An Expeditious Synthesis of 2-Aryl- and 2-Alkylquinazolin-4(3*H*)-ones

Axel Couture,* Hélène Cornet, Pierre Grandclaudon

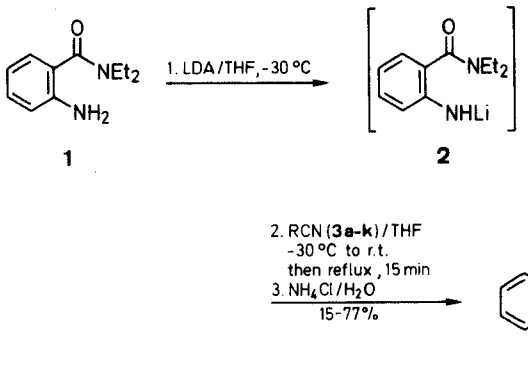
Laboratoire de Chimie Organique Physique, URA CNRS N° 351, Université des Sciences et Techniques de Lille Flandres-Artois, F-59655 Villeneuve d'Ascq Cedex, France

2-Aryl- and alkylquinazolin-4(3*H*)-ones are readily accessible by reaction of the lithium 2-(diethylaminocarbonyl)anilide with appropriate aryl and alkyl nitriles.

Quinazolin-4(3*H*)-ones or tautomeric hydroxyquinazolines, especially their 2-aryl or alkyl derivatives, are a class of fused heterocycles of considerable interest owing to the remarkable diversity of their biological activities.[1,2] Indeed, some of these compounds possess soporofic, diuretic and antiinflammatory properties.[3] Recently the anticonvulsive and antihypoxic activities of various 2-substituted quinazolinones have been reported[4] and it has been demonstrated that incorporation of a styryl moiety at the 2-position of the bicyclic framework gave rise to a promising new class of antimitotic anticancer agents.[5] Paradoxically the synthetic methods for the elaboration of this bicyclic system of rather simple structure are not general in scope and involve multistep, and often low-yielding, reaction sequences. The main synthetic routes to such compounds consist in preliminary amidation of 2-aminobenzonitrile,[6] 2-aminobenzoic acid[1] or ethyl 2-aminobenzoate.[7] The oxidative ring closure of the intermediates under acidic conditions affords the desired quinazolinones in various yield.[8] They are also accessible by condensation of appropriate aromatic imino chlorides with the sodium derivative of urethane,[9] by ring closure of sophisticated carboxamidines in boiling quinoline[10] or by the recently reported aza-Wittig reactions from α-azido substituted aromatic imides[11] or from aromatic iminophosphoranes and isocyanates.[12] Different one-step syntheses have been also described but the condensation of 2-aminobenzoic acid with amides,[13] thioamides[14] or nitriles requires either high temperatures or must be effected in a sealed tube at 200°C.[15]

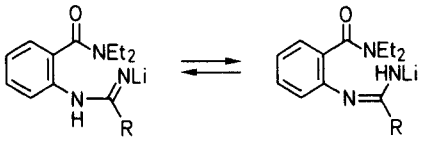
In this paper we report a novel, general and effective approach to the 2-aryl- and 2-alkylquinazolin-4(3*H*)-ones **4a–k**. Our strategy consists in reacting aromatic, heteroaromatic and aliphatic nitriles **3a–k** with the lithium derivative **2** of 2-amino-*N*,*N*-diethylbenzamide (*N*,*N*-diethylanthranilamide, **1**) (Scheme). The starting amide **1** is readily and quantitatively accessible from the commercial methyl 2-aminobenzoate by treatment with the lithium derivative of diethylamine. The anion of 2-amino-*N*,*N*-diethylbenzamide (**2**) is generated with lithium diisopropylamide (LDA) in anhydrous tetrahydrofuran. It is preferable to carry out this experiment at low temperature (– 30°C) to prevent self-condensation of the lithiated species **2**.

The addition of the appropriate nitriles **3a–k** is also effected at this temperature but the obtention of the desired annulation products requires refluxing of the reaction mixture for 15 minutes. The reaction is quenched with water and work up affords satisfactory yields of the cyclocondensation products **4a–k**. High



1 2 4a-k

3, 4	R	3, 4	R
a	Ph	**g**	2-FC_6H_4
b	1,3-benzodioxol-5-yl	**h**	3-FC_6H_4
c	2-thienyl	**i**	styryl
d	2-furyl	**j**	Me
e	4-$F_3CC_6H_4$	**k**	*c*-C_6H_{11}
f	3-$F_3CC_6H_4$		



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efficiencies are generally obtained by use of aryl and heteroaryl nitriles and with cinnamonitrile **3i** (Table). Despite the presence of the acidic α protons in the enolizable aliphatic nitriles **3j,k** which renders them susceptible to *trans*-metalation with **2** and subsequent self-condensation,[16] moderate but good yields of 2-alkylquinazolinones **4j,k** are obtained upon reaction of **2** with the nitriles **3j,k**.

