Acid-Catalyzed Air-Oxidative Fragmentation of the Carbon–Carbon Bond in 2-Aryl-1-tetralones

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ABSTRACT: Catalytic auto-oxidation with air is a highly desirable method for green synthesis. Described here is a method for acid-catalyzed one step air-oxidative fragmentation of 2-aryl-1-tetralones to alkyl-2-(3-oxo-3-aryl) benzoates in the presence of alcohol. This method was then demonstrated using concise synthesis of a key intermediate of antiasthma drug Montelukast sodium. Moreover, the paradoxical nature of the reaction in which ester forms but only within a low concentration threshold of alcohol helps in understanding the mechanism of the reaction.

INTRODUCTION

Fragmentation reactions are highly efficient in building molecular complexity from simpler molecular assembly. These aesthetically pleasing reactions are efficient by virtue of their high atom economy and step minimization potential in a synthetic sequence. On the other hand, auto-oxidation reaction is used as the green synthetic method in which air oxygen is a renewable oxidant. Hence, the synthetic method involving auto-oxidative fragmentation is highly desirable for efficient green synthesis. O₂ is widely used as economic and environment-friendly oxidant in the production of bulk chemical from simpler petroleum-derived hydrocarbons. However, because of lack of selectivity and control, O₂ is not commonly used as oxidant in chemical laboratory and pharmaceutical industry. It is known that carbonyl compounds undergo auto-oxidation under basic conditions to form α-hydroperoxides, which undergo C–C bond cleavage in both acidic and alkaline condition. Ishikawa et al. while reporting aryl migration in air oxidation of 2-aryl-1-tetralone also mentioned few examples in which the fragmentation product was obtained, most notably 2-phenyl-1-tetralone 1 was converted to benzoic acid derivative 2 as sole product in the presence of the TsOH catalyst (Scheme 1).

The abovementioned one step reaction slowly proceeded to form a diarylpropane framework without any sensitizer, light or pure oxygen. Intrigued by these reported findings, and because of the absence of further reports in the literature for this transformation, a study was conducted to find out the synthetic scope for acid-catalyzed air-oxidative fragmentation of 2-aryl-1-tetralones, which were easily accessed from 1-tetralone via palladium-catalyzed α-arylation methods.

RESULTS AND DISCUSSION

Reaction optimization with 1 under various conditions was performed which is summarized in Table 1. When the reaction was performed in toluene at 80 °C the reaction was complete within 72 h and the benzoic acid derivative 2 formed in 88% yield. Temperature of 80 °C in toluene was found to be optimum as increasing (entry 2) or decreasing (entry 3) reaction temperature, the reaction became slower and yield went down. The reaction also proceeded in tetrahydrofuran (THF) with good yield. Trifluoroacetyl in toluene and HCl in THF also catalyze the conversion with good yield. When relatively weak acetic acid was used as solvent, the reaction proceeded but with only 38% yield of 2 (other byproducts formed was not characterized). No reaction was observed when the reaction was run either in methanol or in mixed solvents of 10% (v/v) of methanol in THF (entry 9) and 10% (v/v) of methanol in toluene (entry 10). Interestingly, when 5% (v/v) methanol in toluene was used as solvent, low yield of methyl ester product 3a instead of 2 was obtained. This result prompted to run the reaction in even lower alcohol concentration in toluene. Accordingly, reaction was run in 2% (v/v) methanol and surprisingly within 8 h starting ketone 2 was consumed completely and 3a formed in 90% yield. Further lowering of methanol concentration resulted incomplete reaction (data not shown). On the other hand switching...
Table 1. Optimization of Acid-Catalyzed Auto-Oxidative Fragmentation of 2-Phenyl-1-tetralone

