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Synthesis of 2-Aryl-6-Substituted Quinolines and Their Use as Fluorescent Brightening Agents

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SUMMARY

*The condensation of 5-bromoisatin (**1a**) with aryl methyl ketones (**2a–2d**) gave 2-aryl-6-bromoquinolines (**3a–3d**), ammonolysis of which gave the 6-amino-2-arylquinoline derivatives (**4a–4d**), which were also converted to the corresponding acetyl derivatives **5a–5d** by reaction with acetic anhydride. Diazotisation of **4a–4d** and coupling with Tobias acid (**6**) gave o-aminoazo dyes (**7a–7d**), which were then oxidatively cyclised to the 2-aryl-6-triazoloquinoline derivatives (**8a–8d**). Treatment of 2-phenyl-6-bromoquinoline-4-carboxylic acid (**3a**) with cuprous cyanide and copper in quinoline gave 2-phenyl-6-cyanoquinoline (**9**) which on condensation with 2-aminophenol (**10**) and 1,2-diaminobenzene (**11**) yielded 2-phenyl-6-(benzoxazol-2-yl)- and 2-phenyl-6-(benzimidazol-2-yl)-quinolines (**12a** and **12b**, respectively). The possible use of compounds **5a–5d**, **8a–8d**, **9** and **12a–12b** as fluorescent brightening agents was studied.*

1 INTRODUCTION

We have previously reported the synthesis of a number of heterocyclic systems and studied their fluorescent properties. Of particular interest as fluorescent brightening agents were 1,3,4-oxadiazoles,[1] pyrido[1,2-*a*]-benzimidazoles,[2–4] fused quinoxalines,[5–8] pyrazolo-1,2,3-triazoles,[9] pyrazolopyridines and pyrazolyl-1,2,3-triazoles,[10] naphthalimidotriazoles and 1,2,3-triazolylnaphthalimides,[11] naphthalimidopyridones[12] and pyrroloquinolines.[13]

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In this present study, we report the synthesis of 2-aryl-6-substituted quinoline derivatives and an evaluation of their fluorescent properties.

2 RESULTS AND DISCUSSION

The basic starting materials, viz. 6-amino-2-arylquinoline derivatives (**4a–4d**) were synthesised by condensation of 5-bromoisatin (**1a**) and aryl methyl ketones (**2a–2d**) and subsequent ammonolysis. 6-Amino-2-phenylquinoline-4-carboxylic acid (**4a**) was also prepared from 5-nitroisatin (**1b**) by condensation with acetophenone (**2a**) and subsequent treatment with strong acid. Phase-transfer catalysis (PTC) was employed for converting **1a** to **3a–3d** and **1b** to **4a**.

