Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 501–504

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

DIAMINE PREPARATION FOR SYNTHESIS OF A WATER SOLUBLE Ni(II) SALEN COMPLEX

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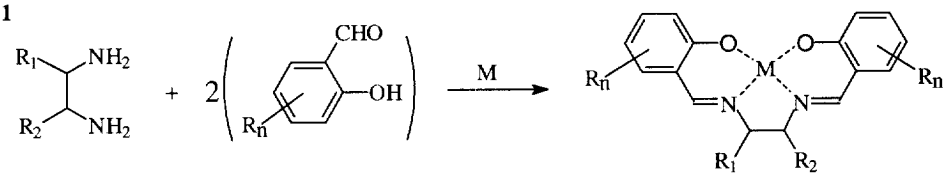
Received 11 November 1998; accepted 24 December 1998

Abstract: A reliable and efficient synthesis of a Ni(II) salen complex useful in probing nucleic acid structure is described and illustrates a general approach for constructing *cis* diamines suitable for assembly into N_2O_2 Schiff base complexes. Two equivalents of an aryllithium reacted with 1,4-dimethylpiperazine-2,3-dione to form the symmetric α-dione. This material was then converted to its dioxime and reduced by $TiCl_4/NaBH_4$ to yield the *meso*-diamine. Condensation of the diamine and salicyladehyde, coordination of nickel and final methylation generated the desired water soluble and redox active complex.

Metal complexes of salen [bis(salicylidene)ethylenediamine] derivatives have become increasingly valuable as reagents and catalysts of many reactions including olefin epoxidation,[1] nucleic acid modification,[2,3] electrochemical reduction,[4] hydroxylation[5] and Diels-Alder transformations.[6] Such complexes are readily assembled from diamines and various salicylaldehyde derivatives (Scheme 1) and are amenable to combinatorial syntheses. For example, a series of libraries based on related Schiff base complexes was recently developed for promoting asymmetric Strecker reactions.[7] The diversity of salen derivatives has typically been

Scheme 1

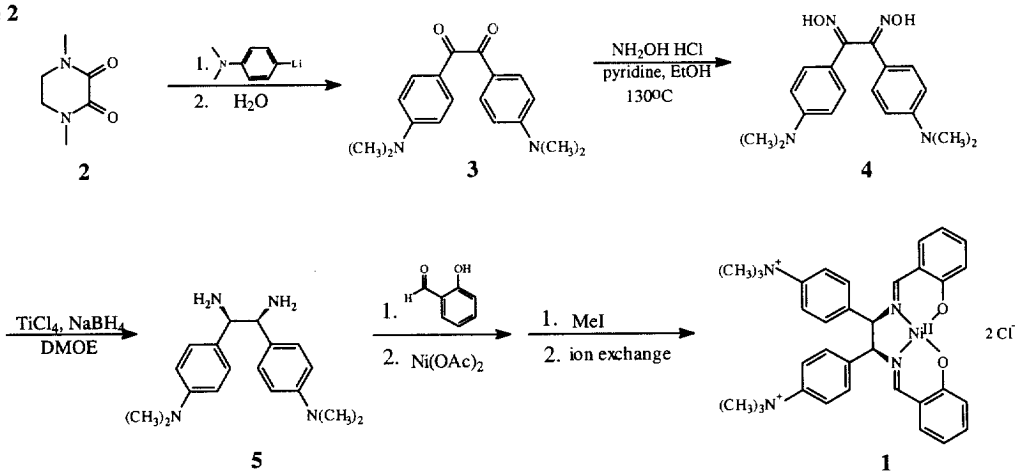


achieved through use of the numerous salicylaldehydes that are available commercially.[7,8] In contrast, only a limited number of *trans* diamines are available, and *cis* diamines are even more uncommon. For example, the *cis* diamine required for producing the first water soluble and cationic nickel salen complex, [N,N'-bis(salicylaldehyde)-*meso*-1,2-bis(4-trimethylaminophenyl)ethylenediimino]nickel(II) **1**,[3] initially relied on two low-yielding and undependable diaza-Cope rearrangements.[9] The resulting complex has proven to be an effective probe of nucleic acid structure since it selectively couples to solvent accessible guanine residues in a manner detectable by both primary extension and piperidine assays.[10]

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00020-7

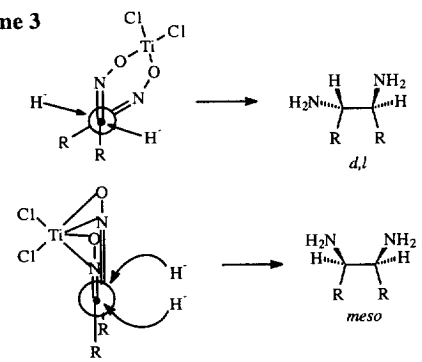
Recent application[10d] of this salen complex has been limited by its difficult preparation. A more efficient method of synthesis has now been achieved through facile production and transformation of a central α-dione. 1,4-Dimethylpiperazine-2,3-dione was treated with two equivalents of *para*-N,N'-dimethylaminophenyl lithium to form the desired α-dione **3** in 48% (Scheme 2) using a method developed by Mueller-Westerhoff and Zhou.[11] Excess hydroxylamine hydrochloride was then added to **3** in a mixed solvent of ethanol and pyridine (37:63), and the reaction was heated to reflux for three hours. The resulting dioxime **4** was recrystallized in $CHCl_3$ and isolated in a 68% yield.[12]

