Ethylenation of aldehydes to 3-propanal, propanol and propanoic acid derivatives

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Methodology has been developed for the synthesis of 3-propanaldehydes through a five-step process in 11–67% yield from aldehydes. Aldehydes were reacted with Meldrum’s acid through a Knoevenagel condensation to give materials that upon reduction with sodium borohydride and subsequent hydrolysis decarboxylation generated the corresponding 3-propanoic acid derivatives. The propanoic acid derivatives were reduced to give 3-propanol derivatives, which were readily oxidised to target 3-propanal derivatives.

Aryl-3-propanaldehydes have demonstrated themselves as synthetically useful in the synthesis of natural products1, chiral tetrahydroquinolines2,3 chemoensors4,5 and in the perfume industry6. As such, facile synthesis of a range of these derivatives would be advantageous.

The chemoselective reduction of cinnamaldehydes to hydrocinnamaldehydes has been reported by Hashizume et al.7 and List et al. via either a palladium catalysed reduction7 or the organocatalysed Hantzsch’s ester reduction8, respectively. The synthesis of cinnamaldehydes has been reported utilising a range of conditions including the Wittig reaction1 from aryl aldehydes and the Heck cross-coupling of aryl halides9–13. Alternatively, the products from the Knoevenagel condensation of aldehydes with Meldrum’s acid can be converted to hydrocinnamaldehydes. Frost et al. reported the hydrosilylation of Meldrum’s acid derivatives (3) either through a one-step14 or two-step15 process, using palladium or molybdenum catalysts and reagents.

A study by Andrews et al. (Glaxo-Smith-Kline (GSK)) reported a four-step synthesis of 3-(anthracen-9-yl)propan-1-ol (6d) on a 20-gram scale. Upon oxidation, this material would give the corresponding aldehyde (7d)16. However, this route was reported to have been carried out on a single substrate, starting with 9-anthraldehyde (1d) affording 3-(anthracen-9-yl)propan-1-ol (6d) in an overall yield of 84% over four steps.

Herein we provide alternative methodology to the established literature and build on previous studies16 for the synthesis of 3-propanal derivatives (Fig. 1) utilising a Knoevenagel condensation, olefin reduction, decarboxylation, carboxylic acid reduction and an alcohol oxidation. Substrate scope is expanded and a range of versatile hydrocinnamaldehyde derivatives are synthesised.

Results and Discussion

The synthesis of condensation products para-nitro (3a), para-dimethylamino (3b) and para-methoxy (3c) could be achieved via the literature reported Knoevenagel condensation of aldehydes 1a–c with Meldrum’s acid (2) in 74–87% yields14. Whilst this method successfully delivered 3a–c in our hands, the use of an aqueous solvent system prevented us from successfully applying the same conditions to substrates with low water solubility such as 9-anthraldehyde (1d). However, this route was reported to have been carried out on a single substrate, starting with 9-anthraldehyde (1d) affording 3-(anthracen-9-yl)propan-1-ol (6d) in an overall yield of 84% over four steps.

A literature reported method for the synthesis of 3n was used17, for which we carried out minor solvent modifications to avoid the use of benzene (Fig. 2, entry 19) giving the desired Knoevenagel condensation products.
Figure 1. General route for the synthesis of hydrocinnamaldehydes.

Figure 2. Substrate scope for the Knoevenangel condensation of aldehydes with Meldrum's acid.

