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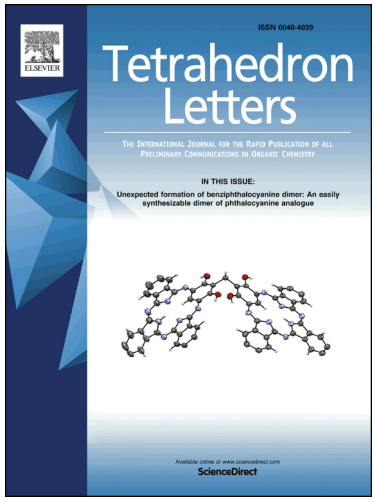

A re-investigation of the Fries rearrangement of 3-chlorophenyl acetate and synthesis of 2-azido-1-(4-(benzyloxy)-2-chlorophenyl)ethanone from 4-bromo-3-chlorophenol

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A re-investigation of the Fries rearrangement of 3-chlorophenyl acetate and synthesis of 2-azido-1-(4-(benzyloxy)-2-chlorophenyl)ethanone from 4-bromo-3-chlorophenol

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Keywords: Fries rearrangement, 3-chlorophenyl acetate, 2-chloro-4-hydroxy-acetophenone, 4-benzyloxy-2-chlorophenacyl azide, Heck reaction

Abstract

The Fries rearrangement of 3-chlorophenyl acetate provided the expected 4-chloro-2-hydroxy-acetophenone as the major product and 2,4-diacetyl resorcinol and 2-chloro-4-hydroxy-acetophenone as minor products. 4-Benzyloxy-2-chloroacetophenone was prepared by a Heck reaction and then elaborated to 4-benzyloxy-2-chlorophenacyl azide.

Phenacyl azides are highly functionalised compounds used as versatile starting materials in medicinal chemistry. For example the azide moiety of these compounds undergoes click chemistry (azide-acetylene cycloaddition)[1] to produce triazoles,[2-4] is reduced to diazo compounds,[5] oxidised to nitro ketones[6] or azidoesters,[7] and undergoes photolysis.[8] The ketone group can undergo condensation with ester enolates[9] or aldehydes,[10] forms heterocycles, such as pyrroles,[11] imidazoles,[12] and oxazoles.[13] In addition there is a huge interest in enantioselective reduction of the keto group of phenacyl azides to form 2-azido-1-arylethanols using either enantioselective reducing agents[14] or biotransformations.[15,16] The azido group of such compounds can then be reduced to provide enantiomerically pure phenethanolamines, useful intermediates for the synthesis of for example β_2 agonists.[17-19]

Phenacyl azides are readily formed from the corresponding bromides, which in turn are prepared by the bromination of acetophenones. We were interested in using the phenacyl azide **1**, or a protected form of it, in one of our medicinal chemistry programmes.

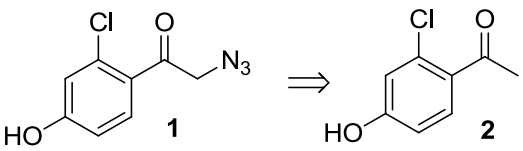
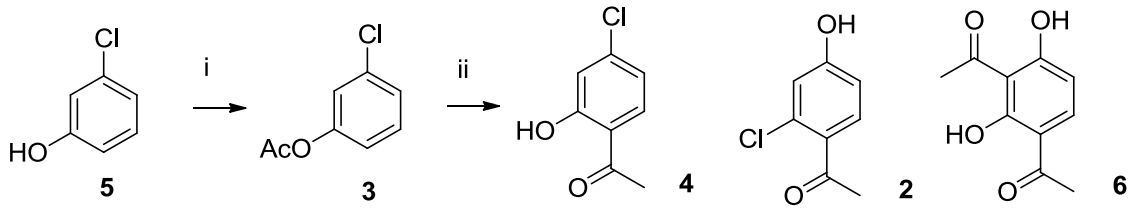


