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New synthetic methodology for construction of the 3,4-dihydroisoquinolinone skeleton: A key structure for isoquinoline alkaloids

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ABSTRACT

We hereby report a new method for preparation of 3,4-dihydroisoquinolin-1(2*H*)-one as well as isoquinolin-1(2*H*)-one skeleton starting from the methyl 2-(3-methoxy-3-oxopropyl)benzoate. The ester functionality, adjacent to the methylene, was regiospecifically converted to the desired acyl azide. The isocyanate was transformed into the monoisocyanate by Curtius rearrangement followed by trapping with aniline. The formed urea derivative was cyclized with NaH to give a 3,4-dihydroisoquinolin-1(2*H*)-one derivative. Incorporation of a double bond into the six-membered ring followed by removal of the substituent resulted in the formation of isoquinolin-1(2*H*)-one skeleton.

1. Introduction

Isoquinolines are the member of alkaloids found in several bioactive natural products (Shamma, 1972; Shamma and Moniot, 1978; Glushkov and Shklyaev, 2001; Krane and Shamma, 1982). Many naturally occurring alkaloids such as dorianine **1** (Shamma, 1972; Shamma and Moniot, 1978), *N*-methylcoryaldine **2** (Lee et al., 1992), thalflavine **3** (Aly et al., 1989), ruprechstyril **4** (Awuah and Capretta, 2010) and narciclasine **5** (Gonzalez et al., 1999) contain isoquinoline backbone ring structure (Fig. 1)

Isoquinolinone skeletons, biogenetically derived from the amino acid phenylalanine, exhibit antidepressant (Sulkovski and Wille, 1969), anti-inflammatory (Kubo et al., 1979), analgesic (Senda et al., 1981), and hypolipidemic (Hasegava et al., 1994) characteristics. Furthermore, they also act as inhibitors of lipoxygenase (Van Duzer and Roland, 1995) and cholesterol biosynthesis (Ashton et al., 1990). The substituted isoquinolinone derivatives are also used as building blocks in organic synthesis.

In view of their great therapeutic value of such motifs in various biologically active compounds, various synthetic methods have been developed for the synthesis of isoquinolinone derivatives. Among the synthetic methods, Gabriel and Colman synthesized isoquinolone derivatives *via* ring enlargement process starting from phthalimide derivatives (Delcey et al., 1995). Another synthetic method to prepare the cyclic amides (Beccalli et al., 2007) involves a palladium-catalyzed three-component coupling reaction between aryl halides, carbon monoxide, and amines. This reaction was modified by using a slight excess amount of carbon monoxide in the form of its molybdenum complex, $Mo(CO)_6$ (Ren and Yamane, 2010). For the synthesis of *N*-substituted isoquinolinones, 2-methoxycarbonylstyrene oxides were reacted with substituted amines to yield 4-hydroxy-1(2*H*)-isoquinolinones (Sugimoto et al., 1995).

In this paper, we describe a novel route for the synthesis of dihydroisoquinolinone skeleton based upon Curtius rearrangement of the azide derived from 2-(2-carboxyethyl)benzoic acid **8**.

2. Results and discussion

The starting material **9** was synthesized from commercially available β-naphtol **6**, which was first oxidized to cinnamic acid derivative **7** by reaction with peroxyacetic acid (Fig. 2). Diacid **7** was then reacted with Raney Nickel in basic aqueous solution to give the desired saturated diacid **8** as described in the literature (Page and Tarbell, 1963; Dengiz et al., 2010). The corresponding diester **9** (Srinivas and Das, 2003) was synthesized by refluxing of diacid **8** in methanol with thionyl chloride.

Our plan for the construction of the desired heterocyclic ring system, dihydroisoquinolinone (Ozcan and Balcı, 2008; Ozcan et al., 2007, 2011; Deliömeroglu et al., 2010), involved an intramolecular cyclization reaction of the isocyanate **13**, generated by *Curtius* rearrangement (Scriven and Turnbull, 1988) of the corresponding acyl azide **12**. For this reason the diester was submitted to hydrolysis reaction. Recently, we reported that the

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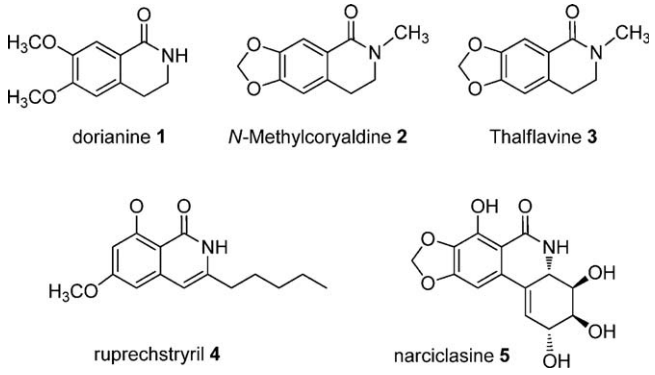

Fig. 1. Structures of some natural products containing isoquinolinone skeleton.

