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# A new short synthesis of 5,6-dimethylxanthenone-4-acetic acid (ASA404, DMXAA)

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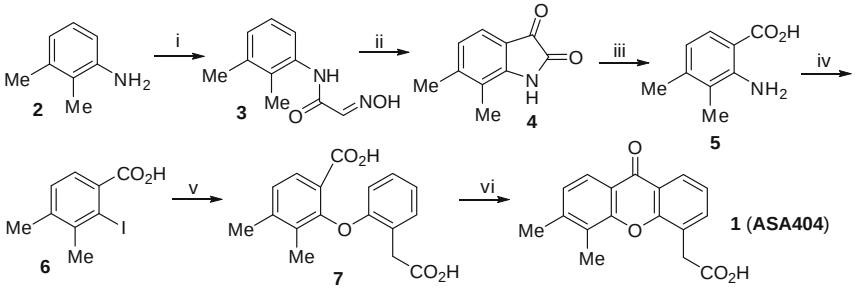
ABSTRACT

A new short synthesis of 5,6-dimethylxanthenone-4-acetic acid (ASA404) is developed. The key steps of the synthesis are dibromination of 3,4-dimethylbenzoic acid, followed by regioselective coupling with 2-hydroxyphenylacetic acid and subsequent cyclodehydration.



5,6-Dimethylxanthenone-4-acetic acid (**1**; ASA404, DMXAA) is the first small-molecule vascular-disrupting agent to enter Phase III trials,[1] which are currently in progress. It selectively attacks established tumour blood vessels through induction of apoptosis in tumour vascular endothelial cells, causing vascular collapse and haemorrhagic necrosis,[2] thereby expanding tumour hypoxia.[3] Phase II studies in non-small cell lung cancer showed that addition of **1** to standard carboplatin/paclitaxel therapy resulted in significant and substantial increases in survival.[4] It has also been suggested for use, in combination with docetaxel, in advanced prostate cancer, on the basis of favourable Phase II results.[5] Since **1** is not a particularly potent drug, with dose levels of up to 4.9 g/m$^2$ reported in human trials,[6] a robust and cost-effective synthesis is of importance. We report here a new, four-step synthesis of **1** from readily available starting materials.

The original synthesis[7] (Scheme 1) proceeded via the key intermediate 2-amino-3,4-dimethylbenzoic acid (**5**). This was prepared from 2,3-dimethylaniline (**2**) by a Sandmeyer[8] condensation with hydroxylamine and chloral hydrate, in a heterogeneous reaction that gave isonitrosoacetanilide **3**, followed by the formation of




**Scheme 1.** Original (Sandmeyer) synthesis of **1.** Reagents and conditions: (i) $Cl_3CCH(OH)_2$, $NH_2OH$, 20–90 °C over 3 h; (ii) $H_2SO_4$, 80 °C, 30 min, 56% over two steps; (iii) $H_2O_2$, KOH, 10 °C, 1 h, 65%; (iv) $HNO_2$, KI, 10–100 °C over 30 min, 65%; (v) 2-hydroxyphenylacetic acid, Cu, TDA-1, 95 °C, 12 h, 63%; (vi) $H_2SO_4$, water (9:1), 80 °C, 10 min, 70%.

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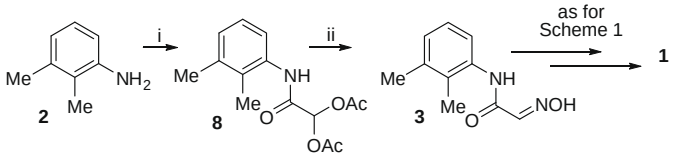
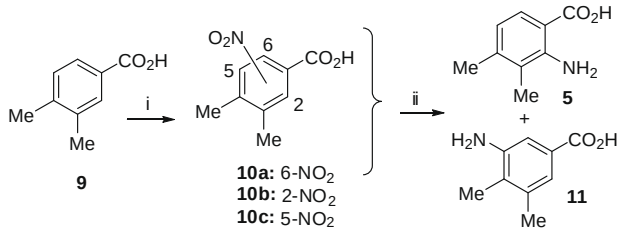
**Table 1**
Comparison of methods for the preparation of **1**

| Method | No. of steps | Overall yield (%) | Reference |
|---|---|---|---|
| Sandmeyer (Scheme 1) | 7 | 15 | 7 |
| Modified isatin (Scheme 2) | 6 | 30 | 10 |
| Nitration (Scheme 3) | 6 | 25 | 12 |
| Dibromination (Scheme 4) | 4 | 51 | This work |




**Scheme 2.** Improved isatin synthesis. Reagents and conditions: (i) $(AcO)_2CHCOCl$, $KHCO_3$, $CH_2Cl_2$, −10 °C to 20 °C, 30 min; (ii) $NH_2OH{\cdot}HCl$, EtOH, $H_2O$, reflux, 2 h, 83% over two steps.




