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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.

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. hydrosilylation[1] 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 it's 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 imidate formation[8] 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 electrophilic[9] 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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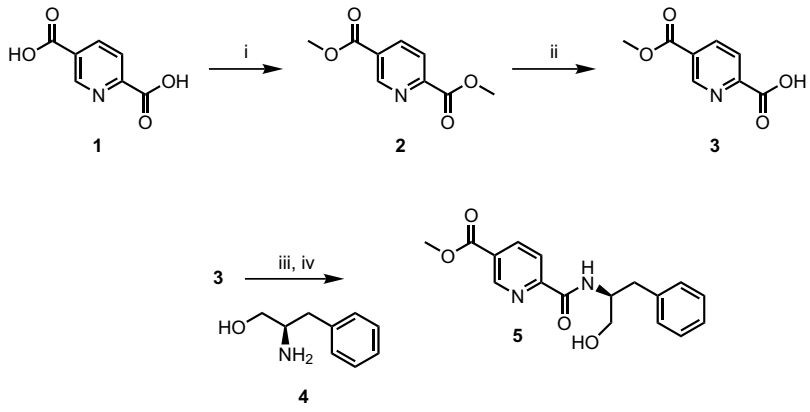
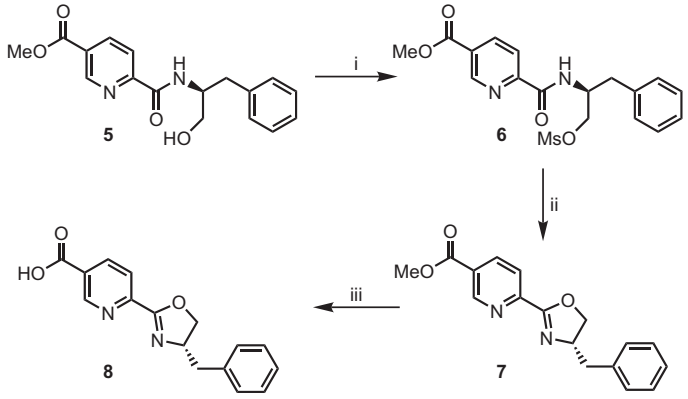
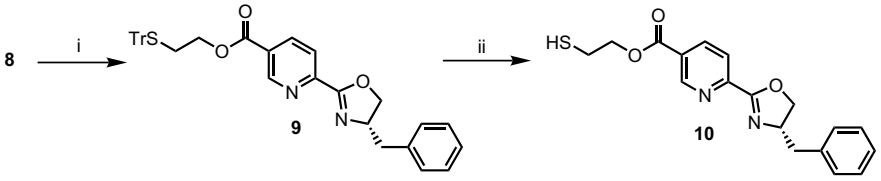


Scheme 1. Reagents and conditions: (i) MeOH, H_2SO_4, reflux, 17.5 h, 91%; (ii) NaOH, MeOH, reflux, 2.5 h, 90%; (iii) $SOCl_2$, reflux, 3 h; (iv) **4**, NEt_3, CH_2Cl_2, rt, 30 min, 64%.



Scheme 2. Reagents and conditions: (i) MsCl, NEt_3, DMAP, CH_2Cl_2, 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, CH_2Cl_2, DMF; (b) $TrSCH_2CH_2$ OH, DMAP, CH_2Cl_2, rt, 22 h, 72%; (ii) TFA, Et_3SiH, CH_2Cl_2, 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.

Acknowledgements

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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); ^{1}H 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 $C_{16}H_{14}N_2O_3$+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); ^{1}H 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 $C_{18}H_{18}N_2O_3S$+Na: 365.0936; found: 365.0944 (M+Na).
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