

(43.6), 181 (36.4), 182 (62.4, $M^+-CH_2CH_2CH_2CH_3$), 183 (22.1), 194 (10.2), 196 (100, $M^+-CH_2CH_2CH_3$), 197 (23.0), 210 (10.3, $M^+-CH_2CH_3$), 224 (16.4, M^+-CH_3), 239 (34.0, M^+); IR (NaCl) ν 3059 (w), 3039 (w), 2956 (s), 2926 (vs), 2856 (s), 1616 (m), 1599 (s), 1558 (m), 1503 (s), 1458 (w), 1426 (w), 1380 (w), 1304 (w), 1079 (w), 823 (s), 753 (s); (*cis* isomer) 1H NMR ($CDCl_3$, 300 MHz) δ 8.13-7.30 (6H, Hs in quinoline), 5.74 (t, 1H, $J=7.64$ Hz, =C-H), 2.20 (s, 3H, =C- CH_3), 2.10 (q, 2H, $J=7.14$ Hz, =C- CH_2), 1.42-1.29 (m, 2H, $-CH_2(CH_2)_2CH_3$), 1.29-1.15 (m, 4H, $-CH_2(CH_2)_2CH_3$), 0.83 (t, 3H, $J=6.48$ Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.87, 147.92, 135.73, 131.44, 129.40, 129.29, 127.39, 126.02, 121.61, 31.49, 29.56, 29.16, 23.87, 22.48, 13.99; MS (*M/Z*) 128 (23.6), 143 (13.9), 156 (16.5), 167 (70.1), 168 (26.4), 180 (44.6), 181 (34.5), 182 (81.4, $M^+-CH_2CH_2CH_2CH_3$), 183 (25.9), 194 (9.9), 196 (100, $M^+-CH_2CH_2CH_3$), 197 (18.9), 210 (17.4, $M^+-CH_2CH_3$), 224 (13.1, M^+-CH_3), 239 (38.8, M^+); IR (NaCl) ν 3059 (w), 2957 (s), 2926 (vs), 2856 (s), 1618 (m), 1598 (s), 1557 (w), 1503 (s), 1460 (w), 1428 (w), 1376 (w), 1140 (w), 1074 (w), 832 (s), 756 (s)

2-(2-Octenyl)isoquinoline 5. Spectral data were obtained from a mixture of the *trans* and *cis* isomers. (*trans* isomer) 1H NMR ($CDCl_3$, 300 MHz) δ 8.55-7.52 (6H, Hs in quinoline), 5.82 (t, 1H, $J=7.38$ Hz, =C-H), 2.15 (s, 3H, =C- CH_3), 1.65 (q, 2H, $J=7.42$ Hz, =C- CH_2), 1.35-1.20 (m, 2H, $-CH_2(CH_2)_2CH_3$), 1.20-1.05 (m, 4H, $-CH_2(CH_2)_2CH_3$), 0.76 (t, 3H, $J=6.8$ Hz, $-CH_3$); MS (*M/Z*) 128 (9.1), 143 (7.6), 154 (11.5), 156 (8.3), 167 (33.0), 168 (12.1), 180 (38.2), 181 (39.0), 182 (34.8, $M^+-CH_2CH_2CH_2CH_3$), 183 (7.0), 194 (7.5), 196 (100, $M^+-CH_2CH_2CH_3$), 197 (16.9), 210 (4.2, $M^+-CH_2CH_3$), 224 (2.1, M^+-CH_3), 239 (24.5, M^+); (*cis* isomer) 1H NMR ($CDCl_3$, 300 MHz) δ 8.52-7.52 (6H, Hs in quinoline), 5.69 (t, 1H, $J=7.11$ Hz, =C-H), 2.34 (q, 2H, $J=7.50$ Hz, =C- CH_2), 2.20 (s, 3H, =C- CH_3), 1.60-1.47 (m, 2H, $-CH_2(CH_2)_2CH_3$), 1.46-1.33 (m, 4H, $-CH_2(CH_2)_2CH_3$), 0.92 (t, 3H, $J=6.95$ Hz, $-CH_3$); MS (*M/Z*) 128 (13.7), 143 (11.9), 154 (22.1), 156 (11.0), 167 (71.8), 168 (40.1), 180 (46.7), 181 (42.6), 182 (95.5, $M^+-CH_2CH_2CH_2CH_3$), 183 (17.1), 194 (9.0), 196 (100, $M^+-CH_2CH_2CH_3$), 197 (16.1), 210 (14.8, $M^+-CH_2CH_3$), 224 (12.1, M^+-CH_3), 238 (15.0, M^+-1), 239 (38.8, M^+).