| entry | solvent 𝑎 | catalyst | temp (°C) | time | product | % yield |
|-------|-----------|----------|-----------|------|---------|---------|
| 1     | toluene   | TsOH·H2O (0.3 equiv) | 80       | 72 h | 2       | 88      |
| 2     | toluene   | 10% (v/v) MeOH in toluene | 100      | 5 d  | 2       | 36      |
| 3     | toluene   | TsOH·H2O (0.3 equiv) | 70       | 5 d  | 2       | 52      |
| 4     | THF       | TFA (1.0 equiv) | 65       | 72 h | 2       | 82      |
| 5     | toluene   | conc HCl (0.3 equiv) | 65       | 72 h | 2       | 75      |
| 6     | THF       | acetic acid | 65       | 72 h | 2       | 78      |
| 7     | acetic acid | acetic acid | 80       | 48 h | 2       | 38      |
| 8     | MeOH      | TsOH·H2O (0.3 equiv) | 65       | 48 h | no reaction |
| 9     | 10% (v/v) MeOH in THF | 65 | 48 h | no reaction |
| 10    | 10% (v/v) MeOH in toluene | 70 | 48 h | no reaction |
| 11    | 5% (v/v) MeOH in toluene | 70 | 48 h | 3a | 15 |
| 12    | 2% (v/v) MeOH in toluene | 70 | 8 h | 3a | 90 |
| 13    | 2% (v/v) MeOH in THF | 65 | 8 h | no reaction |
| 14    | 2% (v/v) EtOH in toluene | 70 | 16 h | 3b | 80 |
| 15    | 2% iPrOH in toluene | 70 | 24 h | 2 | 22 |

*All reactions were run with 0.05 molar concentration of starting ketone. *aReactions were heated in silicon oil bath, temperatures mentioned are oil bath temperatures. *bYields reported are isolated yield. *cNo significant Pr ester product was observed.

to ethanol the ethyl ester 3b formed in good yield even though reaction took longer time. However, switching to bulkier 2-propanol, no isopropyl ester was observed after prolonged reaction time instead low yield of 2 was obtained. The latter result indicates of steric constrains of alcohol for the transformation. When the reactions (entries 12 and 15) were run in the dark no significant change in yield observed (data not shown).

Optimization results in Table 1 suggest that alcohol concentration beyond a threshold inhibits the reaction and such threshold concentration may vary in different solvents. Further screening of the catalyst and solvent with varying alcohol ratio would be synthetically useful. However, with good yield obtained in toluene, TsOH combination within limited screening, focus of this study was shifted to the aromatic group for the new transformation. Thus reaction was carried out on α-aryl tetralones with varying electronic nature of the α-aryl group, summarized in Table 2.

All the reactions were performed in 2% (v/v) of methanol in toluene. It was generally observed that electron-donating substituent increases the reaction rate while rate decreases with the electron-deficient aryl group. Thus, reaction time is relatively longer in ortho and para tolyl compounds (entries 1 and 2) compared to 1 (Table 1, entry 12), whereas with para methoxy compound, reaction became faster, but lower yield was obtained (entry 3). Reaction also proceeded faster in case of α-naphthalene compound (entry 6). In contrast, slower reaction was observed in case of p-chloro, and 3-carboxy-aldehyde-substituted compounds (entries 4 and 7) even though good yields were obtained. The catalyst amount was increased to 1.3 equiv for the α-pyridine compound; as with 0.3 equiv of the catalyst, no reaction was observed (data not shown) probably because of basic nitrogen of pyridine (entry 5). Under the reaction condition, the acetal group of compound 4h also hydrolyzed to give product 5g (entry 8). Interestingly, when the reaction with 4h was performed without methanol, a small amount of 5g was obtained along with mostly 4g (entry 9).

This indicates that methanol generated from the hydrolysis of acetal is enough to form the ester product.

The generality of the abovementioned method was demonstrated in three step synthesis of a key intermediate 11 toward synthesis of Montelukast sodium, a selective LTD4 antagonist, used for the treatment of asthma.11 3-bromobencilaldehyde 6 was condensed with 7-chloroquinidine 7 in acetic anhydride to get 8 with 92% yield. Palladium-catalyzed coupling of 8 with 1-tetralone gave α-aryl product 10, which readily underwent oxidative fragmentation to form methyl benzoate product 11 in 82% yield.12 Alternatively, product 11 was also obtained via condensation of aldehyde 5g (from entry 7, Table 2) with 7-chloroquinaldine 7 in acetic acid albeit in moderate 58% yield (Scheme 2).