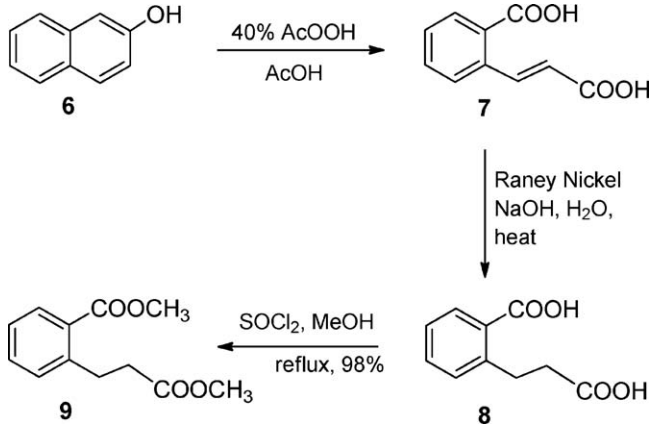

Fig. 2. Synthesis of methyl 2-(3-methoxy-3-oxopropyl)benzoate **9**.

reactivity of the ester groups, connected to a furan ring, is different (Koza et al., 2009, 2010). The ester functionality adjacent to the methylene group in **9** is more reactive than the aromatic one. For regiospecific hydrolysis, the diester **9** was treated with K_2CO_3 at 60 °C for 2 h. The desired monoester **10** was formed in 86% yield (Fig. 3).

The most general and versatile synthesis of acyl azides involves the reaction of acyl chlorides with NaN_3 in an aqueous medium. The monoester **10** was treated with oxalyl chloride in methylene chloride followed by addition of a solution of NaN_3 in water. This azide formation method was successful and provided acyl azide **12** in 83% yield. Finally, **12** was refluxed in benzene to give the corresponding isocyanate derivative **13** in high yield. Isocyanate **13** was chosen as a model compound to explore further reactions. Treatment of **13** with aniline in methylene chloride gave the urethane derivative **14** in 65% yield.

Finally, we focused our effort to the ring closure reaction of **14**, already bearing the necessary functionalities as shown in Fig. 4. The ring-closure reaction of **14** was accomplished by treatment with NaH in THF at 0 °C. The NMR spectral studies indicated that the cyclization product **16** was formed as the product in 70% yield. In the cyclization reaction of **15**, two cyclization products, **15** and **18**, are expected as a result of the attack of the two different amide functionalities to the ester carbonyl group. The formation of the six-membered ring was preferred over the eight-membered ring **18** (Fig. 5).

For conversion of 3,4-dihydroisoquinolin-1(2*H*)-one skeleton **15** into isoquinolinone **17**, urea derivative **15** was treated with *N*-bromosuccinimide (NBS) in the presence of radical initiator, azaisobutyronitrile (AIBN) at reflux temperature of benzene. Brominated isoquinolinone derivative **16** was isolated after column chromatography in 70% yield. For removal of the amide functionality and introduction of a double bond into the molecule, the brominated compound **17** was reacted with potassium *t*-butoxide to give the isoquinolinone **17** in 74% yield.

In conclusion, we have developed a new synthetic methodology for the construction of *N*-substituted 3,4-dihydroisoquinolin-1-(2*H*)-one derivative. The isocyanate **13** can be trapped with different nucleophiles so that the substituents attached to *N*-atom can be controlled. Furthermore, by starting from at benzene ring substituted diesters **9**, further substituted dihydroisoquinolin-1-(2*H*)one derivatives can be synthesized. Application of this methodology opens up a new area for the synthesis of various substituted isoquinolinone derivatives. Furthermore, introduction of a double bond into the six-membered ring opens up new routes of synthesizing of various at benzene ring as well as at nitrogen atom substituted isoquinolinone derivatives.

