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# Practical Synthesis of 4-Chloro-2-(2-naphthyl)quinoline, a Precursor to Triple-Helix DNA Intercalators

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**Abstract:**
**Several synthetic approaches to the title compound and analogs have been evaluated. This compound is a practical precursor to *N*-substituted 2-(2-naphthyl)quinolin-4-amines, the triple-helix DNA specific intercalators.**

The triple-helix structure of nucleic acids is formed by binding a single strand of DNA in the major groove of duplex DNA. The interaction is highly base sequence specific but is quite unstable under normal physiological conditions.[1] Various biotechnology applications have led to an increased interest in stabilization of the triplex DNA form. For example, the formation of a stable triplex structure between a short oligonucleotide and a specific sequence in a long duplex DNA can be used to inhibit expression of the specific gene.[2] Alternatively, with an appropriate cleaving group attached to the third-strand oligomer, highly specific cleavage of DNA can be achieved.[3]

One approach to enhance triplex stability is to design compounds that bind strongly and specifically to triplex DNA but weakly to duplex DNA.[4] Another strategy is to tether such compounds to the triplex-forming oligonucleotide, so that the triplex structure can be stabilized efficiently by intramolecular interactions.[5]

Several DNA intercalators are known to interact nonselectively with triple and double DNA structures or stabilize the triple helix relative to the corresponding duplex with various selectivities.[4] Compound **2** (Scheme 1) and other $N^4$-substituted 2-(2-naphthyl)quinolin-4-amines are far superior in their triplex stabilization ability and the triplex/duplex binding selectivity than any other triplex intercalators reported to date.[6] These unfused biaromatic derivatives bind to and stabilize strongly and selectively T·AT triplets of the triple-helix DNA in the presence of duplex DNA of any sequence.[7]

In this paper we critically examine several synthetic approaches to such triplex DNA intercalators. The preparation of a standard intercalator **2** and the synthesis of compound **9** (Scheme 1) with a terminal hydroxy group for the attachment to the 5′-end of an oligonucleotide[8] by using phosphoramidite chemistry serve as examples. A similar strategy can be used for the synthesis of analogs of **9** containing a terminal 1,2-diol functionality for linking to the 3′-end of an oligonucleotide.[9]

Quinoline **2** has been obtained previously by two methods, shown in Scheme 1, namely, (i) lithium 2-(dimethylamino)-ethylamide mediated cyclization of ketimine **1** derived from 2-(trifluoromethyl)aniline and acetonaphthone[10] and (ii) nucleophilic displacement of fluoride in 4-fluoroquinoline **3** with *N*,*N*-dimethylethylenediamine.[11] Unfortunately, the short and efficient route (i) is not applicable to the preparation of other quinolines substituted with a primary alkylamino function at position 4.[12]

The attractiveness of the second method (ii) as a general route to 4-(substituted alkylamino)quinolines is severely hampered by the low yield of 4-fluoroquinoline **3** obtained by the reaction of 2-(trifluoromethyl)aniline with the lithium enolate of acetonaphthone and a tedious purification that requires several consecutive chromatographic separations.[11] Our numerous attempts to optimize the synthesis of **3** did not succeed. The 33% yield of **3** obtained on a 200-mg scale[11] decreased to 5−15% for the reactions conducted on a 2-g scale under a variety of experimental conditions. These experiments included the published conditions and reactions conducted in different solvents (ether, hexanes, and ether/hexanes, in the presence and absence of hexamethylphosphoramide) with varying ratios of the reagents and at varying temperatures.