Presumably these heterocyclization reactions proceed via the intermediacy of species like **5** or the tautomeric form **6** arising from the nucleophilic attack of the preformed anion **2** on the reactive nitrile moiety of **3a–k**. The annulation reaction that gives rise to **4a–k** is actually the result of the nucleophilicity of the transient amide anion and of the great sensitivity of the *N*,*N*-diethylcarboxamide group with respect to nucleophilic attack, a precedented phenomenon.[17,18]

In conclusion the reactions of aliphatic, aromatic and heteroaromatic nitriles with the anion of 2-amino-*N*,*N*-diethylbenzamide offers a new and convenient synthetic approach to 2-aryl- and 2-alkylquinazolin-4(3*H*)-ones. Although the yields are sometimes modest, this is overcome somewhat by the availability of the starting materials and by the simplicity and generality of the process.

Table. 2-Aryl- and 2-Alkylquinazolin-4(3*H*)-ones **4a–k** Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr) ν (cm^{-1}) C=O	^{1}H-NMR (DMSO-d_6/TMS)[c] δ, J (Hz)	MS (70 eV)[d] *m/z* (%)
4a	75	235–236 (EtOH)	236–238[7,20]	1660	7.5–8.3 (m, 9H$_{arom}$), 12.5 (s, 1H, NH)	222 (M^+, 100), 119 (92)
4b	77	278–279 (DMF)	279[20]	1660	6.15 (s, 2H, CH_2), 7.0–8.2 (m, 7H$_{arom}$), 12.3 (s, 1H, NH)	266 (M^+, 56), 119 (100)
4c	48	288–289 (EtOH)	287–288[1,10]	1670 (br)	7.1–8.2 (m, 7H, H$_{phenyl}$ + H$_{thiophene}$), 12.6 (s, 1H, NH)	288 (M^+, 100), 119 (83), *111* (80), 110 (63)
4d	63	222–223 (DMF)	220[21]	1660	6.7 (dd, J = 3.5, 1.8, 1H$_{furan}$), 7.4–8.2 (m, 6H, H$_{phenyl}$ + H$_{furan}$), 12.5 (s, 1H, NH)	212 (M^+, 100), 119 (4)
4e	43	306–308 (EtOH)	$C_{15}H_9F_3N_2O$ (290.2)	1660	7.4–8.4 (m, 8H$_{arom}$), 12.7 (s, 1H, NH)	290 (M^+, 25), 119 (100)
4f	45	247–248 (EtOH)	$C_{15}H_9F_3N_2O$ (290.2)	1670	7.5–8.5 (m, 8H$_{arom}$), 12.7 (s, 1H, NH)	290 (M^+, 100), 119 (85)
4g	15	163–164 (EtOH)	$C_{14}H_9FN_2O$ (240.2)	1680	7.3–8.2 (m, 8H$_{arom}$), 12.5 (s, 1H, NH)	240 (M^+, 25), 119 (100)
4h	55	264–265 (EtOH)	$C_{14}H_9FN_2O$ (240.2)	1670	7.4–8.2 (m, 8H$_{arom}$), 12.6 (s, 1H, NH)	240 (M^+, 100), 119 (84)
4i	72	223–226 (DMF)	220–228[5]	1665	7.0 and 8.0 (dd, 2H, J = 16.5, H$_{vinyl}$), 7.4–8.2 (m, 8H$_{arom}$), 12.3 (s, 1H, NH)	248 (M^+, 62), 247 (100), 119 (5)
4j	52	237–238 (EtOH)	237–239[3,22]	1670	2.3 (s, 3H, CH_3), 7.3–8.1 (m, 4H$_{arom}$), 12.2 (s, 1H, NH)	160 (M^+, 100), 119 (16)
4k	37	224–226 (EtOH)	225[1]	1670	1.3–2.8 (m, 11H$_{cyclohexyl}$), 7.3–8.1 (m, 4H$_{arom}$), 12.3 (s, 1H, NH)	232 (M^+, 100), 119 (31)

[a] Uncorrected, measured with a Reichert-Termopan.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.23, N ±0.38.
[c] Recorded on a Bruker WP 60 spectrometer.
[d] Obtained on a Riber 10-10 spectrometer.

2-Amino-*N,N*-diethylbenzamide (1):

The 2-amino-*N,N*-diethylbenzamide **(1)** is prepared by adapting and noticeably optimizing a previously reported procedure.[19] A solution of lithium diethylamide in anhydrous Et_2O is obtained by addition of BuLi in hexane (1.6 M, 66 mmol, 41 mL) to Et_2NH (4.8 g, 66 mmol) in Et_2O at 0 °C. The mixture is stirred under Ar for 15 min and a solution of freshly distilled methyl 2-aminobenzoate (5 g, 33 mmol) in Et_2O (20 mL) is added dropwise at 0 °C. The lemon yellow mixture is then refluxed for 1 h. After cooling an aq sat. NH_4Cl solution (100 mL) is added and the organic layer separated. The aqueous solution is extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers are washed with water and dried (Na_2SO_4). Evaporation of the solvents furnishes an oily product which slowly solidifies on standing. Recrystallization from hexane at 0 °C affords 2-amino-*N,N*-diethylbenzamide **(1)**; yield: 6.1 g (97%).