3. Experimental

3.1. General

Melting points are uncorrected. Infrared spectra were obtained from KBr pellets on an FT-IR Bruker Vertex 70 instrument. The ^1H and ^{13}C NMR spectra were recorded on a Bruker-Biospin (DPX-400) instrument. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck), and TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates. Elemental analyses were carried out on a Leco-932 model CHNS analyzer.

3.2. Methyl 2-(3-methoxy-3-oxopropyl)benzoate 9

To a stirred solution of diacid **8** (2.0 g, 10.3 mmol) in methanol (30 mL) was added thionyl chloride (1.02 mL, 12.36 mmol) and

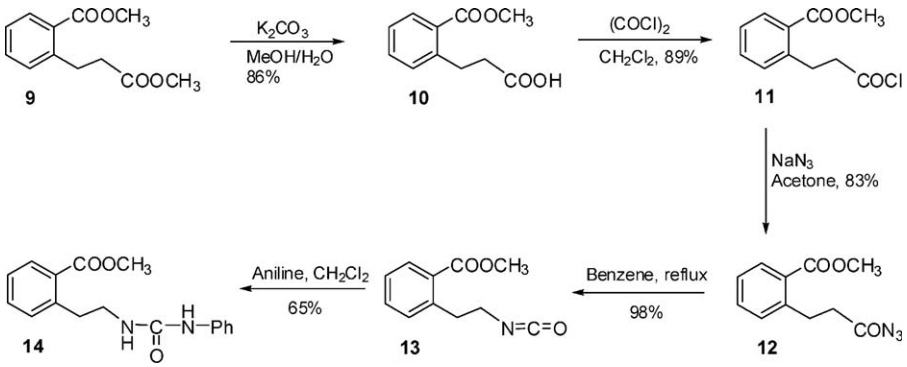

Fig. 3. Synthesis of urea derivative **14** starting from the diester **9**.

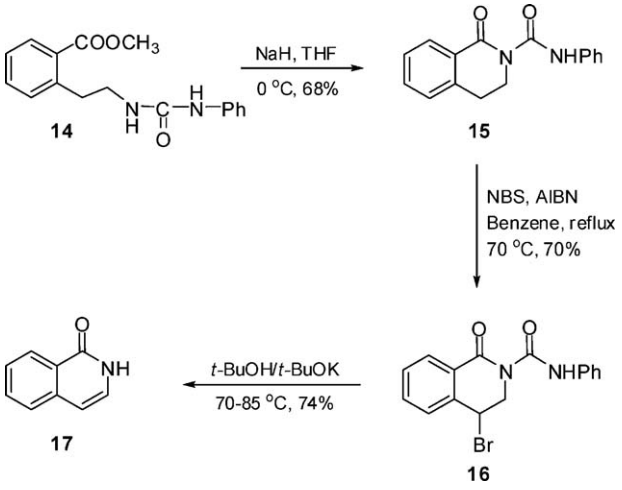

Fig. 4. Synthesis of isoquinolin-1(2*H*)-one (**17**).

solution was heated up to reflux temperature (70–80 °C). The reaction was monitored by TLC. After the completion of the reaction (4 h), methanol and excess thionyl chloride were evaporated to give diester **9** (2.14 g, 9.6 mmol, 94%) as a pale yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (d, $J_{5,6}$ = 8.0 Hz, 1H, H-6), 7.40 (t, $J_{4,3} = J_{4,5}$ = 6.5 Hz, 1H, H-4), 7.25 (m, 2H, H-3 and H-5), 3.86 (s, 3H, –OCH_3), 3.63 (s, 3H, –OCH_3), 3.25 (t, $J_{7,8}$ = 7.0 Hz, 2H, H-8) 2.65 (t, $J_{7,8}$ = 7.0 Hz, 7.0 Hz, H-7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.2, 167.4, 142.4, 132.9, 131.0, 130.8, 129.3, 126.3, 51.9, 51.4, 35.4, 29.8; IR (KBr, cm^{-1}) 3726.4, 2952.1, 2256.3, 1718.9, 1601.7, 1576.8, 1489.6, 1366.3, 1257.8, 1131.3, 907.5, 648.1.

