Synthesis of 4-methoxysalicylaldehyde via selective monomethylation of 2,4-dihydroxybenzaldehyde

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4-Methoxysalicylaldehyde, a naturally occurring product, has a range of industrial applications in the preparation of organic compounds, drugs and therapeutic agents. 4-Methoxysalicylaldehyde can be synthesised via selective monomethylation of 2,4-dihydroxybenzaldehyde in toluene in the presence of $NaHCO_3$ in higher yield using cheaper reagents with little production of dimethylation product compared to previous methods. The location of the methoxyl group was confirmed by conversion to 3-acetyl-7-methoxycoumarin by condensation with ethyl acetoacetate.

Keywords: 4-methoxysalicylaldehyde, synthesis, monomethylation, 3-acetyl-7-methoxycoumarin

4-Methoxysalicylaldehyde is a naturally occurring compound present in the roots and bark of *Periploca sepium*.[1] It is also a useful building block for the synthesis of a large number of organic molecules and natural products such as chalcones, flavanones, and coumarins.[2–5] In addition, 4-methoxysalicylaldehyde has a range of industrial applications in the preparation of organic compounds, drugs, and therapeutic agents. There are three main methods for the synthesis of 4-methoxysalicylaldehyde starting from resorcinol described in the literature. The first is formylation of 3-methoxyphenol by paraformaldehyde in the presence of the $MgCl_2$-Et_3N base system (Fig. 1).[6–8] The second is demethylation of 2,4-dimethoxybenzaldehyde in the presence of Lewis acid or other reagent (Fig. 2).[9-12] These two methods suffer from shortcomings with regard to multistep reaction (*e.g.*, demethylation of 2,4-dimethoxybenzaldehyde) and costly reagents (*e.g.*, $MgCl_2$-Et_3N, LiCl, $CeCl_3$, BCl_3, and a volatile thiol). Most importantly, the selective formylation or demethylation is not easy and is always accompanied by an isomer.

The third method that appears to be more attractive involves methylation of 2,4-dihydroxybenzaldehyde in alkali condition. The formation of intermolecular hydrogen bond of the phenolic OH group at the 2-position with carbonyl oxygen of aldehyde makes the methylation of the 2-OH more difficult than the 4-OH. Methods relevant to this transformation include K_2CO_3–MeI in acetone under reflux,[3,13] $NaHCO_3$–CH_3Br in DMF under reflux,[14] K_2CO_3–methyl *p*-toluenesulfonate in CH_3CN under reflux,[4] and K_2CO_3–Me_2SO_4 in acetone under reflux.[5] Unfortunately, all the syntheses of 4-methoxysalicylaldehyde in alkali condition published to date suffer from one or more the following disadvantages involving using costly reagents (*e.g.* CH_3I, CH_3Br, and 18-crown-6), low boiling point solvent that is inappropriately recycled in industry (*e.g.* acetone), the formation of a dimethyl product, and a low yield (53–65%). Consequently we considered new reaction conditions for the preparation of 4-methoxysalicylaldehyde. We now report the use of toluene as an efficient solvent and $NaHCO_3$ as a base for the formation of the 4-monomethyl product formation in excellent yield.

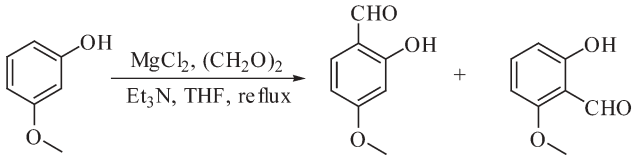

Fig. 1 Formylation of 3-methoxyphenol.

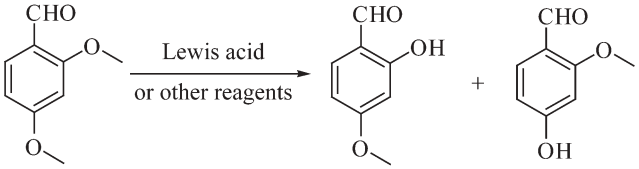

Fig. 2 Demethylation of 2,4-dimethoxybenzaldehyde.

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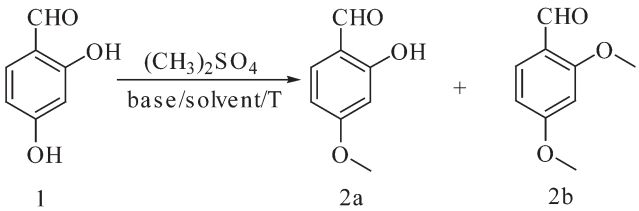
Results and discussion

The 2,4-dihydroxybenzaldehyde **1** was readily prepared via a Vilsmeier reaction. Initial attempts to effect the monomethylation of **1** and Me_2SO_4 for 5 h in the presence of K_2CO_3 in DMF at 70 °C gave the undesired 2,4-dimethoxybenzaldehyde **2b** exclusively (Table 1, entry 1). A decrease in temperature to 40 °C also gave **2b** as the predominate product (entry 2). No reaction was observed when the base was replaced by $NaHCO_3$, even after stirring at 40 °C for 10 h (entry 3). To our delight, when changing the solvent from DMF to acetone, the desired 4-methoxysalicylaldehyde **2a** was obtained in a 51% yield as the major product together with undesired 2,4-dimethoxybenzaldehyde **2b** as the minor product (entry 4). However, the rapid evaporation of the volatile acetone is always hazardous to human health. In addition, the problem of recycling the acetone raised some environmental concerns. Nevertheless, the result showed that $NaHCO_3$ as a base was feasible for the course of this reaction to produce **2a** as the major product. Next, toluene is introduced in the reaction, which has been