We focused our attention on 2-arylquinolin-4(1*H*)-ones that could be transformed into the corresponding quinolines substituted with other nucleofugal groups at position 4. A method described by Staskun[13] failed to produce the desired 2-(2-naphthyl)quinolin-4(1*H*)-one (**5**). The successful synthetic route to **5** involves potassium *tert*-butoxide mediated cyclization of ketimine **1**.[14] This reaction furnished a mixture

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(1) For reviews, see: (a) Hélene, C. *Curr. Opin. Biotechnol.* **1993**, *4*, 29. (b) Sun, J.-S.; Hélene, C. *Curr. Opin. Struct. Biol.* **1993**, *3*, 345.
(2) Grigoriev, M.; Praseuth, D.; Guieyesse, A. L.; Robin, P.; Thuong, N. T.; Hélene, C.; Harel-Bellan, A. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 3501.
(3) Moser, H. E.; Dervan, P. B. *Science* **1987**, *238*, 645.
(4) Kan, Y.; Armitage, B.; Schuster, G. B. *Biochemistry* **1997**, *36*, 1461 and references cited therein.
(5) Washbrook, E.; Fox, K. R. *Biochem. J.* **1994**, *301*, 569.
(6) (a) Strekowski, L.; Gulevich, Yu.; Baranowski, T. C.; Parker, A. N.; Kiselyov, A. S.; Lin, S.-Y.; Tanious, F. A.; Wilson, W. D. *J. Med. Chem.* **1996**, *39*, 3980. (b) Strekowski, L.; Gulevich, Yu.; Van Aken, K.; Wilson, W. D.; Fox, K. R. *Tetrahedron Lett.* **1995**, *36*, 225. (c) Wilson, W. D.; Tanious, F. A.; Mizan, S.; Yao, S.; Kiselyov, A. S.; Zon, G.; Strekowski, L. *Biochemistry* **1993**, *32*, 10614.
(7) (a) Cassidy, S. A.; Strekowski, L.; Fox, K. R. *Nucleic Acids Res.* **1996**, *24*, 4133. (b) Chandler, S. P.; Strekowski, L.; Wilson, W. D.; Fox, K. R. *Biochemistry* **1995**, *34*, 7234. (c) Cassidy, S. A.; Strekowski, L.; Wilson, W. D.; Fox, K. R. *Biochemistry* **1994**, *33*, 15338.
(8) Will, D. W.; Pritchard, C. E.; Brown, T. *Carbohydr. Res.* **1991**, *216*, 315.
(9) Grzybowski, J.; Will, D. W.; Randall, R. E.; Smith, C. A.; Brown, T. *Nucleic Acids Res.* **1993**, *21*, 1705.
(10) Wilson, W. D.; Zhao, M.; Patterson, S. E.; Wydra, R. L; Janda, L.; Strekowski, L. *Med. Chem. Res.* **1992**, *2*, 102.
(11) Strekowski, L.; Kiselyov, A. S.; Hojjat, M. *J. Org. Chem.* **1994**, *59*, 5886.
(12) For example, the treatment of **1** with a lithium reagent derived from 3-(dimethylamino)propylamine failed to produce a quinoline. A lithium dialkylamide mediated cyclization of **1** and related ketimines is a general method for *N*,*N*-dialkylquinolin-4-amines: Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R.L.; Harden, D. B.; Lipowska, M.; Cegla, M. T. *J. Org. Chem.* **1992**, *57*, 196. *N*-Alkyl-2-(2-naphthyl)quinolin-4-amines are better triple-helix DNA intercalators than the corresponding *N*,*N*-dialkyl analogs: ref 6a.
(13) Staskun, B. *J. South African Chem. Inst.* **1956**, *9*, 89.

