying amounts (ca. 2–14 mol%), which disappeared as the reaction ran towards completion, to leave virtually



Scheme 5 Relative rate screening of catalysts for toluene reaction.



Figure 1 Relative rates for Scheme 5 under a range of catalysts.

exclusively the desired product **11**. LCMS analysis of this intermediate species indicated m/z of 484, which equates to the mass of **11** plus an additional acyl fragment. This piece of evidence, together with the fact that this species appeared to go on to give product with no detectable by-product lead us to postulate that this transient species may be the enol acetate **13** (Scheme 6).

Entry	8	R =	σ_{p}^{6}	$BF_3 \cdot OEt_2$ (1.7	BF ₃ ·OEt ₂ (1.7 mol%) ^a		Bi(OTf) ₃ (3.3 mol%) ^e	
				para (%) ^b	Conversion (%) ^c (yield, %) ^d	para (%) ^b	Conversion (%) ^c	
1	а	NO ₂	0.78	83	68	83	80	
2	b	SO ₂ Me	0.73	83	87 (72)	86	72	
3	c	CF ₃	0.54	88	97	86	81	
4	d	OCF ₃	0.35	94	81	90	98	
5	e	Cl	0.23	94	94	91	82	
6	f	Br	0.23	95	85	91	85	
7	g	F	0.06	95	97	92	88	
8	h	SMe	0.00	99	94 (49)	97	86	
9	i	<i>i</i> -Pr	-0.15	98	76	97	64	
10	j	Me	-0.17	97	88	96	82	
11	k	OMe	-0.27	99	78	99	85	

Table 3 Selectivity Correlation for Reactions of Benzoic Acids

^a Reaction performed in 2 volumes anisole, 5 volumes toluene at 80 °C.

^b Determined by ¹H NMR ratio of *ortho/para-*products.

^c Conversion of 8a-k to ortho- and para-products by HPLC.

^d Isolated yield of analytically pure material.

^e Reactions performed in 7 volumes anisole at 80 °C.



Scheme 6 Formation and reaction of postulated enol acetate.

Spectroscopic evidence (¹H NMR) was used to further support this hypothesis. Analysis of the reaction mixture at the mid point of the reaction showed olefinic signals at ca. $\delta = 6.6$ ppm which were entirely absent when the reaction had run to completion. Similar enol acetates have been reported as impurities in previous work.¹

It is interesting that the analogous enol acetate is not formed to the same degree during reactions with anisole. Presumably, the degree of enol acetate formation reflects the difference in the kinetics of mixed anhydride reacting with either solvent or initially formed product, with the difference being accounted for by the reduction in nucleophilicity moving from anisole to toluene. Thus, reaction of mixed anhydride with the initially formed product is favored in toluene over reaction with solvent.

Upon complete consumption of the starting material **5b** and intermediate **13**, the reaction catalysed by triflic acid was crystallized with IMS to give an 83% isolated yield. The reaction catalysed by $Yb(OTf)_3$ was isolated in an analogous fashion to give an 81% yield.

In conclusion we have demonstrated a correlation between electronic properties of the acid component and regioselectivity in the substoichiometrically catalysed Friedel–Crafts acylation. We have applied this reaction to an improved preparation of a pharmaceutical intermediate with considerable reduction in resultant waste. To a slurry of 4-(methylsulfonyl)phenylacetic acid 1 (5 g, 1 wt) in toluene (35 mL, 7 vol) was added TFAA (6.39 mL, 2 equiv) and the solution heated to 80 °C. After 60 min, 3 mol% catalyst (TfOH in this example) were added, and the solution was stirred at 80 °C until complete by HPLC analysis (100 min). Industrial methylated spirit (IMS, 35 mL, 7 vol) was added over 20 min, effecting crystallisation. The slurry was held at reflux for 1 h, cooled to 20-25 °C over 60 min, then chilled to 0-5 °C. The slurry was stirred for 60 min then filtered. The solids were washed with IMS $(2 \times 2 \text{ vol})$ and dried in vacuo at 50-60 °C to give 2-[4-(methylsulfonyl)phenyl]-1-ptolylethanone 11 as a cream white crystalline solid (5.60 g, 83%). IR: 3023, 3002, 2924, 1934, 1683, 1294, 1144 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 2.43 (3 H, s), 3.05 (3 H, s), 4.38 (2 H, s), 7.30 (2 H, d, J = 8 Hz), 7.47 (2 H, d, J = 8 Hz), 7.90 (2 H, d, J = 2 Hz), 7.92 (2 H, d, J = 2 Hz). ¹³C NMR (100 MHz, CDCl₃): $\delta = 21.74, 44.61,$ 44.97, 127.68, 128.63, 129.57, 130.72, 133.72, 139.07, 141.15, 144.72, 195.92. LCMS (ES⁺): m/z (%) = 289 (100) [M + H]⁺. HRMS: m/z calcd for C₁₆H₁₇O₃S: 289.0898 ($\Delta M = 5.0$ ppm); found: 289.0913 [M + H]+.

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