Table 1 Optimisation of solvent, base, and temperature



Entry	Solvent	Base	*T*/°C	*t*/h	**2a**/%[a]	**2b**/%[a]	**1**/%[b]
1	DMF	K_2CO_3	70	5	–	92	–
2	DMF	K_2CO_3	40	5	3	86	–
3	DMF	$NaHCO_3$	40	10	–	–	100
4	Acetone	$NaHCO_3$	Reflux	10	51	33	–
5	Toluene	$NaHCO_3$	60	10	–	–	100
6	Toluene	$NaHCO_3$	70	10	16	–	62
7	Toluene	$NaHCO_3$	80	10	57	–	30
8	Toluene	$NaHCO_3$	90	10	83	3	–
9	Toluene	$NaHCO_3$	100	10	63	17	–

[a] Isolated yield. [b] Recovery of starting material.

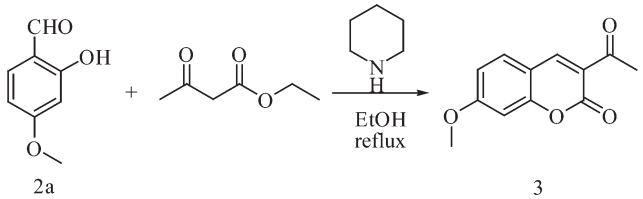
widely accepted by industry due to its high boiling point and environmentally friendly process for fully recycling the solvent. We conducted the reaction in toluene at temperatures ranging from 60 to 100 °C. The results indicated that the temperature played a crucial role, because the methylation, whether monomethylation or dimethylation, did not occur below 70 °C (entry 5). In contrast, the reaction gave a useful result at 70 °C, in which no dimethylation product **2b** was found (entry 6). However, the conversion of starting material **1** was very low. A further increase in the temperature to 80 °C improved the conversion of **1** (entry 7). A reaction temperature of 90 °C was considered to be most suitable to afford desired monomethylation **2a** in toluene (entry 8). Further increasing the temperature to 100 °C, the reaction still went efficiently to provide **2a** as the major product but it was accompanied by the formation of an amount of the undesired dimethylation product **2b** (entry 9).

Although we have proved that monomethylation has occurred under the reaction conditions, we have not yet proved whether or not our compound is 4-methoxysalicylaldehyde **2a** because the structures of **2a** and 4-hydroxy-2-methoxybenzaldehyde have very similar NMR spectra. Consequently, we cannot distinguish these two compounds only according to ^{1}H NMR and ^{13}C NMR data. To confirm the structure of our compound, we studied the reaction of **2a** and ethyl acetoacetate under the basic conditions (Scheme 1). From the results obtained it was clear that the structure of our compound is **2a** since 3-acetyl-7-methoxycoumarin **3** was obtained as the product in high yield.

In conclusion, we have developed a new protocol for the synthesis of 4-methoxysalicylaldehyde using toluene as solvent in the presence of $NaHCO_3$. Compared to the previously reported methods, the advantage of the method described here is that the yield of the product is higher and the reagent is cheaper and there was only a small production of dimethylation product. Particularly noteworthy is that the reaction can be performed in toluene, which allows the fully solvent recycle. This will make the present method potentially useful for industrial applications. With these advantages, we believe the method presented herein will be a valuable complement to existing methods of 4-methoxysalicylaldehyde.

Experimental

Reagents were used as purchased without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz in $CDCl_3$ with chemical shift (δ) given in ppm relative to TMS as internal standard. High resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI).



Scheme 1 Synthesis of 3-acetyl-7-methoxycoumarin.

4-Methoxysalicylaldehyde (**2a**): A solution of 2,4-dihydroxybenzaldehyde (276 mg, 2 mmol), $NaHCO_3$ (840 mg, 10 mmol), and dimethylsulfate (0.9 mL, 10 mmol) in toluene (10 mL) was stirred at 90 °C for 10 h. The reaction mixture was cooled to room temperature and the solid $NaHCO_3$ was filtered and washed with additional toluene. The solvent (toluene) was recycled and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 1/1, v/v) to afford 4-methoxysalicylaldehyde **2a** (458 mg, 83% yield) as a colourless oil, which crystallised to a solid overnight in a freezer, m.p. 39–40 °C (ref.[15] 41–42 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 9.72 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 6.54 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 166.9, 164.6, 135.3, 115.2, 108.4, 100.6, 55.7. HRMS (ESI): *m/z* Calcd for $C_8H_9O_3$ $[M + H]^+$: 153.0552; found: 153.0551. Spectral data matched the reported data.[3]

3-Acetyl-7-methoxycoumarin (**3**): A catalytic amount of piperidine was added to a mixture of **2a** (304 mg, 2 mmol) and ethyl acetoacetate (260 mg, 2 mmol) in ethanol. The mixture was refluxed for 6 h. After cooling to room temperature, the mixture was concentrated and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 2/1, v/v) to afford 3-acetyl-7-methoxycoumarin **3** (370 mg, 85% yield) as yellow crystals. m.p. 170–171 °C (lit.[16] 169 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H), 3.92 (s, 3H), 2.70 (s, 3H). Data matched the reported data.[16]

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