Practical and Efficient Synthesis of Tris(4-formylphenyl)amine, a Key Building Block in Materials Chemistry

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Abstract: A short, practical and efficient preparation of tris(4-formylphenyl)amine, a key building block in materials chemistry, is described. It involves a two-flask synthesis from triphenylamine, which requires shorter overall time than the direct one-flask threefold Vilsmeier–Haack formylation, while giving higher yields. The reaction levels off at the disubstitution stage, due to the deactivation of the bis-iminium intermediate, but hydrolysis of the latter into a less deactivated dialdehyde allows the third formylation to occur. The simple experimental protocol makes this method more convenient than the previously reported procedures.

Key words: materials chemistry, building block, aldehydes, electrophilic aromatic substitutions, Vilsmeier–Haack reaction

The popularity of tris(4-formylphenyl)amine (**1**; Figure 1) as a building block is rapidly growing in materials chemistry. It is used for the synthesis of many materials, with various applications, including electrophotographic photoreceptors,[1,2] hole transport materials,[3–5] TiO_2 electrode sensitizers for solar cells,[6] polymers for non-doping emitting materials,[7] dendrimers,[8,9] octupoles for second harmonic generation (SHG),[10,11] as well as octupolar, multibranched and dendritic chromophores for two-photon absorption (TPA).[12–22]

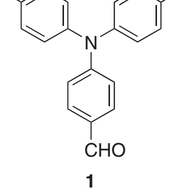

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Figure 1

However, there was until now, no practical and efficient synthesis of **1** described in the literature. The shortest pathway could be the direct threefold Vilsmeier–Haack formylation of triphenylamine (**2**), but regardless of some erroneous patents,[3,23] the reported yields remained finally low, ranging between 6–7%[4,7] and 18% (using 40 equiv of $POCl_3$ at 95–100 °C for 48 h).[24] Tris(4-formylphenyl)amine (**1**) could also be prepared from tris(4-lithiophenyl)amine and DMF, but no procedure or yield was given.[11] Finally, the two last pathways, involving a three-step sequence[8] (based on triple bromination, cyanation and controlled reduction) or a four-step sequence[16] (based on monoformylation, double bromination, protection of the aldehyde, and double bromine-lithium exchange with *t*-BuLi followed by treatment with DMF), are difficult to scale up (Scheme 1).

A shorter, simple and reliable synthesis of **1** was therefore required. Despite that the Vilsmeier–Haack formylation of triphenylamine was low-yielding in **1**, 4-formyltriphenylamine (**3**) could be obtained using a single equivalent of $POCl_3$ in 94% yield, and 4,4′-diformyltriphenylamine (**4**) was reported to be obtained in 71% yield using 10 equivalents of $POCl_3$.[24] It was obvious that the introduction of electron-withdrawing groups on the triphenylamine deactivates the system too much for allowing the third substitution to proceed significantly. The reactions levels off at the disubstitution stage and competes with other degradation pathways.

Our basic idea was that under the Vilsmeier–Haack conditions, the intermediates (as for example the bisiminium **4a**) leading to dialdehyde **4** were even more deactivated than **4**, and that, consequently, a hydrolysis at this stage should be performed, before attempting the third substitution (Scheme 2).

We describe in this paper the optimization of the synthesis of dialdehyde **4** and the investigation of the reaction conditions for the conversion of **4** into **1**.

Repeating the same conditions as in ref.[24] (Table 1, entry 1), we were not able to reproduce the reported results (i.e. 3% of **3** and 71% of **4**). Indeed, in our hands, the main product was the monoaldehyde **3**, along with a smaller amount of the expected dialdehyde **4**. Using larger excess of phosphorus oxychloride and longer reaction times led to the full conversion of triphenylamine (**2**) into **4** and **1** (entries 2 and 3), but also to degradation. It should be noted that increasing the temperature from 95 °C (entry 2) to 105 °C (entry 3) does not lead to an increase in the yield of **1**. In addition, the yield of **4** significantly decreases, the degradation processes being favored. Finally, an important parameter was found to be the $POCl_3$/DMF ratio, and comparison between entries 2 and 4 is illustrative for that purpose.