2-(1-Octenyl)quinoline 6 (*trans* isomer) 1H NMR ($CDCl_3$, 300 MHz) δ 8.07-7.43 (6H, Hs in quinoline), 6.83 (dt, 1H, $J=15.9$, 6.42 Hz, =C-H), 6.71 (d, 1H, $J=15.9$ Hz, =C-H), 2.32 (q, 2H, $J=7.2$ Hz, =C- CH_2), 1.57-1.49 (m, 2H, $-CH_2(CH_2)_3CH_3$), 1.40-1.20 (m, 6H, $-CH_2(CH_2)_3CH_3$), 0.90 (t, 3H, $J=6.7$ Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.50, 138.07, 136.11, 130.96, 129.47, 129.05, 127.38, 125.77, 118.65, 33.05, 31.70, 28.94, 28.84, 22.59, 14.08; MS (*M/Z*) 128 (10.2), 143 (27.5), 154 (6.4), 155 (11.8), 156 (21.8), 167 (70.3), 168 (73.0), 169 (25.8), 180 (20.3), 182 (100, $M^+-CH_2CH_2CH_2CH_3$), 183 (20.4), 196 (21.1, $M^+-CH_2CH_2CH_3$), 210 (27.7, $M^+-CH_2CH_3$), 224 (5.6, M^+-CH_3), 238 (11.2, M^+-1), 239 (25.9, M^+); IR (NaCl) ν 3058 (w), 3039 (w), 2956 (s), 2927 (vs), 2855 (s), 1616 (m), 1598 (s), 1557 (w), 1504 (s), 1466 (w), 1427 (m), 1313 (w), 968 (s), 816 (w), 782 (w), 750 (s).

References

- Alvarado, Y.; Boutry, O.; Gutierrez, E.; Monge, A.; Nicasio, M. C.; Poveda, M. L.; Perez, P. J.; Ruiz, C.; Bianchini, C.; Carmona, E. *Chem. Eur. J.* 1997, 3, 860 and references cited therein.
- (a) Lim, Y.-G.; Kim, Y. H.; Kang, J.-B. *J. Chem. Soc., Chem. Commun.* 1994, 2267. (b) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *Chem. Commun.* 1996, 585. (c) Lim, Y.-G.; Kang, J.-B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* 1996, 2201.
- Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* 1995, 117, 5371.
- (a) Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* 1995, 679. (b) Fujii, N.; Kakiuchi, F.; Chatani, N.; Murai, S. *Chem. Lett.* 1996, 939. (c) Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* 1997, 425/
- Claret, P. A. In *Comprehensive organic chemistry, the synthesis and reactions of organic compounds*; Barton, D.; Ollis, W. D. Eds.; Pergamon: Oxford, 1979; Vol. 4, p 166.
- Dupont, J.; Halfen, R. A. P.; Zinn, F. K.; Pfeffer, M. J. *Organomet. Chem.* 1994, 484, C8-C9.

Facile Synthetic Method for 2,6-Di(aminomethyl)pyridine as Building Block for Macrocyclic Ligands

Heung-Jin Choi*, In-Kyu Lee, and Nam-Sik Yoon†

Department of Industrial Chemistry, Kyungpook National University, Taegu 702-701, Korea
 †*Department of Dyeing and Finishing, Kyungpook National University, Taegu 702-701, Korea*
 Received June 20, 1997

Increasing interests of supramolecular chemistry have led to design new macrocyclic ligands for many purposes. 2,6-Di(aminomethyl)pyridine synthon as ligand site and building block was often utilized in many macrocyclic polyamine ligands.¹⁻³ However, direct incorporation of 2,6-

di(aminomethyl)pyridine moiety into macrocycles has barely been reported apparently because of synthetic difficulty of 2,6-di(aminomethyl)pyridine, **4**. Indirect incorporation of the moiety in the ligands was mostly done by reducing corresponding amides from 2,6-pyridinedicarbonyl chloride, **1**

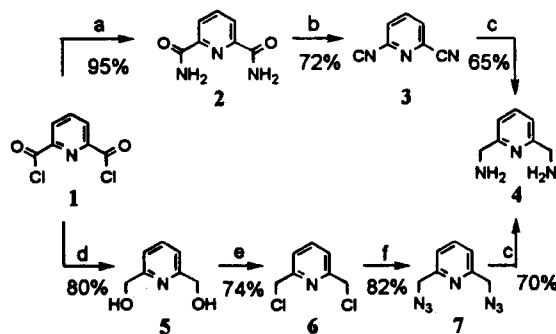
and amines² or by reducing the corresponding Schiff bases from 2,6-pyridinedicarboxaldehyde and amines.³

