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A Rapid Parallel Synthesis of 2-Dialkylamino-4(3H)-quinazolinones

Ming Wu DING*, Ying LIU, Gui Feng ZHANG, Shang Jun YANG

College of Chemistry, Central China Normal University, Wuhan 430079

Abstract: 2-Dialkylamino-4(3H)-quinazolinones **4** were rapidly synthesized by a solution-phase parallel synthetic method, which includes aza-Wittig reaction of iminophosphorane **1** with aromatic isocynate to give carbodiimide **2** and subsequent reaction of **2** with various aliphatic secondary amine in a parallel fashion.

Keywords: 4(3H)-Quinazolinone, aza-Wittig reaction, iminophosphorane, parallel synthesis.

Many 4(3H)-quinazolinones possess biological and pharmaceutical activities. For example, some of them exhibited good antiinflammatory and noncompetitive AMPA receptor antagonistical activities[1-3], whereas others exhibited good anticancer and antiviral activities[4-6]. Among them, 2-amino-4(3H)-quinazolinones were found to show significant fungicidal activities or used as potential potassium channel openers[7-9].

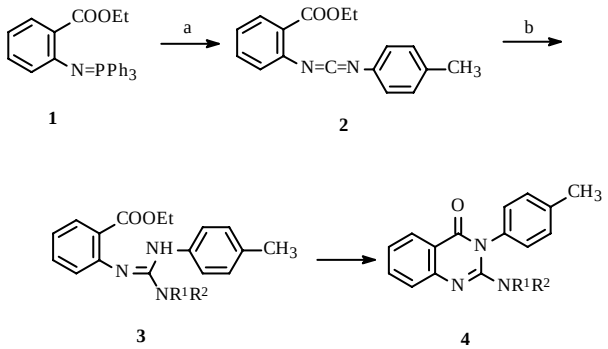
Recently, combinatorial synthesis of libraries containing small organic molecules has become a rapid evolving area of research[10]. It includes solid-phase and solution-phase synthetic techniques. Although a solid phase synthetic method for 4(3H)-quinazolinones has been reported[11], there is no solution phase synthetic route to 2-amino-4(3H)-quinazolinones. In our work on synthesis of biologically active quinazolinones, we developed a facile synthesis of 2-amino-4(3H)-quinazolinones[12]. Here we report an efficient solution-phase parallel synthesis of some new derivatives of 4(3H)-quinazolinones.

The iminophosphorane **1** reacted with tolyl isocyanates to give carbodiimide **2**. After removing the by-product Ph_3PO by recrystallization, the solution of **2** was divided equivalently into several parts to which were added various aliphatic secondary amines separately. The resulted solution was stood at room or refluxing temperature for 12-18 hours to give quinazolinones **4** in satisfactory yields. The formation of **4** can be rationalized in terms of an initial nucleophilic addition to give the guanidine intermediate **3**, which cyclized to give **4**. The results are listed in **Table 1**.

The structure of **4** has been confirmed by spectral data ^{1}H NMR, IR and MS. For example, the ^{1}H NMR spectrum data in **4a** showed the signals of NCH_2 at 3.08 ppm as quaternary absorption. The other signals appeared at δ8.11~7.13 (m, 8H, Ar-H),

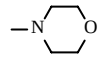
* E-mail: ding5229@yahoo.com.cn

Scheme 1



(a) 4-methylphenylisocyanate, CH_2Cl_2, 0-5℃, 12 h; (b) HNR^1R^2, CH_2Cl_2, r.t.-110℃, 12-18h, 71%-93%.

Table 1 Preparation of 2-dialkylamino-4(3H)-quinazolinones **4**

	NR^1R^2	Condition	Yield (%)	Purity (%)	mp (°C) or n_{20}^D	Elementary analysis (%, Calcd.) C	H	N
4a	NEt_2	r.t./12hr	91	97	90-92	74.05(74.24)	6.80(6.89)	13.93(13.67)
4b	N(*n*-Pr)$_2$	r.t./12hr	83	94	1.5582	75.25(75.19)	7.33(7.51)	12.42(12.53)
4c	N(*n*-Bu)$_2$	r.t./12hr	85	96	1.5438	76.21(76.00)	8.28(8.04)	11.51(11.56)
4d	N(*n*-C_5H_{11})$_2$	r.t./12hr	83	95	1.5464	76.54(76.69)	8.68(8.49)	10.91(10.73)
4e	N(*i*-Pr)$_2$	110℃/12hr	71	94	1.5560	75.31(75.19)	7.58(7.51)	12.37(12.53)
4f	N(*i*-Bu)$_2$	r.t./18hr	80	95	1.5496	76.15(76.00)	8.12(8.04)	11.36(11.56)
4g		r.t./12hr	93	98	129-130	75.13(75.21)	6.84(6.63)	13.10(13.16)
4h		r.t./12hr	88	99	147-149	71.04(71.01)	5.84(5.96)	13.15(13.08)

2.39 (s, 3H, CH_3Ph), 0.85 (t, 6H, J = 6.8 Hz, 2CH_3). The IR of **4a** showed the strong stretching resonance peak of quinazolinone C=O at 1680 cm^{-1}. The MS of **4a** showed M^+ at *m/z* 307 with 81% abundance.

