Mandelic Acid as Synthetic Equivalent of Benzoyl Carbanion. Synthesis of Nitrobenzophenones

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Abstract: Nitrobenzophenones are prepared from a mandelic acid dioxolanone. The sequence starts with the aromatic nucleophilic substitution of the enolate of the dioxolanone onto *p*-fluoronitrobenzenes, followed by hydrolysis of the acetal moiety and oxidative decarboxylation of the resulting α-hydroxyacids. The whole sequence involves the use of mandelic acid as synthetic equivalent of the benzoyl carbanion.

Key words: acetals, nucleophilic aromatic substitutions, ketones, oxygen, oxidations, decarboxylation

The presence of the benzophenone scaffold in the framework of natural and synthetic compounds with important physiological activities, such as antimalaria,[1] antiinflammatory,[2] anticancer[3] or antibiotic,[4] continues to spur synthetic efforts regarding their preparation.[5] Most of the classical synthetic protocols for benzophenones involve Friedel–Crafts benzoylations between an aromatic substrate and an electrophilic reagent. These reactions are catalysed by acidic catalysts (generally used in excess of molar amounts) and do not proceed successfully with aromatic substrates having electron-withdrawing groups.[6] An alternative route involves the substitution on the arene by the action of an appropriate nucleophilic species. Recently, we have reported the use of different mandelic acid derivatives as synthetic equivalents of benzoyl carbanion.[7] In this communication we describe a new application of this strategy in the synthesis of benzophenones **5**. Our synthesis started with aromatic nucleophilic substitution of the enolate of (*S*,*S*)-dioxolanone (**1**) onto aromatic nitro compounds **2**, followed by hydrolysis of the acetal moiety present in **3** and oxidative decarboxylation of the resulting *bis*-aryl-α-hydroxyacids **4** (Scheme 1).

Aromatic nucleophilic substitution with carbanions can be achieved by a number of procedures, such as the nucleophilic substitution to arene-transition metal carbonyl complexes,[8] transition metal catalysed aromatic nucleophilic substitution of aryl halides,[9] and aromatic substitution via nucleophilic addition to electron-deficient arenes (including vicarious[10] and *ipso*[11]).

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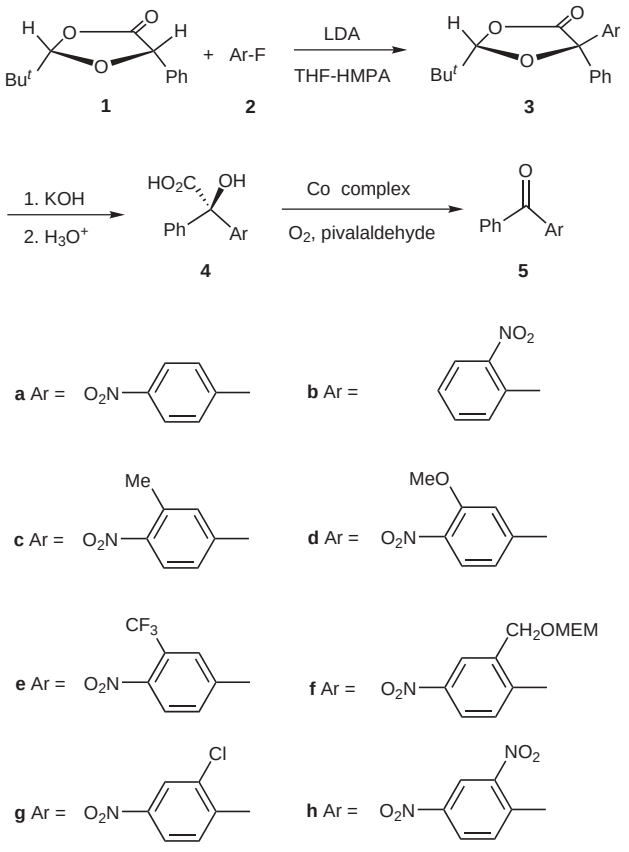
The starting materials in our synthesis were commercially available aromatic nitrocompounds having a leaving group in either the *ortho* or *para* position with respect to the nitro group.

