A Convenient Synthesis of 5-Methylbenzo[*c*]phenanthridin-6(5*H*)-one

Won-Jea Cho,* In Jong Kim,† and Sun-Ja Park

College of Pharmacy, Chonnam National University, Yongbong-dong 300, Buk-gu, Kwangju 500-757, Korea
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0943, Japan
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Many natural benzo[*c*]phenanthridine alkaloids such as nitidine, fagaronine have been investigated as plausible antitumor agents over the last two decades.[1] Although benzophenanthridine alkaloids display significant antitumor activity and progress toward understanding the mode of action has been made, clinical utility has been limited by the acute toxicity, narrow spectrum and weak water solubility.[2]

The bulk of reported benzophenanthridine synthetic studies to date have involved multistep sequences for assembly of the target molecules as well as lack of generality for synthesizing substituted molecules.[3] In order to study structure-activity relationships of these compounds the efficient synthetic procedures are needed.

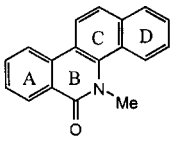
We recently reported the synthesis of 3-arylisoquinoline derivatives with biological evaluation of them.[4] The synthetic strategy involved the coupling reaction of *N*-methyl-*o*-toluamide with benzonitrile derivatives.[5] We planned to apply this method to the synthesis of benzophenanthridine skeleton **1** which could be derived from appropriate 3-arylisoquinoline intermediate.

Our strategy is based on the formation of 3-arylisoquinoline **16** which could be transformed to benzophenanthridine skeleton *via* intramolecular enamide ring formation. For the synthesis of crucial intermediate **16**, 3-(2-hydroxymethyl)-phenylisoquinoline **12** was chosen as a synthetic precursor which could be converted to **16**.

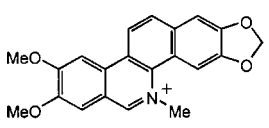
2-Methylbenzonitrile **2** was treated with *N*-bromosuccinimide (NBS) in the presence of 1,1'-azobis(cyclohexanecarbonitrile) (VAZO®)[6] to afford the benzylbromide **3** in 75% yield.[7] The brominated benzonitrile was then converted to acetate followed by deacetylation with K_2CO_3/H_2O-MeOH to give 2-hydroxymethylbenzonitrile **4** which was then reacted with benzyl chloride/60% NaH to give 2-benzyloxymethylbenzonitrile **5** in 80% yield. *N*-Methyl-*o*-toluamide **7** was basified with two equivalent *n*-butyl lithium to form the dianion which was reacted with **5** to produce the 3-(2-benzyloxy)phenylisoquinolin-1(2*H*)-one **8** in 46% yield.[8] For removing the benzyl protection group, **8** was hydrogenated with 5% Pd-C under 1 atm hydrogen. However, the 3-(2-methyl)-phenylisoquinolin-1(2*H*)-one **9** was obtained as a major product (73% yield) instead of a desired 3-(2-hydroxymethyl)phenyl-1(2*H*)-one **12** (11% yield). Therefore, we decided to modify the benzyl protection group to 4-methoxybenzyl moiety because it can be selectively removed by DDQ oxidation without acting on normal benzyl group.