Figure 1. Retrosynthesis of **1**

At the time this work was initiated the precursor acetophenone **2** was not commercially available. However, there was one report for its preparation,[20] where 3-chlorophenyl acetate **3** underwent a Fries rearrangement to provide two regioisomeric acetophenones. The products were separated by steam distillation, which provided 4-chloro-2-hydroxyacetophenone **4** in 50-60% yield depending on the reaction temperature, and the regioisomer 2-chloro-4-hydroxyacetophenone **2** as the minor product. Even though this procedure gave a mixture, it was decided to use it and isolate enough quantities of **2** for our studies. Our synthesis started from 3-chlorophenol **5**, which was converted into the acetate ester **3**, before being added slowly to $AlCl_3$ at 150 °C for 1 h in the absence of any solvent as reported previously[20] (Scheme 1). The reaction gave a mixture, which was separated by column chromatography on silica to provide the major product 4-chloro-2-hydroxyacetophenone **4** (62%), 2-chloro-4-hydroxyacetophenone **2** (8%), 3-chlorophenol **5** and a new product **6**. This new product was found to be a mixture by NMR and GCMS (CI; CH_4) t_R=4.80 min, 43.1%, *m/z* 129, 131 (3:1) $(M+H)^+$, t_R=6.06 min, 54.5%, *m/z* 195 $(M+H)^+$ and t_R=6.15 min, 2.4%, *m/z* 225, 227 (3:1) $(M+H)^+$. The first peak to elute had the mass-ion of 3-chlorophenol, whereas the second peak did not contain chlorine (no Cl isotope). ^1H, ^{13}C NMR, HSQC, HMBC and NOE spectra were recorded, and from the observed correlations (Fig. 2) and the mass-ion, the structure of **6** was assigned as 1,1'-(2,4-dihydroxy-1,3-phenylene)diethanone, which was previously prepared by the Friedel-Crafts acylation of resorcinol as independently reported by two groups.[21,22] The trace impurity (*m/z* 225, 227) in our mixture was not identified.



Scheme 1. *Reagents and conditions*: i) Ac_2O (1.02 equiv.), H_2SO_4 (cat.), 17 h, 20 °C, 99%; ii) $AlCl_3$ (1.5 equiv.), 150 °C, 1 h, **4** (62%), **2** (8%), **6** (6%), **5** (6%).

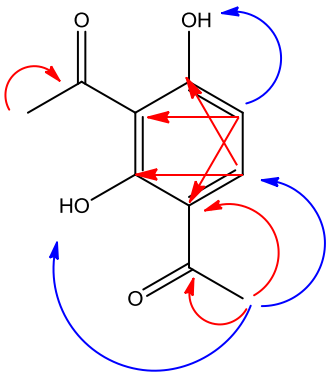
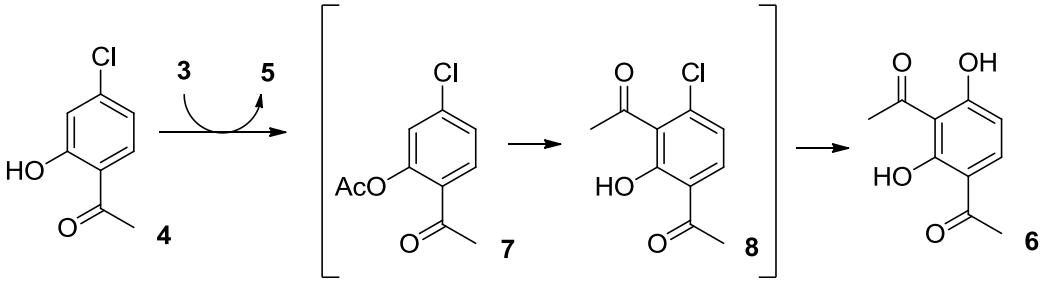


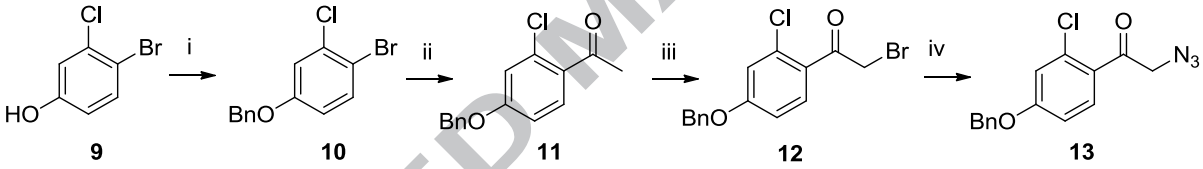
Figure 2. Observed correlations for **6**. Red arrows HMBC, blue arrows NOE

A proposed mechanism for the formation of diketone **6** is outlined in Scheme 2. Presumably **3** is acting as the acetyl source, either trans-acetylating **4** to form **7** and releasing 3-chlorophenol **5**, followed by a second Fries rearrangement to provide the chloro-diketone **8** or alternatively, direct Friedel-Crafts acylation of **4** with **3** to provide **8** and **5**. This might explain the presence of 3-chlorophenol in the reaction mixture. The formation of **6** might arise from **8** following work-up and substitution of chloride *via* a S_NAr reaction. It is conceivable that the minor Fries rearrangement product **2** could also undergo acylation/rearrangement/S_NAr reaction to provide another regioisomer of **6**. Irrespective of the exact mechanism we have not detected any other regioisomer of **6**.



