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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-C₂-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 and Michael reactions. In the late 1990s, C₁-symmetric PyOX was also found to be an outstanding ligand in Pd-catalyzed allylic alkylation reactions, being superior to the C₂-symmetric ligands (e.g. PyBOX) due to its ability to form two different palladium complexes. The metal complex forming ability of the PyOX-core also confers biological activity, e.g. as iron chelators.

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, 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. 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 ZnCl₂, CuCl₂ or Cd(OAc)₂. The common route to the PyOX-core involves imidate formation 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 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.

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. 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. 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.

Cyclization 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. 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. 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.

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

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To prove the versatility of the carboxy functionality in 8, a mercapto tail was attached to the acid. The tail, S-tritylmercaptoethanol, 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.

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 or functionalized glass in various applications.

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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References and notes


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) 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) TrSCH2CH2OH, DMAP, CH2Cl2, rt, 22 h, 72%; (ii) TFA, Et3SiH, CH2Cl2, rt, 10 min, 91%.


12. Data for compound 8: Rf = 0 (67%, EtOAc/hexane); mp = 136–137 °C; [α]25°D = 22.0 (c 0.5, MeOH); 1H NMR δH (400 MHz, DMSO-d6) 9.10 (dd, J1 = 0.8 Hz, J2 = 2.1 Hz, 1H), 8.36 (dd, J1 = 2.1 Hz, J2 = 8.2 Hz, 1H), 8.10 (dd, J1 = 0.8 Hz, J2 = 8.2 Hz, 1H), 7.32–7.19 (m, 5H), 4.64 (m, 1H), 4.49 (dd, J1 = 8.4 Hz, J2 = 9.2 Hz, 1H), 4.16 (dd, J1 = 8.1 Hz, J2 = 8.2 Hz, 1H), 3.01 (dd, J1 = 6.4 Hz, J2 = 13.7 Hz, 1H), 2.84 (dd, J1 = 7.1 Hz, J2 = 13.7 Hz, 1H); 13C NMR: δC (100 MHz, DMSO-d6) 165.8, 161.8, 150.1, 149.2, 138.0, 137.8, 129.3, 129.1, 128.2, 126.3, 71.9, 67.4, 62.2, 52.7, 40.8. El-HRMS m/z calc'd for C18H18N2O3S+Na: 365.0902; found: 365.0944 (M+Na).


14. Data for compound 10: Rf = 0.23 (50%, EtOAc/hexane); mp = 108.5–109 °C; [α]25°D = 25.6 (c 0.5, CH2Cl2); 1H NMR δH (400 MHz, CDCl3) 9.29 (dd, J1 = 0.5 Hz, J2 = 2.0 Hz, 1H), 8.39 (dd, J1 = 2.1 Hz, J2 = 8.2 Hz, 1H), 8.14 (dd, J1 = 0.7 Hz, J2 = 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, J1 = 9.1 Hz, J2 = 9.2 Hz, 2H), 4.26 (dd, J1 = 7.9 Hz, J2 = 8.4 Hz, 1H), 3.50 (dd, J1 = 5.1 Hz, J2 = 13.7 Hz, 1H), 2.92 (td, J1 = 6.7 Hz, J2 = 8.4 Hz, 2H), 2.80 (dd, J1 = 9.0 Hz, J2 = 13.9 Hz, 1H), 1.54 (t, J = 8.6 Hz, 1H); 13C NMR: δC (100 MHz, CDCl3) 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; El-HRMS m/z calc'd for C16H14N2O3+Na: 305.0902; found: 305.0912 (M+Na).