2-[(4-Methoxybenzyl)oxy]methylbenzonitrile **6** was prepared from the compound **3** with 4-methoxybenzylalcohol and 60% NaH in 60% yield. The coupling reaction of *N*-methyl-*o*-toluamide **7** with **6** was carried out under the above condition to provide the desired 3-arylisoquinoline **10** in 35% yield. Methylation of **10** with MeI/60% NaH in tetrahydrofuran (THF) afforded the *N*-methylated product **11** in 56% yield without producing *O*-methylated compound. As expected, 4-methoxybenzyl group on **11** was selectively removed by DDQ treatment to yield 3-(2-hydroxymethyl)-phenylisoquinolin-1(2*H*)-one **12** which was oxidized with pyridinium dichlomate (PDC) in CH_2Cl_2 to give aldehyde **13** in 43% two-step yield. Wittig reaction of **13** with methyltriphenylphosphonium bromide afforded the styrene compound **14** in 65% yield. The styrene moiety was oxyfunctionalized by treating thallium trinitrate in MeOH to give the acetal **15** in 48% yield. The hydrolysis of acetal **15** was performed with 10% HCl to provide the final 5-methylbenzo-[*c*]phenanthridin-6(5*H*)-one **1** in 95% yield. This reaction could be rationalized that the hydrolysis produced the aldehyde **16** and the following intramolecular enamide-aldehyde cyclization occurred under the acidic condition.[9] After the ring formation, dehydration and the consecutive dehydrogenation would easily occur thus producing a fully aromatized ring system of benzo[*c*]phenanthridine skeleton.

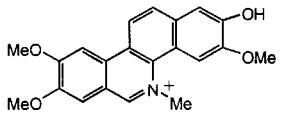
This newly developed method could be applied for the synthesis of natural benzo[*c*]phenanthridine alkaloids because the substitued *N*-methyl-*o*-tolunitrile and benzonitrile derivatives seem to be easily prepared. The total synthesis of some natural benzo[*c*]phenanthridine alkaloids is under investigation.



5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (**1**)