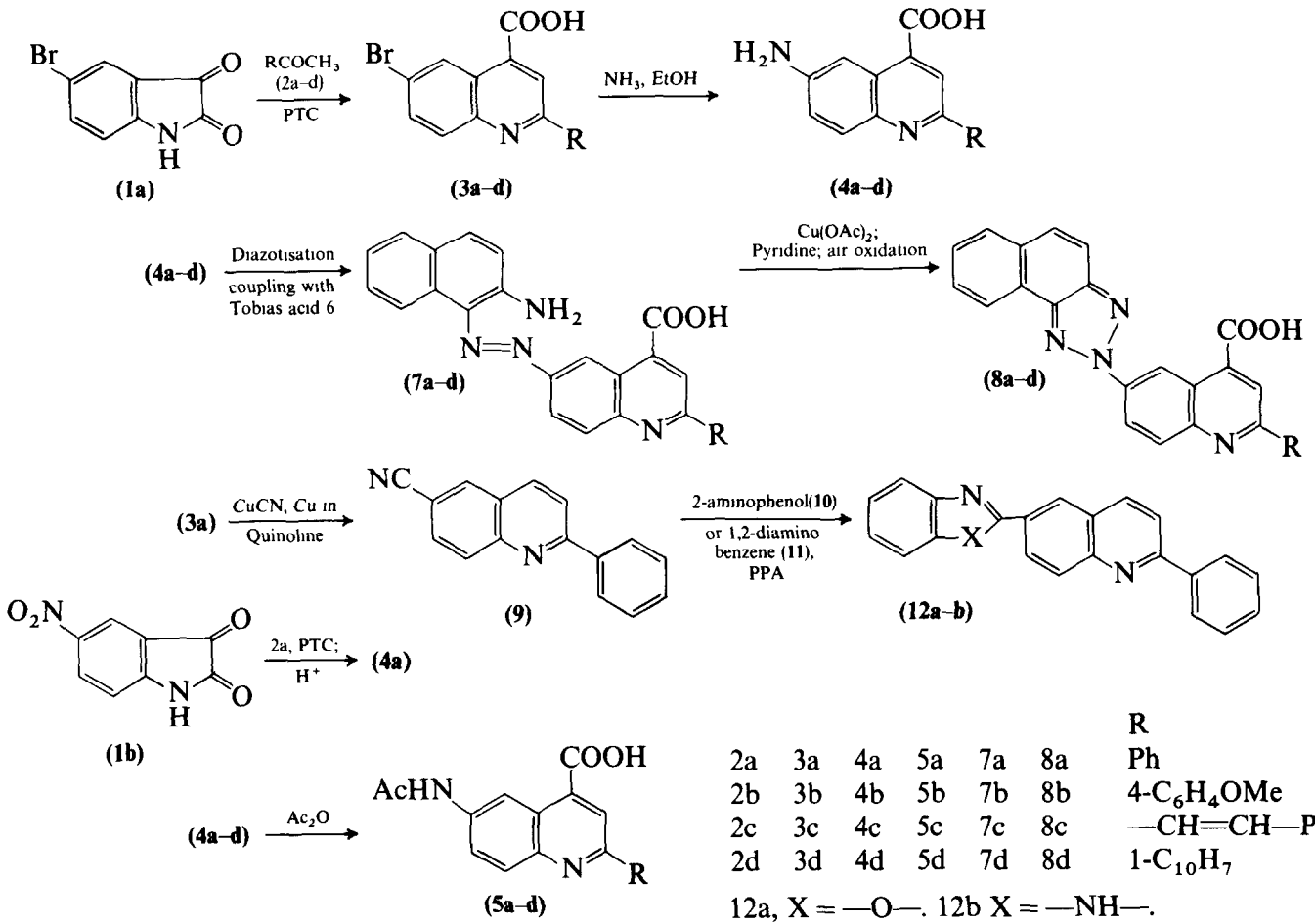
The 6-amino-2-arylquinolines (**4a–4d**) on acetylation afforded the corresponding 6-acetamido derivatives (**5a–5d**). 2-Aryl-6-(1,2,3-triazolo[4,5-*a*]naphth-2-yl)quinolines (**8a–8d**) were synthesised from **4a–4d** by diazotisation and coupling with Tobias acid (**6**) and subsequent oxidative cyclisation of the resulting *o*-aminoazo dyes (**7a–7d**). Substituents present in the 2-position were phenyl, 4-methoxyphenyl, styryl and 1-naphthyl.

6-Cyano-2-phenylquinoline (**9**), a typical representative of the 2-aryl-6-cyanoquinolines, was prepared by cyanation and simultaneous decarboxylation of **3a** using cuprous cyanide and copper in quinoline at 230–240°C. The mass spectrum of **9** showed the molecular ion peak (m^+/e) at 230, in agreement with its molecular weight, thus confirming the structure. Compound **9** was subsequently converted to 6-(benzoxazol-2-yl)-2-phenylquinoline (**12a**) and 6-(benzimidazol-2-yl)-2-phenylquinoline (**12b**) by fusion with 2-aminophenol (**10**) and 1,2-diaminobenzene (**11**), respectively, in polyphosphoric acid at 180–185°C.

The IR spectra of the compounds were recorded in nujol mull and showed absorption bands for the principal functional groups, viz. ν_{NH} at 3320 cm^{-1} and 3220 cm^{-1} for **4a–4d**; ν_{NH} at 3280 cm^{-1} for **5a–5d**; $\nu_{C=O}$ (amido group) at 1710 cm^{-1} for **5a–5d**; $\nu_{C=O}$ (of carboxylic acid group) at 1720 cm^{-1} to 1730 cm^{-1} for **4a–4d**, **5a–5d** and **8a–8d**; and ν_{CN} at 2240 cm^{-1} for **9**.

