Tetrahedron 65 (2009) 8165–8170

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The synthesis of substituted phenols from pyranone precursors

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ARTICLE INFO

Article history:
Received 10 April 2009
Received in revised form 6 July 2009
Accepted 28 July 2009
Available online 6 August 2009

Keywords:
Phenol
Pyranone
Maltol
2,6-Dimethylpyranone
Chelidonic acid
Pronucleophile
Isotopes

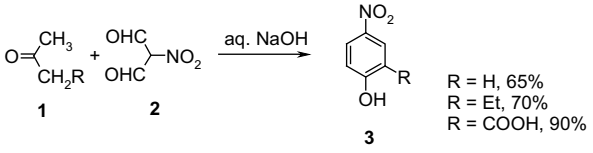
ABSTRACT

The syntheses of various substituted phenols from pyranone precursors, namely 4*H*-pyran-4-one, 3-(benzyloxy)-2-methyl-4*H*-pyran-4-one (benzyl-maltol), 2,6-dimethyl-4*H*-pyran-4-one and diethyl 4-oxo-4*H*-pyran-2,6-dicarboxylate (diethyl chelidonate) are presented. A variety of pronucleophiles were used in combination with *tert*-butanol as solvent and potassium *tert*-butoxide as base, using conventional heating methods and microwave conditions.

1. Introduction

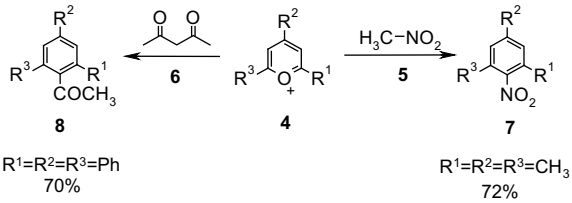
Many natural products such as polyketides, coumarins and flavonoids contain mono-phenolic or polyphenolic moieties.[1] New methodology for the preparation of phenols is therefore potentially valuable in natural product synthesis. Traditional methods for the preparation of phenols[2] include hydrolysis of diazonium salts, Baeyer–Villiger oxidation, displacement of aromatic halides and oxidation of aryl boronates. More recent methods include the catalytic C–H activation/borylation/oxidation procedure developed by Maleczka and Smith[3] and palladium-catalysed C–O bond formation.[4]

An alternative strategy involves the construction of the benzene nucleus from acyclic, non-aromatic precursors with the substituents already in place.[5] This offers a way of overcoming the problems associated with direct introduction of ring substituents, which often leads to isomeric mixtures. The reaction of an acetone derivative **1** with nitromalondialdehyde **2** to provide *p*-nitrophenol **3** is an important reaction of this type (Scheme 1).[6] Its significance is increased by the fact that replacement of acetone by methyl alkyl ketones, or homologous dialkyl ketones, gives rise to 1,2,4-tri- or 1,2,4,6-tetra-substituted derivatives.[7]



Scheme 1. Synthesis of *p*-nitrophenol derivatives from acetone derivatives and nitromalondialdehyde.[6]

Another strategy is the synthesis of benzene derivatives from heterocyclic precursors, which undergo either a rearrangement or an extrusion process. Oxygen-containing heterocycles such as pyrylium salts are particularly susceptible to nucleophilic attack and serve as useful precursors to polysubstituted aromatic compounds. The advantage of this approach is that substituents present in the heterocycle are incorporated into the aromatic product in a regiospecific manner. Scheme 2 shows the reaction of a pyrylium salt **4** with nitromethane **5**[8] or acetylacetone **6**[9] to give an aromatic



Scheme 2. Synthesis of polysubstituted aromatic compounds from pyrylium salts.[8,9]

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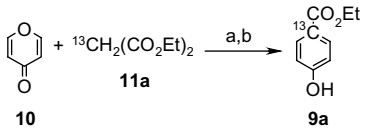
doi:10.1016/j.tet.2009.07.083

nitro compound **7** or ketone **8**, respectively. After addition of the nucleophile, ring opening occurs followed by ring closure and elimination of water to give the product.

It is known that pyran-4-ones can serve as useful precursors for phenols, where the pyranone carbonyl ultimately becomes the phenolic hydroxyl group. This method was used by Steglich and co-workers for the synthesis of isotopically labelled phenols.[10] Scheme 3 shows the synthesis of ethyl 4-hydroxy[1-^{13}C]benzoate **9a** from 4*H*-pyran-4-one **10** using diethyl [2-^{13}C]malonate **11a** as the source of isotopic label (Scheme 3).



Scheme 3. Reagents and conditions: (a) ^{t}BuOH, KO^{t}Bu, reflux; (b) 1 M HCl, reflux, 80%.[10]

This reaction does not appear to have been studied since the time of Steglich's publications.[10,11] We envisaged that the scope of this reaction could be extended to include the use of other pyran-4-one substrates and nucleophiles. This would allow the preparation of a range of *para*-substituted phenols from simple heterocyclic precursors.

