Pergamon

Tetrahedron Letters 42 (2001) 2265–2267

TETRAHEDRON LETTERS

Synthesis of pyrimidine based metal ligands

Paul D. Jones and Timothy E. Glass*

The Pennsylvania State University, University Park, PA 16802, USA

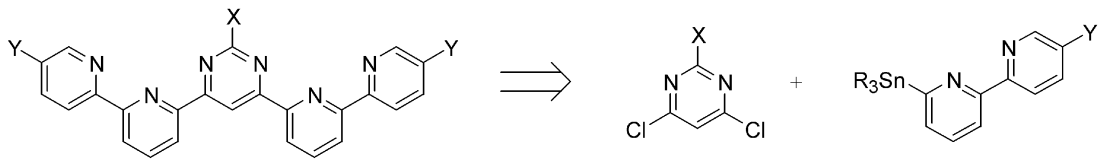
Received 11 December 2000; accepted 17 January 2001

Abstract—A convenient synthesis of a pyrimidine based bis-tridentate metal ligand is presented. The pyrimidine core is constructed via cyclization of an amidine and a substituted propenone. A Stille coupling appends the terminal pyridyl units. The general methodology presented is amenable to functionality at several positions on the ligand framework.

Oligopyridine metal ligands have been widely utilized in the construction of supramolecular structures.[1] Lehn has utilized these ligands in the formation of molecular cages, racks, helicates, ladders and grids. In particular, pyrimidine based bis-tridentate ligands such as **1a–c** have been shown to be useful for constructing a number of supramolecular metal complexes as well as helical stands.[2]

Pyrimidine based ligands such as **1a–c** are typically prepared by palladium mediated cross-coupling of a bipyridine sub-unit (**3**) to a central dichloropyrimidine ring (**2**)[3] (Fig. 1). The range of functionality available in compound **1** is therefore restricted to the availability of the coupling partners.

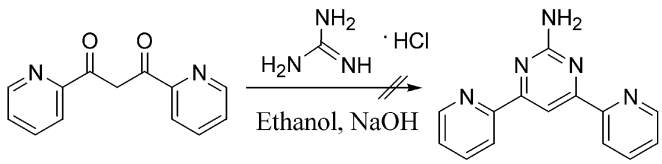
We have been interested in utilizing this class of ligands for preparing molecular hosts. Toward this end we required various hydrogen bonding functionality at the 2-position of the pyrimidine (e.g. **1d**). However, the coupling methodology typically employed for this class of compounds was not amenable to this substitution pattern. Therefore we explored more general strategies that would facilitate introduction of functional groups (X and Y, compound **1**).



1a X = H, Y = H
1b X = Ph, Y = Me
1c X = 9-anthryl, Y = H
1d X = C(O)NH$_2$, Y = H

2 **3**

Figure 1. Pyrimidine based ligands.



4 **5**

(1)

* Corresponding author. E-mail: teg@chem.psu.edu

0040-4039/01/$ - see front matter
PII: S0040-4039(01)00091-0

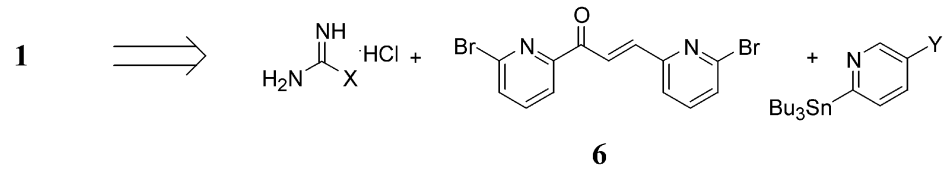
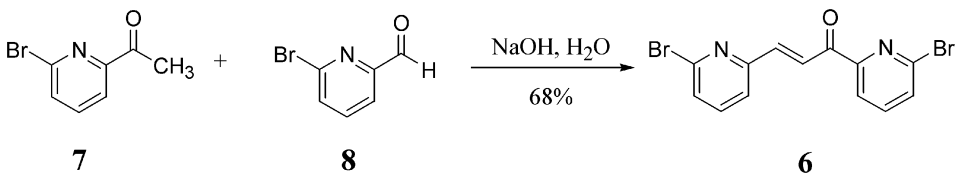


Figure 2. A convergent approach to compound **1**.

Various methods are available for the preparation of pyrimidines.[4] Condensation of a β-diketone with guanidine or amidine is a common method. However, pyridyl substituted diones such as **4** (Eq. (1)) fail to condense with either guanidines or amidines. Alternatively, condensation of amidines with α,β-unsaturated ketones provides pyrimidines after oxidation.[5] Therefore, compound **1** could be derived in a convergent manner from diarylenone **6**, the appropriate amidine and a substituted pyridyl tin reagent (Fig. 2). Thus, compound **6** would serve as a base structure allowing substituted pyrimidines to be prepared from the enone portion, and substituted pyridines to be coupled to the aryl bromide.

Thus, enone **6** was prepared by the condensation of ketone **7**[6] and aldehyde **8**[7], each of which was derived from dibromopyridine (Eq. (2)). As enone **6** was unstable to Stille coupling conditions, the pyrimidine was constructed first.