In the course of developing tetraamide macrocycles for ionophores, the diamine **4** is essential to form amide bonds with 2,3-*O*-isopropylidene-*L*-tartaryl chloride.⁴ A synthetic method of **4** from 2,6-di(chloromethyl)pyridine, **6** by Gabriel synthetic method has been reported. However, this method requires phthalimide synthetic auxiliary which complicate extraction of the basic product **4** from aqueous work up. Furthermore, mass yield is low because of the relatively low molecular weight of product **4** compared with the high molecular weight of the phthalimide precursor.⁵

Interestingly direct reduction of 2,6-pyridinedicarboxamide **2** to **4** with reducing reagents such as LiAlH₄ and BH₃-THF did not give the product partly because **2** is very insoluble in reaction medium and reaction intermediate could form chelates with metal reagents. In consequence, unidentifiable polymeric and insoluble basic polyamine byproducts were isolated. However, reduction of 2,6-pyridinedicarbonitrile, **3** prepared from dehydration of **2** gave high yield of **4** under catalytic hydrogenation. Scheme 1 shows two different synthetic approaches to **4**.

2 was mixed with phosphorus pentoxide in a sublimator and the mixture was heated under vacuum up to 200 °C. The pyridinedicarbonitrile **3** was easily sublimed in 72% yield without any additional work up procedure. Aqueous work up complicates recovery of the basic product **3** from large amount of phosphoric acid solution. Catalytic hydrogenation of **3** in the presence of Raney nickel at room temperature gave **4** in 65% yield. It was observed that the yield is very dependent on the reaction temperature. For example, at the elevated temperature of 80 °C, a mixture of amines were obtained. It has been well known that secondary amines are often side products in the reduction of nitrile under catalytic hydrogenation.⁶ Thus, the dinitrile **3** could form various amines. Many reducing agents including LiAlH₄ and BH₃-THF can also reduce nitriles to primary amines but catalytic hydrogenation with Raney nickel offers better result in this case. Metal hydride reagents can form undesirable complexes due to the strongly basic and tridentate complexing properties of the product **4**.

As comparable synthetic method, the amine synthesis by azide reduction was performed from the same starting material **1**. Although 2,6-pyridinedimethanol **5** is available, the diol **5** was prepared from reduction of freshly prepared acid



Scheme 1. (a) NH₄OH. (b) P₂O₅, 200 °C. (c) H₂ (10 atm), Raney Ni, methanol. (d) LiAlH₄, THF, -30 °C. (e) SOCl₂. (f) NaN₃, triethylbenzylammonium chloride, acetonitrile.

chloride **1** with LiAlH₄ in THF at -30 °C. Direct reduction of 2,6-pyridinedicarboxylic acid with LiAlH₄ in THF did not work due to insolubility of the acid. 2,6-Di(chloromethyl)pyridine **6** was easily prepared by treating diol **5** with SOCl₂. Treating **6** with sodium azide in acetonitrile in the presence of triethylbenzylammonium chloride as phase transfer catalyst afforded 2,6-di(azidomethyl)pyridine in yield of 82%. The azide **7** was reduced to **4** under the same reduction condition applied on the reduction of nitrile **3**. Overall yield of 44% from three reaction steps by nitrile reduction method is better than overall yield of 34% from four reaction steps by azide reduction in spite of the reduction step of nitrile given only 65% yield. The amine synthesis by nitrile reduction is superior for solvent usage and work up of product which can form complexes with metal reagents.

2,6-Di(aminomethyl)pyridine **4** which has potential applications in the field of supramolecular chemistry could be easily synthesized from readily available 2,6-pyridinedicarboxylic acid through nitrile reduction.

Experimental

2,6-Pyridinedicarboxamide, 2. To vigorously stirred ammonium hydroxide (28%, 120 mL), was slowly added a solution of 2,6-pyridinedicarbonyl chloride, **1** (12.24 g, 60 mmol) in THF (10 mL). The mixture was stirred for one hour and the white solid precipitate was filtered and washed with water. The crude product (9.40 g, 95%) was dried under reduced pressure: mp 305-308 °C (dec.) (lit.^{2b} mp 304-306 °C).

