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A Facile and Selective Synthesis of 2-Alkylamino-4(3*H*)-quinazolinones

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ABSTRACT

The carbodiimides **2**, obtained from aza–Wittig reactions of iminophosphorane **1** with aromatic isocyanates, reacted with aliphatic primary amines to give mainly 2-alkylamino-4(3*H*)-quinazolinones **4** with unusual selectivity.

4(3*H*)-Quinazolinones are important heterocycles bearing good antimicrobial, antiinflammatory, antifungal activities.[1–4] Some of them showed significant anticancer and AMPA receptor antagonistical activities.[5–7] Although there are many known methods for the synthesis of 4(3*H*)-quinazolinones,[8–12] the 2-alkylamino derivatives were not easily

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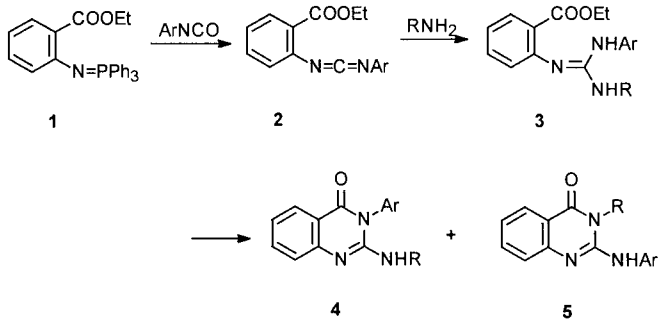
accessible by general routes. We have reported a facile and selective synthesis of 2-alkylamino-3,5-dihydro-4*H*-imidazol-4-ones via the reaction of aliphatic primary amine with functionalized carbodiimides under mild conditions.[13] This method was further utilized to synthesis 2-alkylamino-4(3*H*)-quinazolinones **4**.

Iminophosphorane **1**[12] reacted with aromatic isocyanates to give carbodiimides **2**, which were allowed to react with aliphatic primary amines to provide mainly quinazolinone **4**, one of the possible regioisomers. We obtained pure **4** from the reaction mixture by recrystallization; isomers **5** were found to exist in minor amount by GC-MS detection. The structure of quinazolinones **4** is mainly deduced from their ^{1}H NMR data. For example, the ^{1}H NMR spectrum in **4a** shows the signals of NH at 4.02 ppm as a wide absorption and NCH_2 at 3.42–3.32 ppm as multiple absorption, which strongly suggest the existence of $NHCH_2CH_2CH_3$ group in **4a**. Moreover, when the sample was treated with deuterated water, the ^{1}H NMR spectrum in **4a** shows the absorption of NCH_2 at 3.37 ppm as triplets with the disappearance of signals of NH absorption. Whenever the primary amine used is small (R = *n*-Pr) or bulky (R = *t*-Bu), the cyclization was achieved all in moderate to good yields with the same selectivity. The results are listed in Table 1.

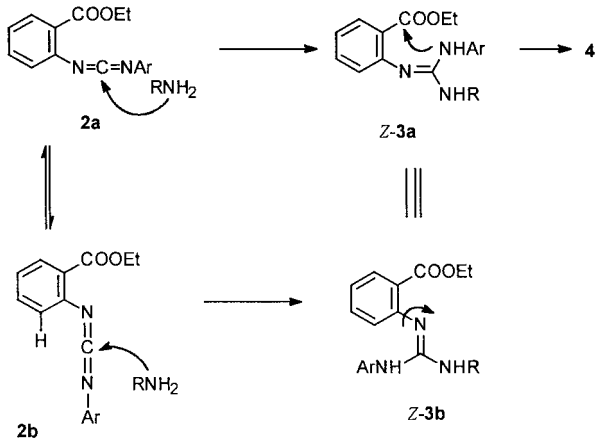


The formation of **4** can be rationalized in terms of an initial nucleophilic addition to give the guanidine intermediate **3** which cyclized to give **4** across the arylamino group rather than the alkylamino one. This will probably due to the geometry of the intermediate **3** which might mainly be *Z*-form suitable for arylamino group to cyclize. It is guessed that the configurations of carbodiimide **2** are mainly coplanar **2a** and **2b** due to the resonance effect. When the aliphatic primary amines react

