Pergamon

Tetrahedron Letters 39 (1998) 1785–1786

TETRAHEDRON LETTERS

# Synthesis of 4-Arylaminoquinazolines *via* 2-Amino-*N*-arylbenzamidines

Wojciech Szczepankiewicz* and Jerzy Suwiński
Institute of Organic Chemistry and Technology,
Silesian Technical University, 44-100 Gliwice, Poland,
e-mail: wojtex@zeus.polsl.gliwice.pl

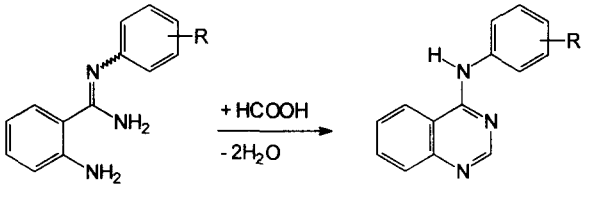
Received 28 November 1997; accepted 18 December 1997

**Abstract:** A new synthesis of twelve 4-arylaminoquinazolines from 2-amino-*N*-arylbenzamidines and formic acid is described. The entering amidines were obtained in the reaction of anthranilonitrile with 50% molar excess of aromatic amines and anhydrous aluminium chloride. 

Recently one can observe a renewed increase of interest in 4-arylaminoquinazolines being connected with reports on a very high activity of 6,7-dimethoxy-4-(3'-bromophenylamino)quinazoline (PD 153035) as a tyrosine kinase inhibitor.[1] Later papers indicate that some analogues of PD 153035 with more complex structures[2] as well as simple derivatives of 4-phenylaminoquinazoline without e.g. methoxy groups[3] also show interesting biological activity. Despite the interest in biological activity of the compounds no progress in their synthesis has been published for several years.

Some 4-arylaminoquinazolines can be obtained in the reactions of 4-halo- or 4-mercaptoquinazolines with aromatic amines.[4,5] Yield of the products usually[6] does not exceed 50%. 4-Arylaminoquinazolines are also produced by melting 4(3*H*)-quinazolone with aromatic amine hydrochlorides in the presence of phosphorus pentaoxide and dimethylcyclohexylamine.[7] Only 4-phenylaminoquinazoline has been obtained by desulfurization of 4-phenylaminoquinazol-2-thione on the Raney nickel W7.[8]

Searching for an effective and general method of 4-arylaminoquinazolines synthesis we have paid an attention to a synthetic usefulness of the reaction of 2-amino-*N*-arylbenzamidines with formic acid (**Scheme**).




**Scheme**

The entering amidines are easily available from the known reaction of anthranilonitrile with aniline and anhydrous aluminium chloride,[9] modified by using 50% molar excess of both latter compounds. The amidines while heating with 85% formic acid are converted[10] into respective 4-arylaminoquinazolines with 70-92% yields (**Table**).

0040-4039/98/$19.00 
*PII:* S0040-4039(97)10864-4

**Table.** Yields of 4-Arylaminoquinazolines Obtained in the Reaction of 2-Amino-*N*-arylbenzamidines with Formic Acid.

| R | Yield [%] | M.p. [°C] | R | Yield [%] | M.p. [°C] |
|---|---|---|---|---|---|
| **H** | 82 | 220-221 | **3-I** | 92 | 232-234 |
| **2-Me** | 70 | 82-84 | **4-Me** | 84 | 191-193 |
| **2-Br** | 73 | 131-132 | **4-Cl** | 92 | 194-195 |
| **3-Me** | 84 | 196-197 | **4-Br** | 91 | 189-90 |
| **3-Cl** | 90 | 199-200 | **3,4-diMe** | 83 | 196.5-8 |
| **3-Br** | 92 | 216-217 | **3,4-diCl** | 92 | 219-220 |

## References and Notes


1. (a) Fry, D.W.; Kraker, A.J.; McMichael, A.; Ambroso, L.A.; Nelson, J.M.; Leopold, W.R.; Connors, R.W.; Bridges, A.J. *Science*, **1994**, *265*, 1093. (b) Traxler, T.M.; Furet, P.; Mett, H.; Buchdunger, E.; Meyer, T.; Lydon, N. *J.Med.Chem.* **1996**, *39*, 2289.
2. Rewcastle, G.W.; Palmer, B.D.; Bridges, A.J.; Showalten, H.D.; Sun, L.; Nelson, J.; McMichael, A.; Kraker, A.J.; Fry, D.W.; Denny, W.A. *J.Med.Chem.* **1996**, *39*, 918.
3. Denny, W.A.; Rewcastle, G.W.; Bridges, A.J.; Fry, D.W.; Kraker, A.J. *Clin.Exp.Pharmacol.Physiol* **1996**, *23*, 424.
4. Lange, N.A.; Sheibley F.E. *J.Am.Chem.Soc.* **1931**, *53*, 3867.
5. Leonard, N.J.; Curtin, D.Y. *J.Org.Chem.* **1946**, *11*, 346.
6. Armarego, W.L.F. *Heterocyclic Compounds, Fused Pyrimidines, Part I, Quinazolines*; Interscience Publisher: New York, **1967**; p. 222.
7. Giris, N.S.; Møller, J.; Pedersen, E.B. *Chemica Scripta* **1986**, *26*, 617.
8. Taylor, E.C.; Ravindranathan, R.V. *J.Org.Chem.* **1962**, *27*, 2622.
9. Cooper, F.C.; Partridge, M.W. *Organic Syntheses* **1956**, *36*, 64.
10. General procedure. An amidine (1 mmole) was heated in 85% formic acid (0.4 ml) at 95°C for two hours. Hot water (2 ml) was added to the obtained solution, and then 2M sodium hydroxide, until weak alkaline reaction. White precipitate was filtered off and recrystallized from ethanol-water mixture.
    The example results (**R** = 3-$BrC_6H_4$). Colourless crystals, yield 92%, m.p. 216-217°C. Elemental analysis calculated for $C_{14}H_{10}BrN_3$: C, 56.02, H, 3.36, N, 14.00; Found C, 56.22, H, 3.18, N, 13.89; MS (*m/z*): $M^+$= 301(37), 300(92), $M^+$= 299(38), 298(81), $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.31-7.41(m,2H,4'+5'), 7.65-7.71(m,1H,6'), 7.82-7.97(m,3H,6+7+8), 8.28-8.29(m,1H,2'), 8.57-8.59 (m,1H,5), 8.70(s,1H,2), 9.90(s,1H,NH).