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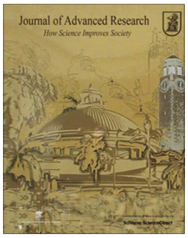

ORIGINAL ARTICLE

Benzoquinoline amines – Key intermediates for the synthesis of angular and linear dinaphthonaphthyridines

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ABSTRACT

A systematic study on the condensation reaction of 2,4-dichlorobenzo[*h*]quinoline and naphth-1-ylamine in the presence of CuI as catalyst to functionalised mono- and di-substituted (naphthalen-1-yl)benzo[*h*]quinoline amines was described. Subsequently these mono- and di-substituted amines on polyphosphoric acid catalysed cyclisation reaction with aromatic/heteroaromatic carboxylic acids led to the construction of angular and linear aromatic/heteroaromatic substituted dinaphthonaphthyridines in good yields.

Introduction

In a quest to obtain lead molecules in the medicinal chemistry, small molecules appended with differently substituted functional groups can be of great interest, due to their potential to create a number of chemical libraries. Among those, nitrogen containing heterocycles such as quinolines and naphthyridines draw special attention due to their wide variety of biological activities. For instance, quinoline based chemical entities were known for their anti-tuberculosis [1,2], antiproliferative [3,4], anthelmintic [5], antibacterial [6] and antioxidant activities [7]. 4-Amino-7-chloroquinoline derivatives and its modified side-chain analogs [8–10] were representative class of antimalarial drugs. Extensive studies were made to obtain biologically active quinolines and naphthyridine analogues starting from chloro quinolines [11]. The synthesis of naphthyridines [12], benzonaphthyridines [13], and dibenzonaphthyridines [14–16] from various starting precursors were also well documented in the literature. Such naphthyridines exhibit remarkable biological activities such as CB_2 selective agonists [17], anti-HIV [18], anticancer [19,20], selective 3-phosphoinositide-dependent kinase-I inhibitors [21] and topoisomerase-I inhibitors [22]. Naphthyridines were also explored as a versatile ligand in the field of inorganic chemistry [23].

Hence, there is a continuous urge to develop new methods for the synthesis of naphthyridines. There are so many reports in the literature about the utility CuI as catalyst. For example, Buchwald explored CuI-catalysed coupling of alkylamines and aryl iodides and also the *N*-arylation of sev-

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eral nitrogen-containing substrates using specific ligands [24,25]. Recently CuI catalysts have been received good attention for *N*-arylation reaction between aryl halides and amines [26,27], which in general are high yielding reactions under mild conditions. It is also quite stable under open atmosphere, less toxic and low cost. *N*-arylation of aromatic heterocycles and amino acids catalysed by CuI catalyst under ligand free conditions were recently reported [28]. These features encouraged our interest in exploring the synthetic utility of CuI as a catalyst for the synthesis of benzoquinoline amine intermediates under ligand free condition.

To the best of our knowledge, there are no literature reports for the synthesis of angular and linear aromatic/heteroaromatic substituted dinaphthonaphthyridines. Keeping the importance of naphthyridine compounds in mind, here in we report the synthesis of titled compounds by the reaction of 2,4-dichlorobenzo[*h*]quinoline *via* benzoquinolin-amine intermediates utilising Bernthsen reaction condition. These functionalised intermediates were prepared by simple amine-halide condensation reaction between 1-naphthylamine and 2,4-dichlorobenzo[*h*]quinoline using CuI as catalyst.

Experimental

General

Melting points (Mp.) were determined on Mettler FP 51 apparatus (Mettler Instruments, Switzerland) and were uncorrected. They were expressed in degree centigrade (°C). A Nicolet Avatar Model FT-IR spectrophotometer was used to record the IR spectra (4000–400 cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV 400 (400 M*Hz* (^{1}H) and 100 M*Hz* (^{13}C)), Bruker AV 500 (500 M*Hz* (^{1}H) and 125 M*Hz* (^{13}C)) spectrometer using tetramethylsilane (TMS) as an internal reference. The chemical shifts were expressed in parts per million (ppm). Mass spectra (MS) were recorded on Auto Spec EI + Shimadzu QP 2010 PLUS GC–MS mass spectrometer. Microanalyses were performed on a Vario EL III model CHNS analyser (Vario, Germany) at the Department of Chemistry, Bharathiar University, Coimbatore – 46, India. The solvent and the reagents used (reagent grade) were purified by standard methods. Anhydrous sodium sulphate was used to dry the solution of organic extracts. Thin layer chromatography (TLC) was performed using glass plates coated with silica gel-G containing 13% calcium sulphate as binder. Ethyl acetate and petroleum ether were used as developing solvents. A chamber containing iodine vapour was used to locate the spots. Separation and purification of the crude products were carried out using chromatographic column packed with activated silica gel (60–120 mesh). In the case of mixture of solvents used for elution, the ratio of the mixture is given in brackets.