An important potential application of this methodology is in the preparation of isotopically labelled compounds. The number of commercially available [^{13}C]-labelled benzene derivatives is relatively small. They are often only available in uniformly ring-labelled form and tend to be expensive. New methods for the construction of benzene derivatives with regioselective placement of isotopes within the ring are therefore potentially useful. Compounds multiply labelled with stable isotopes are valuable as internal standards in LC–MS[13,14] and GC–MS[15] analysis.

In this paper, we report an improved method for the synthesis of *para*-substituted phenols from 4*H*-pyran-4-one **10** and a variety of carbon nucleophiles. The results of experiments with other pyran-4-ones are also presented. Both conventional and microwave heating were employed and results compared. This approach has already been used by Botting and co-workers for the preparation of [1,3,5-^{13}C]gallic acid.[12]

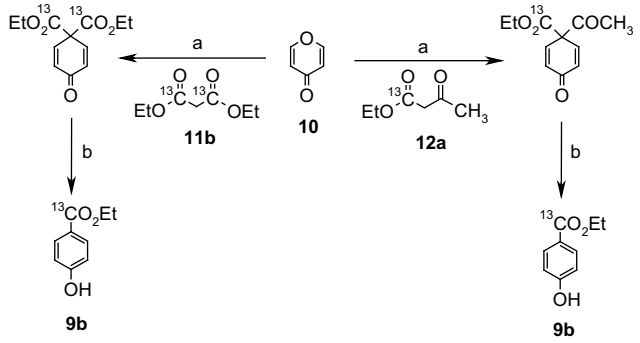
2. Results and discussion

Table 1 shows the pronucleophiles studied and their respective pK_a values compared to *tert*-butanol.

Previous work had shown that ethyl 4-hydroxy[1-^{13}C]benzoate **9a** was obtained in 85% yield by heating 4*H*-pyran-4-one **10** (1.6 equiv) and diethyl [2-^{13}C]malonate **11a** (1.0 equiv) with potassium *tert*-butoxide (1.3 equiv) in *tert*-butanol at reflux (Scheme 3).[10,11] After varying the number of equivalents of pyranone, pronucleophile and base, we found the optimum conditions to be 1.7 equiv of pyranone, 1 equiv of diethyl malonate and 1.3 equiv of base with a reflux time of 3 h, followed by a further hour at reflux after addition of acid. Ethyl 4-hydroxybenzoate **9** was obtained in 94% crude yield and did not require further purification. Interestingly, the same product was obtained in 65% yield when the reaction was carried out using ethyl acetoacetate **12** in place of diethyl malonate **11**. The acetyl group was selectively removed in refluxing aqueous acid. There was no evidence for the formation of 4-hydroxyacetophenone by loss of the ester group. Although only carried out on unlabelled substrates thus far, this selectivity will be of use when considering the synthesis of ^{13}C-labelled compounds as shown in Scheme 4. Use of diethyl [1,3-$^{13}C_2$]malonate **11b** would ultimately result in loss of half of the isotopically labelled carbon during acid reflux. However if ethyl [1-^{13}C]acetoacetate **12a** was used, all of the isotopic label would be retained.

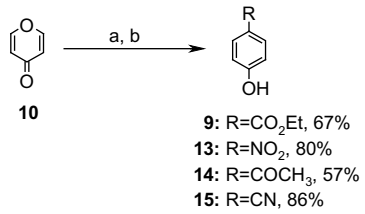
Table 1
Pronucleophiles and pKa values relative to *tert*-butanol

Pronucleophile	pK_a value
Acetylacetone	9
Ethyl cyanoacetate	9
Nitromethane	10
Ethyl acetoacetate	11
Diethyl malonate	13
^{t}BuOH	18



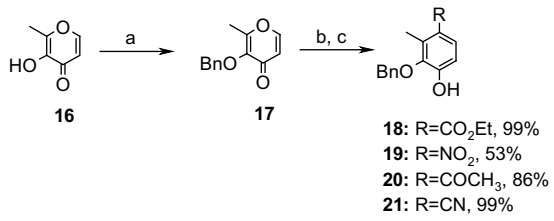
Scheme 4. Proposed reagents and conditions: (a) ^{t}BuOH, KO^{t}Bu, reflux; (b) 1 M HCl, reflux.

The results of experiments with other pronucleophiles are shown in Scheme 5. The pyranone reacted more slowly with nitromethane **5** and acetylacetone **6** and longer reaction times were required. After heating for 20 h at reflux, reaction with nitromethane **5** gave 4-nitrophenol **13** in 80% yield. Similarly reaction with acetylacetone **6** gave 4-hydroxyacetophenone **14** in 95% yield. Reaction of the pyranone with ethyl cyanoacetate was particularly slow. However 4-hydroxybenzonitrile **15** was obtained in 78% yield after heating at reflux for 27 h in the presence of 3 equiv of base and 1.6 equiv of ethyl cyanoacetate.



