Amidines: synthesis from *o*-alkenylanilines and cyclization in polyphosphoric acid

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Condensation of 2-[(*E*)-pent-3-en-2-yl]-4-, 2-[(*E*)-pent-2-en-2-yl]-4-, or 2-(cyclopent-1-enyl)-6-methylaniline with 1-chloro-1-(*N*-methylimino)- or 1-chloro-1-(*N*-phenylimino)ethane affords the corresponding amidines. Cyclization of the *N*-methylimino derivatives in polyphosphoric acid gives 3,4-dihydroquinazolines in high yields.

Key words: 2-(alk-2-enyl)anilines, 2-(alk-1-enyl)anilines, amidines, intramolecular cyclization, 3,4-dihydroquinazolines.

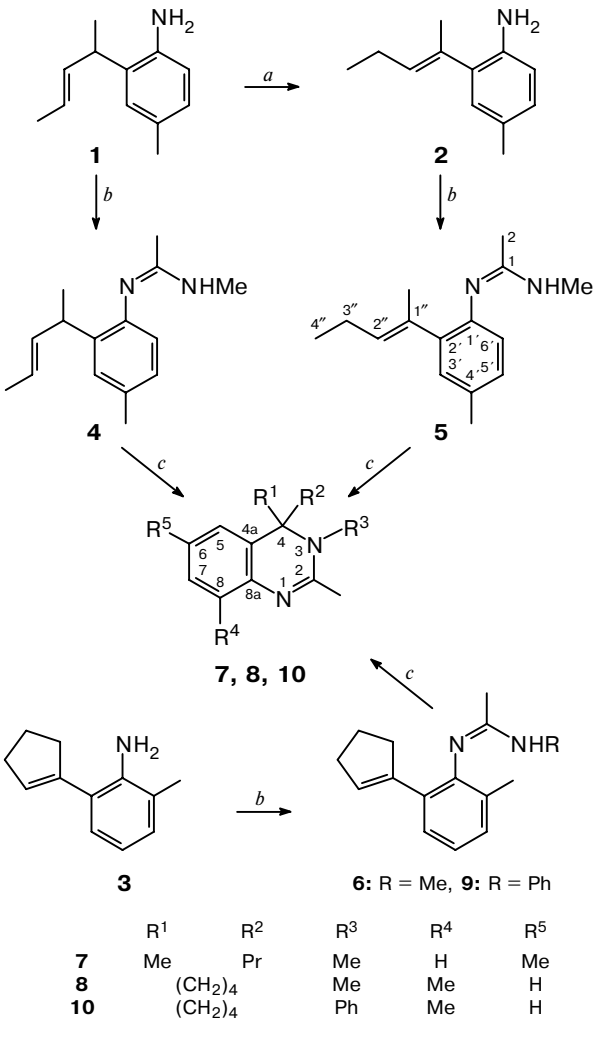
Quinazolines, which exhibit a variety of biological properties, are of noticeably increasing interest in recent years.[1—12] The methods for preparing compounds of this class mostly involve derivatives of anthranilic and aminocinnamic acids, 3,1-benzooxazines, or 2-aminomethylanilines. The use of derivatives of anthranilic acid[1—5] or 3,1-benzooxazines[6—8] affords quinazolin-4-ones, while cyclization of *N'*-phenyl-*N''*-acylureas in polyphosphoric acid (PPA) gives quinazolin-2-ones.[13] 3,4-Dihydroquinazolines are usually synthesized from 2-aminomethylanilines[9,10] or by addition of alkyl isocyanates to organic 2-aminocinnamates.[11]

In continuation of our work on heterocyclization of alkenylarylamines, we synthesized amidines from *o*-alkenylanilines and studied their cyclization into 3,4-dihydro-1,3-quinazolines under the action of PPA. Thus, condensation of 2-[(*E*)-pent-3-en-2-yl]-4- (**1**),[14] 2-[(*E*)-pent-2-en-2-yl]-4- (**2**),[15] and 2-(cyclopent-1-enyl)-6-methylaniline (**3**)[16] with *N*-methylimino-1-chloroethane[17] in benzene at 80 °C lead to amidines **4**—**6** in high yields (Scheme 1). Semiempirical quantum-chemical calculations (AM1) suggest[18] a *Z*-configuration of their double bond, because such a structure is more stable (by ~13 kJ) than the *trans*-arrangement of the phenyl and methylamino groups.

When kept in PPA at 150—160 °C for 4 h, amidines **4** and **5** undergo cyclization into quinazoline **7**, while amidine **6** gives quinazoline **8**. The cyclization of amidine **4** into quinazoline **7** starts with a shift of the double bond toward the aromatic ring to give a vinyl derivative **5** (identified in the reaction mixture by GLC). An analogous shift of the double bond is well known when amine **1** itself reacts with PPA at 100—140 °C. The reaction occurs in several steps to give, through alkenylaniline **2** as a first intermediate,[19] a mixture of 2-ethyl-2-methylindoline and 1-amino-4,4-dimethylindane.[20]

Replacement of the MeNH group in the amidine by the PhNH group (when passing from compound **6** to **9**)

Scheme 1



	R^1	R^2	R^3	R^4	R^5
7	Me	Pr	Me	H	Me
8	$(CH_2)_4$		Me	Me	H
10	$(CH_2)_4$		Ph	Me	H

Reagents and conditions: *a*. KOH, 300 °C; *b*. MeC(Cl)NMe or MeC(Cl)NPh, C_6H_6, 80 °C; *c*. PPA, 150—160 °C.