3.3. 3-(2-(Methoxycarbonyl)phenyl)propanoic acid 10

To a stirred solution of diester **9** (2.14 g, 9.6 mmol) in 50 mL of methanol/H_2O (1:1) was added excess potassium carbonate (3.0 g, 21 mmol) and the resulting solution was stirred at 60 °C for 2 h. After the completion of the reaction, the mixture was cooled to room temperature and the solution was acidified by dropwise addition of HCl solution. The unreacted starting material **9** and the monoester **10** were extracted with ethyl acetate. The organic phase was extracted with aqueous NaOH solution (10%, 3 × 25 mL). The aqueous phase was acidified and then extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed to give the monoester **10** (1660 mg, 86%), Mp: 70–71 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.12 (br s, 1H, –COOH), 7.95 (d, $J_{3,4}$ = 7.6 Hz, 1H, H-3), 7.45 (t, $J_{4,5} = J_{5,6}$ = 7.6 Hz, 1H, H-5), 7.31 (m, H-4 and H-6) 3.91 (s, 3H, –OCH_3), 3.31 (t, $J_{7,8}$ = 7.7 Hz, 2H, H-8) 2.66 (t, $J_{7,8}$ = 7.7 Hz, 2H, H-7); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.2, 167.4, 142.4, 132.9, 131.0, 130.8, 129.3, 126.3, 51.2, 35.4, 29.8; IR (KBr, cm^{-1}) 3300–3000, 1678, 1599, 1492, 1308, 1215, 1150, 809, 680, 536.

3.4. Methyl 2-(3-chloro-3-oxopropyl)benzoate 11

To a stirred solution of 3-(2-(methoxycarbonyl)phenyl)propanoic acid (**10**) (1.0 g, 4.8 mmol) in 25 mL of dichloromethane was added oxalyl chloride (0.5 mL, 5.76 mmol) and stirred at room temperature for 1 h. After completion of the reaction, solvent was evaporated to give the acyl chloride (0.97 g, 4.27 mmol, 89%) **11**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (br d, $J_{3,4}$ = 7.8 Hz, 1H, H-3), 7.41 (dt, $J_{4,5} = J_{5,6}$ = 7.7 Hz, $J_{3,5}$ = 1.5 Hz, 1H, H-5), 7.30 (dt, $J_{3,4} = J_{4,5}$ = 7.8 Hz, $J_{4,6}$ = 1.4 Hz, 1H, H-4), 7.28 (d, $J_{5,6}$ = 7.5 Hz, 1H, H-6), 3.88 (s, 3H, –OCH_3), 3.29 (AA′BB′-system, 4H, H-7 and H-8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.2, 167.4, 140.7, 132.6, 131.4, 131.2, 129.0, 127.0, 52.1, 48.4, 30.2.

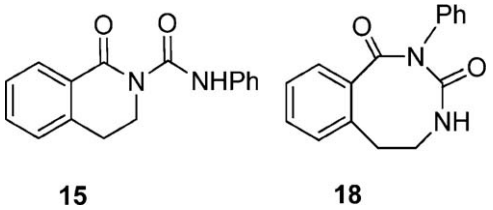

Fig. 5. Possible cyclization products of **14**.

3.5. Methyl 2-(3-azido-3-oxopropyl)benzoate 12

To a solution of methyl 2-(3-chloro-3-oxopropyl)benzoate (**11**) (0.97 g, 4.27 mmol) in acetone (25 mL) was added a solution of sodium azide (1.5 g, 23 mmol) in water (25 mL) dropwise at 0 °C and stirred for 1 h at 0 °C. The mixture was extracted with ethyl acetate (3 × 25 mL), and the combined extracts was washed with saturated sodium bicarbonate and water, and dried over $MgSO_4$. After concentration of the solvent, acyl azide **12** (0.84 g, 83%), unstable at room temperature, was obtained as a pale yellow viscous liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J_{3,4}$ = 7.8 Hz, 1H, H-3), 7.41 (br t, $J_{4,5} = J_{5,6}$ = 7.7 Hz, 1H, H-5), 7.2–7.3 (m, H-4 and H-6), 3.88 (s, 3H, –OCH_3), 3.58 (t, $J_{7,8}$ = 6.8 Hz, 2H, H-7a), 2.71 (t, $J_{7,8}$ = 6.8 Hz, 2H, H-8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 179.7, 167.4, 141.9, 139.7, 131.0, 130.8, 129.3, 126.3, 52.1, 43.8, 38.3; IR (KBr, cm^{-1}) 2956, 2152 (N_3), 1742, 1689, 1600, 1437, 1300, 1046, 850, 741.