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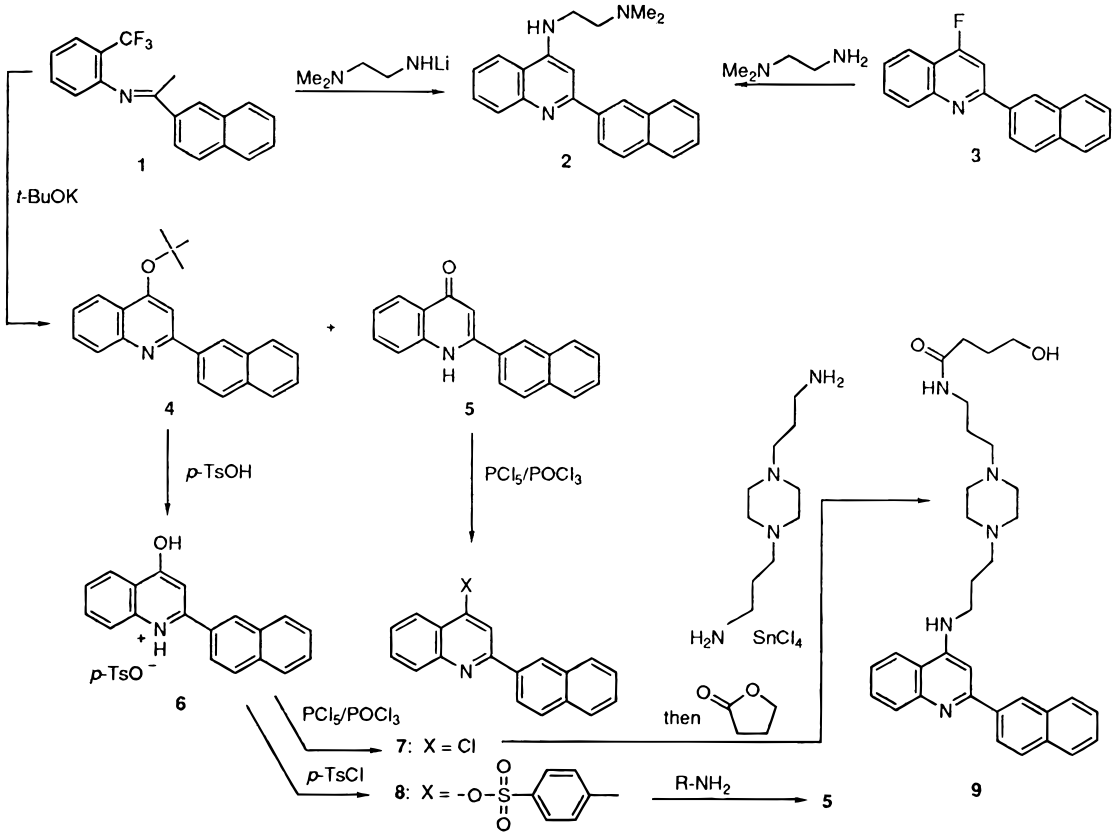
***Scheme 1***




of a 4-*tert*-butoxyquinoline **4** and quinolin-4(1*H*)-one **5** in 51% and 15% yields, respectively. The *tert*-butoxy derivative **4** was efficiently converted into **6** (93% yield), a *p*-toluenesulfonate salt of **5**, by treatment with *p*-toluenesulfonic acid. The subsequent reaction of either **5** or **6** with phosphorus oxychloride afforded 4-chloro-2-(2-naphthyl)-quinoline (**7**) in 75% yield. The use of phosphorus pentachloride (1 equiv) in a mixture with phosphorus oxychloride improved the efficiency of this reaction to 86%. Larger amounts of phosphorus pentachloride did not increase the yield of **7** but caused potential safety hazards during workup. Substitution of *p*-toluenesulfonyl chloride for $POCl_3$ furnished 2-(2-naphthyl)-4-[(*p*-tolylsulfonyl)oxy]quinoline (**8**). Unfortunately, the treatment of **8** with a primary amine did not cause displacement of the sulfonate group but resulted in cleavage of the S−O bond and gave quinolinone **5** quantitatively. Our initial attempts at displacing chloride from **7** by primary amines also did not succeed. Thus, in contrast to the reactivity of its fluoro analog **3**, the 4-chloroquinoline **7** was inert in attempted reactions with amines at 120 °C. After 6 h at 150 °C, the starting material **7** was still present and a large number of products had formed, as observed by TLC analysis. The nucleophilic displacement of chloride easily took place, however, in the presence of a catalytic amount of tin tetrachloride.[15] Such a treatment of **7** with *N*,*N*-dimethylethylenediamine gave the known intercalator **2**. In the synthesis of the desired triplex DNA intercalator **9**, compound **7** was treated with an excess of 1,4-bis(3-aminopropyl)piperazine in the presence of $SnCl_4$ followed by a reaction of the resultant intermediate monosubstituted amine, without purification, with $\gamma$-butyrolactone. The efficiencies of the reactions conducted with 0.5 g of **7** or scaled up to 5 g were virtually identical. The yield of the two-step transformation of **7** to **9** was 56%, and the overall yield of **9** from **1** was 27%.