nitidine



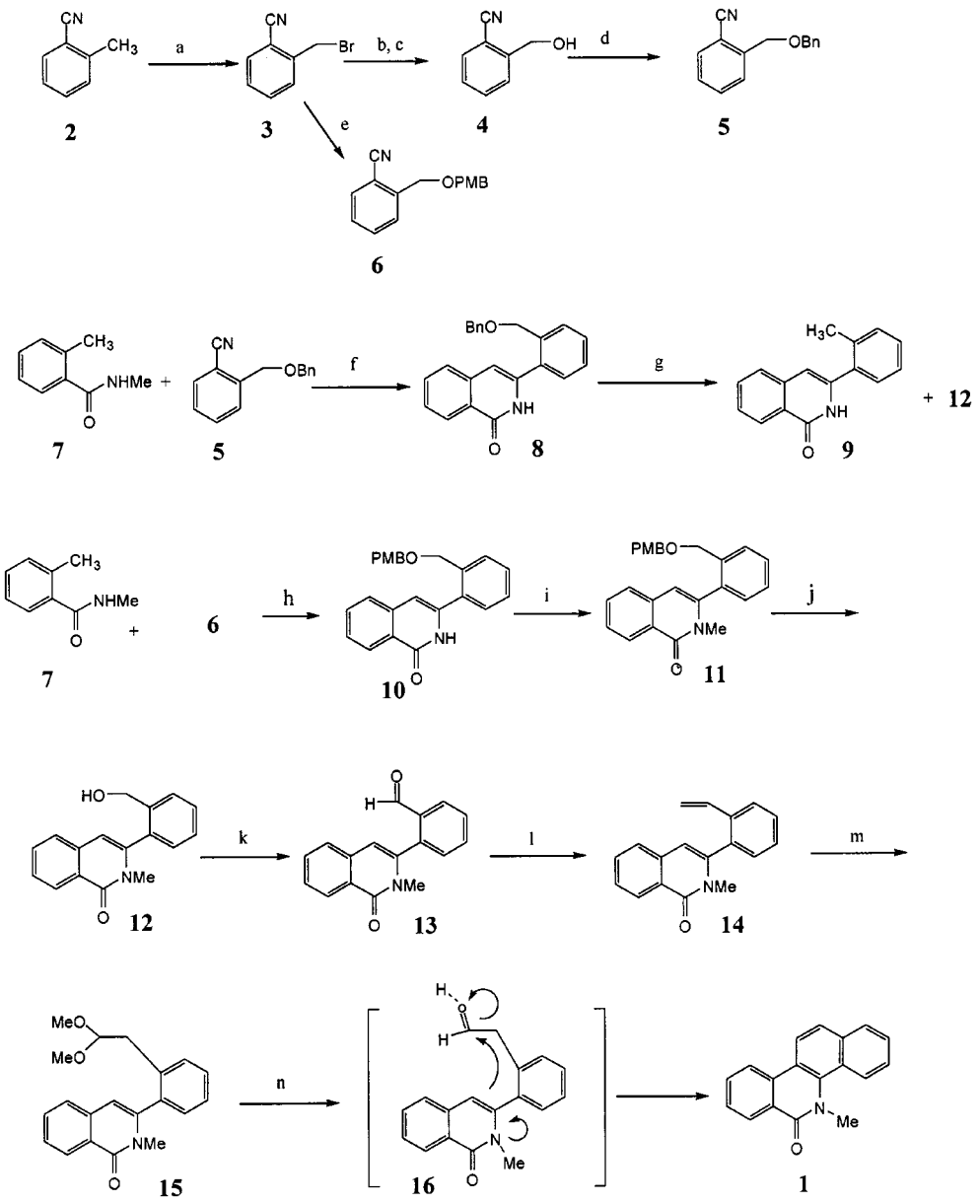
fagaronine

Scheme 1. Representative Antitumor Benzo[*c*]phenanthridine Alkaloids.

Experimental Section

Melting points were determined on an Electrothermal

*Corresponding Author. Tel: +82-62-530-2933; Fax: +82-62-530-2911; E-mail: wjcho@chonnam.chonnam.ac.kr



Scheme 2. Synthesis of Benzo[*c*]phenanthridine Skeleton. *Reagents and Yields*: a: NBS, CCl_4, VAZO®, 75% b: NaOAc, EtOH, 88% c: K_2CO_3, MeOH-H_2O, 62% d: BnCl, 60% NaH, 80% e: 4-MeO-C_6H_4-CH_2OH, 60% NaH, THF, 60% f: *n*-BuLi, THF, -50 °C, 46% g: 5% Pd-C, H_2, MeOH, 73% (**9**), 11% (**12**) h: *n*-BuLi, THF, -50 °C, 35% i: 60%NaH, MeI, 56% j: DDQ, CH_2Cl_2-H_2O, 52% k: PDC, CH_2Cl_2, cat. AcOH, 82% l: $Ph_3P^+CH_3\ Br^-$, *n*-BuLi, THF, 65% m: $Tl(NO_3)_3 \cdot 3H_2O$, MeOH, 48% n: 10% HCl, MeOH, 95%

IA9200 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra (^1H NMR) were recorded on a Varian 300 spectrometers, using TMS as the internal standard; chemical shifts are reported in parts per million (δ) and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Perkin-Elmer 783 spectrometer and a Nicolet instrument using KBr pellets. Elemental analyses were performed on a CaHo Erba elemental analyser. Solvents were routinely distilled prior to use. Anhydrous tetrahydrofuran (THF) was distilled from sodium-benzophenon ketyl. Column chromatography was performed on Merck silica gel 60 (70-230 mesh). TLC was carried out using plates coated with silica gel 60F 254 purchased from Merck Co. Reagents were obtained from commercial suppliers and were used without purification.

2-{[(4-Methoxybenzyl)oxy]methyl}benzonitrile (6). To a solution of *p*-methoxybenzyl alcohol (552 mg, 4.0 mmol) in THF (50 mL) was added 60% NaH (263 mg, 6.6 mmol) at 0 °C under N_2 atmosphere and the reaction mixture was stirred for 1h. After an ice bath was removed, 2-(bromobenzyl)benzonitrile (**3**) (640 mg, 3.3 mmol) in THF (10 mL) was added to this mixture which was then stirred overnight at 60 °C. The reaction mixture was cooled to room temperature and quenched with water (20 mL). The mixture was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residual oil which was purified by