| Entry | Substituent (R) | Conditions | Yield |
|-------|----------------|------------|-------|
| 1     | 4-NO₂-C₆H₄ (3a) | H₂O, 75 °C, 2 h<sup>18</sup> | 79%   |
| 2     | 4-NO₂-C₆H₄ (3a) | Pyridine, rt, 15 h | 74%   |
| 3     | 4-NMe₂-C₆H₄ (3b) | H₂O, 75 °C, 2 h<sup>18</sup> | 87%   |
| 4     | 4-NMe₂-C₆H₄ (3b) | Pyridine, rt, 15 h | 93%   |
| 5     | 4-OMe-C₆H₄ (3c) | H₂O, 75 °C, 2 h<sup>18</sup> | 75%   |
| 6     | 4-OMe-C₆H₄ (3c) | Pyridine, rt, 15 h | 91%   |
| 7     | 9-Anthryl (3d) | H₂O, 75 °C, 2 h | 0%    |
| 8     | 9-Anthryl (3d) | Pyridine, rt, 15 h<sup>16</sup> | 93%   |
| 9     | 2-Furyl (3e) | Pyridine, rt, 15 h | 91%   |
| 10    | 1-Pyrenyl (3f) | Pyridine, rt, 15 h | 88%   |
| 11    | C₆H₅- (3g) | Pyridine, rt, 15 h | 74%   |
| 12    | 4-Me-C₆H₄ (3h) | Pyridine, rt, 15 h | 73%   |
| 13    | 4-OH-C₆H₄ (3i) | Pyridine, rt, 15 h | 67%   |
| 14    | 2-HCC-C₆H₄ (3j) | Pyridine, rt, 15 h | 56%   |
| 15    | 2-Br-C₆H₄ (3k) | Pyridine, rt, 15 h | 55%   |
| 16    | 3-Indole (3l) | Pyridine, rt, 15 h | 48%   |
| 17    | 2-Naphthyl (3m) | Pyridine, rt, 15 h | 34%   |
| 18    | 4-CF₃-C₆H₄ (3n) | Pyridine, rt, 15 h | 0%<sup>6</sup> |
| 19    | 4-CF₃-C₆H₄ (3n) | Pyridinium acetate (10 mol%), Toluen, 50 °C, 36 h<sup>17</sup> | N.D.<sup>5</sup> |
| 20    | C₆F₅- (3o) | Pyridinium acetate (10 mol%), Toluen, 50 °C, 36 h | N.D.<sup>5</sup> |

<sup>1</sup>The crude material thus obtained contained more than 20 signals in the 19F NMR spectrum and no aldehyde remaining.
<sup>2</sup>Conditions are judged by <sup>1</sup>H NMR spectroscopy.
<sup>3</sup>Compounds were taken to the next step without purification.

<sup>4</sup>Compounds were taken to the next step without purification.

<sup>5</sup>N.D. = not determined.
products. The same procedure also yielded the novel pentafluorophenyl derivative (3o, Fig. 2, entry 20). Both the para-trifluoromethyl (3n) and pentafluoro (3o) derivatives were not purified at this stage due to instability of the substrates during attempted purification protocol, which included recrystallisation and flash column chromatography. Instead, when full conversion was determined to have been reached by $^1$H NMR spectroscopic analysis of the crude reaction mixtures for these reactions, they were taken forward to the next step.

With alkene containing compounds 3a–o in hand, the next step was reduction of the conjugated double bonds introduced through the Knoevenagel condensation. This was successfully carried out according to the method reported for the synthesis of 4d by Andrews et al., giving high yields (87–99%) for 4a, c–h, j–l, n–o. The 4-dimethylamino derivative (4b) gave a lower than expected yield of 75%, minor decomposition was observed. In the case of compounds 4c (Fig. 3, entry 3) and 4h (Fig. 3, entry 8) methanol led to ring opening of the Meldrum’s moiety to the dimethyl malonate, whereas under otherwise identical conditions the use of ethanol furnished the desired compounds. Therefore, ethanol was selected as the preferable solvent for manipulation of 3 to 4 from this point.

The hydrolysis and decarboxylation of derivatives 4 was required in order to synthesise 5, this was achieved with the method reported for the synthesis of 5d by Andrews et al., in acceptable to good yields (48–98%, Fig. 4) for 5a–h, j, l–n, o.

For the synthesis of the para-methyl (5b) and para-methoxy (5c) derivatives from 4h and 4c, respectively, undesired side-products were detected. In order to minimise the formation of the side-products, the reaction was run initially at room temperature for one hour, followed by heating to reflux for a further 4 hours. The desired compounds were obtained after work-up without requiring further purification. Furthermore, under the standard reaction conditions the synthesis of 2-furyl derivative 5e from 4e led to the formation of the desired compound alongside a minor undesired side-product, the desired compound was poorly soluble in common laboratory solvents and therefore this impurity was taken through to the LiAlH$_4$ reduction. The low yield for the synthesis of 5e was not pursued.