Preparation of 2,4-dichlorobenzo[h]quinoline (3)

An equimolar mixture of naphth-1-ylamine (**1**, 0.01 mol), malonic acid (**2**, 0.01 mol) and 40 mL of phosphorous oxychloride was refluxed on water bath for 8 h and the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into crushed ice and neutralised with diluted solution of sodium hydroxide to give a white precipitate, which was filtered, dried and purified by silica column chromatography. The product was eluted with hexane, to obtain **3** as a white solid; Mp.: 70–72 °C; Yield: 45%; IR (KBr, cm^{-1}) ν_{max}: 1581 (C=N); ^{1}H NMR (400 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.62 (s, 1H, C_3—H), 7.74–8.08 (m, 5H, C_5, C_6—C_9—H), 9.22 (dd, 1H, J_o = 8.20 *Hz*, J_m = 1.20 *Hz*, C_{10}—H); Anal. Calcd. for $C_{13}H_7Cl_2N$ (247): C, 62.93; H, 2.84; N, 5.65%; Found: C, 63.00; H, 2.78; N, 5.61%.

General procedure for the reaction of naphth-1-ylamine (1) with 2,4-dichlorobenzo[h] quinoline (3); preparation of 4-chloro-N-(naphth-1-yl)benzo[h]quinolin-2-amine (4) and N^2,N^4-di(naphth-1-yl)benzo[h]quinolin-2,4-diamine (5)

A mixture of 2,4-dichlorobenzo[*h*]quinoline (**3**, 0.010 mol), naphth-1-ylamine (**1**, 0.010 mol) and CuI (10 mol%) was heated in 20 mL of DMSO at 120 °C for an hour. After the completion of the reaction, water was added into the reaction mixture. The resultant precipitate was washed with water, dried and purified by column chromatography (neutral alumina). Compound **4** was eluted with petroleum ether: ethyl acetate (99:1) whereas compound **5** was eluted with ethyl acetate: methanol (95:5). Both the compounds were recrystallised using methanol.

4-Chloro-N-(naphth-1-yl)benzo[h]quinolin-2-amine (4)

White amorphous powder; Mp.: 126–128 °C; Yield: 45%; IR (KBr, cm^{-1}) ν_{max}: 3066 (NH), 1636 (C=N); ^{1}H NMR (500 M*Hz*, $CDCl_3$) (ppm) δ_H: 7.02 (s, 1H, C_2—NH), 7.17 (s, 1H, C_3—H), 7.54–7.84 (m, 8H, C_8, $C_{2'}$—$C_{8'}$—H), 7.91 (t, 1H, *J* = 8.00 *Hz*, C_9—H), 7.96 (d, 1H, *J* = 8.00 *Hz*, C_6—H), 8.01 (d, 1H, *J* = 8.50 *Hz*, C_7—H), 8.15 (d, 1H, *J* = 9.00 *Hz*, C_5—H), 9.20 (dd, 1H, J_o = 8.00 *Hz*, J_m = 1.50 *Hz*, C_{10}—H); ^{13}C NMR (125 M*Hz*, $CDCl_3$) (ppm) δ_C: 109.17 (C_3), 119.11 (C_{4a}), 121.15 ($C_{2'}$), 121.25 ($C_{4'}$), 122.12 ($C_{8'}$), 124.50 ($C_{5'}$), 124.89 (C_5), 125.95 ($C_{7'}$), 126.08 ($C_{6'}$), 126.50 ($C_{3'}$), 126.52 (C_{10}), 126.59 (C_6), 127.77 (C_9), 128.38 (C_8), 128.64 (C_7), 129.34 ($C_{8a'}$), 130.22 ($C_{4a'}$), 134.38 (C_{10a}), 134.75 (C_{6a}), 135.14 ($C_{1'}$), 143.75 (C_{10b}), 147.06 (C_4), 155.68 (C_2); MS *m*/*z* (%) 354 (M + H, 100), 356 (M + 2, 31); Anal. Calcd. for $C_{23}H_{15}ClN_2$ (354): C, 77.85; H, 4.26; N, 7.89%; Found: C, 77.79; H, 4.23; N, 7.82%.

N^2,N^4-Di(naphth-1-yl)benzo[h]quinolin-2,4-diamine (5)

Pale brown solid; Mp.: > 300 °C; Yield: 51%; IR (KBr, cm^{-1}) ν_{max}: 3136, 3054 (NH), 1629(C=N); ^{1}H NMR (500 M*Hz*, DMSO-d_6) (ppm) δ_H: 6.51 (s, 1H, C_3—H), 7.01–8.19 (m, 18H, C_6—C_9, $C_{2'}$—$C_{8'}$ & $C_{2''}$—, $C_{8''}$—H), 8.77 (d, 1H, C_5—H, *J* = 8.00 *Hz*), 9.38 (d, 1H, C_{10}—H, *J* = 8.50 *Hz*), 10.74 (s, 1H, C_4—NH), 11.45 (s, 1H, C_2—NH), 14.13 (s, 1H, N_1—H); ^{13}C NMR (125 M*Hz*, DMSO-d_6) (ppm) δ_C: 86.26 116.36, 120.07, 121.05, 122.45, 122.82, 123.46, 125.16, 125.39, 126.30, 127.06 (2C), 127.20, 127.37, 128.27, 128.72, 128.95 (3C), 129.13, 129.32, 130.02, 132.35, 134.14, 134.34 (4C), 134.50, 134.88, 135.69, 152.88, 155.57; MS *m*/*z* (%) 462 (M + H, 100); Anal. Calcd. for $C_{33}H_{23}N_3$ (461): C, 85.87; H, 5.02; N, 9.10%; Found: C, 85.94; H, 4.99; N, 9.07%.