2-Aryl- and 2-Alkylquinazolin-4(3*H*)-ones 4a–k; General Procedure:

A solution of LDA is prepared at −30 °C by addition of BuLi in hexane (1.6 M, 6.3 mL, 10 mmol) to *i*-Pr_2NH (1.7 mL, 10 mmol) in THF (20 mL). The mixture is stirred under Ar for 15 min and a solution of 2-amino-*N,N*-diethylbenzamide (**1**, 1.92 g, 10 mmol) in THF (10 mL) is added dropwise. To the resulting yellow solution, the appropriate nitrile **3** (11 mmol) dissolved in THF (5 mL) is added over a period of 5 min. The mixture is allowed to warm to r.t. and then gently refluxed for 15 min. After cooling, water (50 mL) is added. The pH of the mixture is then adjusted to 5–6 by addition of NH_4Cl. Except for **4j** and **4k**, the crude product is isolated by filtration, washed several times with water, dried under vacuum and recrystallized from EtOH or DMF. The reaction mixture obtained by reaction of **2** with the aliphatic nitriles **3j, k** is extracted with CH_2Cl_2 (2 × 50 mL). The organic layer is washed with water and dried (Na_2SO_4). The crude product is finally recrystallized from EtOH.

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(1) Bogentoft, C.; Kronberg, L.; Danielsson, B. *Acta Pharm. Suec.* **1969**, *6*, 485 and references cited therein.
(2) Brown, D.J. in: Katritzky and Rees *Comprehensive Heterocyclic Chemistry*, Vol. 3, Boulton, A.J.; McKillop, A. (eds.), Pergamon Press, Oxford, 1985, pp. 148–149 and references cited therein.
(3) *Neth. Appl. Patent* 295501 (1965) Nordisk Droge- and Kemikalieforretning AIS; *C.A.* **1965**, *63*, 18113.
(4) Hori, M.; Iemura, R.; Hara, H.; Ozaki, A.; Sukamoto, T.; Ohtaka, H. *Chem. Pharm. Bull.* **1990**, *38*, 1286.
(5) Jiang, J.B.; Hesson, D.P.; Dusak, B.A.; Dexter, D.L.; Kang, G.J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721.
(6) Bogert, M.T.; Hand, W.F. *J. Am. Chem. Soc.* **1902**, *24*, 1032.
(7) Stephen, H.; Wadge, G. *J. Chem. Soc.* **1956**, 4420.
(8) Armarego, W.L.F. in: *The Chemistry of Heterocyclic Compounds*, Vol. 24, Brown, D.J. (ed.), Interscience, N.Y., 1967, pp. 69–218.
(9) Shah, R.C.; Ichaparia, M.B. *J. Chem. Soc.* **1936**, 431.
(10) Papadopoulos, E.P. *J. Org. Chem.* **1974**, *39*, 2540.
(11) Takeuchi, H.; Haguvara, S.; Eguchi, S. *Tetrahedron*, **1989**, *45*, 6375.
Takeuchi, H.; Matsushita, Y.; Eguchi, S. *J. Org. Chem.* **1991**, *56*, 1535.
(12) Wamhoff, H.; Wintersohl, H.; Stölben, S.; Paasch, J.; Zhu, N.-j.; Guo, F. *Liebigs Ann. Chem.* **1990**, 901.
(13) von Niementowski, S. *J. Prakt. Chem.* **1895**, *51*, 564.
(14) Endicott, M.M.; Wick, E.; Mercury, M.L.; Sherrill, M. *J. Am. Chem. Soc.* **1946**, *68*, 1299.
(15) Gotthelf, P.; Bogert, M.T. *J. Am. Chem. Soc.* **1901** *23*, 611.
(16) Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, 1974, pp. 116–121.
(17) Jahangir; Clark, R.D. *J. Org. Chem.* **1987**, *52*, 5378.
(18) Date, M.; Watanabe, M.; Furukawa, S. *Chem. Pharm. Bull.* **1990**, *38*, 902.
(19) Petyunin, P.A.; Kozhevnikov, Y.V. *Zh. Obshch. Khim.* **1960**, *30*, 2028.
(20) Smith, K.; Stephen, H. *Tetrahedron* **1957**, *1*, 38.
(21) Andrisano, R.; Modena, G. *Gazz. Chim. Ital.* **1950**, *80*, 228.
(22) Patel, V.S.; Patel, S.R. *J. Indian. Chem. Soc.* **1965**, *42*, 531.