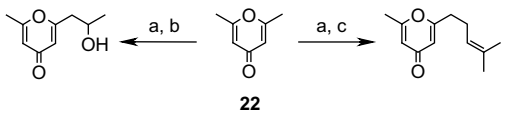
Scheme 5. Reagents and conditions: (a) ^{t}BuOH, KO^{t}Bu, pronucleophile, reflux; (b) 1 M HCl, reflux.

Encouraged by these results we wished to extend the scope of this methodology to other pyran-4-ones. Maltol **16** is one of the few commercially available substituted pyran-4-ones. Use of substituted pyran-4-one substrates would facilitate the synthesis of polysubstituted phenols with a substitution pattern derived from the pyranone starting material. In the case of maltol, the synthesis of polyphenols such as catechols could be achieved. In order to prevent unwanted side reactions, the 3-hydroxy group was first protected as the benzyl ether **17**. Scheme 6 outlines the reactions carried out using this pyranone. Initially, the reaction of **17** with diethyl malonate **11** resulted in poor conversion to **18**. However the yield was improved to 73% by use of 3 equiv of base, 1.6 equiv of pronucleophile and a reaction time of 47 h. The reaction of **17** with nitromethane **5** and acetylacetone **6** resulted in low yields of **19** and **20** under all conditions studied. After prolonged heating (>40 h) in the presence of 2.3 equiv of base and 1.6 equiv of pronucleophile, phenols **19** and **20** were isolated in 20% and 10% yield, respectively. However, reaction with ethyl cyanoacetate was more successful, with **21** being obtained in 93% yield under conditions identical to those used for the preparation of **18**.



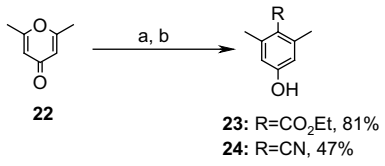
Scheme 6. Reagents and conditions: (a) Benzyl bromide, aq NaOH, MeOH, reflux, 20 h, 98%; (b) ^{t}BuOH, KO^{t}Bu, pronucleophile, reflux; (c) 1 M HCl, reflux.

Benzyl-maltol **17** is relatively electron rich compared to 4*H*-pyran-4-one **10** due to the presence of the oxygen at the 3-position. This may offer a possible explanation for the poor reactivity of **17** with some nucleophiles. However there was also evidence that the pyranone starting material was being converted into other products by a competing pathway. It is known that pyranones with alkyl groups in the 2- and 6-positions, such as 2,6-dimethyl-4*H*-pyran-4-one **22**, can be deprotonated.[16,17] Side-chain deprotonation followed by reaction with electrophiles has been exploited in the synthesis of more complex pyranones, such as those shown in Scheme 7. Alternative protecting groups for the 3-hydroxy group were also examined, including Boc and acetate, however, in these cases complex mixtures of products were obtained due to increased side reactions and cleavage of protecting groups during the acid hydrolysis step.



Scheme 7. Reagents and conditions: (a) LDA, THF, −78 °C; (b) CH_3CHO (47%); (c) $BrCH_2CH{=}C(CH_3)_2$ (yield not given).[16,17]

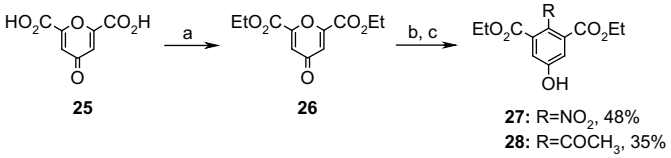
In our experiments the addition of more base improved conversion to phenolic products in some cases, but also resulted in the generation of unwanted side-products. Deprotonation of the methyl groups followed by reaction with other species in the reaction mixture may account for this. In order to investigate the effects of alkyl substituents on the reaction with pronucleophiles some reactions with 2,6-dimethyl-4*H*-pyran-4-one **22** were examined, as shown in Scheme 8.



Scheme 8. Reagents and conditions: (a) ^{t}BuOH, KO^{t}Bu, pronucleophile, reflux; (b) 1 M HCl, reflux.

Ethyl 4-hydroxy-2,6-dimethylbenzoate **23** was obtained in 18% yield after heating at reflux for 44 h in the presence of 3 equiv of base and 1.6 equiv of diethyl malonate **11**. Under similar conditions **24** was obtained from ethyl cyanoacetate in 57% yield. These yields were much lower than those obtained with unsubstituted 4*H*-pyan-4-one **10**. These results support the hypothesis that the pyranone starting material **22** was being consumed by the pathway described above. Reactions of **22** with nitromethane **5** and acetylacetone **6** gave complex mixtures of products, with none of the desired phenols being observed.