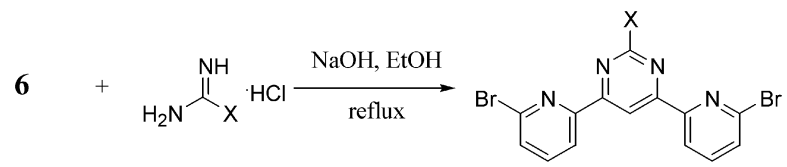


Compound **6** was cyclized with three different amidine hydrochlorides as well as guanidine hydrochloride to give the corresponding pyrimidine (Table 1). Optimal conditions entailed using sodium hydroxide base in refluxing ethanol for 4 h. Aryl, alkyl and amine substituted pyrimidines can be easily generated from this sequence, although the electron rich amidines generally give higher yields than the electron poor. Presumably the initially formed dihydropyrimidine is air oxidized during the course of the reaction as this intermediate was never observed, and pyrimidine **10** was the only isolated product.

The synthesis of compound **1d** was completed as shown in Scheme 1.[9] Hydrolysis of acetal **10a** in THF/$HCl_{(aq)}$ readily produces the aldehyde **11**. Conversion of compound **11** to ester **12** is accomplished with cyanide and MnO_2.[10] Stille coupling with tributyltin pyridine appended the terminal pyridine rings. Amidation of compound **13** with saturated MeOH/NH_3 gave the final product, **1d**.

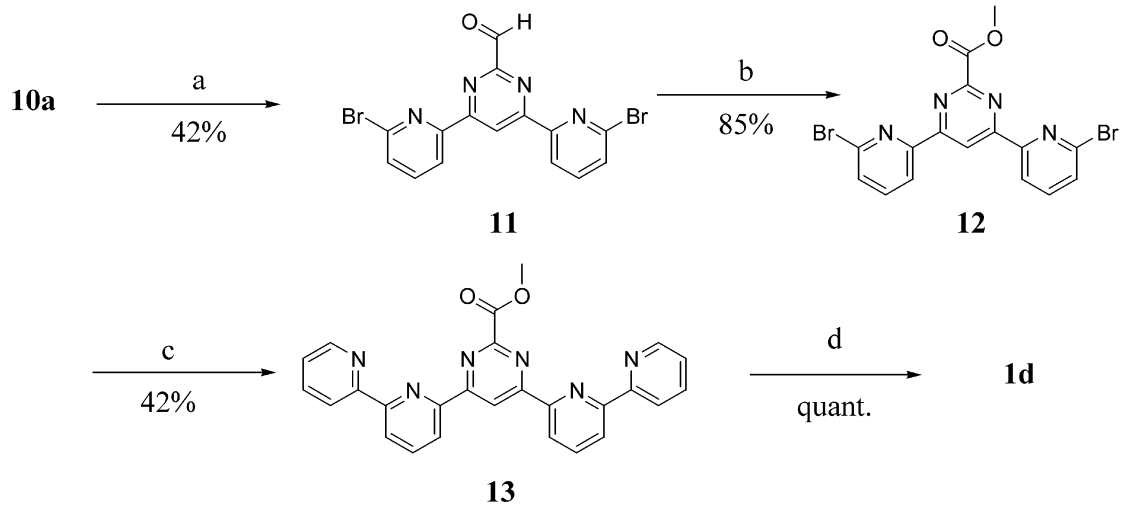
In conclusion, we have developed a novel route to functionalized oligopyridine ligands. This route relies on the cyclization of an amidine with a bis(bromopyridyl)propenone to form a pyrimidine ring. Final Stille coupling of the terminal pyridyl units provides a bis-tridentate metal ligand with opportunities for introducing functionallity in various positions. The coordination chemistry of this class of ligands (e.g. **1d**) is ongoing in our laboratory.

Table 1.



Amidine	X	Yield (%)
9a[a]	$(EtO)_2CH$	47
9b	Me	52
9c	Ph	53
9d	NH_2	85

[a] Prepared according to Ref. 8.



Scheme 1. (a) HCl, THF, reflux; (b) MnO_2, KCN, MeOH, HOAc, reflux; (c) 2-pyridyl tributyltin, $Pd(PPh_3)_4$, toluene, 105°C; (d) $MeOH/NH_3$.

Acknowledgements

This work was supported by The Pennsylvania State University.

