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A FACILE SYNTHESIS OF INDOLOQUINAZOLINES

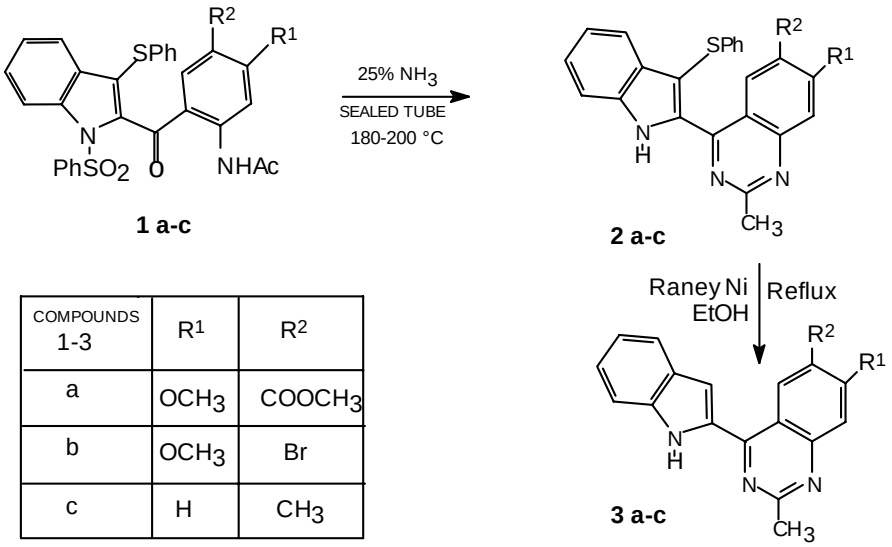
Nagappan Arumugam[a] and Panayencheri C. Srinivasan[*b]

[a]R&D Department, Amrutanjan Ltd., Chennai-600 004, India E-mail: arumugam50@yahoo.co.in. [b]Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai - 600 025, India Fax : 91- 44 -235 2494. E-mail : pancol2000@yahoo.co.in.

Abstract- 4-[Indol-2'-yl]quinazolines were synthesized from 2-[*o*-acetamido-benzoyl]indoles and 25% ammonia by heating in a sealed tube at 180 - 200 °C for 2 h.

Recently quinazolines have been identified as inhibitors of CDK4/D1 and CDK2/E.[1] 2-Thiazolidinyl-triazinoquinazolines[2] have potent anti-inflammatory activity. A series of 2-arylquinazolinones[3] was synthesized and evaluated for anticancer activity.[4] Investigation of diuretic activity in other heterocyclic systems has demonstrated that the benzothiadiazine-1,1-dioxide system is not unique in its effect on diuresis, natriuresis and chloruresis and a series of corresponding 7-chloro-6-sulfamyl-4(8*H*)-quinazolinones and 7-chloro-6-sulfamyl-1,2,3,4-tetrahydro-4-quinazolinones are reported[5] which have diuretic activity equal to or better than the benzothiadiazine-1,1-dioxides. In continuation of our studies towards the synthesis of biologically active heterocycles we report here a convenient synthesis of 4 -[indol-2'-yl]quinazolines from 2-[*o*-acetamidobenzoyl]indoles.[6]

Scheme



1 a-c **2 a-c** **3 a-c**

COMPOUNDS 1-3	R^1	R^2
a	OCH_3	$COOCH_3$
b	OCH_3	Br
c	H	CH_3

Treatment of **1a-c** with 25% ammonia solution[7] at 180-200 °C in a sealed tube for 2 h gave 4-[3'-phenylthioindol-2-yl]quinazolines (**2a-c**). Use of dry ammonia gas instead of 25% ammonia solution results in the completion of the reaction in 30 - 45 min at the same temperature. These afforded 4-[indol-2'-yl]quinazolines (**3a-c**) on treatment with Raney Ni in boiling ethanol.

EXPERIMENTAL

Compound (2a-c). General procedure:

A mixture of compound (**1a-c**) (5 mmol) in THF (10 mL) and 25% aq. ammonia solution (5 mL) was taken in a sealed tube and heated in an oil bath at 180 – 200 °C for 2 h. Then the sealed tube was cooled to 25 °C and the THF was distilled off under reduced pressure. The pH was adjusted to 2 with 20% hydrochloric acid. It was then extracted with chloroform (2x50 mL). The chloroform layer was then washed with water (2x50 mL) and dried over anhydrous sodium sulfate. The solvent was distilled off to give a residue, which was chromatographed on silica gel column using 20% ethyl acetate in hexane as an eluent.

