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COMMUNICATION

A more efficient synthesis of 4,4',4"-tricarboxy-2,2':6',2"-terpyridine†

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We report in this paper a new route for the synthesis of 4,4',4''-tricarboxy-2,2':6',2''-terpyridine. This synthetic pathway has a lower ecological impact with respect to yield, atom economy, solvent and chemicals used and wastes generated when compared to a previously reported method. In addition it uses furfural, which can be obtained from renewable sources. The title compound can be used to prepare complexes that are valuable for applications in Dye Sensitized Solar Cells.

Dye-sensitized solar cells¹⁻³ (DSSC) have been widely studied over the past decades. Based on sensitized nanocrystalline TiO₂, the DSSC concept, developed by Grätzel and coworkers,⁴ is a low cost promising technology to produce electricity. While organic dyes have been investigated for a few years,^{5,6} polypyridyl ruthenium dyes are known to be the best sensitizers for DSSC.⁷

N3 Dye (Fig. 1), which is a bipyridine-based dye,⁴ was initially used, providing DSSC with efficiencies near 10%. The tricarboxy-terpyridine based complex "Black dye" (Fig. 1) was introduced later⁸ as an even more efficient sensitizer that reached a solar energy conversion efficiency over 10%. This sensitizer shows a strong and large absorption over the visible range and a good grafting onto TiO₂ films. Many others complexes bearing this ligand[‡] have been synthesized and investigated with good



Fig. 1 The structures of N3-dye (left) and Black-Dye (right).

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† Electronic supplementary information (ESI) available: Experimental procedures and detailed green metrics calculations. See DOI: 10.1039/c1gc15808b overall efficiencies. For comparison, a similar complex bearing only one acid function on the terpyridine has been characterized with solar energy conversion efficiency about half of that reached by the 'black dye'.⁹ The three carboxylic acid functions allow strong anchoring on the TiO_2 surface and afford an improved withdrawing effect that can explain such performances.

Preparation of "Black-Dye" and analogous complexes requires the 4,4',4''-tricarboxy-2,2':6',2''-terpyridine ligand **1** (Fig. 2) to be synthesized.



Fig. 2 The chemical structure of 4,4',4"-tricarboxy-2,2':6',2"-terpyridine.

Ligand **1** has been previously prepared by self condensation of 4-picoline or 4-ethylpyridine to afford alkyl terpyridines followed by potassium dichromate oxidation.^{8,10-12} As a part of our work dedicated to the preparation of new sensitizers for DSSC, we propose herein a new route for the preparation of **1**.

This new pathway (Scheme 1) starts with preparation of ethyl 2-acetyl isonicotinate 2 by radical acylation of ethylisonicotinate. Introduction of the acetyl group was chosen since acetylpyridine derivatives are widely used as starting materials for the preparation of terpyridines.¹³⁻¹⁶ In addition, isonicotinate derivatives have been successfully used for the preparation of 4,4"-carboxy-functionalized terpyridines.17-19 In order to introduce the carboxy group at position 4' of the terpyridine, a furyl substituent, which can be considered as a latent carboxylic acid,²⁰ was introduced. In fact this methodology has been used many times in the terpyridine series.²¹⁻²⁴ Therefore 2 was reacted with furfural and potassium hydroxide in the presence of aqueous ammonia.²⁵ This one pot protocol was selected owing to its simplicity and the use of environmentally benign solvents, such as ethanol and water. In addition, this steps uses furfural as a reagent, which can be isolated from biomass.²⁶ Since the reaction is performed in a basic media, hydrolysis of the two esters is concomitant with terpyridine formation and the dicarboxylate salt 3 was obtained. To date, the nature of



Scheme 1 The new synthetic pathway A for the preparation of 1.

the counter cation is not clearly determined (K⁺ or NH₄⁺?). Any effort to obtain pure **3** failed and elemental analysis of the crude product differs from calculated values. Therefore yield calculation was made on the basis of a potassium salt, which gave the lowest value. Nevertheless, work is ongoing to determine the exact nature of **3**. In order to gain further information concerning the structure of compound **3**, its corresponding diacid **4** (Fig. 3) was isolated for analytical purposes. Oxidation of the furyl ring is performed on crude **3**. A first experiment was made in refluxing water as a solvent, and **1** was isolated in 35% yield after 4 h of reaction. Nevertheless, the reaction proved to be as efficient as if made at room temperature by simply increasing the reaction time to 24 h.

The environmental impact of this method was compared to the original synthesis (pathway B) of 1 (Scheme 2).

Self coupling of 4-alkylpyridine in the presence of palladium as a catalyst afforded a mixture of bipyridine and terpyridine derivatives.^{27,28} This methodology was employed for the prepa-







Scheme 2 The original route to 1 (pathway B).

ration of 4,4',4''-triethyl-2,2':6',2''-terpyridine **5** using palladium on carbon as the catalyst, with a 20% yield. Since compound **6** was also obtained during this process, a separation step is required. The latter was accomplished by sublimation of **6** from the mixture. The final step involved oxidation of ethyl substitutents with potassium dichromate to afford the desired carboxy-terpyridine **1** in 36% yield.