References

1. Lehn, J.-M. *Supramolecular Chemistry–Concepts and Perspectives*; VCH: Weinheim, 1995.
2. (a) Funeriu, D. P.; Lehn, J.-M.; Fromm, K. M.; Fenske, D. *Chem. Eur. J.* **2000**, *6*, 2103–2111; (b) Hannan, G. S.; Arana, C. R.; Lehn, J.-M.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1122–1124; (c) Hannan, G. S.; Arana, C. R.; Lehn, J.-M.; Baum, G.; Fenske, D. *Chem. Eur. J.* **1996**, *2*, 1292–1302; (d) Hanan, G. S.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *J. Chem. Soc., Chem. Commun.* **1995**, 765–766.
3. (a) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Riviè, E.; Lehn, J.-M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169–182; (b) Hasenknopf, B.; Lehn, J.-M.; Baum, G.; Fenske, D. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 1397–1400; (c) Hanan, G. S.; Arana, C. R.; Lehn, J.-M.; Fenske, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1122–1124; (d) Schubert, U. S.; Eschbaumer, C. *Org. Lett.* **1999**, *1*, 1027–1029.
4. (a) Al-Hajjar, F. H.; Sabri, S. S. *J. Heterocycl. Chem.* **1982**, *19*, 1087–1092; (b) Alker, D.; Campbell, S. F.; Cross, P. E.; Burgess, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 2381–2388; (c) Hurst, D. T. *An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines*; John Wiley & Sons: New York, 1980 Chapter 2.
5. Muller, T. J. J.; Braun, R.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967–1970.
6. Peterson, M. A.; Mitchell, J. R. *J. Org. Chem.* **1997**, *62*, 8237–8239.
7. Meth-Cohn, O.; Jiang, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3737–3746.
8. Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412–418.
9. All new compounds gave satisfactory spectroscopic analysis. Representative spectral data are given for compounds **10a**, **11**, **12**, **13** and **1d**:**10a**: Mp = 184–186°C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) = 9.21 (s, 1H), 8.58 (dd, J = 6, 1 Hz, 2H), 7.73 (t, J = 8 Hz, 2H), 7.59 (dd, J = 7, 1 Hz, 2H), 5.70 (s, 1H), 3.85 (m, 4H), 1.32 (t, J = 9 Hz, 6H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) = 165.8, 163.4, 155.2, 142.0, 139.2, 130.0, 121.2, 113.6, 102.7, 63.0, 15.3. HRMS (APCI): m/z = 492.9862 $(M+H)^+$ calcd for $C_{19}H_{19}Br_2N_4O_2$, 492.9874.
11: Mp = 167–168°C. ^{1}H (360 MHz, $CDCl_3$) δ (ppm): 10.04 (s, 1H), 9.60 (s, 1H), 8.61 (dd, J = 7.5, 1 Hz, 2H), 7.79 (t, J = 8 Hz, 2H), 7.67 (dd, J = 7.0, 0.8 Hz, 2H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm): 191.2, 164.1, 159.2, 154.2, 142.3, 139.5,130.7, 121.3, 116.2. HRMS (APCI): m/z = 418.9124 $(M+H)^+$, calcd for $C_{15}H_9Br_2N_4O$, 418.9143.
12: Mp = 200–202°C. ^{1}H (400 MHz, $CDCl_3$) δ (ppm) = 9.38 (s, 1H), 8.61 (dd, J = 8, 1 Hz, 2H), 7.77 (t, J = 8 Hz, 2H), 7.65 (dd, J = 8, 1 Hz, 2H), 4.11 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) = 164.2, 163.8, 156.6, 154.3, 142.2, 139.4, 130.5, 121.3, 115.9, 53.5. HRMS (APCI): m/z = 448.9249 $(M+H)^+$, calcd for $C_{16}H_{11}Br_2N_4O_2$, 448.9248.
13: Mp = 260–263°C. ^{1}H (400 MHz, $CDCl_3$) δ (ppm) = 9.94 (s, 1H), 8.80 (d, J = 4 Hz, 2H), 8.75 (d, J = 8 Hz, 2H), 8.71 (dd, J = 8, 0.8 Hz, 2H), 8.63 (dd, J = 8, 0.8 Hz, 2H), 7.91 (td, J = 8, 2 Hz, 2H), 7.40 (ddd, J = 12, 4, 1.2 Hz, 2H), 4.15 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) = 165.0, 164.6, 156.8, 155.9, 155.8, 152.6, 149.3, 138.3, 136.8, 124.1, 123.1, 122.3, 121.2, 115.6, 53.5. HRMS (APCI): m/z = 447.1559 $(M+H)^+$, calcd for $C_{26}H_{19}N_6O_2$ 447.1569.
1d: Mp = 270–273°C (decomp.). ^{1}H (300 MHz, 1:1 (vol.) d_4 THF: d_6 DMSO) δ (ppm) = 9.93 (s, 1H), 8.87 (d, J = 13 Hz, 2H), 8.85 (d, J = 13 Hz, 2H), 8.73 (d, J = 13 Hz, 2H), 8.70 (dt, J = 18 Hz, 2H), 8.50 (br, 1H), 8.24 (t, J = 10 Hz, 2H), 8.09 (t, J = 10 Hz, 2H), 7.80 (br, 1H), 7.49 (dd, J = 8.4 Hz, 5.1 Hz, 2H). ^{13}C (75 MHz, 1:1 (vol) d_4-THF: -d_6 DMSO) δ (ppm) = 163.0, 162.8, 154.4, 154.0, 151.4, 148.1, 137.3, 135.8, 123.1, 121.4, 121.0, 119.1, 112.1. HRMS (ESI) m/z = 432.1592 $(M+H)^+$, calcd for $C_{25}H_{18}N_7O$, 432.1573.
10. Lai, G.; Anderson, W. K. *Synth. Commun.* **1997**, 1281–1284.