Compound (2a): (61%), mp: 110 – 112 ˚C (hexane –ethyl acetate, 1:1); IR (KBr): 3425, 1718, 1616, 1400, 1192 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 2.23 (s, 3H), 3.68 (s, 3H), 3.98 (s, 3H), 7.08 - 8.48 (m, 10H, arom), 8.38 (s, 1H), 9.37 (s, 1H). MS: m/z (%) 455(M^+, 64.2), 101(51.9), 71(100), 55(54.1). Anal. Calcd for $C_{26}H_{21}N_3O_3S$: C, 68.55; H, 4.65; N, 9.22. Found: C, 68.73; H, 4.86; N, 9.51.

Compound (2b): (58%), mp: 108 -110 ˚C (hexane-ethyl acetate, 1:1); IR (KBr): 3078, 1550, 1487, 1338 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 2.75 (s, 3H), 3.95 (s, 3H), 6.97 – 7.59 (m, 10H, arom), 8.23 (s, 1H), 9.71 (s, 1H). MS: m/z (%) 476(M^+, 100), 475(62.6), 474(78), 109(51.9), 95(54.8), 85(32.5), 83(46.3), 78(66.6), 56(46.6). Anal. Calcd for $C_{24}H_{18}N_3OBrS$: C, 60.51; H, 3.81; N, 8.82. Found: C, 60.78; H, 3.65; N, 9.01.

Compound (2c): (62%), mp: 204 - 206 ˚C (hexane-ethyl acetate, 1:1); IR (KBr): 3406, 1539, 1458,740 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 1.85 (s, 3H), 2.39 (s, 3H), 7.28 –7.99 (m, 11H, arom), 8.24 (s, 1H), 9.59 (s, 1H). MS: m/z (%) 381 (M^+, 100), 367(11.1), 339(10.6), 304(53), 289(32.5), 190(20.4), 157(20.3), 110(14.2), 889(9.7), 63(5). Anal. Calcd for $C_{26}H_{21}N_3O_3S$: C, 75.56; H, 4.98; N, 11.01. Found: C, 75.87; H, 4.85; N, 10.84 .

Compound (3a-c). General procedure:

A mixture of Raney Ni (5 g) and compound (**2a-c**) (1 g) in dry ethanol (50 mL) was refluxed for 2 h. The completion of the reaction was confirmed by periodic TLC analysis. Raney Ni was filtered off and the ethanol was removed by distillation. It was then crystallized from hexane-ethyl acetate (1:1).

Compound (3a): (82%), mp: 120 – 122 ˚C; IR (KBr): 3425, 1724, 1624, 1527, 1404, 1239, 1091, 720 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 2.88 (s, 3H), 4.01 (s, 3H), 4.06 (s, 3H), 7.33 – 7.77 (m, 6H, arom), 9.13 (s, 1H), 9.79 (s, 1H). MS: m/z (%) 347(M^+, 100), 333(6.4), 288(22.8), 217(13.2), 190(10.8), 89(12.5), 63(6.6). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.89; N, 12.10. Found: C, 69.43; H, 4.75; N, 12.25.

Compound (3b): (72%), mp: 172 – 174 ˚C; IR (KBr): 3406, 1616, 1222 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 2.87 (s, 3H), 3.99 (s, 3H), 7.26 – 7.50 (m, 6H, arom), 8.56 (s, 1H), 9.85 (s, 1H). MS: m/z (%) 289(M^+-79, 100), 258(12.5), 204(150.5), 173(10.7), 144(12.1), 117(18.9), 89(49.2). Anal. Calcd for $C_{18}H_{14}N_3OBr$: C,

58.71; H, 3.83; N, 11.41. Found: C, 58.97; H, 3.67; N, 11.71.

Compound (3c): (78%), mp: 223 - 225 ˚C; IR (KBr): 3406, 2904, 1539, 1458, 1123 cm^{-1}. ^1H NMR ($CDCl_3$/TMS): 2.62 (s, 3H), 2.89 (s, 3H), 7.26 –7.90 (m, 7H, arom), 8.46 (s, 1H), 9.82 (s, 1H). MS: m/z (%) 273 (M^+, 59.5), 258(49.6), 217(23.8), 203(16.5), 89(100), 77(71.2) Anal. Calcd for $C_{18}H_{15}N_3$: C, 79.10; H, 5.49, N, 15.37. Found: C, 79.42, H, 5.38, N, 15.58.

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