Scheme 2. Proposed mechanism for the formation of **6**

Having failed to isolate substantial quantities of acetophenone **2** using the published method we next investigated Heck chemistry starting from the commercially available 4-bromo-3-chlorophenol **9** as outlined in Scheme 3. Thus, treatment of **9** with benzyl bromide in the presence of potassium carbonate gave benzyl ether **10**, which was then reacted with ethyl vinyl ether in the presence of $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine to provide the protected acetophenone **11**. Treatment of **11** with trimethylphenylammonium tribromide in THF at room temperature gave the phenacyl bromide **12**, together with 4-bromo-1-butanol (arising from cleavage of THF by the brominating agent). Reaction of **12** with sodium azide in DMF at room temperature afforded the required phenacyl azide **13**.[23]



Scheme 3. *Reagents and conditions*: i) BnBr (1 equiv.), K_2CO_3 (1.06 equiv.), DMF (1 mL/mmol), 20 °C, 24 h, 99%; ii) (a) ethyl vinyl ether (1 mL/mmol), $Pd(OAc)_2$ (0.02 equiv.), P(*o*-$MeC_6H_4)_3$ (0.1 equiv.), Et_3N (2 equiv.), DMF (1 mL/mmol), 100 °C, 5 h, 47%, (b) 2M HCl-EtOAc (1:1; 5 mL/mmol), 20 °C, 15 h; iii) PhN^+Me_3 Br_3^- (1 equiv.), THF (3.5 mL/mmol), 20 °C, 1.5 h; iv) NaN_3 (2 equiv.), DMF 0.5 mL/mmol), 20 °C, 2 h, 77% (over two steps).

In conclusion, the reaction of 3-chlorophenyl acetate **3** with $AlCl_3$ at 150°C provided mainly the Fries rearrangement product **4** together with a small quantity of **2** and a mixture of the unexpected diketone **6** and chlorophenol **5**. The phenacyl azide **13** was prepared from 4-bromo-3-chlorophenol **9** *via* a sequence of protection, Heck reaction, bromination and azide displacement.

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Declaration

The authors are/were GSK employees, have given approval to the manuscript, and have no competing financial interests.

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23. Characterisation data:

4-Chloro-2-hydroxyacetophenone (4): LCMS (System A) t_R=2.63 min, 97%; (System B) t_R=7.55 min, ES–ve *m/z* 169, 171 $(M–H)^-$; ^{1}H NMR ($CDCl_3$, 400 MHz) 12.4 (1H, s), 7.66 (1H, d, *J* 8 Hz), 7.00 (1H, d, *J* 2 Hz), 6.88 (1H, dd, *J* 8, 2 Hz), 2.62 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) 203.4 (CO), 162.7 (C-2), 141.4 (C-4), 131.7 (C-6), 119.2 (C-5), 118.1 (C-3), 118.0 (C-1), 26.2 (CH_3); NOE observed from OH (12.4 ppm) to the doublet *J* 2 Hz at 7.00 ppm (3-H); HMBC correlations observed from 2-OH to C1 (118.0 ppm) and CO (203.4 ppm) and from CH_3 (2.62 ppm) to CO and C1.

2-Chloro-4-hydroxyacetophenone (2): LCMS (System B) t_R=5.82 min, 100%, ES+ve *m/z* 171, 173 $(M+H)^+$, ES–ve *m/z* 169, 171 $(M–H)^-$; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.65 (1H, d, *J* 9

Hz), 7.12 (1H, br), 6.95 (1H, d, *J* 2 Hz), 6.81 (1H, dd, *J* 9, 2 Hz), 2.66 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) 201.4, 159.7, 134.2, 132.5, 131.0, 118.0, 114.3, 30.6.

3-Chlorophenol (**5**) ^{1}H NMR ($CDCl_3$, 400 MHz) 7.14 (1H, t, *J* 8 Hz), 6.90 (1H, ddd, *J* 8, 2, 1.5 Hz), 6.84 (1H, t, *J* 2 Hz), 6.72 (1H, ddd, *J* 8, 2, 1.5 Hz), 5.50 (1H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) 156.4, 134.8, 130.4, 121.0, 115.9, 114.5; LCMS (System A) t_R=2.95 min, ES–ve *m/z* 127, 129 $(M–H)^-$.

