Pergamon

Tetrahedron Letters 40 (1999) 4779–4782

TETRAHEDRON LETTERS

A Convenient Set of Bidentate Pyridine Ligands for Combinatorial Synthesis

Fen Wang and Alan W. Schwabacher*[1]
Department of Chemistry, University of Wisconsin-Milwaukee
Milwaukee, WI 53201

Received 15 April 1999; accepted 6 May 1999

Abstract: *Synthesis is reported of five pyridine-containing bidentate ligands bearing nucleophilic groups at different positions. Their efficient solid-phase alkylation was demonstrated in the synthesis of a small library. These ligands are attractive building blocks for the construction of libraries of metal-binding compounds for various purposes.*

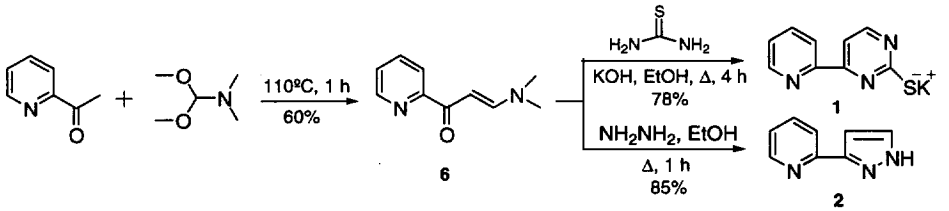
Keywords: combinatorial chemistry, alkylation, pyridines, peptides, polypeptides

2,2'-Bipyridine is among the most studied of bidentate ligands due to its affinity for a wide range of metals[2], and the useful properties of its complexes.[3,4,5] Geometric differences among ligands can lead to interesting variations in their metal complex properties. Imperiali has prepared amino acids with appended bipyridine ligands, and shown that the metal-binding abilities of peptides incorporating these amino acids vary with the orientation of the tether.[6] Ghadiri has incorporated bipyridines into peptides to direct the assembly of triple helix bundles.[7] Our group has designed and synthesized flexible molecules that bind metal ions to become organized into hosts and bind organic guests.[8] Combinatorial synthesis has led to an enhanced ability to prepare compounds having desired properties, because of the large numbers of variants that can be investigated.[9]

We report here synthesis of the five 2,2'-bipyridine analogs **1-5**, as well as their compatibility with combinatorial library synthesis by efficient alkylation on a Merrifield resin. Another approach to combinatorial synthesis of bipyridines has recently appeared.[10]

Syntheses for compounds **1-2** are outlined in Scheme I.[11] Acetylpyridine was converted to 3-dimethylamino-1-pyridine-2-yl-propenone **6** by heating with N, N'-dimethylformamide dimethyl acetal at 110°C.[12] Compound **6** was then transformed either with thiourea into pyridylpyrimidine thiolate **1**,[13,11] or with hydrazine into pyrazolylpyridine **2**.[14]

Scheme I

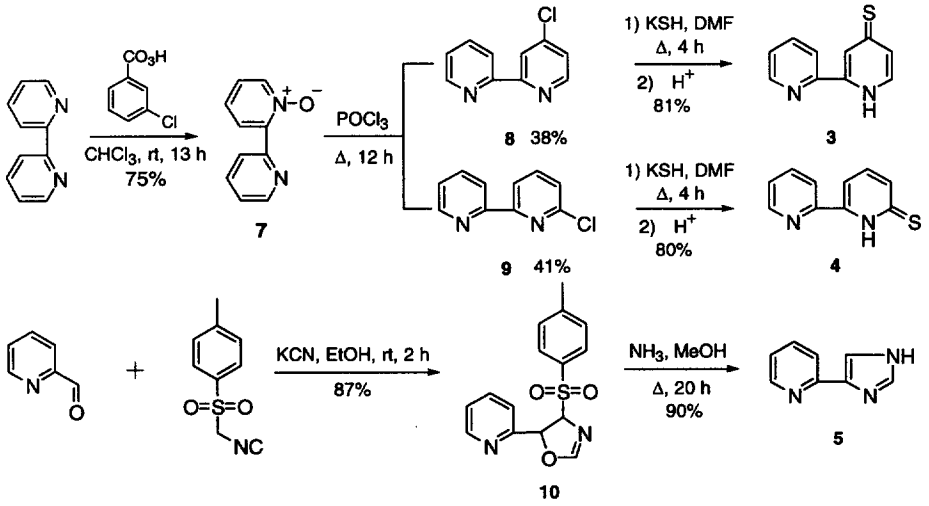


The isomeric pair of bipyridine thiones **3**[11] and **4**[11] (Scheme II) was obtained by oxidation of bipyridine to its mono-N-oxide,[15] reflux in $POCl_3$ to give separable[16] chlorides **8** and **9**,[17] followed by