2,6-Pyridinedicarbonitrile, 3. A mixture of **2** (1.0 g, 6.1 mmol) and P₂O₅ (2.0 g, 14.1 mmol) was well ground in a mortar, and charged in a sublimation apparatus. After flushed with nitrogen the sublimation apparatus was heated at 200 °C for 20 min. And then under vacuum the product was sublimed to give **3** as white solid (0.57 g, 72%): mp 130 °C (lit.^{2b} mp 130 °C).

2,6-Pyridinedimethanol, 5. To a suspension of LiAlH₄ (2.5 g, 67.2 mmol) in THF (200 mL) at -30 °C, was slowly added a solution of **1** (6.0 g, 29.4 mmol) in THF (20 mL) over one hour. The mixture was further stirred for 12 hours at -30 °C, and then for additional 12 hours at room temperature. After a saturated aqueous Na₂SO₄ solution (15 mL) was added slowly, the organic layer was separated and the aqueous layer was extracted with ethyl ether (15 mL × 3). The combined ether solution was dried over MgSO₄ and concentrated by a rotary evaporator. The residue was dried under vacuum to yield **5** as a slightly yellow solid (3.27 g, 80%): mp 113-115 °C (lit.^{5,7} mp 114-116 °C).

2,6-Di(chloromethyl)pyridine, 6. To thionyl chloride (20 mL) cooled at 0 °C, was slowly added diol **5** (2.0 g, 14.4 mmol). The resulting solution was heated at reflux for 4 hours. After excess thionyl chloride was distilled off, benzene (20 mL) was added to the residue. The formed white solid was filtered, and then dissolved in 35%-HCl (10 mL). The solution was neutralized with a saturated NaHCO₃ solution and the white precipitate was collected by filtration and washed with water, and then dried under vacuum to give **6** (1.88 g, 74%) as colorless crystals: mp 76 °C (lit.^{5,8}

mp 74-75 °C).

2,6-Di(azidomethyl)pyridine, 7. A mixture of dichloride **6** (1.8 g, 10 mmol), sodium azide (3.3 g, 50 mmol) and triethylbenzylammonium chloride (0.2 g, 0.5 mmol) in acetonitrile (50 mL) was heated at reflux for 30 min. The solvent was removed by a rotary evaporator. To the residue was added methylene chloride (50 mL) and the insoluble material was removed by filtration. The filtrate was washed with brine, dried over MgSO₄. The solution was concentrated and then dried under vacuum to give **7** (1.55 g, 82%) as a pale brown liquid: ¹H NMR (CDCl₃, 300 MHz) δ 7.74 (t, *J*=7.8 Hz, 1H, Ar-*H*), 7.29 (d, *J*=7.8 Hz, 2H, Ar-*H*) and 4.47 (s, 4H, ArCH₂); ¹³C NMR (CDCl₃, 75 MHz) δ 155.6 (*C*2, *C*6 of Ar), 137.7 (*C*4 of Ar), 120.8 (*C*3, *C*5 of Ar) and 55.1 (ArCH₂); IR (neat) 3068 w, 2928 m, 2877 w, 2099 vs, 1594 s, 1458 s, 1279 s, 800 m, 760 m and 656 m cm⁻¹.

2,6-Di(aminomethyl)pyridine, 4

Synthesis from 3. A mixture of dinitrile **3** (2.6 g, 20 mmol) and Raney nickel (2 g) in ethanol (30 mL) was charged in an autoclave. The autoclave was closed, evacuated, flushed with hydrogen three times and then pressurized to 10 atm. The autoclave was stirred with a magnetic stirrer at room temperature for 12 hours. The catalyst was removed by filtration and washed with water. The filtrate was concentrated *in vacuo*. The residue was distilled under vacuum (70 °C, 2 mmHg) to give **4** (1.78 g, 65%) as an icy solid:

Synthesis from 7. Under same reaction condition as above, diazide **7** (0.41 g, 2.17 mmol) afforded 0.21 g of **4** (70%): mp 29-31 °C (lit.⁵ mp 30 °C); ¹H NMR (CDCl₃, 300 MHz) δ 7.60 (t, *J*=7.8 Hz, 1H, Ar-*H*), 7.13 (d, *J*=7.8 Hz, 2H, Ar-*H*), 3.96 (s, 4H, ArCH₂), 1.72 (s, 4H, NH₂); ¹³C NMR (CDCl₃, 75 MHz) δ 161.1 (*C*2, *C*6 of Ar), 136.8 (*C*4 of Ar), 118.9 (*C*3, *C*5 of Ar) and 47.4 (ArCH₂); IR (neat) 3348 m, 3292 m, 3063 w, 2920 m, 1604 vs, 1577 vs, 1459 s, 1372 m, 1313 s, 795 s cm⁻¹; mass spectrum, *m/z* (rel in-

tensity). 138 (*M*+1, 25), 137 (*M*⁺, 11), 122 (10), 121 (100), 120 (26); Anal. Calcd for C₇H₁₁N₃: C, 61.29; H, 8.08; N, 30.63. Found: C, 60.96; H, 8.42; N, 30.27.