The aromatic nucleophilic substitution was first tested with *p*-halonitrobenzenes in order to optimise the reaction conditions (Scheme 2, Table 1). Compound **1** was deprotonated with a LDA solution at –78 °C in THF, and then *p*-chloronitrobenzene **2a** (X = Cl) was added to the resulting enolate solution. Under these conditions none of the expected product was obtained (entry 1). Instead, compound **6** was obtained in 40% yield and 30% of the starting material was recovered. Compound **6** is the aldol product of dioxolanone (**1**) and pivalaldehyde. The presence of pivalaldehyde in the reaction mixture is not completely clear, but since formation of compound **6** is only



Scheme 1

Table 1 Reaction of 1,3-Dioxolan-4-one (**1**) with *p*-Halonitrobenzenes **2a**

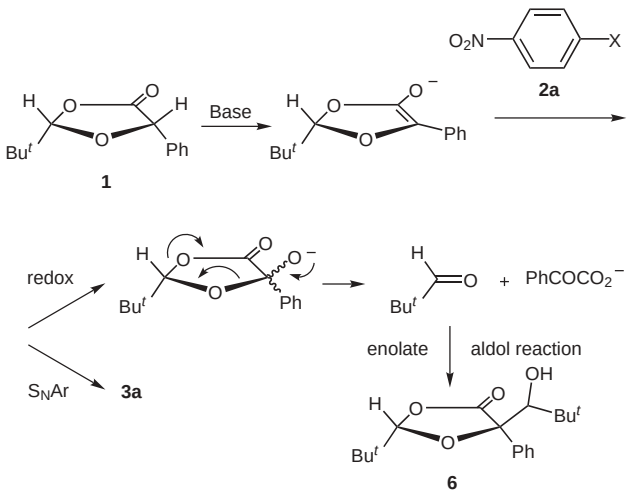
Entry	**2a** (X)	Solvent	Additive	Base	**3a** (Yield)	**6** (Yield)
1	Cl	THF	–	LDA		40% (30%)[a]
2	Cl	THF	HMPA (3 equiv)	LDA	30%	40%
3	F	THF	HMPA (3 equiv)	LDA	85%	
4	Br	THF	HMPA (3 equiv)	LDA	27%	30%
5	F	THF	HMPA (3 equiv)	*t*-BuLi	50%	
6	F	THF		NaHMDS	–[b]	
7	F	DMF		NaH	35%	

[a] Recovered **1** in brackets.
[b] Enolate decomposition.

observed after the addition of the nitrocompound, we believe that it most likely results from a redox process between the enolate of **1** and the nitro group,[11b,12] which would take place faster than the addition of the enolate to the aromatic ring (Scheme 2). As a matter of fact, the use of 3 equivalents of HMPA, an additive that increases the reactivity of enolates toward nucleophilic substitution,[13] allowed to obtain the desired product **3a** in 30% yield, although accompanied with 40% of **6** (entry 2). The formation of compound **6** could be prevented only when *p*-fluoronitrobenzene **2a** (X = F) was used as arylating reagent (entry 3) while the use of *p*-bromonitrobenzene **2a** (X = Br) did not provide satisfactory results (entry 4).

The use of *tert*-butyllithium instead of LDA gave poorer results. Sodium bases gave also disappointing results. Thus, NaHDMS in THF (entry 6) brought about decomposition of the enolate, even at –78 °C, while the combination NaH–DMF[11b] (entry 7) gave low yields of the expected product. It was also observed the tendency of compound **3a** to decompose upon prolonged reaction times or higher temperatures. Accordingly, a short reaction time (5–10 min) and quenching at –78 °C was established as the best experimental protocol. *p*-Cyano- and *p*-trifluoromethyl fluorobenzenes were also tested as arylating reagents. However none of these electron-withdrawing groups was able to induce nucleophilic substitution with the enolate of **1** under the optimised conditions (LDA–THF–HMPA).