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00885-0

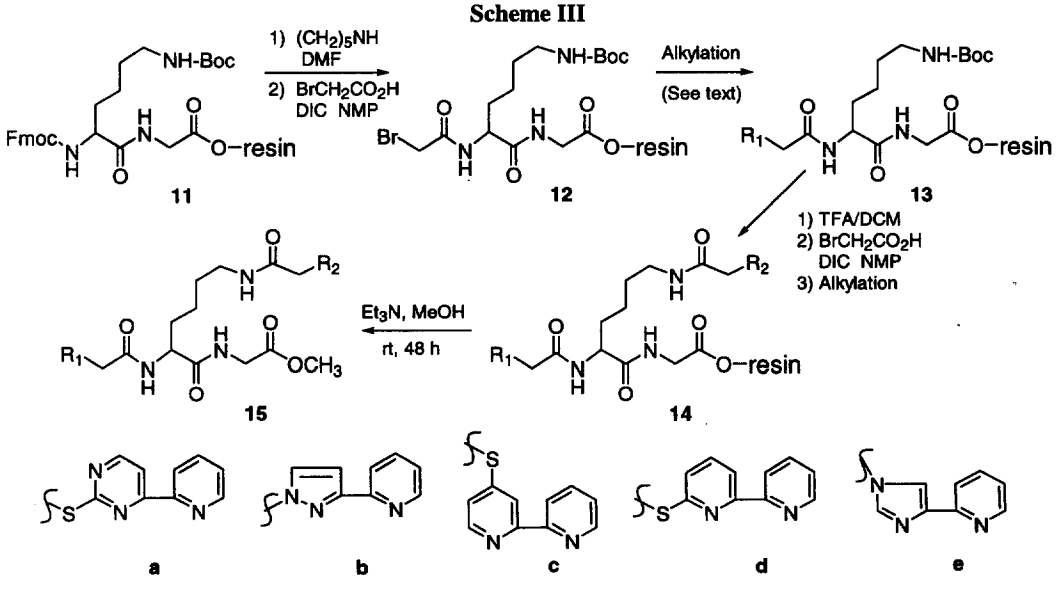
displacement with KSH in DMF at reflux.[18] Pyridine carboxaldehyde was treated with tosylmethyl isocyanide[19] to form oxazoline **10**, which without purification was heated with ammonia saturated dry methanol in a resealable tube to give 2-(1H-imidazole-4-yl) pyridine **5**.

Scheme II



Conditions for alkylation of **1-5** were investigated in solution with ethyl α-bromoacetate, and then applied to solid-phase synthesis. α-FMOC-ε-BOC-Lys-Gly-O-resin **11** was prepared by standard methods using Merrifield resin,[20,21] and converted to its bromoacetamide **12** by sequential treatment with piperidine and $BrCH_2CO_2H$/DIC as shown in Scheme III.

Scheme III



Substitution of bromide to form compounds **13** was carried out in each case by shaking the resin for 12 h. at rt in a ca. 0.1 M DMF solution of **1**, **3**, **4**, or the Na^+ salt of **2** or **5** (generated by 30 min exposure to sodium hydride).[22] Each compound **13** was converted to its bromoacetamide, and then treated in the same way with compounds **1-5** to yield 25 different compounds **14**. Cleavage from the resin with triethylamine in methanol gave the library of 25 compounds **15** (Table 1).

All products were characterized by HPLC, ^1H NMR[23] and by FAB mass spectrometry. All compounds gave UV spectra that quantitatively matched those predicted by adding spectra of the two ligand chromophores; these spectra allowed HPLC yield determinations.[24] The HPLC purities for all products were >90% and overall yields calculated based on resin glycine loading[25] averaged about 60%.