In summary, we have described a practical method for the synthesis of 4-chloro-2-(2-naphthyl)quinoline (**7**) and shown that compound **7** is a good substrate for the preparation of triple-helix DNA intercalators. Products, such as **9**, that are compatible with phosphoramidite chemistry can be used in the preparation of triple-helix DNA intercalator−oligonucleotide conjugates.[8,9]

## Experimental Section

Melting points (Pyrex capillary) are uncorrected. $^1$H NMR (300 MHz) and $^{13}$C NMR (75.4 MHz) spectra were taken with TMS as an internal reference. Proton−proton coupling constants smaller than 2 Hz are not reported. Ketimine **1** was obtained as reported previously.[10]

**Reaction of Ketimine 1 with Potassium *tert*-Butoxide.** A mixture of **1** (10 g, 32 mmol) and *t*-BuOK (17 g, 150 mmol) in anhydrous THF (500 mL) was heated under reflux under a nitrogen atmosphere for 1 h. Cooling to 23 °C was followed by quenching with water (6.0 mL) and filtration. Concentration of the filtrate on a rotary evaporator to 50 mL followed by dilution with hexanes (40 mL) gave a

(14) For related cyclizations, see: Janda, L.; Nguyen, J.; Patterson, S. E.; Strekowski, L. *J. Heterocycl. Chem.* **1992**, *29*, 1753.

(15) The nucleophilic displacement of chloride in **7** is apparently facilitated by complexation of the ring nitrogen atom of **7** by the Lewis acid ($SnCl_4$). The reaction is also clean and similarly efficient, albeit slower (4 h at 140 °C under otherwise similar conditions), in the presence of boron trifluoride−dimethyl sulfide complex. The mercuric dichloride mediated reaction requires even harsher conditions (8 h at 140 °C) and produces many byproducts.

precipitate of **5**, which was filtered off and crystallized from methanol. Flash chromatography of the THF/hexanes solution (silica gel; hexanes/triethylamine, 95:5) gave an analytically pure sample of compound **4**, which was additionally purified by crystallization from hexanes. Crude compound **4** was used for the subsequent reaction.

**4-(*tert*-Butoxy)-2-(2-naphthyl)quinoline (4)**: 1.06 g (51%); mp 76−78 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.64 (s, 9 H), 7.19 (s, 1 H), 7.41 (t, $J$ = 8 Hz, 1 H), 7.46 (m, 3 H), 7.63 (t, $J$ = 8 Hz, 1 H), 7.83 (m, 1 H), 7.93 (m , 2 H), 8.06 (d, $J$ = 8 Hz, 1 H), 8.14 (d, $J$ = 8 Hz, 1 H), 8.19 (d, $J$ = 8 Hz, 1 H), 8.45 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.9, 80.7, 105.1, 122.6, 123.2, 125.2, 125.3, 126.3, 126.6, 126.9, 127.7, 128.5, 128.8, 129.3, 129.8, 133.4, 133.7, 137.8, 149.8, 158.1, 160.1. Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.39; H, 6.59; N, 4.45.

