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Synthesis of a novel carboxy functionalized PyOX-ligand

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Abstract—A short and convenient synthesis of a carboxy functionalized PyOX-core is presented. The carboxy functionality offers a wide variety of possibilities for further modification. In this paper, the core is functionalized with a mercapto tail.
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In the late 1980s, non- C_2 -symmetric oxazoline ligands and especially the 2-(2'-pyridyl)oxazolines (PyOX) were shown to be excellent ligands in asymmetric synthesis. Chiral PyOX-ligands have been used in, e.g. hydrosilylation¹ and Michael reactions.² In the late 1990s, C_1 -symmetric PyOX was also found to be an outstanding ligand in Pd-catalyzed allylic alkylation reactions,³ being superior to the C_2 -symmetric ligands (e.g. PyBOX) due to its ability to form two different palladium complexes.^{3a} The metal complex forming ability of the PyOX-core also confers biological activity, e.g. as iron chelators.⁴

We present herein a new and convenient method to construct PyOX-ligands substituted with functionalities suitable for further conversion, e.g. to nanomaterials. Our approach is based on amido alcohol formation, mesylation and base-assisted cyclization. To our knowledge, this general method has only been tried by Meyers,⁵ using long reaction times. In our hands, the cyclization in this one-pot protocol required very long reaction times and prolonged heating to complete, which led to dark coloured reaction mixtures, as also observed by Wuts.⁶ PyOX-ligands have usually been prepared by longer synthetic routes from 2-pyridyl nitriles by heating with an amino alcohol in a solvent with a metal salt catalyst like $ZnCl_2$,^{7a} $CuCl_2$ ^{7b} or $Cd(OAc)_2$.^{7c} Another common route to the PyOX-core involves imide formation⁸ and further reaction with the desired amino alcohol.

Amido alcohol **5** was constructed from L-phenylalaninol **4** and pyridine-2,5-dicarboxylic acid **1** as follows. Exhaustive esterification of **1**, followed by selective hydrolysis of the more electrophilic⁹ ester at the 2-position of the diester **2** gave the monoacid **3**. The acid was then converted to the corresponding acid chloride and reacted with amino alcohol **4**. In the case of 2-pyridyl acids, the coupling is very selective using equimolar amounts of amino alcohol and acid and no ester by-products were observed after recrystallization. This was, however, not the case when the corresponding benzoic acids were used.¹⁰(Scheme 1)

Cyclization of **5** was performed in two steps for three reasons: ease of purification, reaction efficiency and ease of reaction monitoring. The similar polarity of amido alcohol **5** and oxazoline **7** makes monitoring on TLC very difficult. The formation and disappearance of mesylate **6**, however, were easily followed by TLC. Mesylation of **5** proceeded very fast using DMAP as catalyst at room temperature, total conversion was always reached within 15 min. The mesylate **6** is stable to aqueous extractions and silica and it was isolated by a simple extraction and recrystallization. It was converted to the PyOX-adduct **7** using DBU as the base.⁶ No by-products were observed in this step, either. It has been reported that base treatment could also yield two by-products: the aziridinyl or the vinylic amide. The aziridinyl amide was formed selectively, if Mitsunobu conditions were used.^{11a} The use of *t*-BuOK as the base has been reported to yield the aziridinyl amide and the corresponding vinyl amide as products, but no oxazoline formation.^{11b} Stoichiometric amounts of base used in the final hydrolysis facilitated the hydrolysis of **7** without decomposition of the PyOX-core, yielding the key intermediate **8**.¹²(Scheme 2)

Keywords: PyOX-ligand; Cyclization; Mesylate; Amido alcohol; DBU; Oxazoline.

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Scheme 1. Reagents and conditions: (i) MeOH, H₂SO₄, reflux, 17.5 h, 91%; (ii) NaOH, MeOH, reflux, 2.5 h, 90%; (iii) SOCl₂, reflux, 3 h; (iv) **4**, NEt₃, CH₂Cl₂, rt, 30 min, 64%.

Scheme 2. Reagents and conditions: (i) MsCl, NEt₃, DMAP, CH₂Cl₂, rt, 3 min, 92%; (ii) DBU, THF, 50 °C, 8 h, 84%; (iii) NaOH, aq MeOH, reflux, 4 h, 71%.

