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AN EFFICIENT SYNTHESIS OF 4-PHENYL-2-AMINOQUINOLINES

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ABSTRACT : An efficient procedure for 3-substituted-4-Phenyl-2-aminoquinolines involving the reaction between a preformed complex of amide 2 and phosphorus oxychloride with o-acetamidobenzophenone is reported. Hitherto unknown ten 4-Phenyl-2-aminoquinolines have been synthesized in 72-88% yield.

Quinolines containing 3-phenyl and 2-amino (especially N-methyl piperazinyl and morpholino) functionalities have been reported to have potent antihypertensive, antidepressant and anticonvulsant activities¹⁻⁶. The 4-phenyl analogues of 2-aminoquinolines possess diverse pharmacological properties, such as antiinflammatory, diuretic⁷, antiulcerogenic, gastric antisecretory⁸ and antidepressant activities⁹. It was therefore planned to synthesize 2-aminoquinolines having 4-phenyl and 3-phenyl (and 3-methyl) functions. These systems have recently attracted considerable attention as potential bioactive agents¹⁰.

The reported methods for the synthesis of 2-amino, 3-substituted or 4-substituted quinolines

$$\begin{array}{c}
 \text{R}_1 \\
 | \\
 \text{C}_6\text{H}_4 \\
 | \\
 \text{C}(=\text{O})\text{NHCOCH}_3 \\
 | \\
 \text{C}_6\text{H}_4 \\
 | \\
 \text{C}(=\text{O})\text{C}_6\text{H}_5
 \end{array}
 +
 \begin{array}{c}
 \text{R}_2 - \text{CH}_2 - \text{C}(=\text{O}) - \text{N}(\text{CH}_2)_4\text{X}
 \end{array}
 \xrightarrow[\text{CHCl}_3, \text{ reflux, 48 h}]{\text{POCl}_3}
 \begin{array}{c}
 \text{R}_1 \\
 | \\
 \text{C}_6\text{H}_4 \\
 | \\
 \text{N} \\
 | \\
 \text{C}_6\text{H}_4 \\
 | \\
 \text{C}_2\text{C}_6\text{H}_5 \\
 | \\
 \text{N}(\text{CH}_2)_4\text{X}
 \end{array}
 \quad \text{3}$$

72 - 88 %

a. $\text{R}_1 = \text{H}$
 b. $\text{R}_1 = \text{Cl}$

a. $\text{R}_2 = \text{H}$
 b. $\text{R}_2 = \text{CH}_3$
 c. $\text{R}_2 = \text{Ph}$
 d. $\text{R}_2 = \text{CH}_3$
 e. $\text{R}_2 = \text{Ph}$
 f. $\text{R}_2 = \text{CH}_3$

a. $\text{X} = \text{H}$
 b. $\text{X} = \text{NCH}_3$
 c. $\text{X} = \text{O}$
 d. $\text{X} = \text{O}$
 e. $\text{X} = \text{CH}_2$
 f. $\text{X} = \text{CH}_2$

a. $\text{R}_1 = \text{H}$
 b. $\text{R}_1 = \text{Cl}$

a. $\text{R}_2 = \text{H}$
 b. $\text{R}_2 = \text{Ph}$
 c. $\text{R}_2 = \text{CH}_3$
 d. $\text{R}_2 = \text{Ph}$
 e. $\text{R}_2 = \text{Ph}$
 f. $\text{R}_2 = \text{CH}_3$

a. $\text{X} = \text{H}$
 b. $\text{X} = \text{NCH}_3$
 c. $\text{X} = \text{O}$
 d. $\text{X} = \text{O}$
 e. $\text{X} = \text{CH}_2$
 f. $\text{X} = \text{CH}_2$

x	U
=	=
a'	a'
d	b

	R ₂	X
a.	Ph	NCH ₃
b.	CH ₃	NCH ₃
c.	Ph	O
d.	CH ₃	O
e.	Ph	CH ₂
f.	CH ₃	CH ₂

R ₁	R ₂	X
a. H	Ph	NCH ₃
b. H	Ph	O
c. H	CH ₃	O
d. H	Ph	CH ₂
e. Cl	Ph	NCH ₃
f. Cl	CH ₃	NCH ₃
g. Cl	Ph	O
h. Cl	CH ₃	O
i. Cl	Ph	CH ₂
j. Cl	CH ₃	CH ₂

involve Tchichibabin type reaction¹⁻⁹ between the desired amine and 2-chloroquinoline the latter being prepared from the respective 3 or 4-phenyl carbostyryl. The present strategy (scheme-1) involves a modified Friedlander's method for the synthesis of 3-substituted-4-phenyl-2-aminoquinolines- a strategy not used earlier.