**2-(2-Naphthyl)quinolin-4(1*H*)-one (5):** yield 1.3 g (15%); mp 290−292 °C (from MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ 3.13 (br s, 1 H), 6.48 (s, 1 H), 7.35 (t, $J$ = 8 Hz, 1 H), 7.63 (m, 2 H), 7.69 (t, $J$ = 8 Hz, 1 H), 7.81 (d, $J$ = 8 Hz, 1 H), 7.93 (d, $J$ = 8 Hz, 1 H), 8.03 (m, 1 H), 8.11 (m, 3 H), 8.46 (s, 1 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 107.8, 118.7, 123.3, 124.5, 124.8, 124.9, 127.0, 127.2, 127.5, 127.7, 128.6, 128.7, 131.5, 131.9, 132.6, 133.6, 140.6, 149.9, 176.9; IR (KBr) $\nu$ 3250, 1630, 1595, 1547, 1508 cm$^{-1}$. Anal. Calcd for $C_{19}H_{13}NO$: C, 84.11; H, 4.83; N, 5.16. Found: C, 83.80; H, 4.69; N, 5.14.

**4-Hydroxy-2-(2-naphthyl)quinolinium *p*-Toluenesulfonate (6).** A solution of crude compound **4** (6.5 g, 20 mmol) and *p*-toluenesulfonic acid (6.0 g, 30 mmol) in THF (150 mL) was heated under reflux for 4 h and then cooled to 0 °C. After standing for 3 h at 0 °C, the precipitate of **6** was filtered off and crystallized from methanol: yield 8.0 g (93%); mp 223−225 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.28 (s, 3 H), 7.10 (d, $J$ = 8 Hz, 2 H), 7.28 (s, 1 H), 7.50 (d, $J$ = 8 Hz, 2 H), 7.71 (m, 3 H), 8.0−8.215 (m, 6 H), 8.33 (d, $J$ = 8 Hz, 1 H), 8.61 (s, 1 H). Anal. Calcd for $C_{26}H_{21}NO_4S$: C, 70.40; H, 4.77; N, 3.16. Found: C, 70.38; H, 4.73; N, 3.11.

**4-Chloro-2-(2-naphthyl)quinoline (7).** A mixture of salt **6** (7.0 g, 15.7 mmol), phosphorus pentachloride (3.2 g, 15.7 mmol), and phosphorus oxychloride (40 mL) was heated under reflux for 1 h, then cooled, and poured onto ice. The mixture was neutralized with a saturated solution of sodium bicarbonate, and the resultant precipitate of crude product **7** was filtered, washed with water, and dried (50 °C/10 mmHg). Purification involved treatment with hot ethyl acetate (180 mL), filtration from an insoluble yellow solid, then concentration of the solution, and crystallization of the residue from hexanes: yield 3.9 g (86%); mp 114−116 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (m, 2 H), 7.58 (t, $J$ = 8 Hz, 1 H), 7.74 (t, $J$ = 8 Hz, 1 H), 7.84 (m, 1 H), 7.94 (m, 2 H), 8.08 (s, 1 H), 8.17 (m, 2 H), 8.28 (d, $J$ = 8 Hz, 1 H), 8.53 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 119.5, 124.3, 125.0, 125.7, 126.8, 127.3, 127.6 (two signals), 128.0, 129.0, 129.2, 130.4, 130.9, 133.7, 134.4, 136.1, 143.5, 149.4, 157.3. Anal. Calcd for $C_{19}H_{12}ClN$: C, 78.75; H, 4.17; N, 4.71. Found: C, 78.75; H, 4.11; N, 4.65.

The treatment of quinoline **5** as described above furnished product **7** in a similar yield.