Air oxidation of 2-aryl-1-tetralone in the absence of light or sensitizer indicates that triplet oxygen (3O2) rather than singlet oxygen (1O2) is the actual oxidizing agent.13 Recently, quantum chemical calculation on enol addition to triplet oxygen was found to be energetically possible via the formation of triplet diradical (stabilized by intramolecular H-bond) followed by intersystem crossing to the singlet state in the formation of α-hydroperoxide.14 Higher alcohol concentration would disrupt such intramolecular H-bonding and might be one possible reason for low concentration threshold found in this study. For conversion of hydroperoxide 12 to ester 3, two reaction paths can be plausible based on earlier literature report (Scheme 3).9

If the reaction follows cyclic path A, then first benzoic acid intermediate 2 would form en route to ester 3. However, high yield of ester formed in the reaction in the presence of low concentration of alcohol suggests that path A involving endoperoxide 13 is unlikely. In fact, when acid 2 was heated in 2% (v/v) methanol in toluene with 0.3 equiv TsOH. H2O for 8 h, no significant amount (<5%) of ester 3 was obtained (data not shown). This together with result from Table 2 (entry 9) suggests the reaction mechanism is acyclic one (path...
Table 2. Auto-Oxidative Fragmentation of 2-Aryl-1-tetralones to Methyl-2-(3-oxo-3-aryl) Benzoates

| Entry | 4 (Ar) | Reaction Time | Products (yield in %) |
|-------|--------|---------------|-----------------------|
| 1     | 4a (Me) | 6 h           | 5a (82%)              |
| 2     | 4b (Me) | 6 h           | 5b (84%)              |
| 3     | 4c (OMe) | 6 h         | 5c (71%)              |
| 4     | 4d (Cl) | 10 h          | 5d (84%)              |
| 5     | 4e (N)  | 6 h           | 5e (82%)              |
| 6     | 4f (Cl) | 6 h           | 5f (85%)              |
| 7     | 4g (CHO) | 10 h      | 5g (81%)              |
| 8     | 4h (OMe) | 12 h         | 5g (81%)              |

*All the reactions were run with 0.05 M concentration of the starting 2-aryl-1-tetralone. *Yields reported are isolated yield. *1.3 equiv of the catalyst was used. *Reaction was run in toluene without MeOH, rest of the reaction mixture contained mostly aldehyde 4g.

B) in which addition of alcohol initially forms hemiacetal 14 which subsequently undergoes C–C bond cleavage to form 3.

### CONCLUSIONS

In conclusion, synthetic utility of novel acid-catalyzed auto-oxidative fragmentation combined with esterification of 2-aryl-1-tetralones have been demonstrated. The reaction condition is relatively mild and only air atmosphere is enough for auto-oxidation. The rate enhancement in the presence of small alcohol concentration not only makes the transformation synthetically more useful but also helps in understanding the mechanism of the reaction.

### EXPERIMENTAL SECTION

**General Information.** Starting materials, reagents, and solvents (dry) were purchased from commercial suppliers and used without further purifications. All reactions were conducted in oven-dried (110 °C) glassware. Progress of reactions was monitored by silica gel thin layer chromatography (TLC) plates (with fluorescent indicator), visualized under UV. Products were purified by flash column chromatography on 100–200 mesh silica gel. H NMR were recorded in Bruker 400 MHz (FT NMR) or Bruker 300 MHz (FT NMR) using tetramethylsilane as an internal reference. 13C NMR were recorded in Bruker 100 MHz (FT NMR) or Bruker 75 MHz (FT NMR). High-resolution mass spectra (HRMS) were measured on an Agilent quadrupole time-of-flight mass spectrometer instrument with an electrospray ionization (ESI) source. Melting points were uncorrected. The known 2-aryl-1-tetralones 1, 4a–f were prepared according to the previously reported protocols. The unknown 2-aryl-1-tetralones 4h, 10 were synthesized following the procedure reported by Palucki and Buchwald.

### General Procedure for the Synthesis of Methyl-2-(3-oxo-3-aryl) Benzoates 3a and 4.
To a solution of α-aryl tetralone (0.50 mmol) in toluene (10 mL) in a two neck round-bottom flask was added MeOH (0.2 mL) and TsOH·H2O (29 mg, 0.15 mmol). The reaction flask was then fitted with a condenser in one neck and air balloon on another neck. The reaction mixture was then heated at 70 °C and monitored by TLC. Upon completion of the reaction, the reaction was cooled to room temperature and to that sodium acetate (0.2
mmol) was added and stirred for 10 min. The reaction mixture was then diluted with ethyl acetate (50 mL) and washed with water (10 mL) and then brine (10 mL). Evaporation of solvent followed by column chromatography (silica gel with ethyl acetate/hexane as an eluent) gave the desired methyl-2-(3-oxo-3-aryl) benzoates.