Finally, we investigated the reactivity of an electron poor 2,6-disubstituted pyranone. Chelidonic acid **25** was converted into diethyl ester **26** as shown in Scheme 9. In this case, the reactions of **26** with diethyl malonate **11** and ethyl cyanoacetate gave complex mixtures of products, with none of the desired phenols being observed. However it was found that the reaction with nitromethane **5** could be carried out under milder conditions than those used for pyanones **17** and **22**. Phenol **27** was obtained in 46% yield after heating at reflux for 24 h in the presence of 3 equiv of base and 1.1 equiv of nitromethane **5**. Reducing the amount of base to 1.1 equiv did not affect the yield significantly. The reaction of **26** with acetylacetone **6** under the same conditions gave only traces of the desired phenol **28** under conventional heating methods.



Scheme 9. Reagents and conditions: (a) EtOH, conc. HCl, reflux, 24 h, 99%; (b) ^{t}BuOH, KO^{t}Bu, pronucleophile, reflux; (c) 1 M HCl, reflux.

Following studies using conventional heating, microwave irradiation was examined as a way of accelerating these reactions. It was anticipated that shorter reaction times would suppress the formation of unwanted side-products and lead to higher yields of the desired phenolic compounds. A wide range of conditions were studied in order to optimise each reaction where the desired product was observed under conventional heating methods. The results are summarised in Table 2.

As expected, microwave irradiation greatly accelerated the reactions with most giving optimum results after 30 min. Microwave experiments with 4*H*-pyran-4-one **10** gave yields similar to those obtained by conventional heating. The main advantage was the shorter reaction time. However substantial improvements in yield were observed with pyanones **17** and **22** when microwave heating was employed. Microwave irradiation did not improve yields significantly in reactions with diethyl chelidonate **26**.

Table 2
Reaction conditions and results for microwave-assisted reactions, including comparison with yields obtained using conventional heating methods

Product	Pyranone	Pyranone (eq)	Pronucleophile (eq)	KO^{t}Bu (eq)	Time (min)	Temp (°C)	Microwave yield (%)	Conventional yield[a] (%)
9	**10**	1.0	1.1	1.1	30	120	67	94
13	**10**	1.0	1.1	1.1	15	120	80	80
14	**10**	1.0	1.1	2.0	30	150	57	95
15	**10**	1.0	1.6	3.0	30	150	86	78
18	**17**	1.0	1.6	2.3	30	120	99	73
19	**17**	1.0	1.6	2.0	30	120	53	20
20	**17**	1.0	1.6	2.3	30	150	86	10
21	**17**	1.0	1.6	2.3	30	120	99	93
23	**22**	1.0	1.6	2.0	30	150	81	18
24	**22**	1.0	1.6	2.0	30	120	47	57
27	**26**	1.0	1.6	2.3	30	120	48	46
28	**26**	1.0	1.6	2.3	30	120	35	2

[a] Using conditions previously discussed and given in Section 4.2.

Interestingly, we observed that the optimum quantities of reactants and base used in the microwave-assisted reactions were not always the same as those required under conventional heating. In experiments with benzyl-maltol **17**, 2–2.3 equivalents of base gave the cleanest reaction profiles. Addition of more base caused the formation of side products. The same observation was found in experiments with 2,6-dimethyl-4*H*-pyran-4-one **22**. 2 equiv of base were optimum under microwave conditions, whereas 3 equiv were detrimental to the reaction, presumably for reasons described earlier. In several cases microwave heating at 150 °C enhanced yields in reactions, which gave poor yields by conventional heating.

3. Conclusion

In summary, we have explored the scope of the base-catalysed reaction of pyran-4-ones with a range of carbon nucleophiles for the synthesis of phenols. Under conventional heating, the most successful results were obtained with 4*H*-pyran-4-one **10** and 3-(benzyloxy)-2-methyl-4*H*-pyran-4-one (benzyl-maltol) **17**. Limited success was achieved with 2,6-dimethyl-4*H*-pyran-4-one **22** and diethyl chelidonate **26**. The use of microwave irradiation accelerated the reactions with most being complete within 30 min. When 4*H*-pyran-4-one **10** was used, there was little difference between the yields obtained using microwave and conventional heating. However substantial improvements in yield were observed with other pyran-4-ones when microwave heating was employed.

This chemistry also has potential application for the regiospecific placement of carbon isotopes into benzene derivatives.