Scheme 2



The crucial reduction of the dioxime was accomplished in a 94% yield[13] with $TiCl_4/NaBH_4$. These conditions inhibited competing production of hydroxylamine and aziridine derivatives[14] and offered chelation control during reduction.[15] ^1H NMR analysis of the crude diamine product indicated a 83:17 ratio of the *meso*:*d,l* diastereomers from integration of their methylene signals (*meso*, 3.86 ppm; *d,l*, 4.00 ppm). Reduction of the *para*-methoxyphenyl analogue under equivalent conditions generated only the *meso* diastereomer since no signals for the *d,l* pair were observed by ^1H-NMR in this case. $TiCl_4$ typically provides excellent stereochemical control during reduction of ketoesters through chelation of the oxygens.[15] However, the *d,l* rather than the *meso* diastereomer would have dominated the product profile if titanium had bound only to the two dioxime oxygens (Scheme 3). In contrast, coordination of both dioxime oxygens and nitrogens would predominantly block one face of the target and yield the *meso* isomer as observed.

Scheme 3



The diastereomeric mixture of diamines was then

condensed with salicylaldehyde in refluxing ethanol. A pale-yellow solid formed after the reaction was cooled. Recrystallization of this material in acetonitrile afforded the desired salen in 35% yield. Only the *meso* isomer was isolated in this manner as suggested by the sole benzylic and imino protons detected by NMR. Complexation of nickel, methylation of the dimethylamino groups and anion exchange to the chloride salt followed published procedures[3] and yielded the desired product in 76%.[16] The nickel(salen) complex has thus been routinely prepared in an overall yield of 8% starting from the α-dione, and greater yields are expected for salen derivatives that do not suffer from the inefficient recrystallization noted above. This approach to salens is currently supporting synthesis of numerous analogues for additional application in nucleic acid modification and manipulation. Similar preparation of unsymmetric salens may be achieved through use of α-diones generated from the appropriate olefins, diols or other synthetic equivalents.

Acknowledgment: We thank Cynthia J. Burrows and James G. Muller for their advice and encouragement and the National Institutes of Health for financial support (GM47531).

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12. Physical data for *meso*-1',2'-bis(4-dimethylaminophenyl)ethylenedioxime (**4**): mp 218°C. ^{1}H NMR (DMSO-d_6), δ 2.87 (s, 12H, CH_3), 6.65 (d, J = 9 Hz, 4H, ArH), 7.28 (d, J = 9 Hz, 4H, ArH), 10.75 (s, 2H, NOH). ^{13}C NMR (5% DCl/D_2O, CH_3CN as reference) δ 46.7, 119.4, 128.6, 133.3, 143.7, 151.4; HR/MS (FAB), *m/z* 327.1821 ($M + H^+$), calc for $C_{18}H_{23}N_4O_2$, 327.1821.

13. Synthesis of *meso*-1',2'-bis(4-dimethylaminophenyl)ethylenediamine (**5**): The dioxime (**4**, 400 mg, 1.2 mmols) was combined with sodium borohydride (360 mg, 9.5 mmols) and placed under a nitrogen atmosphere. 1,2-Dimethoxyethane (10 mL, dried over potassium/sodium and distilled onto 4 Å molecular sieves) was then included, and the mixture was cooled with a salt water/ice bath. $TiCl_4$ (1.1 g, 5.7 mmols) was added dropwise. The solution initially appeared dark brown but turned dark green during the reaction period of 24 h at room temperature. Sodium hydroxide (3 M, 35 mL) was introduced slowly to quench the reaction and raise the pH to 10. The resulting solution and blue solid was combined with $CHCl_3$ (50 mL) and filtered. The solid was washed with additional $CHCl_3$ (25 mL). The organic phases were washed twice with water, twice with brine and finally evaporated under reduced pressure to yield 340 mg (94% crude yield) of a yellow crystalline solid. mp: 162-163°C (recrys. 174°C; lit:[9b] 174°C). ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 4H, NH_2), 2.93 (s, 12H, $N(CH_3)_2$), 3.86 (s, 2H, CH), 6.72 (dd, J = 7 Hz, J = 2 Hz, 4H, ArH), 7.30 (dd, J = 7 Hz, J = 2 Hz, 4H, ArH). ^{13}C NMR ($CDCl_3$): δ 40.6, 62.3, 112.6, 128.3, 131.1, 150.1. LR/MS (FAB): 299 ($M + H^+$).

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16. The physical properties of **1** are equivalent to those published previously.[3] ^{1}H NMR (DMSO-d_6): δ 3.55 (s, 18H, N^+-CH_3), 5.29 (s, 2H, C-H), 6.49 (t, J = 7 Hz, 2H, ArH), 6.79 (d, J = 9 Hz, 2H, ArH), 7.14 (d, J = 7 Hz, 2H ArH), 7.23 (t, J = 9 Hz, 2H, ArH), 7.60 (d, J = 8 Hz, 4H ArH), 7.64 (s, 2H, C=N-H), 7.85 (d, J = 8 Hz, 4H, ArH). ^{13}C NMR (DMSO-d_6): δ 56.5, 74.5, 114.8, 120.0, 120.2, 120.5, 130.3, 134.6, 137.8, 147.1, 163.6, 164.3.