In this method amides 2a-f were complexed with POCl_3 (1:1 ratio) in dry chloroform and heated with o-acetamidobenzophenones 1a-b, to yield crude products, which were purified by column chromatography over silica gel. The spectral and analytical data indicated them to be the hitherto unknown 3-substituted-4-phenyl-2-aminoquinolines 3a-1 in 72-88% yield (vide experimental).

Experimental

To a solution of amide 2a-f^{11,12-14} (0.001 mol) in dry chloroform (5 ml), POCl_3 (0.001 mol) was added and the mixture stirred at room temperature for 24 hr. To this was then added o-acetamidobenzophenone 1a-b (0.001 mol). The mixture was refluxed till the latter was consumed (TLC, 48 Hr.). The cooled mixture was poured in 10% Na_2CO_3 solution (10 ml), warmed on water bath (30 min) and cooled.

The product obtained was extracted with ethylacetate (2 x 10 ml). The ethylacetate extract was washed, dried (Na_2SO_4) and evaporated. The

product obtained was passed through a column of silica gel and eluted with petether : ethylacetate (90:10) mixture to afford the compounds. The spectral and analytical data is given below :

- 3a** : m.p. 181° , IR (Nujol) : 1580, 1550, PMR(CDCl_3) : 2.25(s, 3H, NCH_3); 2.30(bt, 4H, $J=6\text{Hz}$, $2\text{CH}_2\text{NCH}_3$); 3.35(bt, 4H, $J=6\text{Hz}$, $2\text{CH}_2\text{NAr}$); 7.30 (s, 5H, ArH); 7.40 (s, 5H, ArH); 7.75(m, 3H, ArH); 8.10(dd, 1H, $J=2, 8\text{Hz}$, C-8H); Yield : 85%, Found : C, 82.49%; H, 6.88%; $\text{C}_{26}\text{H}_{25}\text{N}_3$ requires C, 82.29%; H, 6.64%.
- 3b** : m.p. 177° , IR(Nujol): 1590, 1550, PMR(CDCl_3) : 3.25(bt, 4H, $J=6\text{Hz}$, $2\text{CH}_2\text{N}$); 3.60(bt, 4H, $J=6\text{Hz}$, $2\text{CH}_2\text{O}$); 7.30(s, 5H, ArH); 7.40(s, 5H, ArH); 7.75(m, 3H, ArH); 8.10(dd, 1H, $J=2, 8\text{Hz}$, C-8H); Yield : 86%, Found : C, 82.09%; H, 6.18%; $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}$ requires C, 81.94%; H, 6.05%.
- 3c** : m.p. 173° , IR(Nujol) : 1590, 1550, PMR(CDCl_3) : 2.15(s, 3H, CH_3); 3.40(bt, 4H, $2\text{CH}_2\text{N}$); 3.95(bt, 4H, $2\text{CH}_2\text{O}$); 7.40(s, 5H, ArH); 7.75(m, 3H, ArH); 8.05 dd, 1H, $J=2, 8\text{Hz}$, C-8H); Yield : 82%, Found : C, 79.00%; H, 6.76%; $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$ requires C, 78.92%; H, 6.62%.
- 3d** : m.p. 154° , IR(Nujol): 1590, 1550, PMR(CDCl_3) : 1.40(m, 6H, 3CH_2); 3.20(m, 4H, $2\text{CH}_2\text{N}$); 7.30(s, 5H, ArH); 7.40(s, 5H, ArH); 7.75(m, 3H, ArH); 8.10(dd, 1H, $J=2, 8\text{Hz}$, C-8H); Yield : 87%,

Found : C, 85.43%, H, 6.88%; $C_{26}H_{24}N_2$ requires C, 85.68%; H, 6.64%.