4. Experimental

4.1. General information

NMR spectra were recorded on a Varian Gemini 2000 (^{1}H 300 MHz, ^{13}C 75.45 MHz) or a Bruker Avance 400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer. ^{13}C NMR spectra were recorded using the PENDANT or DEPTQ sequence and internal deuterium lock. Chemical shifts (δ) in ppm are given relative to Me_4Si, coupling constants (J) are given in Hz. IR spectra were recorded on a Perkin–Elmer series 1420 FT IR spectrophotometer. The samples were prepared as Nujol mulls or thin films between sodium chloride discs and recorded in cm^{-1}. Low resolution and high resolution electrospray mass spectra were recorded on a Micromass LC-T (time-of-flight). Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. Analytical TLC was carried out on Merck 5785 Kieselgel 60F_{254} fluorescent plates. The components were observed under ultraviolet light (254 nm). All chemicals were used as delivered from Sigma–Aldrich unless otherwise indicated. *tert*-Butanol was dried by stirring with 3 Å molecular sieves overnight, followed by filtration. All microwave-assisted reactions were carried out on a Biotage Initiator-60, using a single mode resonator, with dynamic field tuning at a maximum power of 300 W at 2.45 GHz. All quoted yields are for crude isolated products, without any further purification. Portions of these materials were purified by Mass Directed Auto Prep (MDAP) when necessary to allow full characterisation of the product.

4.2. Experimental procedures

4.2.1. General procedure for reactions using conventional heating methods. A solution of the pyranone and pronucleophile in dry ^{t}BuOH (20 mL) was heated to reflux under argon. KO^{t}Bu (1 M solution in ^{t}BuOH) in a further volume of dry ^{t}BuOH (30 mL) was added drop-wise. The resulting mixture was heated under reflux for the desired time after which 1 M HCl was added. The reaction solution was then heated under reflux for a further 1 h. The solvent was removed at reduced pressure, and water (40 mL) was added to the residue. The aqueous phase was extracted with diethyl ether or ethyl acetate (3×30 mL). The combined organic phase was washed with water (2×30 mL), brine (30 mL), dried ($MgSO_4$), and solvent removed at reduced pressure to give the product.

*4.2.1.1. Ethyl 4-hydroxybenzoate (**9**).* Using the general procedure with 4*H*-pyran-4-one **10** (1 g, 10.4 mmol), diethyl malonate **11** (1 g, 6.2 mmol) or ethyl acetoacetate **12** (1.17 g, 9 mmol), KO^{t}Bu (8.2 mL, 8.2 mmol), and 3 h reflux time. Extractions were with diethyl ether. Product **9** was recovered as an orange solid (0.96 g, 94% from diethyl malonate, or 0.64 g, 65% from ethyl acetoacetate). Mp 111–111.5 °C (lit[18] 112–115 °C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, t, J=7.0 Hz, CH_3), 4.36 (2H, q, J=7.0 Hz, CH_2), 6.90 (2H, d, J=8.0 Hz, H-3 and 5), 7.97 (2H, d, J=8.0 Hz, H-2 and 6); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*H$_3$), 61.0 (*C*H$_2$), 115.2 (*C*H-3,5), 122.5 (*C*-1), 131.9 (*C*H-2,6), 160.3 (*C*-4), 167.1 (*C*=O).

*4.2.1.2. 4-Nitrophenol (**13**).* Using the general procedure with 4*H*-pyran-4-one **10** (1 g, 10.4 mmol), nitromethane **5** (0.7 g, 11.5 mmol), KO^{t}Bu (11.5 mL, 11.5 mmol), and 5 h reflux time. Extractions were with diethyl ether. Product **13** was recovered as an off-white solid (1.16 g, 80%). Mp 109–110 °C (lit[19] 110–115 °C); δ_H (400 MHz, DMSO-d_6) 6.90 (2H, d, J=9.2 Hz, H-2 and 6), 8.10 (2H, d, J=9.2 Hz, H-3 and 5), 8.26 (1H, s, OH); δ_C (100 MHz, DMSO-d_6) 115.9 (*C*H-2,6), 131.1 (*C*H-3,5), 139.1 (*C*-4), 164.7 (*C*-1).

*4.2.1.3. 4-Hydroxyacetophenone (**14**).* Using the general procedure with 4*H*-pyran-4-one **10** (0.95 g, 9.88 mmol), acetylacetone **6** (2.69 g, 19.76 mmol), KO^{t}Bu (19.8 mL, 19.8 mmol), and 20 h reflux time. Extractions were with diethyl ether. Product **14** was recovered as a yellow solid (1.29 g, 95%). Mp 105–105.5 °C (lit[19] 106–108 °C); δ_H (400 MHz, $CDCl_3$) 2.60 (3H, s, CH_3), 6.97 (2H, d, J=9.0 Hz, H-3 and 5), 7.92 (2H, d, J=9.0 Hz, H-2 and 6), 8.17 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 26.3 (*C*H$_3$), 115.6 (*C*H-3,5), 129.4 (*C*-1), 131.2 (*C*H-2,6), 161.5 (*C*-4), 198.8 (*C*=O).