The 2-aryl-6-substituted quinolines **5a–5d**, **8a–8d**, **9** and **12a–12b** were pale yellow to brown in colour and exhibited intense blue to greenish-blue fluorescence in daylight in most common organic solvents.

The absorption and fluorescence emission maxima of the compounds **5a–5d**, **8a–8d**, **9** and **12a–12b** in DMF solution are shown in Table 1. The absorption maxima of the compounds varied from 292 to 367 nm. The fluorescence emission maxima of compounds **5a**, **5c**, **8a–8d**, **9** and **12b** were in the blue region (432 to 442 nm) and those of the compounds **5b**, **5d** and **12a** were in greenish-blue region (448 to 456 nm). Thus, 6-acetamidoquinoline-4-carboxylic acid substituted in the 2-position by phenyl and styryl substituents



						R
2a	3a	4a	5a	7a	8a	Ph
2b	3b	4b	5b	7b	8b	4-C_6H_4OMe
2c	3c	4c	5c	7c	8c	—CH=CH—Ph
2d	3d	4d	5d	7d	8d	1-$C_{10}H_7$

12a, X = —O—. 12b X = —NH—.

Scheme 1

TABLE 1
Absorption and Fluorescence Emission Spectra of 2-Aryl-6-substituted Quinolines

Compound	*Absorption max. (nm)*	*Fluorescence emission max. (nm)*	*log ε*
5a	352	440	4·17
5b	347	456	3·83
5c	350	438	3·43
5d	292	448	4·27
8a	367	441	3·88
8b	294	437	4·10
8c	298	432	4·13
8d	297	440	4·17
9	352	436	4·26
12a	337	452	4·29
12b	356	432	4·44

resulted in fluorescence in the blue region, whereas the presence of 2-(4-methoxyphenyl) and 2-(1-naphthyl) substituents shifted the fluorescence to the greenish-blue region. The 6-(naphtho[1,2-*d*]-1,2,3-triazol-2-yl)-quinoline-4-carboxylic acids containing 2-phenyl, 2-(4-methoxyphenyl), 2-styryl and 2-(1-naphthyl) substituents exhibited fluorescence in the blue region. 2-Phenylquinolines containing 6-cyano and 6-(benzimidazol-2-yl) substituents fluoresced in the blue region but the corresponding 6-(benzoxazol-2-yl) derivative fluoresced in the greenish-blue.

3 EXPERIMENTAL

All melting points are uncorrected and are in °C. Absorption and fluorescence emission spectra in DMF solutions were recorded on a Beckman Model 25 spectrophotometer and an Aminco Bowman spectrophotofluorimeter respectively. Infrared spectra were recorded on a Perkin–Elmer Model 397 spectrometer in nujol mull.

3.1 Preparation of starting materials

5-Bromoisatin (**1a**),[14] 5-nitroisatin (**1b**),[15] 4-methoxyacetophenone (**2b**)[16] and benzalacetone (**2c**)[17] were prepared by known methods.

3.2 6-Bromo-2-phenylquinoline-4-carboxylic acid (3a)

A mixture of acetophenone (**2a**) (1·8 g, 0·015 mol), aqueous sodium hydroxide solution (33%, 16 ml, 0·015 mol), TEBA (1·14 g, 0·005 mol) or

PEG 400 (2 ml) and benzene (50 ml) was stirred for 0·5 h. 5-Bromoisatin (**1a**) (2·26 g, 0·01 mol) was added in portions and the reaction mixture was refluxed with vigorous stirring until the reaction was complete (5 h, checked by tlc). Benzene was removed by distillation and the residue was added to water (100 ml). The alkaline solution was neutralised with dilute acetic acid and the solid which separated was filtered, dried and crystallised from ethanol as pale yellow needles (78%), m.p. 241° (dec). Calculated for $C_{16}H_{10}NO_2Br$: C, 58·5; H, 3·0; N, 4·3; Br, 24·4. Found: C, 58·5; H, 3·1; N, 4·2; Br, 24·1%.