Green metrics were calculated for both routes. The first parameter to be evaluated is overall yield. The new method exhibits a 36% yield over the three steps while original method was limited to 7.2% (over two steps). Clearly, pathway A provides a great improvement.

The second important parameter that was estimated is atom economy²⁹ (AE). The latter for pathway A was found to be 14.12% while the calculated AE for pathway B is 8.23%. Despite the fact that the first step in route B is very efficient in terms of atom economy, the overall process is penalized by the oxidation that requires large amounts of potassium dichromate and

sulfuric acid. When regarding each step separately in pathway A, one can observe that each step has a limited efficiency. Nevertheless, the whole process has a better AE than route B.

The E factors³⁰ were calculated for both pathways. Calculations for a multistep synthesis can be made using a tree analysis.³¹ In the present case, another protocol was used. Namely, the E factor was calculated for each step, reported in the next one and so on till the end of the process. By applying this method, the E factor was found equal to 106.6 g waste per g final product for pathway A. Estimation for pathway B was made on the basis of amounts reported in litterature.¹¹ When doing calculations, two problems appeared with pathway B. The first one is the Pd catalyst. Of course it can be reused for multiple experiments and this fact should be taken into account in calculations. The second problem relies in that the starting 4-ethylpyridine is not entirely consumed and therefore its excess could be recovered and reused. Since there is no data dealing with these two points, two scenarios were envisioned. The first one assumes no reclaiming of both catalysts and 4ethylpyridine. Obviously the latter is the worst case possible and is not suitable for comparison. The second scenario is based on twenty uses of catalyst (average 0.2 g per experiment) and full recovery of unused 4-ethylpyridine. The amount of the latter was calculated by taking into account the amount of intermediate 5 that is formed, but neglect the bipyridine by-product (no data available concerning quantities of this molecule). As a consequence, the amount of 4-ethylpyridine that could be recovered is overestimated and real E factor should be lower than the calculated value. So the E factor for pathway B was found to be 336.36 g waste per g of final product, according to the "best" scenario. Values for both pathways are high, but the new route has an E factor that is approximately one third of that of the original process, which is a great improvement. This can be explained by the use of less solvent in work-up procedures and less reagents in the oxidation step conjugated to a better overall yield.

While not directly related to environmental impact, price for the product is also an important parameter. In fact, if one wants solar energy to develop further, it is necessary to keep DSSC's cost as low as possible to be competitive. This implies price control for all fabrication stages, including dye synthesis. The price for the final product was estimated to be $4.66 \in g^{-1}$ using pathway A and $5.61 \notin g^{-1}$ with pathway B (in the best case). It is interesting to note that electrical consumption was not included in cost calculation. Nonetheless, the first step in pathway B requires 9 days heating at 170 °C, which is much more than the total heating time in pathway A (including work-up and purification). Therefore the new route is clearly less energy greedy than the original one.

Finally, EcoScale parameter³² was used as an additional tool for environmental impact assessment. EcoScale is interesting because it includes points such as toxicity and hazards of reagents and solvents, price, setup and purification. The higher the EcoScale is, the better the process is. Pathway A has a value of 19,1 while it was estimated to be 3,6 for pathway B. again the new route appears to be better. This could be partly explained by the use of a toxic and carcinogenic Cr(vI) salt for the oxidation³³ that is avoided with the new route. In addition, the overall yield for pathway B is much lower compared to that of

Table 1 Green metrics summary for the two proces

	Pathway A	Pathway B
Yield (overall %)	36	7.2
Atom economy (%)	14.99	8.23
E factor $(g g^{-1})$	106.06	336.36
EcoScale	19.1	3.6
$Cost \ (\in g^{-1})$	4.66	5.61

route A. All the results for the green metrics are summarized in Table 1.

In conclusion, we have developed a new process for the preparation of the ligand 4,4',4"-tricarboxy-2,2':6',2"-terpyridine. The principles of green chemistry are fully applied since this new route generates less waste and avoids the use of dangerous chromium salts. It also employs a reagent (furfural) that could be obtained from renewable sources. Furthermore, the obtained compound can be used for the preparation of sensitizers useful in the field of solar cells with the final aim of producing "green" electricity. Future work will focus on further characterization of intermediate **3**, and on preparing new sensitizers that include ligand **1** in order to enhance performance of DSSCs. In addition, owing to recent literature, it should be possible to further improve the synthesis of **1**, for example by modifying the oxidation of the alkyl chains.^{34,35}

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Notes and references

[‡] A SciFinder search performed on January 2011 indicates more than 300 substances including this ligand.

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