*4.2.1.4. 4-Hydroxybenzonitrile (**15**).* Using the general procedure with 4*H*-pyran-4-one **10** (0.96 g, 10.0 mmol), ethyl cyanoacetate (2.13 g, 16.0 mmol), KO^{t}Bu (30 mL, 30.0 mmol), and 27 h reflux time. Extractions were with ethyl acetate. Product **15** was recovered as a red solid (0.926 g, 78%). Mp 109–109.5 °C (lit[20] 109–110 °C); δ_H (400 MHz, DMSO-d_6) 6.90 (2H, d, J=8.7 Hz, H-3 and 5), 7.64 (2H, d, J=8.7 Hz, H-2 and 6), 10.62 (1H, s, OH); δ_C (100 MHz, DMSO-d_6) 101.0 (*C*-1), 116.4 (*C*H-3,5), 119.5 (*C*N), 134.2 (*C*H-2,6), 161.6 (*C*-4); HRMS (CI): MH$^+$, found 120.0449, C_7H_6NO requires 120.0450.

*4.2.1.5. 3-(Benzyloxy)-2-methyl-4H-pyran-4-one (Bn-maltol) (**17**).* To a stirring solution of maltol **16** (6.55 g, 51.9 mmol) in MeOH (57 mL) were added successively NaOH (2.28 g, 57.1 mmol) in water (5.2 mL) followed by benzyl bromide (10.21 g, 59.7 mmol). The mixture was heated at reflux for 20 h. The solvent was then removed at reduced pressure to give a yellow oil, which was dissolved in DCM (50 mL) and washed with 5% aqueous NaOH solution (50 mL) and water (50 mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent was removed at reduced pressure to give **17** as a pale yellow oil (10.96 g, 98%). Subsequent recrystallisation from diethyl ether gave **17** as colourless needles (9.94 g, 89%). Mp 55.5–56 °C (lit[21] 53–55 °C); δ_H (300 MHz, $CDCl_3$) 2.09 (3H, s, CH_3), 5.16 (2H, s, CH_2), 6.37 (1H, d, J=5.7 Hz, H-5), 7.25–7.36 (5H, m, H-Ar), 7.60 (1H, d, J=5.7 Hz, H-6); δ_C (75.45 MHz, $CDCl_3$) 14.8 (*C*H$_3$), 73.5 (*C*H$_2$), 117.1 (*C*H-5), 128.3 (*C*H-12), 128.4 (*C*H-10,10′), 129.0 (*C*H-11,11′), 136.9 (*C*-9), 143.8 (*C*-3), 153.5 (*C*H-6), 159.8 (*C*-2), 175.1 (*C*=O); HRMS (CI): MH$^+$, found 217.0863, $C_{13}H_{13}O_3$ requires 217.0865.

*4.2.1.6. Ethyl 3-(benzyloxy)-4-hydroxy-2-methyl benzoate (**18**).* Using the general procedure with benzyl-maltol **17** (1 g, 4.6 mmol), diethyl malonate **11** (1.18 g, 7.4 mmol), KO^{t}Bu (13.8 mL, 13.8 mmol), and 47 h reflux time. Extractions were with diethyl ether. Product **18** was recovered as an orange oil (0.961 g, 73%). υ_{max}/cm^{-1} 3400, 2981, 1731, 1277; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, t, J=7.2 Hz, CH_3), 2.62 (3H, s, CH_3), 4.33 (2H, q, J=7.2 Hz, CH_2), 4.88 (2H, s, CH_2), 6.81 (1H, d, J=8.6 Hz, H-6), 7.37–7.46 (5H, m, H-Ar), 7.72 (1H, d, J=8.6 Hz, H-5); δ_C (100 MHz, $CDCl_3$) 14.2 (*C*H$_3$), 14.3 (*C*H$_3$), 60.5 (*C*H$_2$), 75.9 (*C*H$_2$–O), 112.4 (*C*H-5), 122.9 (*C*H-6), 128.3 (*C*H-10,10′), 128.8 (*C*H-11,11′), 134.4 (*C*-1), 136.4 (*C*H-12), 144.6 (*C*-9), 152.4 (*C*-3), and 167.1 (*C*=O); HRMS (CI): MH$^+$, found 287.1281, $C_{17}H_{19}O_4$ requires 287.1283.

*4.2.1.7. 2-(Benzyloxy)-3-methyl-4-nitrophenol (**19**).* Using the general procedure with benzyl-maltol **17** (1 g, 4.6 mmol), nitromethane **5** (0.45 g, 7.4 mmol), KO^{t}Bu (10.6 mL, 10.6 mmol), and 44 h reflux time. Extractions were with ethyl acetate. Product **19** was recovered as an orange oil (0.238 g, 20%). υ_{max}/cm^{-1} 2926, 1714, 1640, 1557; δ_H (400 MHz, $CDCl_3$) 2.62 (3H, s, CH_3), 4.93 (2H, s, CH_2), 6.87 (1H, d, J=9.1 Hz, H-6), 7.40–7.47 (5H, m, H-Ar), 7.86 (1H, d, J=9.1 Hz, H-5), 8.00 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 13.8 (*C*H$_3$), 76.5 (*C*H$_2$), 112.8 (*C*H-5,6), 123.1 (*C*H-12), 128.3 (*C*H-10,10′), 129.2 (*C*H-11,11′); HRMS (CI): MH$^+$, found 260.0970, $C_{14}H_{14}NO_4$ requires 260.0923.