Compounds **3b–3d** were prepared following the above procedure.

3.3 6-Bromo-2-(4-methoxyphenyl)quinoline-4-carboxylic acid (3b)

Crystallised from ethanol as pale yellow needles (82%), m.p. 220–223°. Calculated for $C_{17}H_{12}NO_3Br$: C, 57·0; H, 3·35; N, 3·9; Br, 22·3. Found: C, 56·55; H, 3·5; N, 4·05; Br, 22·1%.

3.4 6-Bromo-2-styrylquinoline-4-carboxylic acid (3c)

Crystallised from ethanol as pale yellow needles (85%), m.p. 286–288° (lit.[18] m.p. 287°). Calculated for $C_{18}H_{12}NO_2Br$: C, 61·0; H, 3·4; N, 3·95; Br, 22·6. Found: C, 61·0; H, 3·3; N, 3·85; Br, 22·3%.

3.5 6-Bromo-2-(1-naphthyl)quinoline-4-carboxylic acid (3d)

Crystallised from ethanol as pale yellow needles (78%), m.p. 228–230°. Calculated for $C_{20}H_{12}NO_2Br$: C, 63·5; H, 3·2; N, 3·7; Br, 21·2. Found: C, 63·2; H, 3·2; N, 3·6; Br, 21·1%.

3.6 6-Amino-2-phenylquinoline-4-carboxylic acid (4a)

Method A

A mixture of 6-bromo-2-phenylquinoline-4-carboxylic acid (**3a**) (9·74 g, 0·03 mol), ethanol (25 ml) and aqueous ammonia (30%, 10 ml) was heated in a sealed tube at 130–140°C for 1 h. On cooling, a crystalline solid was filtered and dried to give reddish-orange needles (68·3%), m.p. 257° (dec) [lit.[19] m.p. 257° (dec)]. The compound was pure and further crystallisation did not improve its melting point. Calculated for $C_{16}H_{12}N_2O_2$: C, 72·7; H, 4·5; N, 10·6. Found: C, 72·6; H, 4·4; N, 10·6%.

Method B

A mixture of 5-nitroisatin (**1b**) (5·8 g, 0·03 mol), acetophenone (3·6 g, 0·03 mol), TEBA (1·14 g, 0·005 mol) or PEG-400 (2 ml), aqueous sodium

hydroxide solution (33%, 12 ml) and benzene (65 ml) was refluxed with vigorous stirring until reaction was complete (8 h, checked by tlc). Benzene was removed by distillation and the red water-insoluble sodium salt was filtered. The solid thus obtained was slowly added to conc. hydrochloric acid (30%, 100 ml). The filtrate was brought to pH 5, when a gelatinous precipitate was formed, which crystallised on standing. The crystalline solid was filtered, dried and recrystallised from aqueous ethanol (30%) as red needles (62%), m.p. 256° (dec) [lit.[19] m.p. 257° (dec)]. Calculated for $C_{16}H_{12}N_2O_2$: C, 72·7; H, 4·5; N, 10·6. Found: C, 72·5; H, 4·7; N, 10·8%.

Compounds **4b–4d** were prepared following the procedure given in Method A.

3.7 6-Amino-2-(4-methoxyphenyl)quinoline-4-carboxylic acid (4b)

Reddish-orange needles (71%), m.p. 245–248° (dec). Calculated for $C_{17}H_{14}N_2O_3$: C, 69·4; H, 4·8; N, 9·5. Found: C, 69·8; H, 5·0; N, 9·8%.

3.8 6-Amino-2-styrylquinoline-4-carboxylic acid (4c)

Orange needles (62%), m.p. > 300°. Calculated for $C_{18}H_{14}N_2O_2$: C, 74·5; H, 4·8; N, 9·65. Found: C, 74·5; H, 4·8; N, 9·7%.