2-(3-Oxo-3-phenyl-propyl)-benzoic Acid Ethyl Ester (3a). Yield 90% (120 mg); light yellow oil; \( R_f = 0.45 \) (10% EtOAc/hexane); \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.97 (1H, d, \( J = 8.2 \) Hz), 7.96 (1H, d, \( J = 8.2 \) Hz), 7.91 (1H, dd, \( J = 8.2, 1.3 \) Hz), 7.54–7.48 (1H, m), 7.45–7.37 (3H, m), 7.35–7.32 (1H, m), 7.28–7.22 (1H, m), 3.87 (3H, s), 3.36 (2H, t, \( J = 4.0 \) Hz), 3.34 (2H, t, \( J = 4.0 \) Hz); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 199.2, 167.6, 143.2, 136.8, 132.8, 131.1, 130.3, 130.7, 129.3, 128.4, 128.0, 126.2, 51.8, 40.4, 29.2; HRMS (ESI) \( m/z \): calcd for C\(_{18}\)H\(_{19}\)O\(_3\) \([(\text{M} + \text{H})^+]\)= 299.1283; found, 299.1274.

2-(3-Oxo-3-phenyl-propyl)-benzoic Acid Ethyl Ester (3b). The general procedure was followed, and ethanol was used instead of methanol. Yield 80% (113 mg); light yellow oil; \( R_f = 0.50 \) (10% EtOAc/hexane); \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.97 (1H, d, \( J = 8.0 \) Hz), 7.97 (1H, d, \( J = 8.2 \) Hz), 7.91 (1H, dd, \( J = 8.0, 1.3 \) Hz), 7.57–7.50 (1H, m), 7.47–7.38 (3H, m), 7.36–7.24 (2H, m), 4.35 (2H, q, \( J = 7.1 \) Hz), 3.36 (4H, s), 1.36 (3H, t, \( J = 7.1 \) Hz); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 199.3, 167.4, 143.0, 136.9, 132.0, 131.0, 130.7, 129.9, 128.5, 128.0, 126.2, 60.9, 40.6, 29.3, 14.2; HRMS (ESI) \( m/z \): calcd for C\(_{18}\)H\(_{19}\)O\(_3\) \([(\text{M} + \text{H})^+]\)= 293.1334; found, 283.1330; 2-(3-Oxo-3-p-toly-propyl)-benzoic Acid Ethyl Ester (5a). Yield 82% (116 mg); white solid; \( R_f = 0.45 \) (10% EtOAc/hexane); mp 61 °C; \( ^1H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.90 (1H, d, \( J = 7.6, 1.6 \) Hz), 7.62 (1H, d, \( J = 7.5 \) Hz), 7.45–7.15 (6H, m), 3.86 (3H, s), 3.40–3.20 (4H, m), 2.48 (3H, s); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 203.2, 167.6, 143.1, 137.9, 137.8, 132.1, 131.7, 131.2, 131.0, 129.7, 128.5, 128.3, 126.2, 125.5, 51.8, 43.2, 29.3, 21.1; HRMS (ESI) \( m/z \): calcd for C\(_{17}\)H\(_{18}\)O\(_2\) \([(\text{M} + \text{H})^+]\)= 283.1334; found, 283.1330.

2-(3-Oxo-3-p-toly-propyl)-benzoic Acid Ethyl Ester (5b). Yield 84% (118 mg); light yellow oil; \( R_f = 0.50 \) (10% EtOAc/hexane); \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.91 (1H, dd, \( J = 7.8, 1.2 \) Hz), 7.87 (2H, d, \( J = 8.2 \) Hz), 7.46–7.20 (5H, m), 3.88 (3H, s), 3.40–3.27 (4H, m), 2.39 (3H, s); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 198.9, 167.7, 143.5, 143.3, 134.3, 133.1, 131.3, 130.7, 129.3, 128.1, 126.1, 51.8, 40.3, 29.3, 21.4; HRMS (ESI) \( m/z \): calcd for C\(_{17}\)H\(_{18}\)O\(_2\) \([(\text{M} + \text{H})^+]\)= 277.1293; found, 283.1333.