1,1'-(2,4-Dihydroxy-1,3-phenylene)diethanone (**6**): ^{1}H NMR ($CDCl_3$, 400 MHz) 14.8 (1H, s), 14.2 (1H, s), 7.82 (1H, d, *J* 9 Hz), 6.40 (1H, d, *J* 9 Hz), 2.80 (3H, s), 2.60 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) 205.7, 203.1, 170.8, 168.2, 137.9, 112.0, 109.8, 109.5, 33.5, 26.2; LCMS (System A) t_R=3.14 min; ES+ve *m/z* 195 $(M+H)^+$; ES–ve *m/z* 193 $(M–H)^-$.

4-(Benzyloxy)-1-bromo-2-chlorobenzene (**10**): ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49 (1H, d, *J* 9 Hz), 7.44-7.33 (5H, m) 7.11 (1H, d, *J* 3 Hz), 6.77 (1H, dd, *J* 9, 3 Hz), 5.04 (2H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) 158.8, 136.4, 135.3, 134.3, 129.1, 128.7, 127.9, 117.2, 115.6, 113.6, 70.9; LCMS (System A) t_R=4.01 min, 98%, ES–ve *m/z* 295, 297, 299 $(M–H)^-$. Found: C, 52.53; H, 3.40. $C_{13}H_{10}BrClO$ requires C, 52.47; H, 3.39%.

1-(4-(Benzyloxy)-2-chlorophenyl)ethanone (**11**): ^{1}H NMR ($CDCl_3$, 400 MHz) 7.67 (1H, d, *J* 8 Hz), 7.45-7.30 (5H, m), 7.02 (1H, d, *J* 2 Hz), 6.91 (1H, dd, *J* 8, 2 Hz), 5.10 (2H, s), 2.64 (3H, s); ^{13}C NMR ($CDCl_3$, 101 MHz) 197.9, 161.1, 135.5, 133.6, 131.8, 130.7, 128.4, 128.1, 127.2, 116.7, 113.2, 70.2, 30.4; LCMS (System A) t_R=3.45 min, 100%, ES+ve *m/z* 261, 263 $(M+H)^+$. Found: C, 68.54; H, 4.96; Cl, 13.52. $C_{15}H_{13}ClO$ requires C, 69.10; H, 5.03; Cl, 13.60%.

1-(4-(Benzyloxy)-2-chlorophenyl)-2-bromoethanone (**12**): ^{1}H NMR ($CDCl_3$, 400 MHz) 7.68 (1H, d, *J* 9 Hz), 7.43-7.35 (5H, m), 7.04 (1H, d, *J* 2.5 Hz), 6.93 (1H, dd, *J* 9, 2.5 Hz), 5.11 (2H, s), 4.54 (2H, s); LCMS (System A) t_R=3.87 min, ES–ve *m/z* 383, 385, 387 $(M–H)^-$.

2-Azido-1-(4-(benzyloxy)-2-chlorophenyl) ethanone (**13**): ^{1}H NMR ($CDCl_3$, 400 MHz) 7.73 (1H, d, *J* 9 Hz), 7.42-7.35 (5H, m), 7.04 (1H, d, *J* 2.5 Hz), 6.94 (1H, dd, *J* 9, 2.5 Hz), 5.11 (2H, s), 4.53 (2H, s); LCMS (System A) t_R=3.58 min, ES+ve *m/z* 302, 304 $(M+H)^+$.

LCMS analysis was conducted on either a Supelcosil LCABZ+PLUS column (System A) (33 mm × 4.6 mm id) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient 0.0–0.7 min 0% B, 0.7–4.2 min 100% B, 4.2–5.3 min 0% B, 5.3–5.5 min 0% B at a flow rate of 3 mL min^{-1} or was performed on a Monolithic C18 column (System B) (50 mm × 4.6 mm) eluting with 0.1% formic acid in water (solvent A) and acetonitrile containing 0.1% formic acid (solvent B) using the following elution gradient: 0.0–3.0 min 5% to 50% B, 3.0 to 5.0 min 50–80% B, 5.0–6.5 min 80 to 95% B, 6.5–8.0 min held at 95% B, 8.0–8.2 min 95 to 5% B, 8.2–10 min 5% B at a flow rate of 0.5 mL/min, detecting with a UV detector between 220–400 nm. The mass spectra were recorded on a Waters ZQ spectrometer using electrospray positive and negative mode (ES+ve and ES–ve).

- A re-examination of the Fries rearrangement of 3-chlorophenyl acetate
- Synthesis of 4-benzyloxy-2-chlorophenacyl azide
- 2,4-diacetyl resorcinol