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

Compound	Ar	R	Conditions	Yield[a] (%)
4a	Ph	*n*-C_3H_7	r.t./12 h	52
4b	Ph	*n*-C_4H_9	r.t./12 h	56
4c	Ph	$PhCH_2$	r.t./12 h	58
4d	Ph	*i*-C_3H_7	r.t./24 h	67
4e	Ph	*t*-C_4H_9	r.t./24 h	81
4f	Ph		r.t./24 h	80
4g	4-Cl-Ph	*n*-C_3H_7	r.t./12 h	56
4h	4-Cl-Ph	*n*-C_4H_9	r.t./12 h	50
4i	4-Cl-Ph	$PhCH_2$	r.t./12 h	53
4j	4-Cl-Ph	*i*-C_3H_7	r.t./24 h	70
4k	4-Cl-Ph	*t*-C_4H_9	r.t./24 h	84
4l	4-Cl-Ph		r.t./24 h	78

[a]Isolated yields based on iminophosphorane **1**.



with **2a**, *Z*-**3a** will be formed for the amine will attack **2a** mainly from the down direction due to the steric hindrance of COOEt group. When the amines react with **2b**, *Z*-**3b** will be formed for the amine will attack **2b** mainly from the right direction due to the steric hindrance of phenyl hydrogen. Actually *Z*-**3a** is equivalent to *Z*-**3b** through the C–N single bond rotation.

EXPERIMENTAL

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a Shimadzu IR-408 infrared spectrometer. NMR were taken on a Varian XL-200 spectrometer. Elementary analysis were taken on a CHN 2400 elementary analysis instrument.

General Preparation of 2-Alkylamino-4(3*H*)-quinazolinones 4

To a solution of iminophosphorane **1** (2.12 g, 5 mmol) in dry methylene dichloride (15 mL) was added aromatic isocyanate (5 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 6~12 h at 0~5°C, the solvent was removed off under reduced pressure and diethyl ether/petroleum ether (1:2, 20 mL) was added to precipitate triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **2**, which was used directly without further purification.

To a solution of **2** prepared above in methylene dichloride (15 mL) was added primary amine (5 mmol). After the reaction mixture was stirred for 12–24 h, the solvent was removed off under reduced pressure and the residual was recrystallized from methylene dichloride/diethyl ether to give 2-alkylamino-4(3*H*)-quinazolinones **4**.

4a. White crystals, m.p. 127–128°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09–7.09 (m, 9H, Ar-H), 4.02 (s, 1H, NH), 3.42–3.32 (m, 2H, NCH_2), 1.57–1.46 (m, 2H, CH_2), 0.85 (t, 3H, $J = 7.3$ Hz, CH_3). MS (*m*/*z*, %): 279 (M^+, 15), 264 (6), 236 (100), 221 (16), 145 (11), 90 (23). Anal. calcd. for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.23; H, 6.05; N, 15.12.

4b. White crystals, m.p. 148–150°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09–7.09 (m, 9H, Ar-H), 3.99 (s, 1H, NH), 3.45–3.36 (m, 2H, NCH_2), 1.50–1.20 (m, 4H, CH_2CH_2), 0.88 (t, 3H, $J = 6.8$ Hz, CH_3). MS (*m*/*z*, %): 293 (M^+, 22), 264 (13), 251 (27), 236 (100), 221 (25), 145 (19), 106 (42). Anal. calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.62; H, 6.65; N, 14.18.

4c. White crystals, m.p. 140–142°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.10–7.02 (m, 14H, Ar-H), 4.64 (d, 2H, $J = 5.8$ Hz, $NHC\underline{H}_2Ph$), 4.38 (s, 1H, NH). MS (*m*/*z*, %): 327 (M^+, 44), 250 (3), 222 (14), 167 (36), 91 (100). Anal. calcd. for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.87; H, 5.13; N, 12.96.