2-[3-(4-Methoxy-phenyl)-3-oxo-propyl]-benzoic Acid Ethyl Ester (5c). Yield 71% (106 mg); viscous oil; \( R_f = 0.40 \) (10% EtOAc/hexane); \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.96 (2H, d, \( J = 9.0 \) Hz), 7.91 (1H, dd, \( J = 7.8, 1.2 \) Hz), 7.45–7.22 (3H, m), 6.91 (2H, d, \( J = 8.9 \) Hz), 3.89 (3H, s), 3.86 (3H, s), 3.39–3.25 (4H, m); \( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 198.0, 167.8, 163.4, 143.4, 132.2, 131.4, 130.8, 130.4, 130.0, 129.5, 126.2, 113.6, 55.4, 52.0, 40.2, 29.5; HRMS (ESI) \( m/z \): calcd for C\(_{17}\)H\(_{18}\)O\(_2\) \([(\text{M} + \text{H})^+]\)= 271.1253; found, 271.1274.

2-[3-(4-Chloro-phenyl)-3-oxo-propyl]-benzoic Acid Ethyl Ester (5d). Yield 84% (127 mg); viscous oil; \( R_f = 0.40 \) (10% EtOAc/hexane); \( ^1H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.88–7.97 (3H, m), 7.50–7.25 (5H, m), 3.89 (3H, s), 3.40–3.25 (4H, m); \( ^13C \) NMR (75 MHz, CDCl\(_3\)): \( \delta \) 198.2, 167.7, 143.1, 139.3, 135.2, 132.3, 131.4, 130.8, 129.5, 129.3, 128.8, 126.4, 52.0, 40.5, 29.4; HRMS (ESI) \( m/z \): calcd for C\(_{17}\)H\(_{17}\)ClO\(_3\) \([(\text{M} + \text{H})^+]\)= 303.0788; found, 303.0791.
2-(3-(3-Formyl-phenyl)-3-oxo-propyl)-benzoic Acid Methyl Ester (5g). It is prepared via the general procedure from 4g. Yield 81% (120 mg); light yellow oil; Rf = 0.45 (10% EtOAc/hexane); 1H NMR (400 MHz, CDCl3): δ 10.07 (1H, s), 8.47 (1H, br), 8.25 (1H, d, J = 7.8 Hz), 8.06 (1H, d, J = 7.8 Hz), 7.94 (1H, dd, J = 7.8, 1.2 Hz), 7.63 (1H, dd, J = 7.6, 7.6 Hz), 7.48–7.25 (3H, m), 3.90 (3H, s), 3.40 (4H, s); 13C NMR (100 MHz, CDCl3): δ 198.1, 191.3, 167.5, 142.7, 137.4, 136.4, 133.4, 133.0, 132.2, 131.3, 130.8, 129.4, 129.2, 129.1, 126.3, 51.8, 40.6, 29.1; HRMS (ESI) m/z: calcd for C18H17O4 ([M + H]+), 280.1171; found, 280.1171.

2-(3-(Bromo-phenyl)-vinyl)-7-chloroquinoline (8). To a solution of 3-bromobenzaldehyde (3.0 g, 16.2 mmol) in acetic anhydride (50 mL) was added 7-chloroquinoline (3.0 g, 16.9 mmol). The reaction mixture was stirred at 80 °C for 8 h. The reaction was then cooled to room temperature and water (5.0 mL) was added. The reaction solvent was evaporated under reduced pressure and the crude solid product was purified by column chromatography using 5% EtOAc in hexane as eluent. Yield 92% (5.08 g); light yellow solid; Rf = 0.60 (10% EtOAc/hexane); mp 126–136 °C; 1H NMR (400 MHz, CDCl3): δ 8.30 (1H, d, J = 8.5 Hz), 8.07 (1H, br), 7.20–7.15 (4H, m), 7.48–7.25 (3H, m), 3.90 (3H, s), 3.40 (4H, s); 13C NMR (100 MHz, CDCl3): δ 198.1, 191.3, 167.5, 142.7, 137.4, 136.4, 133.4, 133.0, 132.2, 131.3, 130.8, 129.4, 129.2, 129.1, 126.3, 51.8, 40.6, 29.1; HRMS (ESI) m/z: calcd for C18H17O4 ([M + H]+), 280.1171; found, 280.1171.

Notes
The author declares no competing financial interest.

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