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Synthesis of 4′-substituted 2,2′:6′,2″-terpyridines via a Mitsunobu reaction

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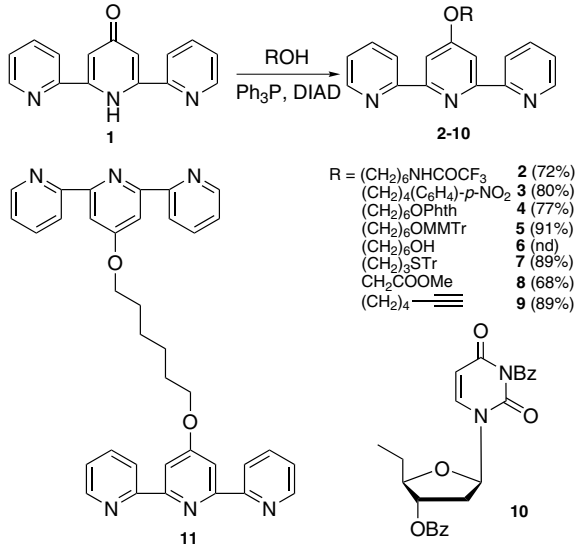
Abstract—Treatment of 2,6-di(pyridin-2-yl)pyridin-4(1*H*)-one with various appropriately protected ω-substituted primary alcohols or a nucleoside (3,3′-*O*-diBz-dUrd) in dry THF in the presence of triphenylphosphine and diisopropylazodicarboxylate gives the corresponding 4′-substituted terpyridines in high yield.

2,2′:6′,2″-Terpyridine and its derivatives are well-known metal complexing ligands.[1] For example, terpyridine-based lanthanide(III) chelates are among the best luminescent europium(III) chelates used as nonradioactive markers in a wide variety of routine and research applications.[2–8] Terpyridine derivatives have also been used as building blocks for supramolecular structures and nanotechnology as well as RNA cleavage agents.[9]

In several applications, preparation of substituted 2,2′:6′,2″-terpyridines is needed. Most conveniently, the substituent is attached at the central pyridine ring, because the synthetic strategies are versatile and well established.[10] For example, for the preparation of 4′-terpyridyl ethers with an ω-substituent, two methods are commonly applied. The method of Newkome and He[11] involves nucleophilic substitution of 4′-chloro-2,2′:6′,2″-terpyridine with various ω-substituted alcohols or thiols in the presence of an excess of KOH in DMSO at elevated temperature.[11–13] Although the reactions proceed in high yield, the rather drastic reaction conditions limit the type of linker that can be used. Furthermore, since an excess of alcohol is often required, the method is not very suitable for direct introduction of complicated or expensive tether molecules.

Another tethering strategy, developed by Constable and co-workers,[14] involves an S_N2 reaction between the nucleophilic 2,6-di(pyridin-2-yl)pyridin-4(1*H*)-one and a tether molecule bearing a good leaving group in its structure. Although this method allows the introduction of even more complicated molecules, such as carbohydrates[15] in moderate yield, the reactions have to be performed under basic conditions at elevated temperatures for prolonged times.

The Mitsunobu reaction is widely applied in the synthesis of arylalkyl ethers.[16] The same reaction was used here for terpyridine derivatization (Scheme 1).



Scheme 1.

Keywords: Terpyridine; Mitsunobu reaction.
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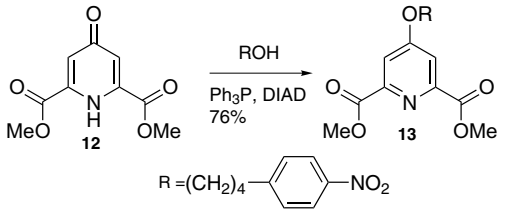
Accordingly, treatment of 2,6-di(pyridin-2-yl)pyridin-4(1*H*)-one **1** with an equimolar amount of appropriately protected ω-substituted primary alcohol or a nucleoside (3,3′-*O*-di-Bz-dUrd) in dry THF in the presence of triphenylphosphine (Ph_3P) and diisopropylazodicarboxylate (DIAD) gave the desired terpyridine derivatives (**2**–**5**, **7**–**10**) in high yields.[17] In all cases, the reaction was complete in a few hours at ambient temperature. Purification was performed on a column of basic aluminum oxide. In contrast, attempts to prepare 4′-(6-hydroxyhexyloxy)-2,2″:6′-2″-terpyridine **6** using unprotected hexane-1,6-diol were less successful: an excess of alcohol had to be used in order to avoid the formation of bis-terpyridine terminated ligand, **11**. Furthermore, oxepane formation[18] was a serious side reaction decreasing the yield of the desired product.