3.6. Methyl 2-(2-isocyanatoethyl)benzoate 13

A solution of methyl 2-(3-azido-3-oxopropyl)benzoate (**12**) (1.0 g, 4.29 mmol) in dry benzene (25 mL) was heated under reflux for 1 h. The solvent was evaporated to give isocyanate **13** (0.82 g, 98% as pale yellow viscous liquid). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (d, $J_{3,4}$ = 7.8 Hz, 1H, H-3), 7.39 (t, $J_{4,5} = J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.16–7.28 (m, H-4 and H-6), 3.82 (s, 3H, –OCH_3), 3.53 (t, $J_{7,8} = J_{7a,b,8b}$ = 6.7 Hz, 2H, H-7) 2.66 (t, $J_{7,8}$ = 6. 7 Hz, H-8); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.4, 139.4, 132.5, 131.0, 130.8, 129.8, 128.3, 122.2, 52.1, 43.8, 36.3; IR (KBr, cm^{-1}) 2953, 2271 (NCO), 1716, 1490, 1353, 1265, 1086, 966.1, 752, 582.

3.7. Methyl 2-(2-(3-phenylureido)ethyl)benzoate 14

To a stirred solution of ethyl 2-(3-isocyanato-3-oxopropyl)-benzoate (**13**) (0.82 g, 4.0 mmol) in methylene chloride (25 mL) was added aniline (600 mg, 6.45 mmol) at room temperature and the resulting mixture was stirred for 2 h at the same temperature. After concentration of solvent, the residue was purified over a silica gel (20 g) column eluting with hexane/ethyl acetate (1:1) to give the urea derivative **14** (775 mg, 65%). White solid, Mp: 131–144 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 7.2 Hz, H-15), 7.38 (dt, J = 7.5 and 1.4 Hz, 1H), 7.30–7.17 (m, 7H), 6.96 (t, J = 7.3 Hz, 1H), 5.4 (br. s, NH, H-10) 3.81 (s, 3H, –OCH_3), 3.42 (dt, J = 7.5 and 6.5 Hz, 2H), 3.09 (t, J = 7.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.2, 156.3, 149.9, 139.2, 132.4, 131.6, 130.8, 129.4, 128.9 (2C), 126.6, 123.0, 120.4 (2H), 52.2, 42.0, 34.9. IR (KBr, cm^{-1}) 3354, 3316, 3022, 2947, 1721, 1629, 1593, 1557, 1443, 1314, 1247, 1108, 1087, 1028, 968; anal. calcd. for $C_{17}H_{18}N_2O_3$; C, 68.44; H, 6.08; N, 9.39. Found: C, 68.53; H, 5.82; N, 9.74.

3.8. 1-Oxo-N-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide 15

To a stirred solution of methyl 2-(2-(3-phenylureido)ethyl)-benzoate (**7**) (0.68 g, 2.28 mmol) in dry THF (25 mL) was added sodium hydride (0.063 g, 2.74 mmol) at 0 °C and the resulting mixture was stirred for 1 h at the same temperature. After

completion of the reaction, water was added dropwise and aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$. Removal of the solvent gave the crude product, which was chromatographed on silica gel (20 g) eluting with hexane/ethyl acetate (3:2) to give dihydroquinolinone derivative **19** (0.41 g, 68%). Mp: 162–163 °C from ethyl acetate/hexane (5:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.78 (bs, –NH), 8.13 (dd, $J_{9,10}$ = 6.8 Hz, $J_{8,10}$ = 1.0 Hz 1H, H-10), 7.58 (dd, $J_{16,17} = J_{19,20}$ = 7.5 Hz, $J_{16,18} = J_{18,20}$ = 1.2 Hz, 2H, H-16, H-20), 7.54 (dt, $J_{7,8} = J_{8,9}$ = 7.5 Hz, $J_{8,10}$ = 1.2 Hz, 1H, H-8), 7.41 (t, $J_{9,10} = J_{8,9}$ = 6.8 Hz, 1H, H-9), 7.35 (t, $J_{17,18} = J_{16,17} = J_{18,19} = J_{19,20}$ = 7.5 Hz, 2H, H-17, H-19), 7.27 (d, $J_{7,8}$ = 7.5 Hz, 1H, H-7), 7.12 (t, $J_{17,18} = J_{18,19}$ = 7.5 Hz, 1H, H-18), 4.25 (t, $J_{2,3}$ = 6.4 Hz, 2H, H-2) 3.05 (t, $J_{2,3}$ = 6.4 Hz, 2H, H-3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.1, 152.6, 140.2, 138.2, 133.8, 129.6, 129.4 (2C), 129.2, 127.7, 127.4, 124.4, 120.8 (2C), 41.9, 28.2; IR (KBr, cm^{-1}) 2924, 1703, 1653, 1596, 1556, 1445, 1392, 1318, 1225, 1151, 898, 737; anal. calcd. for $C_{16}H_{14}N_2O_2$; C, 72.16; H, 5.30; N, 10.52; O, 12.02. Found: C, 72.16; H, 5.19; N, 10.55.