*4.2.1.8. 1-(3-(Benzyloxy)-4-hydroxy-2-methylphenyl)ethanone (**20**).* Using the general procedure with benzyl-maltol **17** (1 g, 4.6 mmol), acetylacetone **6** (1.01 g, 7.4 mmol), KO^{t}Bu (10.6 mL, 10.6 mmol), and 42 h reflux time. Extractions were with ethyl acetate. Product **20** was recovered as an orange oil (0.118 g, 10%). υ_{max}/cm^{-1} 3032, 1719, 1648, 1255, 1187; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 2.57 (3H, s, CH_3), 4.88 (2H, s, CH_2), 6.83 (1H, d, J=8.6 Hz, H-5), 7.39–7.45 (5H, m, H-Ar), 7.54 (1H, d, J=8.6 Hz, H-6), 8.02 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 14.4 (*C*H$_3$), 29.3 (*C*H$_3$), 75.9 (*C*H$_2$), 112.1 (*C*H-5), 128.1 (*C*H-10,10′), 129.0 (*C*H-11,11′), 130.9 (*C*H-6), 133.4 (*C*-1), 136.3 (*C*H-12), 145.1 (*C*-9), 152.3 (*C*-3), 200.0 (*C*=O); HRMS (CI): MH$^+$, found 257.1176, $C_{16}H_{17}O_3$ requires 257.1178.

*4.2.1.9. 3-(Benzyloxy)-4-hydroxy-2-methylbenzonitrile (**21**).* Using the general procedure with benzyl-maltol **17** (1 g, 4.6 mmol), ethyl cyanoacetate (1.07 g, 7.4 mmol), KO^{t}Bu (13.8 mL, 13.8 mmol), and 47 h reflux time. Extractions were with ethyl acetate. Product **21** was recovered as an orange/red oil (1.13 g, 93%). υ_{max}/cm^{-1} 2929, 2216, 1456, 1376; δ_H (400 MHz, $CDCl_3$) 2.51 (3H, s, CH_3), 4.92 (2H, s, CH_2), 6.84 (1H, d, J=8.5 Hz, H-5), 7.33 (1H, d, J=8.5 Hz, H-6) 7.39–7.47 (5H, m, H-Ar); δ_C (100 MHz, $CDCl_3$) 14.9 (*C*H$_3$), 76.1 (*C*H$_2$), 105.3 (*C*-1), 114.2 (*C*N), 118.2 (*C*H-5), 128.3 (*C*H-10,10′), 129.1 (*C*H-11,11′), 130.1 (*C*-2), 131.6 (*C*H-6), 135.9 (*C*H-12), 144.5 (*C*-9), 153.3 (*C*-3); HRMS (CI): MH$^+$, found 240.1017, $C_{15}H_{14}NO_2$ requires 240.1025.

*4.2.1.10. Ethyl 4-hydroxy-2,6-dimethyl benzoate (**23**).* Using the general procedure with 2,6-dimethyl-4*H*-pyran-4-one **22** (1 g, 8.1 mmol), diethyl malonate **11** (2.1 g, 12.9 mmol), KO^{t}Bu (24.3 mL, 24.3 mmol), and 44 h reflux time. Extractions were with ethyl acetate. Product **23** was recovered as an orange solid (0.283 g, 18%). Mp 65–65.5 °C (lit[22] 62 °C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, t, J=7.1 Hz, CH_3), 2.29 (6H, s, 2×CH_3), 4.37 (2H, q, J=7.1 Hz, CH_2), 8.50 (2H, s, H-3 and 5); δ_C (100 MHz, $CDCl_3$) 14.3 (*C*H3), 20.1 (*C*H$_3$), 60.8 (*C*H$_2$), 114.5 (*C*H-3,5), 136.7 (*C*-2,6), 153.6 (*C*-4), 169.9 (*C*=O).

*4.2.1.11. 4-Hydroxy-2,6-dimethylbenzonitrile (**24**).* Using the general procedure with 2,6-dimethyl-4*H*-pyran-4-one **22** (0.67 g, 5.4 mmol), ethyl cyanoacetate (1.15 g, 8.6 mmol), KO^{t}Bu (16.2 mL, 16.2 mmol), and 47 h reflux time. Extractions were with ethyl acetate. Product **24** was recovered from the organic phase as an orange/red oil (0.449 g, 57%), and as an off-white solid after purification. Mp 176–176.5 °C (lit[23] 177.5–177.7 °C); υ_{max}/cm^{-1} 3234, 2220, 1608, 1585, 1457, 1321, 1262, 1147, 845, 717, 705; δ_H (400 MHz, $CDCl_3$) 2.48 (6H, s, 2×CH_3), 6.69 (2H, s, H-3 and 5); δ_C (100 MHz, $CDCl_3$), 20.8 (*C*H$_3$), 105.2 (*C*-1), 114.6 (*C*H-3,5), 117.7 (*C*N), 144.6 (*C*-2,6), 158.8 (*C*-O); HRMS (CI): M$^-$, found 146.0611, $C_9H_8O_6N$ requires 146.0606.