The compounds synthesized were characterized by ESI-TOF MS and ^1H NMR, and the spectra were in accordance with the proposed structures. The site of terpyridine alkylation was confirmed as $O^{4'}$-based on the ^1H NMR chemical shifts of the terpyridine 3′- and 5′-protons (ca. 8.0 ppm)[11–13] as well as on the chemical shifts of the linker α-methylene groups, which appeared as triplets at ca. 4.2 for compounds **2**–**7** and **9**, and as a singlet at 4.88 ppm for compound **8**. The sugar 5′- and 5″-protons of the nucleoside derivative **10**, in turn, appeared as doublets of doublets at 4.73 and 4.68 ppm, respectively.

As demonstrated here, the present method is suitable for the introduction of various functional groups, such as amino, ester, hydroxy, aminooxy, mercapto, alkyne, and carboxylic acid to the terpyridine structure. Because the reaction conditions are mild and only an equimolar amount of the tether molecule is required, introduction of rather complicated structures, such as nucleosides is possible. The only requirements are that the tether molecule has a hydroxy group in its structure and that other functional groups are protected. When required, the protecting groups can be removed by standard procedures.[19] However, it is worth noting that it is not possible to tether *N*-protected serine esters to **1** via the Mitsunobu reaction, because the amino acid undergoes dehydration to give the corresponding dehydroamino acid.[20] Thus, exploitation of the present tethering strategy to peptide chemistry requires the use of amino acid derivatives where the intramolecular reaction is not possible, such as appropriately protected homoserines.[21]

The present tethering strategy is not limited to the preparation of terpyridine 4′-ethers, but is applicable to pyridine derivatization as well. For example, reaction of chelidamic acid dimethyl ester[22] **12** with 4-(4-nitrophenyl)-butan-1-ol in the presence of Ph_3P and DIAD gave the corresponding C4-derivatized pyridine **13**[23] (Scheme 2).



Scheme 2.

In summary, a versatile method for the preparation of 4′-functionalized 2,2′:6′,2″-terpyridines via Mitsunobu alkylation is demonstrated. The synthesis of various terpyridine and pyridine-based metal chelates exploiting the presented tethering strategy is in progress in our laboratory.

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17. *Representative procedure*. 2,6-Bis(pyridin-2-yl)pyridin-4(1*H*)-one (3.0 g, 12.2 mmol), 4-(4-nitrophenyl)butan-1-ol (2.65 g, 13.57 mmol), and Ph_3P (3.56 g, 13.57 mmol) were dissolved in dry THF (50 mL). DIAD (2.67 mL, 13.57 mmol) was added dropwise and the mixture was stirred for 2 h at room temperature and then concentrated. Purification on activated basic aluminum oxide (150 mesh, Brockmann I) using dichloromethane as the eluent followed by precipitation from diethyl ether yielded compound **3** as a white powder (4.2 g, 80%). Mp 115–116 °C. ^1H NMR ($CDCl_3$): δ 8.70 (2H, m); 8.63 (2H, td,

$J < 1$ and 7.9); 8.16 (2H, d, J 8.8); 8.01 (2H, s); 7.86 (2H, dt, J 1.8 and 6.1); 7.37 (2H, d, J 8.8); 7.34 (2H, m); 4.27 (2H, t, J 5.5); 2.83 (2H, t, J 7.1); 1.91 (4H, m). ESI-TOF MS: $[M+H]^+$ obsd 427.177; calcd for $C_{25}H_{23}N_4O_3^+$ 427.177.

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23. Synthesized as described for compound **3**, but purification was performed on silica gel (eluent 1% (v/v) MeOH in CH_2Cl_2) followed by precipitation from diethyl ether. Compound **13**: Mp. 111 °C. ^{1}H NMR ($CDCl_3$): δ 8.07 (2H, d, J 8.8); 7.72 (2H, s); 7.29 (2H, d, J 8.8); 4.10 (2H, t, J 5.9). 3.93 (6H, s); 2.74 (2H, t, J 7.1); 1.85 (4H, m). ESI-TOF MS $[M+H]^+$ obsd 389.1347; calcd for $C_{19}H_{21}N_2O_7^+$ 389.1349.