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AN EFFICIENT SYNTHESIS OF 4-PHENYL-2-AMINOQUINOLINES

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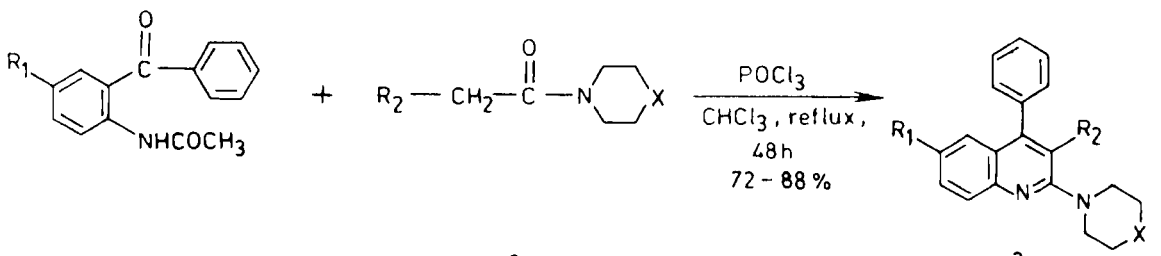
ABSTRACT : An efficient procedure for 3-substituted-4-Phenyl-2-aminoquinolines involving the reaction between a preformed complex of amide 2 and phosphorus oxychloride with o-acetamidobenzophenone is reported. Hitherto unknown ten 4-Phenyl-2-aminoquinolines have been synthesized in 72-88% yield.

Quinolines containing 3-phenyl and 2-amino (especially N-methyl piperazinyl and morpholino) functionalities have been reported to have potent antihypertensive, antidepressant and anticonvulsant activities[1-6]. The 4-phenyl analogues of 2-amino-quinolines possess diverse pharmacological properties, such as antiinflammatory, diuretic[7], antiulcerogenic, gastric antisecretory[8] and antidepressant activities[9]. 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 agents[10].

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

Scheme 1



1

a. R_1 = H
b. R_1 = Cl

2

	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

3

	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 reaction[1-9] between the desired amine and 2-chloroquinoline the latter being prepared from the respective 3 or 4-phenyl carbostyril. 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-i 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=6Hz,$2CH_2NCH_3$); 3.35(bt,4H,J=6Hz,$2CH_2NAr$);7.30 (s,5H,ArH); 7.40 (s,5H,ArH); 7.75(m,3H,ArH); 8.10(dd,1H,J=2,8Hz, C-8H); Yield : 85%, Found : C,82.49%; H,6.88%; $C_{26}H_{25}N_3$ requires C,82.29%; H, 6.64%.

3b : m.p. 177°, IR(Nujol): 1590,1550, PMR($CDCl_3$) : 3.25(bt,4H,J=6Hz,$2CH_2N$); 3.60(bt,4H,J=6Hz, $2CH_2O$; 7.30(s,5H,ArH); 7.40(s,5H,ArH); 7.75(m,3H, ArH); 8.10(dd,1H,J=2,8Hz, C-8H); Yield : 86%, Found : C,82-09%; H,6.18%; $C_{25}H_{22}N_2O$ 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,$2CH_2N$); 3.95(bt,4H, $2CH_2O$); 7.40(s,5H,ArH); 7.75(m,3H,ArH); 8.05 dd,1H,J=2,8Hz,C-8H): Yield : 82%, Found : C, 79.00%;H,6.76%; $C_{20}H_{20}N_2O$ 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,$2CH_2N$); 7.30(s, 5H,ArH); 7.40(s,5H,ArH); 7.75(m,3H,ArH); 8.10(dd,1H,J=2,8Hz,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°, IR(Nujol): 1580,1550, 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=2Hz, C-5H); 7.35(s,5H,ArH); 7.45(s,5H,ArH); 7.70(dd,1H, J=2,8Hz, C-7H); 8.10 (d,1H,J=8Hz, 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°, IR(Nujol): 1580,1550, 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 andC-7H); 7.75(s,5H,ArH); 8.10(d,1H, J=8Hz, 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°, IR(Nujol) : 1590,1550, PMR($CDCl_3$): 3.30(bt,4H,$2CH_2N$); 3.65(bt,4H,$2CH_2O$); 7.10 (d,1H,J=2Hz, C-5H); 7.35(s,5H,ArH); 7.45(s,5H,. ArH);7.70(dd,1H,J=2,8Hz, C-7H); 8.10(d,1H, J=8Hz, 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°, IR(Nujol): 1590,1550, 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, PMR($CDCl_3$): 1.40(m,6H,3CH_2); 3.20(m,4H,2CH_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%.

3j : m.p. 138°, IR(Nujol): 1590,1550, PMR($CDCl_3$): 1.75(m,6H,3CH_2); 2.15 (s,3H,CH_3); 3.30(m,4H, 2CH_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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