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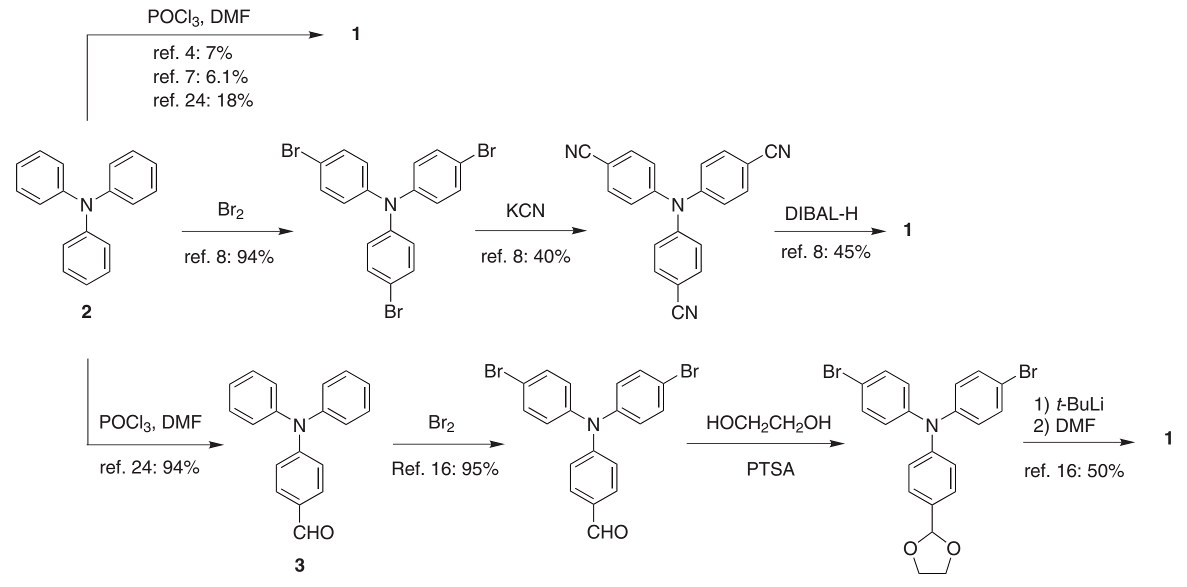
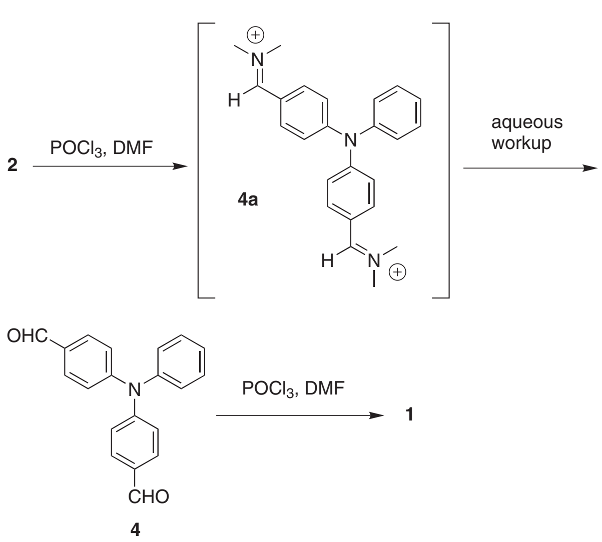


Scheme 1

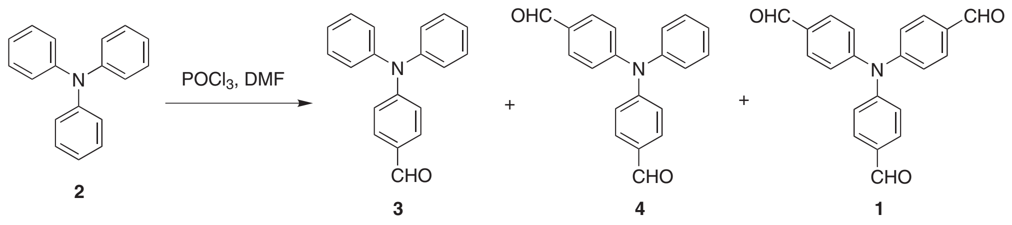


Scheme 2

Indeed, a slight variation of this ratio from 21:25 to 25:23 reduced the degradation very significantly, and the expected dialdehyde **4** could thus be obtained in 81% yield along with 10% of trialdehyde **1** (Table 1, entry 4).

The conversion of dialdehyde **4** into the trialdehyde **1** under Vilsmeier–Haack conditions was then examined. It was first found that the reaction temperature should be kept below 100 °C and that the best reaction time was 1.5 hours. For longer reaction times, the slight increase in conversion was counterbalanced by a parallel increase of the degradation. The optimization of the amounts of phosphorus oxychloride and DMF is summarized in Table 2. We started with a fixed amount of 100 equivalents of $POCl_3$ (Table 2, entries 1–4), varying the quantity of DMF; reduction of the excess of DMF led to very significantly improved conversion rates and yields of **1**, together with lowering of the degradation. For a fixed $POCl_3$/DMF ratio, decreasing the amount of phosphorus oxychloride, from 100 equivalents to 50 equivalents (entry 5 vs. entry 3, and entry 6 vs. entry 4) did not decrease the conversion

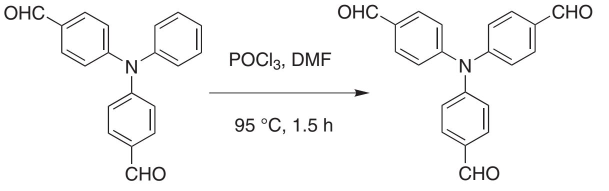
Table 1 Direct Vilsmeier–Haack Formylation of Triphenylamine