### Table 1: Reduction of Knoevenangel products to afford saturated Meldrum’s derivatives.

| Entry | Substituent (R) | Solvent | Yield |
|-------|----------------|---------|------|
| 1     | 4-NO$_2$-C$_6$H$_4$- (4a) | EtOH | 99% |
| 2     | 4-NMe$_2$-C$_6$H$_4$- (4b) | MeOH | 75% |
| 3     | 4-OMe-C$_6$H$_4$- (4c) | EtOH | 91% |
| 4     | 9-Anthryl (4d) | MeOH | N.D. |
| 5     | 2-Furyl (4e) | EtOH | 87% |
| 6     | 1-Pyrenyl (4f) | MeOH | 95% |
| 7     | C$_5$H$_{11}$- (4g) | EtOH | 99% |
| 8     | 4-Me-C$_6$H$_4$- (4h) | EtOH | 94% |
| 9     | 2-HCC-C$_6$H$_4$- (4j) | EtOH | 88% |
| 10    | 2-Br-C$_6$H$_4$- (4k) | EtOH | 88% |
| 11    | 3-Indole (4l) | EtOH | 91% |
| 12    | 4-CF$_3$-C$_6$H$_4$- (4n) | EtOH | 98% (2 steps) |
| 13    | C$_6$F$_5$- (4o) | EtOH | 99% (2 Steps) |

N.D. – Not determined, compound was taken to the next step containing residual water.

Figure 3. Reduction of Knoevenangel products to afford saturated Meldrum’s derivatives.
of 3-indole derivative 5l was most likely due to product loss during reaction work-up because of the probable zwitterionic nature of 5l having some water solubility.

In order to synthesize 7, isolated 5a–h, j–l, n–o should first be converted to the corresponding primary alcohols 6a–h, j–l, n–o before oxidation to aldehydes 7a–h, j–l, n–o. The reduction of 5b–d, f–h, j–l was carried out with lithium aluminium hydride (LiAlH4) in THF to give the primary alcohols in 83% to 99% yields (Fig. 5). The reduction of 5e to 6e was attempted with lithium aluminium hydride (LiAlH4) however partial fluorine displacement was observed. Pentafluoro derivative 5o underwent a nucleophilic aromatic substitution (SNAr) displacing one of the fluorine substituents to give 8o in an approximate 4:1 ratio 6o:8o (Fig. 6), similar observations are reported in the literature with related substrates19. When para-trifluoromethyl derivative 6n was exposed to LiAlH4 it underwent a hydride-fluorine exchange to give the para-difluoromethyl compound 8n (Fig. 6) in an approximate 1:1 ratio 6n:8n by 1H NMR spectroscopic analysis. Fluorine substitution by hydride within trifluoromethyl groups has been previously reported with related substrates20.

| Entry | Substituent (Ar) | Yield       |
|-------|-----------------|-------------|
| 1     | 4-NO2-C6H4-     | 65%         |
| 2     | 4-NMe2-C6H4-    | 91%         |
| 3     | 4-OMe-C6H4-     | 93%         |
| 4     | 9-Anthryl       | 80% (2 steps)|
| 5     | 2-Furyl         | ≤ 94%a      |
| 6     | 1-Pyrenyl       | 98%         |
| 7     | C6H11-           | 57%b        |
| 8     | 4-Me-C6H4-      | 81%b        |
| 9     | 2-HCC-C6H4-     | 86%a        |
| 10    | 2-Br-C6H4-      | 81%b        |
| 11    | 3-Indole        | 48%         |
| 12    | 4-CF3-C6H4-     | 63%         |
| 13    | C6F5-           | 91%         |

Figure 4. Decarboxylation to synthesise hydrocinnamic acid derivatives.

| Entry | Substituent (Ar) | Yield       |
|-------|-----------------|-------------|
| 1     | 4-NO2-C6H4-     | 65%         |
| 2     | 4-NMe2-C6H4-    | 91%         |
| 3     | 4-OMe-C6H4-     | 93%         |
| 4     | 9-Anthryl       | 80% (2 steps)|
| 5     | 2-Furyl         | ≤ 94%a      |
| 6     | 1-Pyrenyl       | 98%         |
| 7     | C6H11-           | 57%b        |
| 8     | 4-Me-C6H4-      | 81%b        |
| 9     | 2-HCC-C6H4-     | 86%a        |
| 10    | 2-Br-C6H4-      | 81%b        |
| 11    | 3-Indole        | 48%         |
| 12    | 4-CF3-C6H4-     | 63%         |
| 13    | C6F5-           | 91%         |

