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Preparation of phenyl-butyraldehydes using a base-catalyzed aromatization of dienones

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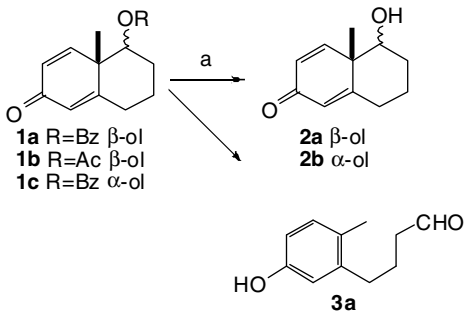
Abstract

Seven aldehydes were prepared using a five-step sequence synthesis. The synthetic strategy involved the use of a novel aromatization reaction of dienones. These key intermediates were prepared following a sequence involving BAR of substituted tetralones, ketones reduction, protection of alcohol, and bis-allylic oxidation. The key step of the route is an aromatization promoted by basic reaction conditions of dienones leading to substituted 4-phenyl butanals.

Arene transformation is still an important research area in organic chemistry and is continuously used as a key step in industrial synthesis. The controlled introduction of substituents and the carbon–carbon bond formation to arenes are of special interest and have many applications in the synthesis of complex molecules.[1] The Friedel–Crafts alkylation even now is the most important reaction to introduce substituents over the aromatic rings, but in general only exhibits moderate regioselectivity. Aryl butanals have been employed along the years for different synthetic applications. They were synthesized by hydroformilation of substituted allyl and propenyl benzene.[2,3] The possibility to form an aromatic ring during the course of a reaction guarantees its exothermicity. This property has been exploited in the oxidation of alicyclic rings producing aromatic or heteroaromatic rings. Recently different research groups have been studying aromatization reactions as a new tool in organic synthesis. Taking advantage of substrates that are susceptible to be aromatized, Walton's and Studer's groups have been using 1-functionalized 2,5-cyclohexadienes as radical precursors that undergo β-scission restoring the aromaticity of the ring.[4] Employing a similar approach, Linker has produced a two-step *ipso*-substitution over aromatic carboxylic acids by means of an acid-catalyzed aromatization.[5] It is also known that monocyclic enones derived from benzoic acid can be transformed into related 4-alkyl and carbalcoxiphenols by acid or basic catalysis.[6] To the best of our knowledge, there is no other application of basic aromatization reaction as a synthetic tool along with those examples.

During the course of our investigations on the applications of the Birch alkylation reaction (BAR) of α-tetralones we had previously found that the hydrolysis of benzoate **1a** produced as the only isolated product aldehyde **3a** instead of the expected alcohol **2a** (Scheme 1). With the purpose of



Scheme 1. Hydrolysis of the dienone ester. Reagents and condition: (a) K_2CO_3, MeOH, rt.

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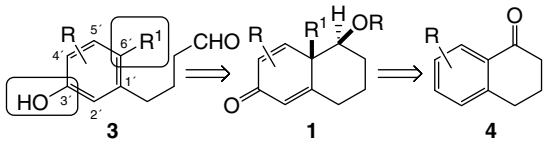


Scheme 2. Synthetic strategy.

studying the scope and limitations of this reaction we decided to test the product formation of acetate **1b** and also the α-benzoate **1c** to find out if the course of the reaction would be affected by the stereochemistry of the alcohol or the acyl group bonded to it. When enones **1b** and **1c** were submitted to hydrolysis under the same reaction conditions the only isolated product was aldehyde **3**, without any traces of alcohols **2a**–**b**, respectively (Scheme 1).

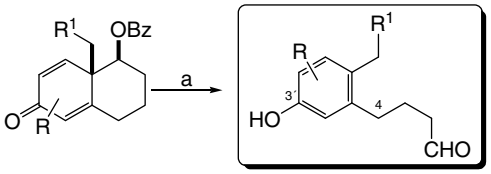
These results demonstrate unequivocally that the reaction product was independent of the nature of the acyl group and of the stereochemistry of the alcohol, as we initially assumed.

With these results in hand, we decided to extend our work on tetralones as synthetic precursors in organic synthesis,[7] using this aromatization reaction to prepare substituted 4-phenyl-butyraldehydes. The aromatization reaction would be used on dienones prepared from tetralones with different patterns of substitution over the aromatic ring. The retrosynthetic analysis of our strategy is shown in Scheme 2. This approach allowed the specific introduction of an alkyl chain and hydroxyl group on the positions 6′ and 3′ of the phenyl butanal, respectively.

To prepare dienones, we focused on the application of BAR on tetralones where the alkyl chain would be introduced followed by carbonyl reduction and protection as benzoate; finalizing by bis-allylic oxidation.