Scheme 3. Reagents and conditions: (i) (a) DIC, CH₂Cl₂, DMF; (b) TrSCH₂CH₂ OH, DMAP, CH₂Cl₂, rt, 22 h, 72%; (ii) TFA, Et₃SiH, CH₂Cl₂, rt, 10 min, 91%.

To prove the versatility of the carboxy functionality in **8**, a mercapto tail was attached to the acid. The tail, *S*-tritylmercaptoethanol,¹³ was coupled with the acid using a standard procedure (Scheme 3) to form the protected mercapto ester **9**. Deprotection of the thiol using TFA with triethylsilane as scavenger yielded the target molecule **10**.¹⁴

A novel key intermediate **8** for the preparation of PyOX-ligands was prepared using a new and simple protocol. Reaction steps were optimized to be clean and moderately to very fast. The first application of intermediate **8** is the mercapto ester **10**, which has a mercapto terminus for attachment to materials such as gold^{15a–c} or functionalized glass^{15c,d} in various applications.¹⁶

This is of great interest for catalyst development and is under investigation in our laboratory and results will be presented in the near future.

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 12. Data for compound **8**: $R_f = 0$ (67%, EtOAc/hexane); mp = 136–137 °C; $[\alpha]_D^{24} + 22.0$ (c 0.5, MeOH); ^1H NMR δ_{H} (400 MHz, DMSO- d_6) 9.10 (dd, $J_1 = 0.8$ Hz, $J_2 = 2.1$ Hz, 1H), 8.36 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.2$ Hz, 1H), 8.10 (dd, $J_1 = 0.8$ Hz, $J_2 = 8.2$ Hz, 1H), 7.32–7.19 (m, 5H), 4.64 (m, 1H), 4.49 (dd, $J_1 = 8.4$ Hz, $J_2 = 9.2$ Hz, 1H), 4.16 (dd, $J_1 = 8.1$ Hz, $J_2 = 8.2$ Hz, 1H), 3.01 (dd, $J_1 = 6.4$ Hz, $J_2 = 13.7$ Hz, 1H), 2.84 (dd, $J_1 = 7.1$ Hz, $J_2 = 13.7$ Hz, 1H); ^{13}C NMR: δ_{C} (100 MHz, DMSO- d_6) 165.8, 161.8, 150.1, 149.2, 138.0, 137.8, 129.3, 129.1, 128.2, 126.3, 123.7, 71.9, 67.4, 62.2, 52.7, 40.8. EI-HRMS m/z calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3 + \text{Na}$: 305.0902; found: 305.0912 (M+Na).
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 14. Data for compound **10**: $R_f = 0.23$ (50%, EtOAc/hexane), mp = 108.5–109 °C; $[\alpha]_D^{24} - 25.6$ (c 0.5, CH_2Cl_2); ^1H NMR δ_{H} (400 MHz, CDCl_3) 9.29 (dd, $J_1 = 0.5$ Hz, $J_2 = 2.0$ Hz, 1H), 8.39 (dd, $J_1 = 2.1$ Hz, $J_2 = 8.2$ Hz, 1H), 8.14 (dd, $J_1 = 0.7$ Hz, $J_2 = 8.2$ Hz, 1H), 7.33–7.23 (m, 5H), 4.70 (m, 1H), 4.50 (t, $J = 6.7$ Hz, 2H), 4.48 (dd, $J_1 = 9.1$ Hz, $J_2 = 9.2$ Hz, 1H), 4.26 (dd, $J_1 = 7.9$ Hz, $J_2 = 8.4$ Hz, 1H), 3.30 (dd, $J_1 = 5.1$ Hz, $J_2 = 13.7$ Hz, 1H), 2.92 (td, $J_1 = 6.7$ Hz, $J_2 = 8.4$ Hz, 2H), 2.80 (dd, $J_1 = 9.0$ Hz, $J_2 = 13.9$ Hz, 1H), 1.54 (t, $J = 8.6$ Hz, 1H); ^{13}C NMR: δ_{C} (100 MHz, CDCl_3) 164.3, 162.5, 150.8, 150.2, 137.8, 137.5, 129.2, 128.6, 127.1, 126.7, 123.6, 72.7, 68.3, 66.7, 41.5, 23.2; EI-HRMS m/z calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3\text{S} + \text{Na}$: 365.0936; found: 365.0944 (M+Na).
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