column chromatography on silica gel with hexane: ethyl acetate = 10 : 1 to give **6** (500 mg, 60%) as a yellow oil. IR neat cm^{-1}: 2250 (CN). ^1H NMR ($CDCl_3$) δ: 7.66-7.36 (4H, m, Ar-H), 7.33 (1H, d, J = 8.7 Hz, Ar-H), 6.90 (1H, d, J = 8.7 Hz, Ar-H), 4.72, 4.59 (each 2H, each s, benzylic H), 3.81 (3H, s, OMe). MS, m/e (%): 253 (M^+, 100), 209 (33), 169 (34).

3-{2-[(Benzyloxy)methyl]phenyl}-1(2*H*)-isoquinolinone (8). To a solution of *N*-methyl-*o*-toluamide (394 mg, 2.6 mmol) in dry THF (20 mL) at 0 °C under N_2 atmosphere was added *n*-BuLi (2.5 *M* in hexane, 3.8 mL, 9.5 mmol) maintaining the reaction temperature never exceeded 20 °C. After the addition was completed, the red orange reaction solution was stirred for 1h at the same temperature. To this solution was slowly added a solution of 2-[(benzyloxy)methyl]benzonitrile (**5**) (736 mg, 3.3 mmol) in dry THF (10 mL) followed by cooling down the reaction mixture to -50 °C which was then stirred for 20 min at the same temperature. The reaction mixture was carefully quenched with water (5 mL) and stirred vigorously for 10 min and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residual oil. Column chromatography on silica gel with hexane: ethyl acetate = 10 : 1 to give 3-{2-[(benzyloxy)-methyl]phenyl}-1(2*H*)-isoquinolinone (**8**) (204 mg, 46%) as a yellow oil. IR neat cm^{-1}: 1640 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 8.46 (1H, d, J = 8.7 Hz, C_8-H), 7.71-6.50 (12H, m, Ar-H), 5.90 (1H, s, C_4-H), 4.81, 4.53 (each 2H, each s, benzylic H). MS, m/e (%): 341 (M^+, 100), 320 (43), 186 (38).

3-(2-Methyl)phenyl-1(2*H*)-isoquinolinone (9). The reaction mixture of 3-{2-[(benzyloxy)methyl]phenyl}-1(2*H*)-isoquinolinone (**8**) (204 mg, 0.6 mmol) in MeOH (40 mL) and 5% Pd-C (20 mg) was treated 1 atm hydrogen overnight at room temperature. The resulting mixture was filtered *in vacuo* and the filtrate was concentrated to give a residue which was purified by column chromatography on silica gel with hexane: ethyl acetate = 2 : 1 to give 3-(2-methyl)phenyl-1(2*H*)-isoquinolinone (**9**) (103 mg, 73%) as a yellow solid, mp: 179.5-180 °C (lit.[4] 179-180 °C).

3-(2-{[(4-Methoxybenzyl)oxy]methyl}phenyl)-1(2*H*)-isoquinolinone (10). This reaction was followed the same reaction condition described in the synthesis of **8** with *N*-methyl-*o*-toluamide (1.1 g, 7.4 mmol) and 2-{[(4-methoxybenzyl)-oxy]methyl}benzonitrile (**6**) to give 3-(2-{[(4-methoxybenzyl)oxy]methyl}phenyl)-1(2*H*)-isoquinolinone (**10**) (760 mg, 35%) as a yellow oil. IR neat cm^{-1}: 1640 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 10.20 (1H, s, NH), 8.45 (1H, d, J = 8.1 Hz, C_8-H), 7.71-6.77 (11H, m, Ar-H), 6.60 (1H, s, C_4-H), 4.67, 4.65 (each 2H, each s, benzylic H), 3.79 (3H, s, OMe). MS, m/e (%): 371 (M^+, 25), 320 (30), 219 (100).