3e : m.p. 231° , \underline{IR} (Nujol): 1580, 1550, \underline{PMR} ($CDCl_3$): 2.25(s, 3H, NCH_3); 2.30(bt, 4H, 2CH_2NCH_3); 3.35(bt, 4H, 2CH_2NAr); 7.10(d, 1H, $J=2\text{Hz}$, C-5H); 7.35(s, 5H, ArH); 7.45(s, 5H, ArH); 7.70(dd, 1H, $J=2, 8\text{Hz}$, C-7H); 8.10(d, 1H, $J=8\text{Hz}$, C-8H); Yield : 72%, Found : C, 75.62%; H, 5.94%; $C_{26}H_{24}ClN_3$ requires C, 75.45%; H, 5.80%.

3f : m.p. 174° , \underline{IR} (Nujol): 1580, 1550, \underline{PMR} ($CDCl_3$): 2.25(s, 3H, CH_3); 2.50(s, 3H, NCH_3); 2.80(bt, 4H, 2CH_2NCH_3); 3.60(bt, 4H, 2CH_2NAr); 7.40(bd, 2H, C-5 and C-7H); 7.75(s, 5H, ArH); 8.10(d, 1H, $J=8\text{Hz}$, C-8H); Yield : 78%, Found : C, 71.68%; H, 6.36%; $C_{21}H_{22}ClN_3$ requires C, 71.69%; H, 6.26%.

3g : m.p. 219° , \underline{IR} (Nujol) : 1590, 1550, \underline{PMR} ($CDCl_3$): 3.30(bt, 4H, 2CH_2N); 3.65(bt, 4H, 2CH_2O); 7.10(d, 1H, $J=2\text{Hz}$, C-5H); 7.35(s, 5H, ArH); 7.45(s, 5H, ArH); 7.70(dd, 1H, $J=2, 8\text{Hz}$, C-7H); 8.10(d, 1H, $J=8\text{Hz}$, C-8H); Yield : 75%, Found : C, 75.03%; H, 5.50%; $C_{25}H_{21}ClN_2O$ requires C, 74.91%; H, 5.24%.

3h : m.p. 145° , \underline{IR} (Nujol): 1590, 1550, \underline{PMR} ($CDCl_3$): 2.15(s, 3H, CH_3); 3.40(bt, 4H, 2CH_2N); 3.95(bt, 4H, 2CH_2O); 7.30(bd, 2H, C-5 and C-7H); 7.65(s, 5H,

ArH); 8.00(d, 1H, J=8Hz, C-8H); Yield : 88%,
 Found : C, 70.83%; H, 5.69; $C_{20}H_{19}ClN_2O$ requires
 C, 70.90%; H, 5.61%.

3i : m.p. 235°, IR(Nujol) : 1590, 1550, $\overline{PMR}(CDCl_3)$:
 1.40(m, 6H, $3\overline{CH_2}$); 3.20(m, 4H, $2\overline{CH_2N}$); 7.15(d, 1H,
 J=2Hz, C-5H); 7.25(s, 5H, ArH); 7.35(s, 5H, ArH);
 7.65(dd, 1H, J=2, 8Hz); 7.95(d, 1H, J=8Hz, C-8H);
 Yield : 83%, Found : C, 78.39%; H, 5.72%;
 $C_{26}H_{23}ClN_2$ requires C, 78.29%; H, 5.77%.

3i : m.p. 138°, IR(Nujol) : 1590, 1550, $\overline{PMR}(CDCl_3)$:
 1.75(m, 6H, $3\overline{CH_2}$); 2.15 (s, 3H, CH_3); 3.30(m, 4H,
 $2\overline{CH_2N}$); 7.30(bd, 2H, C-5 and C-7H); 7.65(s, 5H,
 ArH); 8.00(d, 1H, J=8Hz, C-8H); Yield : 80%,
 Found : C, 74.64%; H, 6.44%; $C_{21}H_{21}ClN_2$ requires
 C, 74.88%; H, 6.24%.

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