Table 1. Results for a library of 25 compounds 15

R_1 \ R_2	a			b			c			d			e		
	Tr (min)[a]	Purity (%)[b]	Yield (%)[c]	Tr (min)	Purity (%)	Yield (%)	Tr (min)	Purity (%)	Yield (%)	Tr (min)	Purity (%)	Yield (%)	Tr (min)	Purity (%)	Yield (%)
a	20.1	96	53	14.2	97	61	16.2	96	49	18.2	92	54	14.0	93	52
b	14.4	92	66	4.20	99	60	7.88	93	64	12.0	95	64	3.93	93	56
c	16.6	91	56	7.72	95	76	12.4	97	61	14.3	93	57	6.68	92	63
d	18.2	92	62	11.7	94	53	14.5	94	70	16.2	95	61	11.4	95	57
e	14.2	95	51	3.98	92	59	7.30	91	66	11.5	95	60	3.65	90	71

a) Tr: HPLC retention time using a Beckman C-18 reverse phase column (4.6 x 250mm, 5μm) at flow rate of 1mL/min. Gradient: 15% B 5 min, 15%-30% B over 10 min, 30% B 10 min. A = 0.05% TFA in H_2O, B = CH_3CN.
b) Purities are HPLC area %, determined by integration at 311 nm.
c) The yields (%) were based on a loading of 0.42mmol/g glycine on the resin (ninhydrin), and on extinction coefficients for the separate ligands.

In summary, we have synthesized five bidentate pyridine-containing ligands as good nucleophiles. A small library of 25 dipeptides, each bearing two bidentate ligands was prepared by solid phase alkylation. These ligands can serve as building blocks, using the library methods presented, for the construction of disparate metal-binding molecules. Their metal-binding abilities, and the properties of their metal complexes, are being investigated.

Acknowledgment: The authors wish to thank the NIH (GM59148) for financial support.

References and notes:

1. Fax: (414) 229-5530, email: awschwab@uwm.edu.
2. Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Plenum: New York, 1974; Constable, E. C. Homoleptic Complexes of 2,2'-bipyridine. In *Advances in Inorganic Chemistry;* Sykes, A. G. Ed.; Academic Press: San Diego, **1989**; Vol. 34.
3. Photochemistry and luminescence: Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; Zelewsky, A. V. *Coordination Chemistry Reviews* **1988,** *84*, 85-277; Balzani, V.; Juris, A.; Venturi, M.; Campagna, S.; Serroni, S. *Chem. Rev.* **1996,** *96*, 759-833.
4. Helix formation: Constable, E. C. *Tetrahedron* **1992,** *48*, 10013-10059.
5. Molecular recognition: Buda, M.; Moutet, J.-C.; Saint-Aman, E.; Cian, A. D.; Fischer, J.; Ziessel, R. *Inorg. Chem.* **1998,** *37*, 4146-4148; Venema, F.; Rowan, A. E.; Nolte, R. J. M. *J. Am. Chem. Soc.*

1996, *118*, 257-258; Szemes, F.; Hesek, D.; Chen, Z.; Dent, S. W.; Drew, M. G. B.; Goulden, A. J.; Graydon, A. R.; Grieve, A.; Mortimer, R. J.; Wear, T.; Weightman, J. S.; Beer, P. D. *Inorg. Chem.* **1996,** *35*, 5868-5879.