Having demonstrated that the stereochemistry of the alcohol does not affect the course of the aromatization, we selected the beta stereochemistry because sodium borohydride reduction provided better yields.[7a] Initially, substituents on the aromatic ring were introduced in the first reaction over tetralones **4a**–**g**, Scheme 3. The chosen alkylating reagents were methyl iodide, methoxy methyl chloride, and allyl bromide that will allow introducing chains with different degrees of oxidation susceptible to be transformed into alcohol, aldehyde, or acids. The BAR provided the expected diene with good yields (70–98%). The ketones were reduced with sodium borohydride to produce β-alcohols exclusively (60–95%), and then were protected as benzoate, using standard protocol to provide benzoates **5a**–**g** (80–98%). Following the reported procedure,[8] bis-allylic oxidation was achieved using PDC, ^{t}BuOOH giving dienones **1a**–**g** (60–85%). The full details on the preparation and characterization of compounds **1a**,**c**–**3a** (Scheme 1) had been previously described.[7a] In all cases, the reaction sequences proceeded efficiently with moderate to high yield, except for the 7-methoxy tetralone which in all attempts of Birch alkylation with MOMCl gave methoxy methyl 4-phenyl butanoate[9] as the sole isolated product in 40% yield from the recovered starting material. It should be pointed out that the presence of allyl or methoxy methyl groups on ring junction makes the chromatographic purification of the dienones difficult in extreme.

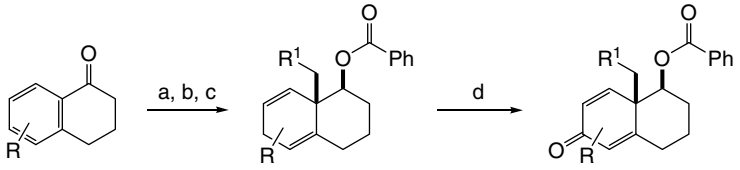
The key step of the path was performed according to the previously optimized conditions[10] using K_2CO_3 as base in MeOH at room temperature. The reaction produced the expected products **3a**–**g** with moderate to good yields (Scheme 4).[11]



1a-g

3a R = H R^1 = H, 94%
3b R = 2,4,6-trimethyl R^1= H, 80%
3c R = 2-MeO, R^1= H, 63%
3d R = H R^1= allyl, 87%
3e R = H R^1= allyl, 94%
3f R = 2,6-dimethyl R^1= H, 80%
3g R = H R^1= H 4-Me, 50%

Scheme 4. Dienones aromatization. Reagents and condition: (a) K_2CO_3, MeOH, rt.

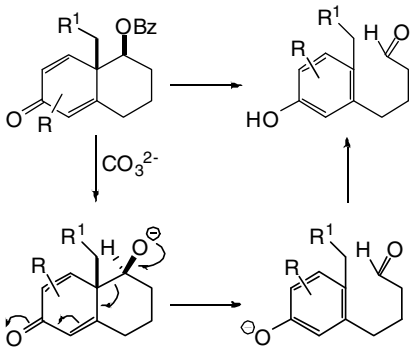


4a R = H
4b R = 5,7-diCH$_3$
4c R = 5-OCH$_3$
4g R = 4-CH$_3$

5a R = H, R^1 = H, 91%[e]
5b R = 5,7-diCH$_3$, R^1 = H, 43%
5c R = 5-OCH$_3$, R^1 = H, 34%
5d R = H, R^1 = OCH$_3$, 75%
5e R = H, R^1 = allyl, 45%
5f R = 5,7-diCH$_3$, R^1 = allyl, 64%
5g R = 4-CH$_3$, R^1 = H, 54%

1a R = H, R^1 = H, 85%
1b R = 5,7-diCH$_3$, R^1 = H, 60%
1c R = 5-OCH$_3$, R^1 = H, 59%
1d R = H, R^1 = OCH$_3$, 73%
1e R = H, R^1 = allyl, 75%
1f R = 5,7-diCH$_3$, R^1 = allyl, 85%
1g R = 4-CH$_3$, R^1 = H, 60%

Scheme 3. Reagents and conditions: (a) (1) NH_3, K, Et_2O, ^{t}BuOH, −78 °C; (2) LiBr; (3) R–X, −78 °C to rt; (b) $NaBH_4$, MeOH, −78 °C, 30 min; (c) PhCOCl, Py, DMAP, 0 °C, 2 h; (d) PDC, ^{t}BuOOH, DCM. [e] Yields of **5a**–**g** are based on **4** (a, b, c steps).



Scheme 5. Proposed mechanism for aromatization under basic conditions.

For some substrates the reaction time was longer than others and that can be explained based on difficulties to produce ester hydrolysis. From the inspection of the structural differences for the transformation of compounds **1** into the final products **3**, there is neither required stereochemistry nor the nature of R substituent for any ester group which would significantly affect the course of the reaction.

From the mechanistic point of view the conversion of dienones **1** to aldehyes **3** under basic conditions suggests the participation of the benzoyloxy group to generate the corresponding alcoxide which promotes the cleavage of the bicyclic dienone to the corresponding phenolate and this takes a proton from the solvent to form the final product **3**. The fragmentation process allows the formation of an aromatic ring that results in gain on resonance stabilization energy, that is, ultimately the driving force of the reaction (Scheme 5). Likewise, it could be also interpreted as the reversal reaction to the *ipso*-alkylation with KO^{t}Bu described by Mander[12] to afford oxodienones from aromatic compounds.