3.9. 4-Bromo-1-oxo-N-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide 16

To a solution of oxo-*N*-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide **(15)** (0.41 g, 1.54 mmol) in dry benzene (10 mL) *N*-bromosuccinimide (0.27 g, 1.54 mmol) and azaisobutyronitrile (0.05 g, 0.03 mmol) were added and the resulting mixture was refluxed for 5 h. Then the mixture was filtered and the solvent was evaporated. The residue was chromatographed on silica gel (20 g) eluting with hexane/ethyl acetate (3:2) to give **16** (0.37 g, 70%) as colorless solid. The obtained product was crystallized from ethyl acetate/hexane (5:1) to give white solid of **16**. Mp: 151–152 °C from ethyl acetate/hexane. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.69 (bs, 1H, –NH), 8.21 (dd, $J_{9,10}$ = 7.8 Hz, $J_{8,10}$ = 1.2 Hz 1H, H-10), 7.62 (dt, J = 7.5 and 1.2 Hz, 1H) 7.63–7.12 (m, 7H), 5.44 (t, J = 3.1 Hz, 1H, H-3) 5.20 (dd, J = 14.9, and 3.1 Hz, 1H, H-2a), 3.93 (dd, J = 14.9, and 3.1 Hz, 1H, H-2b); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.3, 151.8, 139.6, 136.8, 134.3, 132.0 (2C), 129.9, 129.8, 127.7, 126.9, 122.0 (2C), 116.9, 48.5, 43.1; IR (KBr, cm^{-1}) 3129, 3033, 1701, 1657, 1592, 1546, 1500, 1486, 1440, 1389, 1292, 1176, 1149, 1014, 958; anal. calcd. for $C_{16}H_{13}BrN_2O_2$; C, 55.67; H, 3.80; N, 8.12. Found: C, 55.45; H, 3.68; N, 8.13.

3.10. Isoquinolin-1(2H)-one 17

To a solution of 4-bromo-1-oxo-*N*-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxamide (**16**) (0.75 g, 2.17 mmol) in *t*-BuOH (10 mL) was added t-BuOK (1.0 g, 8.92 mmol) and the mixture was refluxed for 15 min. Removal of the solvent followed by column chromatography on silica gel (15 g) eluting with hexane/ethyl acetate (3:2) gave **17**. The obtained product was crystallized from ethyl acetate/hexane (5:1) to give white solid **17** (0.240 g, 76%). Mp: 205–206 °C from ethyl acetate (n-hexane, Lit Mp = 203–204 °C) (Takaki et al., 1978). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.19 (bs, 1H, NH), 8.34 (d, $J_{7,8}$ = 7.9 Hz, 1H, H-8), 7.60 (dt, $J_{7,8} = J_{6,7}$ = 7.9 Hz, $J_{5,7}$ = 1.3 Hz, 1H, H-7), 7.48 (d, $J_{5,6}$ = 7.8, 1H, H-5), 7.44 (dt, $J_{6,7} = J_{5,6}$ = 7.8 Hz, $J_{6,8}$ = 1.1 Hz, 1H, H-6), 7.00 (bt, $J_{1,9} = J_{9,10}$ = 7.3 Hz, 1H, H-9), 6.44 (d, $J_{9,10}$ = 7.3 Hz, 1H, H-10); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 138.1, 133.0, 127.5, 127.2, 127.1, 126.3, 107.5, 99.9; IR (KBr, cm^{-1}) 3517, 3205, 3004, 2253, 1735, 1534, 1476, 1437, 1370, 1335, 1216, 1163, 1111, 1074, 937.

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