The nucleophilic aromatic substitution reaction with the enolate of **1** was carried out with a number of fluoronitrobenzenes **2** under similar conditions (Table 2). In the case of *o*-fluoronitrobenzene (**2b**) (entry 2) the reaction proceeded but only with modest yield. Therefore we centered our study with *p*-substituted fluoronitrobenzenes. The presence of an additional group on the aromatic ring was also studied. When this group was in *meta* position respect the fluorine atom, the reaction worked well regardless of its electronic nature. Thus, fair to good yields of the corresponding compounds **3** were obtained with 2-methyl-4-fluoronitrobenzene (entry 3), 2-methoxy-4-fluoronitrobenzene (entry 4) and 2-trifluoromethyl-4-fluoronitrobenzene (entry 5). The reaction was also carried out with *p*-fluoronitrobenzenes substituted in the *ortho* position with respect the fluorine atom in order to determine possible steric effects (entries 6–8). Again, the reaction proceeded readily in all the cases, including the bulky MEM-protected benzyl alcohol group (entry 6), without much influence of the electron-donating (entries 6 and 7) or electron-withdrawing (entry 8) features of the additional substituent.



Scheme 2

Although irrelevant for the synthesis of benzophenones, it is worth remarking that the nucleophilic aromatic substitution reaction here described is completely diastereoselective, the nitro aromatic ring being exclusively introduced *anti* to the *t*-butyl group of the dioxolanone ring.[16]

The next step in the synthetic sequence was the cleavage of the acetal moiety, which was achieved upon basic hydrolysis with ethanolic KOH and reprotonation to give the corresponding hydroxyacids **4**, with good yields. In the case of the dinitroderivative **3h**, benzophenone **5h** was

Table 2 Synthesis of Nitrobenzophenones **5** from Dioxolanone (**1**) and Fluoronitrobenzenes **2**

Entry	**2** (X = F)	**3** (Yield)	**4** (Yield)	**5** (Yield)
1	**2a**	85%	94%	82%[a]
2	**2b**	37%	78%	90%[a]
3	**2c**	82%	87%	87%[b]
4	**2d**	75%	93%	80%[b]
5	**2e**	75%	64%	95%
6	**2f**	80%	80%	65%
7	**2g**	66%	81%	91%
8	**2h**	90%	–	63%[c,d]

[a] Identical to a commercially available sample.
[b] Ref.[14]
[c] Ref.[15]
[d] Product obtained during hydrolysis of **3h**.

directly obtained from the reaction mixture. In this case, the presence of two strongly electron-withdrawing nitro groups facilitates decarboxylation of the α-hydroxyacid **4h** because of mesomeric stabilisation by the nitro groups at *ortho* and *para* positions of the resulting hydroxybenzyl carbanion, which is then oxidised by oxygen to ketone **5h** under the hydrolysis conditions.[11c,17]

For the decarboxylation of the rest of the hydroxyacids **4** we used a catalytic system developed in our laboratory which employs oxygen as terminal oxidant in the presence of pivalaldehyde and a catalytic amount of a Co(III) complex **7** (Figure 1).[7] Under these conditions, benzophenones **5** were obtained with good yields from hydroxyacids **4**.

In summary, we present here a new method for the synthesis of nitrobenzophenones. The overall sequence eventually involves mandelic acid as an 'umpoled' equivalent of the benzoyl anion, and it is an alternative to the electrophilic Friedel–Crafts benzoylation of electron-deficient nitrobenzenes which normally does not work well. It is also convenient to note that, unlike in the Friedel–Craft reaction, in this case the carbonyl group is provided by the nucleophilic component of the reaction.