*Compound taken forward containing impurities; Modified conditions: Pyridine/H2O (3:1), 1 h at rt followed by 4 h reflux.
Reduction of 5a and 5k to 6a and 6k was carried out using borane to give the desired compounds in 86% and 74%, respectively (Fig. 7). This procedure provides an alternative, milder, method to reduce carboxylic acids when incompatible with LiAlH₄. Thus, this procedure should also be applicable to fluorinated derivatives 5n and 5o and has previously been demonstrated in the literature²¹, ²².

Hydrocinnamyl alcohol derivatives 6a,c,d,f–h,j,k,o were converted to aldehydes 7a,c,d,f–h,j,k,o using a Swern oxidation in 29–89% yield (Fig. 8). The oxidation of 4-dimethylamino derivative 6b to 7b and 3-indole derivative 6l to 7l was unsuccessful, a complex mixture of unidentifiable by-products alongside the desired compound precluded satisfactory synthesis and isolation. Oxidation of a mixture of 6o and 8o led to the formation of the desired aldehyde 7o in acceptable yield (29%) and the by-product from the oxidation of 8o could be separated with column chromatography.

| Entry | Substituent (R) | Yield  |
|-------|-----------------|--------|
| 1     | 4-NMe₂-C₆H₄⁻ | 93%    |
| 2     | 4-OMe-C₆H₄⁻ | 95%    |
| 3     | 9-Anthryl  | 99%    |
| 4     | 2-Furyl  | 0%     |
| 5     | 1-Pyrenyl | 99%    |
| 6     | C₆H₁₃⁻  | 57%    |
| 7     | 4-Me-C₆H₄⁻ | 83%    |
| 8     | 2-HCC-C₆H₄⁻ | 53%    |
| 9     | 3-Indole  | 66%    |
| 10    | 4-CF₃-C₆H₄⁻ | ≤96%³ |
| 11    | C₆F₅⁻    | ≤57%² |

³Reaction conditions led to partial fluorine substitution.

**Figure 5.** Reduction of carboxylic acids to afford hydrocinnamyl alcohol.

**Figure 6.** By-products formed during the lithium aluminium hydride reduction of fluorinated hydrocinnamic acids.
Figure 7. Borane reduction of 4-nitro 5b and 2-bromo 5k derivatives.

Figure 8. Swern oxidation of cinnamoyl alcohols to give corresponding hydrocinamaldehyde derivatives.

| Entry | Substituent (R)       | Yield |
|-------|-----------------------|-------|
| 1     | 4-NO₂-C₆H₄⁻ (7a)      | 84%   |
| 2     | 4-NMe₂-C₆H₄⁻ (7b)     | N.D.⁹ |
| 3     | 4-OMe-C₆H₄⁻ (7c)      | 84%   |
| 4     | 9-Anthryl (7d)        | 89%   |
| 5     | 1-Pyrenyl (7f)        | 66%   |
| 6     | C₆H₁₁⁻ (7g)           | 46%   |
| 7     | 4-Me-C₆H₄⁻ (7h)       | 83%   |
| 8     | 2-HCC-C₆H₄⁻ (7j)      | 77%   |
| 9     | 2-Br-C₆H₄⁻ (7k)       | 75%   |
| 10    | 3-Indole (7l)         | N.D.⁹ |
| 11    | C₆F₅⁻ (7o)            | 29%   |

⁹ Reaction conditions led to formation of an inseparable by-product
The outlined five-step synthesis of aldehydes was successful in providing a range of derivatives in acceptable yields (11–67%, Fig. 9). Our studies found that a single set of conditions were not applicable to all substrates but tailoring of reaction conditions can give a diverse range of derivatives. By-products were observed in the LiAlH₄ reduction of 6n and 6o, the decarboxylation of 4d and 4h but modifications to the synthetic procedure can minimise their formation. Experimental procedures are detailed in the Supplementary Information.

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Figure 9. Summary of five step synthesis of hydrocinnamaldehyde derivatives with overall yields.
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