These 4-aryl-butanals are important building blocks to construct bioactive natural products or their analogs. As an example of that, the methyl ether of compound **3a** had been previously prepared by Taber's group as an intermediate in (−)-astrogorgiadiol synthesis.[13]

Conclusions: We have developed an efficient synthetic procedure (five steps, 42% average overall yield) to prepare new substituted phenolic aldehydes by means of a protocol of dearomatization by BAR methodology, and aromatization in a further stage under basic conditions.

Acknowledgments

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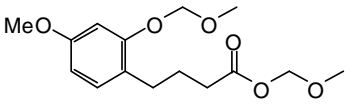
9. 
10. *General procedure to aldehydes preparation*. To a solution of dienone **1** (1 mmol) in MeOH (35 mL), K_2CO_3 (3 mmol) was added and the reaction mixture was maintained with magnetic stirring at room temperature until complete. The reaction was quenched with brine and methanol was concentrated in vacuo. The aqueous layer was extracted with Et_2O (3 × 25 mL) and EtOAc (25 mL), combined organic extracts were dried (anhyd Na_2SO_4) and evaporated in vacuo to give a residue that was purified by column chromatography.
11. All new compounds were characterized on the basis of IR, ^{1}H, ^{13}C NMR and HRMS data. Spectral data for selected compounds:
4-(3-Hydroxy-2,4,6-trimethyl phenyl)-butanal (**3b**). Colorless oil (80%), $R_f = 0.51$ (hexane/EtOAc 70:30). IR (film) ν 3474, 3007, 2949, 2882, 1716, 1480, 1456, 1410, 1386, 1246, 1212, 1094, 1012, 869 cm^{-1}. ^{1}HNMR δ (ppm) 9.81 (t, 1H, $J = 1.0$, CHO), 6.80 (s, 1H, Ar-H-5), 4.71 (s, 1H, OH), 2.64 (t, 2H, $J = 5.4$ Hz, H-4), 2.54 (dt, 2H, $J = 4.7$, 1.0 Hz, H-2), 2.24 (s, 3H, CH_3-6), 2.23 (s, 3H, CH_3-2), 2.21 (s, 3H, CH_3-4), 1.79 (q, 2H, $J = 4.8$ Hz, H-3). ^{13}CNMR δ (ppm, $CDCl_3$) 202.4 (CHO), 150.4 (Ar-C-3), 137.0 (Ar-C-1), 129.8 (Ar-C-5), 127.5 (Ar-C-6), 121.8 (Ar-C-2), 120.4 (Ar-C-4), 43.8 (C-2), 29.2 (C-4), 21.9 (C-3), 19.3 (CH_3-6), 15.7 (CH_3-4), 11.8 (CH_3-2). ESI-HRMS Calcd for (M+H$^+$) $C_{13}H_{19}O_2$, 207.1380; found, 207.1377.
4-(6-Allyl-3-hydroxy-2,4-dimethylphenyl)butanal (**3f**). White solid (80%), $R_f = 0.30$ (hexane/EtOAc 80:20). IR (film) ν 3476, 3077, 2932, 2870, 1717, 1637, 1579, 1480, 1412, 1389, 1212, 1095, 912, 874, 684 cm^{-1}. ^{1}HNMR δ (ppm) 9.81 (t, 1H, $J = 0.8$ Hz, CHO), 6.80 (s, 1H, ArH-5), 5.95 (m, 1H, –CH_2CH=CH_2), 5.04 (dd, 1H, $J = 6.3$, 1.0 Hz, –CH_2CH=CH_2), 4.96 (dd, 1H, $J = 2.0$, 1.0 Hz, –CH_2CH=CH_2), 4.69 (d, 1H, $J = 1.6$ Hz, –OH), 3.33 (d, 2H, $J = 4.1$ Hz, –CH_2CH=CH_2), 2.64 (t, 1H, $J = 5.5$ Hz, H-4), 2.62 (d, 1H, $J = 4.1$ Hz, H-4), 2.54 (dt, 2H, $J = 4.7$, 0.8 Hz, H-2), 2.24 (s, 3H, CH_3-Ar-4), 2.22 (s, 3H, CH_3-Ar-2), 1.79 (m, 2H, H-3). ^{13}CNMR δ (ppm) 202.3 (C=O), 150.8 (Ar-C-3), 138.2 (–CH_2CH=CH_2), 137.0 (Ar-C-1), 129.4 (Ar-C-6), 129.3 (Ar-C-5), 121.9 (Ar-C-2), 120.6 (Ar-C-4), 115.6 (–CH_2CH=CH_2), 43.9 (C-2), 37.3 (–CH_2CH=CH_2), 28.8 (C-4), 22.6 (C-3), 15.8 (CH_3-4), 11.9 (CH_3-4). ESI-HRMS Calcd for (M+H$^+$) $C_{15}H_{20}O_2$: 233.1537; found, 233.1542.
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