Acknowledgment. This work was financially supported by Kyungpook National University Research Fund 1996.

References

- (a) Alpha, B.; Anklam, E.; Deschenaux, R.; Lehn, J.-M.; Pietraskiewicz, M. *Helv. Chim. Acta* **1988**, *71*, 1042. (b) Lehn, J.-M. *Pure Appl. Chem.* **1980**, *52*, 2441.
- (a) Wehner, W.; Vögtle, F. *Tetrahedron Lett.* **1976**, *30*, 2603. (b) Jones, B. A.; Bradshaw, J. S.; Brown, P. R.; Christensen, J. J.; Izatt, R. M. *J. Org. Chem.* **1983**, *48*, 2635.
- (a) Basallote, M. G.; Martell, A. E. *Inorg. Chem.* **1988**, *27*, 4219. (b) Nelson, M. S. *Inorg. Chim. Acta* **1982**, *62*, 39. (c) Burnett, M. G.; McKee, V.; Nelson, S. M.; Drew, M. G. B. *J. Chem. Soc., Chem. Commun.* **1980**, 829. (d) Menif, R.; Chen, D.; Martell, A. E. *Inorg. Chem.* **1989**, *28*, 4633. (e) Lions, F.; Martin, K. V. *J. Am. Chem. Soc.* **1957**, *79*, 2733.
- Choi, H.-J.; Kwack, M.-O.; Song, H. *Syn. Comm.* **1997**, *27*, 1273-1280.
- Buhleier, E.; Wehner, W.; Vögtle, F. *Liebigs Ann. Chem.* **1978**, 537.
- (a) Freifelder, M. *J. Am. Chem. Soc.* **1960**, *82*, 2386. (b) Gould, F. E.; Johnson, G. S.; Ferris, A. F. *J. Org. Chem.* **1960**, *25*, 1658. (c) Carothers, W. H.; Jones, G. A. *J. Am. Chem. Soc.* **1925**, *47*, 3051.
- Bradshaw, J. S.; Nakatsuji, Y.; Huszthy, P.; Wilson, B. E.; Dalley, N. K.; Izatt, R. M. *J. Heterocycl. Chem.* **1986**, *23*, 353.
- (a) Weber, E.; Vögtle, F. *Angew. Chem.* **1980**, *92*, 1067. (b) Weber, E.; Vögtle, F.; Josel, H. P.; Newkome, G. R.; Puckett, W. E. *Chem. Ber.* **1983**, *116*, 1906. (c) Weber, E.; Josel, H. P.; Puff, H.; Franken, S. *J. Org. Chem.* **1985**, *50*, 3125.

A New Route to the Synthesis of Terbinafine

Seok Jong Lee*, Jae Ho Lee, Kyong Up Baik, and Myung Hwan Park

R&D Center, Daewoong Pharmaceutical Co. Ltd., 223-23 Sangdaewondong, Sungnam 462-120, Korea
Received July 31, 1997

Terbinafine **1**, one of an antifungal agents selectively inhibiting fungal squalene epoxidase, exhibits strong antimycotic activity and is currently used for the treatment of skin mycoses.¹ Terbinafine is an allylamine derivative with an (*E*)-1,3-enyne structural moiety that has developed from studies on structural-activity relationships since the accidental discovery of naftifine² (Figure 1).

To date, various synthetic methods for terbinafine **1** have been reported as follows: 1) condensation³ of an allylic bromide with the secondary amine, 2) DIBAL-H reduction⁴ of

1,3-diyne, and 3) palladium catalyzed cross coupling.⁵

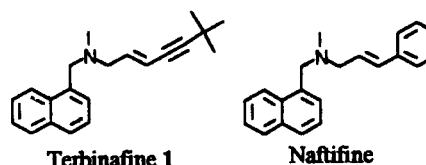


Figure 1.