3-(2-{[(4-Methoxybenzyl)oxy]methyl}phenyl)-2-methyl-1(2*H*)-isoquinolinone (11). 60% NaH (442 mg, 18.4 mmol) was added portionwise to a solution of 3-(2-{[(4-methoxy-benzyl)-oxy]methyl}phenyl)-1(2*H*)-isoquinolinone (**10**) (1.7 g, 4.6 mmol) in THF (50 mL) at 0 °C under nitrogen. The mixture was stirred for 1h at 0 °C and then CH_3I (780 mg, 5.5 mmol) was added. The reaction mixture was warmed to 60 °C and stirred for 2h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel with hexane: ethyl acetate = 6 : 1 to give 3-(2-{[(4-methoxybenzyl)oxy]methyl}phenyl)-2-methyl-1(2*H*)-isoquinolinone (**11**) (1.0 g, 56%) as a yellow oil. IR neat cm^{-1}: 1660 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 8.45 (1H, d, J = 6.0 Hz, C_8-H), 7.67-7.24 (7H, m, Ar-H), 7.09 (2H, d, J = 8.7 Hz, Ar-H), 6.70 (2H, d, J = 8.7 Hz, Ar-H), 6.38 (1H, s, C_4-H), 4.44-4.28 (4H, m, benzylic H), 3.72 (3H, s, OMe), 3.26 (3H, s, NMe). MS, m/e (%): 385 (M^+, 100), 324 (18), 323 (17).

3-[2-(Hydroxymethyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (12). DDQ (1.2 g, 5.4 mmol) was added portionwise to a mixed solution of 3-(2-{[(4-methoxybenzyl)oxy]methyl}-phenyl)-2-methyl-1(2*H*)-isoquinolinone (**11**) (1 g, 3.6 mmol) in water (4 mL)/methylene chloride (70 mL) at room temperature. After the reaction mixture was stirred overnight, saturated aqueous $NaHCO_3$ (10 mL) was added to the mixture which was then extracted with methylene chloride. The organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel with hexane: ethyl acetate = 2 : 1 to give 3-[2-(hydroxymethyl)-phenyl]-2-methyl-1(2*H*)-isoquinolinone (**12**) (470 mg, 52%) as a colorless solid, mp: 115.5 °C. IR ($CHCl_3$) cm^{-1}: 3350 (OH), 1650 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 8.32 (1H, d, J = 8.1 Hz, C_8-H), 7.66-7.18 (7H, m, Ar-H), 6.40 (1H, s, C_4-H), 3.64 (3H, s, OH), 3.18 (3H, s, NMe). MS, m/e (%): 265 (M^+, 65), 260 (73), 258 (76), 235 (96), 234 (100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.75; H, 5.72 ; N, 5.26.

3-[2-(Formyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (13). PDC (1.4 g, 3.8 mmol) was added portionwise to a solution of 3-[2-(hydroxymethyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (**12**) (470 mg, 1.9 mmol) in methylene chloride (20 mL) at room temperature. The reaction mixture was stirred overnight at the same temperature and filtrated through celite. The resulting filtrate was concentrated *in vacuo* to give a residue which was purified by column chromatography on silica gel with hexane: ethyl acetate = 2 : 1 to give 3-[2-(formyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (**13**) (410 mg, 82%) as a colorless oil. IR neat cm^{-1}: 1700 (CHO), 1660 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 10.01 (1H, s, CHO), 8.48 (1H, d, J = 8.1 Hz, C_8-H), 8.08-7.45 (7H, m, Ar-H), 6.45 (1H, s, C_4-H), 3.31 (3H, s, NMe). MS, m/e (%): 263 (M^+, 48), 235 (21), 234 (100).