**Scheme 3.** Nitration route. Reagents and conditions: (i) fuming $HNO_3$, −5 °C, 5 min, 94% (ii) $H_2$, Pd, C, 20 °C, 10 h, 98%.

isatin **4** and its subsequent hydrolysis to give **5**. Not unexpectedly for a substrate with an *ortho* electron-donating group,[9] the first step gave **3** as a crude product of low purity, limiting the overall yield of **1** in the seven-step process to about 15% (Table 1). A later[10] improved method for the preparation of **5** by the acylation of **2** with 2,2-diacetoxyacetyl chloride and in situ hydrolysis of the aldehyde diacetate **8** to the aldehyde (Scheme 2) improved the overall yield of **1** to about 30% in a six-step process (Table 1).

A second alternative route to **5** via the reported[11] direct nitration of 3,4-dimethylbenzoic acid (**9**), followed by reduction, was also explored[12] (Scheme 3). The initial mixture of the three nitro isomers (**10a–10c**; ratio 1:2:1) obtained was purified by crystallisation to give a 3.4:1 mixture of **10b** and **10c** only. Hydrogenation of this mixture, followed by crystallisation gave **5** in 42% overall yield from **9**, resulting in an overall yield of **1** of about 25% in six steps (Table 1). While this was broadly comparable to Scheme 2, the careful fractional crystallisation of isomer mixtures required was a potential drawback for large-scale synthesis.

A completely different approach to the synthesis of **1** (Scheme 4) was prompted by a publication[13] showing that 3,4-dimethylbenzoic acid (**9**) could be brominated directly to give 2,5-dibromo-3,4-dimethylbenzoic acid **(12)** as the main product. We found that the 5-Br group in **12** activated the 2-Br to allow regioselective coupling with anilines or phenols, and moreover was easily removed by hydrogenation. Thus bromination of **9** with bromine and silver nitrate, as reported, gave the 2,5-dibromo derivative **12** in good yield after a single crystallisation from ethanol.[14] Coupling of **12** with 2-hydroxyphenylacetic acid using the previously reported method[7] gave bromo diacid **13**, which was cyclodehydrated with concd $H_2SO_4$ to bromoxanthenone **14**,[15] which was purified by crystallisation. Hydrogenation of **14** gave **1** in an overall yield of 51% in four steps (Table 1). The last two steps in the process can be reversed, hydrogenating **13** to give the known[7] diacid **7**, which is then cyclodehydrated to **1** in similar overall yield.[16] Alternatively, bromination of **9** with NBS in sulfuric acid, which was successfully used for 5,8-dibromoquinoline,[17] gave a similar result[18] thus avoiding the use of expensive silver nitrate. Traces of dibromo isomers and of monobromo and tribromo impurities in this preparation of **12** did not couple, allowing the preparation of pure **7** by the above route.

In conclusion, an efficient and general synthesis of 5,6-dimethylxanthenone-4-acetic acid (ASA404, DMXAA) is developed using 3,4-dimethylbenzoic acid as starting material. This four-synthetic step process employs relatively inexpensive reagents, does not involve any heterogeneous, low-temperature or exothermic reactions and produces only crystalline intermediates, making it easily scalable.