The above solution-phase parallel synthetic method provides a high-speed synthesis of 2-dialkylamino-4(3H)-quinazolinones. Due to the easily accessible and versatile starting material, this method has the potential in synthesis of many biologically and pharmaceutically active quinazolinones derivatives.

General Procedure for parallel synthesis of 2-dialkylamino-4(3H)-quinazolinones **4**: to a solution of iminophosphorane **1**[12] (10.2 g, 24 mmol) in dry methylene dichloride (80 mL) was added 4-methylphenyl isocyanate (3.19 g, 24 mmol) under nitrogen at 0-5°C. After the reaction mixture was stood for 12 hours at 0-5°C, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 160 mL) was added to precipitate triphenylphosphine oxide. After filtration, the filtrate was condensed and methylene dichloride was added to make a solution of carbodiimide **2** (80 mL), which was divided into eight parts (10 mL each part). To each part of **2** prepared was added separately diethylamine (0.31 mL, 3 mmol), or di-*n*-propylamine (0.42 mL, 3 mmol), or di-*n*-butylamine (0.51 mL, 3 mmol), or di-*n*-pentylamine (0.61 mL, 3 mmol), or di-

Table 2 IR, MS and ^{1}H NMR of **4**

	IR (KBr, cm^{-1})	MS (*m/z*, %)	^{1}H NMR ($CDCl_3$, 200MHz, δ, ppm)
4a	1680, 1566, 1473, 1266	307 (M^+, 81), 278 (99), 235 (100), 208 (48), 188 (89), 119 (64)	8.11~7.13 (m, 8H, Ar-H), 3.08 (q, 4H, J = 6.8 Hz, $2NCH_2$), 2.39 (s, 3H, CH_3Ph), 0.85 (t, 6H, J = 6.8 Hz, $2CH_3$)
4b	1686, 1560, 1474, 1251	335 (M^+, 76), 306 (66), 292 (98), 264 (85), 235 (86), 202 (87), 174 (100), 132 (87)	8.12~7.10 (m, 8H, Ar-H), 3.03 (q, 4H, J = 6.8 Hz, $2NCH_2$), 2.40 (s, 3H, CH_3Ph), 1.28-0.82 (m, 10H, $2CH_2CH_3$)
4c	1686, 1561, 1474, 1299	363 (M^+, 99), 320 (62), 306 (99), 263 (98), 216 (93), 174 (93), 90 (100)	8.11~7.12 (m, 8H, Ar-H), 3.01 (q, 4H, J = 6.6 Hz, $2NCH_2$), 2.40 (s, 3H, CH_3Ph), 1.25-0.81 (m, 14H, $2CH_2CH_2CH_3$)
4d	1687, 1560, 1474, 1264	391 (M^+, 57), 348 (40), 320 (100), 278 (51), 264 (68), 230 (90), 105 (34)	8.10~7.11 (m, 8H, Ar-H), 3.02 (q, 4H, J=6.6 Hz, $2NCH_2$), 2.39 (s, 3H, CH_3Ph), 1.29-0.80 (m, 18H, $2(CH_2)_3CH_3$)
4e	1686, 1561, 1473, 1245	335 (M^+, 49), 292 (100), 277 (70), 235 (80), 145 (61)	8.10~7.09 (m, 8H, Ar-H), 3.42-3.60 (m, 2H, 2NCH), 2.37 (s, 3H, CH_3Ph), 1.09 (d, 12H, J = 7.2 Hz, $4CH_3$)
4f	1686, 1566, 1475, 1246	363 (M^+, 95), 320 (95), 305 (95), 276 (94), 264 (100), 201 (61), 145 (92)	8.14~7.12 (m, 8H, Ar-H), 2.90 (d, 4H, J = 6.8 Hz, $2NCH_2$), 2.39 (s, 3H, CH_3Ph), 1.75-0.80 (m, 14H, $2CH(CH_3)_2$)
4g	1681, 1563, 1453, 1255	319 (M^+, 58), 290 (45), 276 (16), 235 (28), 174 (100)	8.10~7.17 (m, 8H, Ar-H), 3.07 (t, 4H, J = 5.0 Hz, $2NCH_2$), 1.41-1.20 (m, 6H, $3CH_2$), 2.40 (s, 3H, CH_3Ph)
4h	1682, 1561, 1473, 1257	321 (M^+, 47), 290 (22), 276 (81), 264 (79), 235 (62), 216 (62), 174 (58), 91 (100)	8.13~7.18 (m, 8H, Ar-H), 3.41 (t, 4H, J = 4.5 Hz, $2OCH_2$), 3.12 (t, 4H, J = 4.5 Hz, $2NCH_2$), 2.40 (s, 3H, CH_3Ph)

iso-propylamine (0.43 mL, 3 mmol), or di-*iso*-butylamine (0.52 mL, 3 mmol), or piperidine (0.30 mL, 3 mmol), or morpholine (0.26 mL, 3 mmol). After the reaction mixture was stood at room temperature for 12-18 hours or refluxed in toluene for 12 hours, the solvent was removed off under reduced pressure and the residue was re-crystallized from methylene dichloride/ petroleum ether or eluted with ether/petroleum ether (1:2) through a short silica gel column to give 2-dialkylamino-4(3H)- quinazolinones **4** separately. The yields of **4** based on iminophosphorane **1** are listed in **Table 1**.

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