2-Methyl-3-(2-vinylphenyl)-1(2*H*)-isoquinoline (14). *n*-BuLi (2.5 *M* in hexane, 1.1 mL, 2.75 mmol) was added to a solution of methyltriphenylphosphonium bromide (893 mg, 2.5 mmol) in THF (50 mL) at room temperature under nitrogen. After 1 h stirring, a solution of 3-[2-(formyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (**13**) (400 mg, 1.5 mmol) in THF (10mL) was added to the above reaction mixture. After 2 h stirring at 60 °C, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over

Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel with hexane: ethyl acetate = 10 : 1 to afford 2-methyl-3-(2-vinylphenyl)-1(2*H*)-isoquinoline (**14**) (254 mg, 65%) as a yellow oil. IR neat cm^{-1}: 1660 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 8.48 (1H, d, J = 8.4 Hz, C_8-H), 7.70-7.26 (7H, m, Ar-H), 6.54 (1H, dd, J = 17.7, J = 11.1 Hz, $\underline{CH}$=CH_2), 6.44 (1H, s, C_4-H), 5.75 (1H, dd, J = 17.7, J = 0.9 Hz, CH=$\underline{CH_2}$), 5.23 (1H, dd, J = 11.1, J = 0.9 Hz, CH=$\underline{CH_2}$), 3.27 (3H, s, NMe). MS, m/e (%): 261 (M^+, 100), 260 (91), 246 (30).

3-[2-(2,2-Dimethoxyethyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (15). A solution of thallium (III) nitrate trihydrate (844 mg, 1.9 mmol) in methanol (10 mL) was added to a solution of 2-methyl-3-(2-vinylphenyl)-1(2*H*)-isoquinoline (**14**) (250 mg, 1.0 mmol) in MeOH (10 mL) at room temperature, and then reaction mixture was warmed to 80-90 °C. After stirred for 1h, the saturated $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with methylene chloride. The combined organic phase was washed with water, brine, dried over Na_2SO_4 and concentrated to dryness to yield the residue which was purified by column chromatography on silica gel with hexane: ethyl acetate = 6 : 1 to give 3-[2-(2,2-dimethoxyethyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (**15**) (147 mg, 48%) as a yellow oil. IR neat cm^{-1}: 1660 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 8.47 (1H, d, J = 9.0 Hz, C_8-H), 7.67-7.23 (7H, m, Ar-H), 6.43 (1H, s, C_4-H), 4.47 (1H, dd, J = 6.3, J = 4.8 Hz, -$\underline{CH}(OMe)_2$), 3.29, 3.23 (each 3H, each s, -OMe x 2), 2.95 (1H, dd, J = 14.4, J = 6.3 Hz, -CH_2-), 2.74 (1H, dd, J = 14.4, J = 4.8 Hz, -CH_2-). MS, m/e (%): 323 (M^+, 52), 308 (11), 293 (27), 291 (53), 276 (33), 261 (41), 260 (100).

5-Methylbenzo[*c*]phenanthridin-6(5*H*)-one (1). A solution of 3-[2-(2,2-dimethoxyethyl)phenyl]-2-methyl-1(2*H*)-isoquinolinone (**15**) (120 mg, 0.4 mmol) and 10% hydrochloric acid (10 mL) in MeOH (25 mL) was heated to reflux overnight. Methanol of reaction mixture was evaporated off and the residue was taken up in methylene chlororide. The solution was washed with water, brine, dried over Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel with hexane: ethyl acetate = 4 : 1 to give 5-methylbenzo[*c*]phenanthridin-6(5*H*)-one (**1**) (97 mg, 95%) as a colorless solid, mp: 135-136 °C. IR (KBr) (cm^{-1}): 1650 (amide carbonyl). ^1H NMR ($CDCl_3$) δ: 8.59 (1H, dd, J = 8.1, J = 1.5 Hz, Ar-H), 8.40-7.53 (9H, m, Ar-H), 4.06 (3H, s, NMe). MS, m/e (%): 259 (M^+, 8), 258 (100). Anal. Calcd for $C_{18}H_{13}NO$: C, 83.38; H, 5.05; N, 5.40. Found: C, 83.45; H, 5.25 ; N, 5.48.

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