**2-(2-Naphthyl)-4-[(*p*-tolylsulfonyl)oxy]quinoline (8).** A solution of salt **6** (4.3 g, 10 mmol) in pyridine (60 mL) was cooled to 0 °C and treated slowly with *p*-toluenesulfonyl chloride (3.4 g, 18 mmol) at such a rate that the temperature did not rise above 5 °C. After being stirred for an additional 3 h at 5 °C, the mixture was diluted with dichloromethane (40 mL) and poured into cold water (200 mL). The organic layer was washed in succession with 1 N hydrochloric acid, a solution of sodium bicarbonate, and water, then dried over sodium sulfate, and concentrated on a rotary evaporator. Chromatography on silica gel eluting with hexanes/*tert*-butyl methyl ether (1:1) followed by crystallization from *tert*-butyl methyl ether gave 3.5 g (79%) of **8**: mp 128−130 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 2.43 (s, 3 H), 7.51 (d, $J$ = 8 Hz, 2 H), 7.62 (m, 3 H), 7.86 (d, $J$ = 8 Hz, 2 H), 7.96 (m, 3 H), 8.02 (m, 1 H), 8.13 (m, 3 H), 8.34 (d, $J$ = 8 Hz, 1 H), 8.65 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.7, 110.5, 121.2, 121.4, 124.7, 126.5, 126.9, 127.0, 127.2, 127.7, 128.6, 128.7, 128.8, 129.5, 130.1, 130.6, 132.2, 133.3, 134.0, 136.0, 146.1, 150.1, 153.8, 157.8. Anal. Calcd for $C_{26}H_{19}NO_3S$: C, 73.39; H, 4.50; N, 3.29. Found: C, 73.12; H, 4.32; N, 3.27.

***N*-[3-[4-[3-(4-Hydroxybutyramido)propyl]piperazino]-propyl]-2-(2-naphthyl)quinolin-4-amine (9).** A mixture of **7** (5.0 g, 17 mmol), 1,4-bis(3-aminopropyl)piperazine (58 mL, 282 mmol), and anhydrous tin tetrachloride (0.8 mL, 6.6 mmol) was stirred and heated to 130 °C under a nitrogen atmosphere for 3.5 h. Removal of the excess of the amine (100 °C/0.2 mmHg) was followed by addition of $\gamma$-butyrolactone (3 mL, 39 mmol) and stirring of the mixture at 80 °C for an additional 2.5 h. After cooling to 23 °C, water (10 mL) was added and the resultant solution was extracted with ethyl acetate (6 × 30 mL). The extract was dried over magnesium sulfate and concentrated, and the residue was crystallized from anhydrous ethyl acetate: yield 5.1 g (56%); mp 177−179 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.5−3.5 (m, 26 H), 4.42 (t, $J$ = 5 Hz, 1 H, exchangeable with $D_2O$), 7.14 (s, 1 H), 7.38 (br, 1 H, exchangeable with $D_2O$), 7.42 (t, $J$ = 8 Hz, 1 H), 7.55 (m, 2 H), 7.65 (t, $J$ = 8 Hz, 1 H), 7.73 (br, 1 H, exchangeable with $D_2O$), 7.91 (d, $J$ = 8 Hz, 1 H), 7.96 (m, 1 H), 8.02 (d, $J$ = 8 Hz, 1 H), 8.09 (m, 1 H), 8.21 (d, $J$ = 8 Hz, 1 H), 8.39 (d, $J$ = 8 Hz, 1 H), 8.70 (s, 1 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 24.9, 26.3, 28.6, 32.1, 36.8, 41.3, 52.7, 53.0, 55.5, 56.1, 60.3, 95.1, 118.0, 121.4, 123.7, 125.0, 126.1, 126.2, 126.4, 127.4, 127.7, 128.5, 129.1, 129.3, 132.9, 133.2, 137.5, 148.2, 150.9, 156.4, 171.9. Anal. Calcd for $C_{33}H_{41}N_5O_2$: C, 73.43; H, 7.65; N, 12.98. Found: C, 73.08; H, 7.71; N, 12.89.

A hemihydrate **9**·$^1/_2H_2O$ was obtained by crystallization of crude **9** from wet ethyl acetate, mp 181−182 °C. Anal. Calcd for **9**·$^1/_2H_2O$: C, 72.22; H, 7.71; N, 12.76. Found: C, 72.19; H, 7.76; N, 12.72.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