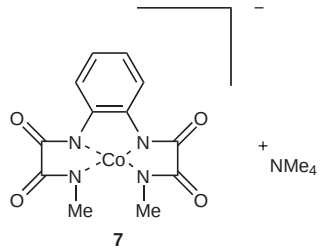


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Figure 1

Nucleophilic Substitution.[18] A solution of dioxolanone (*S,S*)-**1**[16a] (220 mg, 1 mmol) in 1.5 mL of dry THF was added to a –78 °C precooled solution prepared from 0.625 mL of a 2 M commercial solution of LDA in heptane–THF–ethylbenzene (1.25 mmol), 0.56 mL of HMPA (3 mmol) and 4 mL of THF. After 30 min, a solution of *p*-fluoronitrobenzene (**2a**, 0.133 mL, 1.25 mmol) in 0.5 mL of THF was added dropwise, and 10 min after, the reaction was quenched with the addition of 2–3 drops of H_2O and silica gel. Once the mixture reached r.t., the solvent was removed and the resulting powder chromatographed on silica gel to give compound **3a** (291 mg, 85%): oil; $[\alpha]_D^{25}$ +44.1 (*c* 2.60, $CHCl_3$). MS (EI): *m/z* (%) = 297 (100) [$M^+ - CO_2$], 280 (30), 228 (48), 211 (58), 165 (58). HRMS found 297.1374, $C_{18}H_{19}NO_3$ required 297.1365. ^{1}H NMR ($CDCl_3$): δ = 1.00 (9 H, s), 5.13 (1 H, s), 7.27 (3 H, m), 7.36 (2 H, m), 7.72 (2 H, d, *J* = 9.0 Hz), 8.17 (2 H, d, *J* = 9.0 Hz). ^{13}C NMR ($CDCl_3$): δ = 23.6 (q), 34.0 (s), 83.7 (s), 108.3 (d), 124.1 (d), 126.3 (d), 127.5 (d), 128.7 (d), 129.0 (d), 137.8 (s), 143.8 (s), 148.2 (s), 171.1 (s).

Cleavage of the Acetal Moiety.[18] Compound **3a** (170 mg, 0.5 mmol) was treated with 5% ethanolic KOH (1.1 mL, 1 mmol) at r.t. until complete reaction of the starting material (TLC). The solution was poured into ice and acidified with 1 M HCl until pH = 2. The aqueous mixture was extracted with EtOAc, the organic layers washed with brine, dried, filtered and concentrated under reduced pressure to give compound **4a** (128 mg, 94%): oil; $[\alpha]_D^{25}$ –45.6 (*c* 0.84, MeOH). MS (EI): *m/z* (%) = 227 (25) [$M^+ - CO_2H_2$], 197 (12), 150 (7). HRMS found 227.0566, $C_{13}H_9NO_3$ required 227.0582. ^{1}H NMR ($CDCl_3$): δ = 7.10 (2 H, br s), 7.37 (5 H, br s), 7.66 (2 H, d, *J* = 8.5 Hz), 8.14 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$): δ = 80.7 (s), 123.2 (d), 126.9 (d), 128.6 (d), 128.7 (d), 129.0 (d), 140.6 (s), 147.7 (s), 147.8 (s), 176.9 (s).

Oxidative Decarboxylation of α-Hydroxyacids.[18] A solution of α-hydroxyacid **4a** (60 mg, 0.22 mmol), Co(III) complex **7** (5.3 mg, 0.013 mmol) and pivalaldehyde (74 μL, 0.66 mmol) in 0.9 mL of acetonitrile was stirred under an oxygen atmosphere until consumption of the α-hydroxyacid **4a** as indicated by TLC. Water was added, the mixture extracted with Et_2O, and the organic layer washed with brine and dried. The reaction products were purified by flash chromatography to give nitrobenzophenones **5a** (40 mg, 82%): oil; MS (EI): *m/z* (%) = 227 (63) [M^+], 150 (15), 105 (100). HRMS found 227.0527, $C_{13}H_9NO_3$ required 227.0582. ^{1}H NMR ($CDCl_3$) δ = 7.51 (2 H, t, *J* = 8.0 Hz), 7.64 (1 H, t, *J* = 8.0 Hz), 7.78 (2 H, d, *J* = 8.0 Hz), 7.91 (2 H, d, *J* = 8.5 Hz), 8.31 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ = 123.5 (d), 128.7 (d), 130.1 (d), 130.7 (d), 133.5 (d), 136.3 (s), 142.9 (s), 149.8 (s), 194.8 (s).

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