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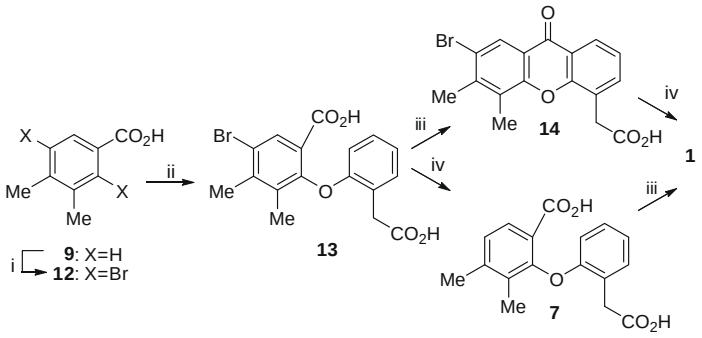
14. *Procedure for dibromination*: A solution of 3,4-dimethylbenzoic acid (**9**) (3.0 g, 20 mmol) in acetic acid (60 mL) was treated with 65% nitric acid (13 mL),


**Scheme 4.** Dibromination route. Reagents and conditions: (i) $Br_2$, AcOH, $HNO_3$, $AgNO_3$, 20 °C, 16 h, 75%; or NBS, $H_2SO_4$, 20 °C, 16 h, 80%; (ii) 2-hydroxyphenylacetic acid, Cu, TDA-1, 85 °C, 4 h, 68%; (iii) $H_2SO_4$, water (9:1), 80 °C, 10 min, 95%; (iv) $H_2$, Pd, C, 99%.

followed by bromine (2.4 mL, 7.49 g, 47 mmol) and a solution of silver nitrate (8.0 g, 47 mmol) in water (50 mL). The mixture was stirred at room temperature overnight, and the precipitate was then collected by filtration and washed with water. The solid was dissolved in ethanol and filtered to remove silver bromide, and the filtrate was concentrated under reduced pressure to give 2,5-dibromo-3,4-dimethylbenzoic acid (**12**) as a white powder (4.5 g, 75%), which was used directly: mp (EtOH) 131–134 °C [lit.[13] mp 195–196 °C]; $^1$H NMR [$(CD_3)_2SO$] $\delta$ 7.68 (s, 1 H), 2.48 (s, 3 H), 2.46 (s, 3 H).

15. *Procedure for coupling and cyclodehydration*: Crude **12** (2.56 g, 8.3 mmol) was converted into its potassium salt and dried thoroughly. The anhydrous disodium salt of 2-hydroxyphenylacetic acid [prepared from the corresponding acid (1.27 g, 8.35 mmol) and Na (284 mg, 12.3 mmol) in MeOH followed by evaporation] was dissolved in anhydrous DMSO (15 mL) and tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1, 1.0 mL) was added. The mixture was stirred at room temperature with the exclusion of moisture until homogeneous. Copper(I) chloride (350 mg) and the powdered potassium salt of **12** were then added, and the reaction mixture was stirred at 85 °C for 4 h. After work up, the crude 5-bromo-2-[2-(carboxyl(methyl)phenoxy]-3,4-dimethylbenzoic acid (**13**) was cyclodehydrated in concd $H_2SO_4$ (55 mL) and water (20 mL) at 90 °C for 30 min, then worked up and the product crystallised from EtOAc/MeOH to give 7-bromo-5,6-dimethyl-9-oxo-9*H*-xanthen-4-ylacetic acid (**14**) (2.0 g, 68% over two steps) as a pale yellow solid: mp 230–231 °C; $^1$H NMR [$(CD_3)_2SO$] $\delta$ 8.12 (s, 1 H), 8.06 (dd, $J$ = 7.9, 1.7 Hz, 1 H), 7.79 (dd, $J$ = 7.3, 1.6 Hz, 1 H), 7.42 (dd, $J$ = 7.6, 7.6 Hz, 1 H), 3.98 (s, 2 H), 2.49 (s, 3 H), 2.48 (s, 3 H); $^{13}$C NMR $\delta$ 175.0, 171.6, 153.6, 152.1, 143.3, 136.9, 128.0, 125.6, 125.3, 124.5, 123.9, 120.2, 120.0, 119.7, 53.3, 20.3, 12.4. Anal. calcd. for $C_{17}H_{13}BrO_4.H_2O$: C, 53.85; H, 3.99. Found: C, 54.19; H, 3.73.
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18. *Alternative bromination with NBS*: NBS (7.1 g, 40 mmol) was added to a solution of **9** (3.0 g, 20 mmol) in concd $H_2SO_4$ (20 mL) at room temperature, and the mixture was stirred overnight at room temperature and poured onto crushed ice (10 × the volume of $H_2SO_4$). The solid was filtered and air-dried and crystallised from EtOH to give **12** in 80% yield.