Entry	$POCl_3$ (equiv)	DMF (equiv)	Reaction temp (°C)	Time (h)	Isolated Yields (%)		
					3	**4**	**1**
1	10.5	25	95	6	57	19	0
2	21	25	95	15	0	49	16
3	21	25	105	15	0	28	17
4	25	23	95	4	1	**81**	10

rate. By finely tuning the $POCl_3$/DMF ratio around 1 (entries 6 and 7), we found that the best results were obtained for a ratio slightly higher than 1, i.e. by using less DMF than phosphorus oxychloride. Finally, by using such a ratio (entries 7–9), the quantity of Vilsmeier–Haack reagent could be reduced to about 20–25 equivalents (such as for entry 8), allowing minimal degradation while keeping the yield of **1** at 94%. When the amount of reagent was further reduced to below 20 equivalents, the mixture became highly viscous, preventing stirring (keeping in mind that the reactions were performed without any solvent),[25] and a decrease of the conversion rate was observed (entry 9).[26]

Table 2 Investigation of the Conversion of Dialdehyde **4** into Trialdehyde **1**



4 **1**

Entry	$POCl_3$ (equiv)	DMF (equiv)	Unreacted **4** (%)[a]	Yield of **1** (%)[a]
1	100	800	34	28
2	100	400	26	40
3	100	200	20	56
4	100	110	12	82
5	50	100	25	63
6	50	55	16	82
7	50	49	3	**95**
8	25	23	6	**94**
9	5	4.9	15	83

[a] Yields determined by HPLC analysis.

In order to reduce the reaction times, the microwave activation was also tested. It appears that although the reaction proceeds indeed faster, in our hands, this process is not as efficient as the thermal one, in terms of yield/degradation rate trade-off, probably due to the absence of a fine local temperature control.

Finally, the two-flask synthesis of trialdehyde **1** from triphenylamine (**2**) was carried out with 52% isolated yield on the gram scale as follows: i) $POCl_3$ (25 equiv), DMF (23 equiv), 95 °C, 4 h; ii) hydrolysis and isolation, but without purification; iii) $POCl_3$ (25 equiv), DMF (23 equiv), 95 °C, 1.5 h. This method could easily be scaled up without any loss of yield.

In summary, we have described a short, practical and efficient preparation of the key building block **1**. This two-flask synthesis requires shorter overall time than the direct one-flask threefold formylations, while giving higher yields. The simple experimental protocol makes this method more convenient than the previously reported procedures.

Phosphorus oxychloride and DMF were dried and distilled prior to use. Reversed phase HPLC analyses were obtained with a Miltonroy CM4000 HPLC instrument using a RP Nova-Park C_{18} column; eluent: CH_3CN–aqueous buffer solution (60:40, 20 mM $AcONH_4$, 1% AcOH); 1 mL/min; 30 °C; UV detection at 254 nm; retention times: t_R (**1**) = 2.79 min, t_R (**4**) : 4.37 min, t_R (**3**) = 8.60 min, t_R (**2**) = 19.66 min. Column chromatography was performed with Merck silica gel Si 60 (40–63 μm, 230–400 mesh). Melting points were determined on an Electrothermal IA9300 digital melting point instrument. NMR spectra were taken on a Bruker ARX 200 spectrometer in $CDCl_3$ solutions; ^1H chemical shifts (δ) are given in ppm relative to TMS as internal standard, and J values are given in Hz.

Investigation of the Conversion of 4 into 1; General Procedure

Phosphorus oxychloride and DMF were added into 20 mL vials containing micro stir bar. Dialdehyde **4** (50 mg, 0.166 mmol) was added, and the mixture was stirred at 95 °C. The reactions were monitored by HPLC after 30 min, 45 min, 1 h, 1.5 h, 3 h and 5 h. The best results were obtained for 1.5 h reaction time.

Tris(4-formylphenyl)amine (1); Two-Flask Procedure from Triphenylamine (2)

Phosphorus oxychloride (9.5 mL, 101.9 mmol) was added dropwise at 0 °C under Ar to DMF (7.26 mL, 93.8 mmol) and the reaction mixture was stirred for 1 h. Triphenylamine (1.00 g, 4.08 mmol) was added, and the resulting mixture was stirred at 95 °C for 4 h. After cooling to r.t., the mixture was poured into ice-water (200 mL), and basified with 1 M NaOH. After extraction with CH_2Cl_2 (200 mL), the organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4) and filtered over a short pad of silica gel. The solvent was then removed under reduced pressure and the residue was added on an ice-cooled mixture of $POCl_3$ (7.6 mL, 81.5 mmol) and DMF (5.78 mL, 74.6 mmol). The resulting mixture was stirred at 95 °C for 1.5 h, and after cooling to r.t., poured into ice-water (200 mL), and basified with 1 M NaOH. After extraction with CH_2Cl_2 (200 mL), the organic layer was washed with water (3 × 50 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by column chromatography (CH_2Cl_2) to yield **1** (0.690 g, 52%, HPLC purity >99%) as a yellow solid; mp 233–235 °C (Lit.[24] 230–232 °C).

^1H NMR (200.13 MHz, $CDCl_3$): δ = 9.95 (s, 3 H), 7.85, 7.26 (AA′XX′, J_{AX} = 8.6 Hz, 12 H).

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