*4.2.1.12. Diethyl 4-oxo-4H-pyran-2,6-dicarboxylate (diethyl chelidonate) (**26**).* To a solution of chelidonic acid **25** (10 g, 54.3 mmol) in ethanol (500 mL) was added conc. HCl (50 mL). The reaction mixture was heated at reflux for 24 h, after which time solvents were removed at reduced pressure. The resulting residue was dissolved in water (100 mL) and diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (2×100 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), and dried ($MgSO_4$). Solvents were removed at reduced pressure to give **26** as a light yellow solid (12.85 g, 99%). Mp 61–61.5 °C (lit[24] 62 °C); δ_H (400 MHz, $CDCl_3$) 1.42 (6H, t, J=7.1 Hz, 2×CH_3), 4.46 (4H, q, J=7.1 Hz, 2×CH_2), 7.17 (2H, s, H-2 and 6).

*4.2.1.13. Diethyl 2-nitro-5-hydroxyisophthalate (**27**).* Using the general procedure with diethyl chelidonate **26** (1 g, 4.2 mmol), nitromethane **5** (0.29 g, 4.62 mmol), KO^{t}Bu (12.6 mL, 12.6 mmol), 24 h reflux time. Extractions were with diethyl ether. Product **27** was recovered as a yellow solid (0.548 g, 46%). Mp 84–84.5 °C; υ_{max}/cm^{-1} 3420, 2989, 2902, 1727, 1655, 1546, 1394, 1376, 1250, 1051, 1021, 1002, 823, 760; δ_H (300 MHz, $CDCl_3$) 1.28 (6H, t, J=7.1 Hz, 2×CH_3), 4.29 (4H, q, J=7.1 Hz, 2×CH_2), 7.46 (2H, s, H-4 and 6); δ_C (100 MHz, $CDCl_3$), 13.6 (*C*H$_3$), 63.1 (*C*H$_2$), 120.6 (*C*H-4,6), 127.0 (*C*-1,3), 142.5 (*C*-2), 157.3 (*C*=O), 163.6 (*C*-5); HRMS (CI): MH$^+$, found 284.0761, $C_{12}H_{14}O_7N$ requires 284.0770.

4.2.2. General procedure for microwave-assisted reactions. A vial containing the pyranone, pronucleophile and KO^{t}Bu in dry ^{t}BuOH (7.5 mL) was treated with microwave irradiation for the desired time at the required temperature, as indicated in Table 2. After this time, 1 M HCl (7.5 mL) was added to the reaction mixture, and microwave irradiation continued for a further 10 min at 120 °C. Solvents were then removed at reduced pressure and water (20 mL) was added. The aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic phase was washed with water (2×20 mL), brine (20 mL), and dried ($MgSO_4$). Solvents were removed at reduced pressure to give the product. Characterisation was as above, with the exception of diethyl 2-acetyl-5-hydroxyisophthalate **28** (see Section 4.2.2.1), which gave only trace amounts using conventional heating methods and therefore was not isolated or characterised at that point.

*4.2.2.1. Diethyl 2-acetyl-5-hydroxyisophthalate (**28**).* Using the general microwave-assisted procedure with diethyl chelidonate **26** and acetylacetone **6** under the conditions given in Table 2. Product **28** was recovered as a yellow solid (344 mg, 35%) mp 66–66.5 °C; υ_{max}/cm^{-1} 3512, 2986, 1724, 1688, 1584, 1283, 1243, 1223, 1203, 1034, 1009, 799; δ_H (400 MHz, $CDCl_3$) 1.37 (6H, t, J=7.2 Hz, 2×CH_3), 2.64 (3H, s, CH_3), 4.34 (4H, q, J=7.2 Hz, 2×CH_2), 7.61 (2H, s, H-4 and 6); δ_C (100 MHz, $CDCl_3$) 14.0 (*C*H$_3$), 32.0 (*C*H$_3$), 62.0 (*C*H$_2$), 121.2 (*C*H-4,6), 129.7 (*C*-1,3), 131.6 (*C*-2), 155.7 (*C*=O), 165.0 (*C*–O); HRMS (CI): M$^-$, found 279.0875, $C_{14}H_{15}O_6$ requires 279.0868.

Acknowledgements

Financial support by the BBSRC and GlaxoSmithKline is gratefully acknowledged.

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