3.9 6-Amino-2-(1-naphthyl)quinoline-4-carboxylic acid (4d)

Red needles (74%), m.p. 233–235°. Calculated for $C_{20}H_{14}N_2O_2$: C, 76·4; H, 4·5; N, 8·9. Found: C, 75·9; H, 4·5; N, 9·1%.

3.10 6-Acetamido-2-phenylquinoline-4-carboxylic acid (5a)

A mixture of 6-amino-2-phenylquinoline-4-carboxylic acid (**4a**) (1·32 g, 0·005 mol), acetic anhydride (3 ml), acetic acid (6 ml) and pyridine (0·3 ml) was heated for 0·5 h on a water-bath. The reaction mixture was then cooled and poured onto an ice–water–ethanol (1:1:1) mixture (30 g), when a pale yellow solid separated. The solid was filtered, dried and crystallised from acetic acid to give pale yellow needles (85%), m.p. > 300°. Calculated for $C_{18}H_{14}N_2O_3$: C, 70·6; H, 4·6; N, 9·15. Found: C, 70·6; H, 4·5; N, 9·1%.

Compounds **5b–5d** were prepared following the procedure given above.

3.11 6-Acetamido-2-(4-methoxyphenyl)quinoline-4-carboxylic acid (5b)

Crystallised from acetic acid as pale yellow needles (84%), m.p. > 300°.

Calculated for $C_{19}H_{16}N_2O_4$: C, 67·9; H, 4·8; N, 8·3. Found: C, 67·4; H, 4·7; N, 8·55%.

3.12 6-Acetamido-2-styrylquinoline-4-carboxylic acid (5c)

Crystallised from acetic acid as yellow needles (82%), m.p. >300°. Calculated for $C_{20}H_{16}N_2O_3$: C, 72·3; H, 4·8; N, 8·4. Found: C, 72·2; H, 4·9; N, 8·4%.

3.13 6-Acetamido-2-(1-naphthyl)quinoline-4-carboxylic acid (5d)

Crystallised from acetic acid as pale yellow needles (83%), m.p. >300°. Calculated for $C_{22}H_{16}N_2O_3$: C, 74·6; H, 4·5; N, 7·9. Found: C, 74·6; H, 4·5; N, 8·1%.

3.14 2-Phenyl-6-(1,2,3-triazolo[4,5-*b*]naphtho-2-yl)quinoline-4-carboxylic acid (8a)

*2-Phenyl-6-(2-aminonaphth-1-yl)azoquinoline-4-carboxylic acid (**7a**)*
6-Amino-2-phenylquinoline-4-carboxylic acid (**4a**) (1·32 g, 0·005 mol) and conc. hydrochloric acid (10 ml) were cooled to 5°C and a previously cooled solution of sodium nitrite (0·38 g, 0·0055 mol) in water (10 ml) was added slowly over 0·5 h. The mixture was stirred for 0·5 h at 0–5°C and excess nitrous acid was destroyed by addition of urea (0·1 g). The mixture was filtered and the filtrate was added slowly at 0–5°C to a solution of Tobias acid (1·12 g, 0·005 mol) in water (10 ml). The pH of the mixture was brought to 6–6·5 by the slow addition of solid sodium carbonate and the mixture was stirred for 4–5 h at 0–10°C. At the end of the coupling, the precipitated dye was filtered and dried. The crude dye was dissolved in boiling aqueous sodium carbonate solution (10%), filtered hot, reprecipitated with dilute acetic acid (20%), filtered and dried. The reprecipitated dye (**7a**), (95%) thus prepared was directly used for triazolysation without further purification.

*Triazolysation of the dye **7a** to the compound **8a***
The dye **7a** was dissolved in pyridine (20 ml) and cupric acetate (1·89 g, 0·011 mol) was added. The mixture was refluxed until the colour of the dye had almost completely disappeared (3h). The reaction mixture was cooled, added with stirring to dilute hydrochloric acid (5%, 100 ml) and the precipitated solid was filtered, washed with water and dried. The solid was dissolved in DMF–acetic acid (1:5) mixture (30 ml), zinc dust (0·2 g) added and the mixture was refluxed for 1 h to remove the last traces of the dye. The hot solution was filtered, cooled and added to water (100 ml). The solid

obtained was filtered, dried and crystallised from DMF–water (1:1) mixture to give pale yellow crystals (79%), m.p. > 300°. Calculated for $C_{26}H_{16}N_4O_2$: C, 75·0; H, 3·85; N, 13·5. Found: C, 74·9; H, 3·6; N, 13·4%.