4d. White crystals, m.p. 118–120°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09–7.09 (m, 9H, Ar-H), 4.40–4.20 (m, 1H, NCH), 3.81 (s, 1H, NH), 1.12 (d, 6H, $J = 5.8$ Hz, $2CH_3$). MS (*m*/*z*, %): 279 (M^+, 29), 236 (100),

221 (18), 145 (16), 90 (28). Anal. calcd. for $C_{17}H_{17}N_3O$: C, 73.10; H, 6.13; N, 15.04. Found: C, 73.31; H, 6.21; N, 14.87.

4e. White crystals, m.p. 145–147°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09–7.10 (m, 9H, Ar-H), 3.89 (s, 1H, NH), 1.37 (s, 9H, $3CH_3$). MS (*m*/*z*, %): 293 (M^+, 10), 236 (100), 221 (7), 145 (12), 77 (16). Anal. calcd. for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.53; H, 6.64; N, 14.39.

4f. White crystals, m.p. 133–135°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09–7.07 (m, 9H, Ar-H), 4.10–3.80 (m, 2H, NCH and NH), 1.96–1.00 (m, 10H, $5CH_2$). MS (*m*/*z*, %): 319 (M^+, 19), 262 (8), 236 (100), 221 (24), 145 (23), 90 (33). Anal. calcd. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.47; H, 6.55; N, 13.27.

4g. White crystals, m.p. 149–151°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.08–7.10 (m, 8H, Ar-H), 3.97 (s, 1H, NH), 3.43–3.33 (m, 2H, NCH_2), 1.59–1.48 (m, 2H, CH_2), 0.87 (t, 3H, $J = 7.3$ Hz, CH_3). MS (*m*/*z*, %): 315 (8), 313 (M^+, 23), 298 (9), 270 (100), 255 (17), 192 (9), 145 (29), 90 (54). Anal. calcd. for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.14; H, 5.11; N, 13.43.

4h. White crystals, m.p. 126–127°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.08–7.10 (m, 8H, Ar-H), 3.95 (s, 1H, NH), 3.47–3.38 (m, 2H, NCH_2), 1.53–1.23 (m, 4H, CH_2CH_2), 0.91 (t, 3H, $J = 7.3$ Hz, CH_3). MS (*m*/*z*, %): 329 (6), 327 (M^+, 20), 298 (12), 285 (25), 270 (100), 255 (17), 140 (47), 90 (58). Anal. calcd. for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found: C, 65.76; H, 5.64; N, 12.75.

4i. White crystals, m.p. 183–184°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.20–7.04 (m, 13H, Ar-H), 4.65 (d, 2H, $J = 6.4$ Hz, $NHC\underline{H}_2Ph$), 4.38 (s, 1H, NH). MS (*m*/*z*, %): 363 (9), 361 (M^+, 26), 256 (6), 201 (17), 145 (9), 91 (100). Anal. calcd. for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.84; H, 4.51; N, 11.47.

4j. White crystals, m.p. 120–122°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07–7.09 (m, 8H, Ar-H), 4.38–4.20 (m, 1H, NCH), 3.76 (s, 1H, NH), 1.14 (d, 6H, $J = 6.8$ Hz, $2CH_3$). MS (*m*/*z*, %): 315 (12), 313 (M^+, 36), 270 (100), 255 (18), 145 (39), 90 (59). Anal. calcd. for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.22; H, 5.08; N, 13.34.

4k. White crystals, m.p. 176–177°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07–7.11 (m, 8H, Ar-H), 3.81 (s, 1H, NH), 1.39 (s, 9H, $3CH_3$). MS (*m*/*z*, %): 329 (3), 327 (M^+, 8), 270 (100), 235 (6), 145 (32), 90 (31). Anal. calcd. for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found: C, 65.84; H, 5.42; N, 12.98.

4l. White crystals, m.p. 103–104°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.06–7.08 (m, 8H, Ar-H), 4.12–3.78 (m, 2H, NCH and NH), 1.98–0.98 (m, 10H, $5CH_2$). MS (*m*/*z*, %): 355 (4), 353 (M^+, 11), 270 (100), 192 (9),

145 (26), 90 (33). Anal. calcd. for $C_{20}H_{20}ClN_3O$: C, 67.89; H, 5.70; N, 11.88. Found: C, 67.72; H, 5.75; N, 11.97.

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