6. Cheng, R. P.; Fisher, S. L.; Imperiali, B. *J. Am. Chem. Soc.* **1996,** *118*, 11349.
7. Mutz, M. W.; Case, M. A.; Wishart, J. F.; Ghadiri, M. R.; McLendon, G. L. *J. Am. Chem. Soc.* **1999,** *121*, 858-859.
8. Schwabacher, A. W.; Lee, J.; Lei, H. *J. Am. Chem. Soc.* **1992,** *114*, 7597; Lee, J.; Schwabacher, A. W. *J. Am. Chem. Soc.* **1994,** *116*, 8382; Schwabacher, A. W.; Stefanescu, A. D.; Rehman, A. *J. Org. Chem.* **1999,** *64*, 1784-1788; Schwabacher, A. W.; Wang, F. submitted
9. Szostak, J. W., *Chemical Reviews*, **1997**, *97*, 347-348; Pirrung, M. C., *ibid*, 473-488; Lam, K. S., Lebl, M., Krchnak, V., *ibid*, 411-448; Nefzi, A., Ostresh, J. M., Houghten, R. A., *ibid*, 449-472; Osborne, S. E., Ellington, A. D., *ibid*, 349-370.
10. Tadesse, S.; Bhandari, A.; Gallop, M. A. *J. Combinatorial Chem.* **1999,** *1*, ASAP.
11. All new ligands were characterized by ^{1}H and ^{13}C NMR, and elemental analysis. Library compounds were characterized as described in Table 1.
12. Kepe, V.; Kocevar, M.; Polanc, S. *J. Heterocycl. Chem.* **1996,** *33*, 1707-1710.
13. Stanek, J.; Caravatti, G.; Capraro, H. G.; Furet, P.; Mett, H.; Schneider, P.; Regenass, U. *J. Med. Chem.* **1993,** *36*, 46-54.
14 Brunner, H.; Scheck, T. *Chem. Ber.* **1992,** *125*, 701.
15. Wenkert, D.; Woodward, R. R. *J. Org. Chem.* **1983,** *48*, 283.
16. Araki, K.; Mutai, T.; Shigemetsu, Y.; Yamada, M.; Nakajima, T. *J. Chem. Soc. Perkin Trans. 2* **1996,** *4*, 613-618.
17. Moran, D. B.; Morton, G. O.; Albright, D. J. *J. Heterocycl. Chem.* **1986,** *23*, 1071.
18. Anderson, S.; Constable, E. C.; Seddon, K. R.; Turp, J. E.; Baggott, J. E.; Pilling, M. J. *J. Chem. Soc. Dalton Trans.* **1985**, 2247-2261.
19. Horne, D. A.; Yakushijin, K.; Buechi, G. *Heterocycles* **1994,** *39*, 139-153.
20. 1) Boc-Gly/Cs_2CO_3/DMF 2) TFA/DCM 3) Fmoc,Boc-Lys/DIC/HOBT/NMP
21. Stewart, J. M.; Young, J. D. *Solid Phase Peptide Synthesis*; Pierce Chemical Co, 1984.
22. All reactions proceeded efficiently as determined by HPLC and MS analysis of cleaved methyl esters. HPLC (solvent system A: 0.05% aqueous TFA, B: CH_3CN, the gradient: 25% B 8 min, 25%-40% B 7min, 40% B 10 min) retention times(min), purities(%) and yields(%) (listed in the order of **a-e**): 18.0, 99, 74; 10.7, 99, 76; 14.7, 98, 71; 6.88, 92, 75; 7.18, 99, 70.
23. ^{1}H NMR ($CDCl_3$) data of **15** ($\mathbf{R_1}$ = **b**, $\mathbf{R_2}$ = **d**) as an example: δ 8.65(dd, 1H, J=4.3, 0.85Hz), 8.60(d, 1H, J=4.4Hz), 8.27(d, 1H, J=8.0Hz), 8.08(dd, 1H, J=7.4, 0.61Hz), 7.90(d, 1H, J=7.9Hz), 7.84(ddd, 1H, J=7.8, 7.7, 1.8Hz), 7.69(ddd, 1H, J=7.8, 7.8, 2.5Hz), 7.69(dd, 1H, J=7.8, 7.8Hz), 7.56(d, 1H, J=2.3Hz), 7.52(dd, 1H, J=5.9, 5.8Hz), 7.32(ddd, 1H, J=7.5, 4.8, 1.1Hz), 7.27(dd, 1H, J=6.1, 0.58Hz), 7.19(ddd, 1H, J=7.4, 4.9, 1.0Hz), 6.97(d, 1H, J=7.6Hz), 6.94(d, 1H, J=2.4Hz), 6.90(dd, 1H, J=5.4, 5.4Hz), 4.91(s, 2H), 4.23(ddd, 1H, J=14, 6.6, 2.9Hz), 3.97(d, 2H, J=5.6Hz), 3.90(d, 2H, J=2.4Hz), 3.71(s, 3H), 3.12(dd, 2H, J=13, 6.4Hz), 1.60(m, 1H), 1.45(m, 1H), 1.24(m, 2H), 1.07(m, 2H).
24. In 30% CH_3CN, 0.035% TFA in H_2O, absorption maxima above 200 nm for the ethyl α-bromoacetate alkylation products as λ_{max} (ε) are: **1**: 311 (4280); 277 (10780); 253 (16880) **2**: 303 (16320); 270 (11720) **3**: 341 (7000); 266 (12200); 228 (14360) **4**: 318 (12540); 250 (7860) **5**: 304 (16300); 243 (9900).
25. Glycine loading on the resin was determined by quantitative ninhydrin test using tetraethylene glycol diamine as standard.