Compounds **8b–8d** were prepared following the procedure given above.

3.15 2-(4-Methoxyphenyl)-6-(1,2,3-triazolo[4,5-*b*]naphtho-2-yl)quinoline-4-carboxylic acid (8b)

Crystallised from DMF–water (1:1) mixture to give pale yellow crystals (63%), m.p. > 300°. Calculated for $C_{27}H_{18}N_4O_3$: C, 72·65; H, 4·0; N, 12·55. Found: C, 72·5; H, 4·2; N, 13·1%.

3.16 2-Styryl-6-(1,2,3-triazolo[4,5-*b*]naphtho-2-yl)quinoline-4-carboxylic acid (8c)

Crystallised from DMF–water (1:1) mixture to give off-white crystals (65%), m.p. > 300°. Calculated for $C_{28}H_{18}N_4O_2$: C, 76·0; H, 4·1; N, 12·7. Found: C, 75·85; H, 3·9; N, 12·5%.

3.17 2-(1-Naphthyl)-6-(1,2,3-triazolo[4,5-*b*]naphtho-2-yl)quinoline-4-carboxylic acid (8d)

Crystallised from DMF–water (1:1) mixture to give pale yellow crystals (61%), m.p. > 300°. Calculated for $C_{30}H_{18}N_4O_2$: C, 77·25; H, 3·9; N, 12·0. Found: C, 77·0; H, 3·7; N, 12·1%.

3.18 6-Cyano-2-phenylquinoline (9)

6-Bromo-2-phenylquinoline-4-carboxylic acid (3·28 g, 0·01 mol), cuprous cyanide (1·03 g, 0·011 mol), copper bronze (0·06 g, 0·001 mol) were pasted with quinoline (5 ml) and the mixture was heated to 230–240°C and maintained at this temperature for 4 h. The mixture was cooled and poured into a solution of hydrated ferric chloride (4 g) and conc. hydrochloric acid (30%, 3 ml) in water (6 ml) and stirred at 60–70°C for 20 min to decompose the complex. The solution was filtered hot, the residue boiled in acetic acid (10 ml) (charcoal), filtered hot and the filtrate poured onto ice-cold water, when a solid separated. The solid was filtered, dried and recrystallised from acetic acid (83%), m.p. 178–180°C. Calculated for $C_{16}H_{10}N_2$: C, 83·5; H, 4·35; N, 12·2. Found: C, 83·3; H, 4·2; N, 12·1%.

3.19 6-(Benzoxazol-2-yl)-2-phenylquinoline (12a)

6-Cyano-2-phenylquinoline (2·3 g, 0·01 mol) was thoroughly mixed with 2-aminophenol (**10**) (1·09 g, 0·01 mol) and the mixture was added to freshly prepared polyphosphoric acid (20 g) at 120°C with stirring. The temperature was then raised to 180–185°C and held there for further 4 h. The hot viscous mixture was cooled to 120°C and added to ice-cold water (200 ml) with stirring. The pH of the mixture was brought to 7–8 by slow addition of solid sodium carbonate, when a brown solid separated. The solid was filtered, washed with water, dried and recrystallised from ethanol to give pale brown crystals (67%), m.p. 235–236°C. Calculated for $C_{22}H_{14}N_2O$: C, 82·0; H, 4·35; N, 8·7. Found: C, 82·1; H, 4·2; N, 8·6%.

Compound **12b** was prepared following the procedure given above.

3.20 6-(1*H*-Benzimidazol-2-yl)-2-phenylquinoline (12b)

Crystallised from ethanol as brown crystals (74%), m.p. >300°. Calculated for $C_{22}H_{15}N_3$: C, 82·2; H, 4·7; N, 13·1. Found: C, 82·3; H, 4·5; N, 13·2%.

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