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decreases the yield of quinazoline from 70% (in the case of product **8**) to 40% (**10**), owing to the formation of by-products.

The structures of the compounds synthesized were determined by spectroscopic methods and confirmed by elemental analysis data. The IR spectra of amidines **4**—**6** and **9** contain an absorption band at 3200 cm^{-1} corresponding to the NH groups. Their ^{13}C NMR spectra show a singlet at δ 156—160 for the N=C—N fragment. The ^{13}C NMR spectra of quinazolines **7**, **8**, and **10** have a characteristic singlet at δ 61—68 for the C(4) atom. In addition, the ^{13}C NMR spectra of spiroheterocycles **8** and **10** exhibit two triplets at δ 23—26 and 38—40 for the C(2′), C(5′) and C(3′), C(4′) atoms, respectively.

Thus, the reactions of *o*-alkenylanilines **1**—**3** with *N*-methyl- or *N*-phenylimino-1-chloroethane easily yield the corresponding amidines, which undergo PPA-promoted cyclization into 3,4-dihydroquinazolines.

Experimental

^1H (300.13 MHz) and ^{13}C NMR (75.47 MHz) spectra were recorded on a Bruker AM-300 instrument with Me_4Si as the internal standard. IR spectra were recorded on a UR-20 instrument. The purity of the products was checked by TLC using Silufol UV-254 plates in C_6H_6—MeOH (19 : 1) as an eluent.

Synthesis of amidines 4—6 and 9 [17] (general procedure). *N*-Methylacetamide or acetanilide (0.02 mol) was added slowly, in small portions, at 0 °C to a solution of PCl_5 (4.8 g, 2.3 mmol) in 20 mL of $CHCl_3$ or C_6H_6. After the reaction was completed, a corresponding alkenylaniline **1**—**3** (0.02 mol) in 10 mL of $CHCl_3$ or C_6H_6 was added. The reaction mixture was refluxed for 2.5 h, cooled to 20 °C, and washed with 10% NaOH. The organic phase was separated, and the products were extracted with $CHCl_3$ (2×10 mL) from the aqueous layer. The combined extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Amidines **4**, **6**, and **9** were isolated by column chromatography on silica gel (10 g) in $CHCl_3$. Amidine **5** was recrystallized from hexane.

1-Methylamino-1-[4′-methyl-2′-(pent-3″-(*E*)-en-2″-yl)phenyl-(*Z*)-imino]ethane (4). Yield 4.3 g (93%); amorphous mass. Found (%): C, 77.89; H, 9.33; N, 11.80. $C_{15}H_{22}N_2$. Calculated (%): C, 78.21; H, 9.63; N, 12.16. IR, ν/cm^{-1}: 3216 (NH). ^1H NMR ($CDCl_3$), δ: 1.2 (d, 3 H, C(1″)H_3, J = 7.0 Hz); 1.6 (d, 3 H, C(5″)H_3, J = 6.1 Hz); 1.7, 2.3, 2.9 (all s, each 3 H, Me); 3.7 (m, 1 H, (H″)); 4.4 (s, 1 H, NH); 5.4 (dq, 1 H, H(3″), $J_{H(3''),Me}$ = 6.0 Hz, $J_{H(3''),H(2'')}$ = 15.4 Hz); 5.5 (dq, 1 H, H(2″), $J_{H(2''),Me}$ = 7.4 Hz); 6.6 (d, 1 H, H(6′), J = 7.1 Hz); 6.8 (s, 1 H, H(3′)); 6.9 (d, 1 H, H(5′)). ^{13}C NMR ($CDCl_3$), δ: 17.4, 17.9, 20.0, 21.0, 28.5 (5 Me); 37.4 (C(2″)); 122.3, 122.7, 126.8, 127.3, 131.8, 136.9, 138.0, 142.3 (C(3″), C(4″), C arom.); 156.0 (C(1)).

1-Methylamino-1-[4′-methyl-2′-(pent-2″-(*E*)-en-2″-yl)phenyl-(*Z*)-imino]ethane (5). Yield 4.5 r (97%), m.p. 95—96 °C (hexane). Found (%): C, 78.02; H, 9.21; N, 11.83. $C_{15}H_{22}N_2$. Calculated (%): C, 78.21; H, 9.63; N, 12.16. IR, ν/cm^{-1}: 3210 (NH). ^1H NMR ($CDCl_3$), δ: 1.0 (t, 3 H, Me, J = 7.6 Hz); 1.6, 1.9 (both s, each 3 H, Me); 2.1 (m, 2 H, CH_2); 2.2, 2.8 (both s, each 3 H, Me); 4.9 (s, 1 H, NH); 5.4 (t, 1 H, C=CH, J = 7.1 Hz); 6.6 (d, 1 H, H(6′), J = 7.8 Hz); 6.8 (d, 1 H, H(5′)); 6.9 (s, 1 H, H(3′)). ^{13}C NMR ($CDCl_3$), δ: 14.2 (C(5″)); 16.3 (C(2)); 17.8 (C(4″)); 20.8 (C(1″)); 21.8 (4 CH_3Ar); 28.5 (NMe); 122.5 (C(3′)); 127.8 (C(5′)); 129.8 (C(3″)); 131.2 (C(2″)); 131.2 (C(6′)); 136.1 (C(4′)); 138.3 (C(2′)); 141.0 (C(1′)); 156.1 (C(1)).

1-Methylamino-1-[2′-methyl-6′-(cyclopent-1-enyl)phenyl-(*Z*)-imino]ethane (6). Yield 4.3 r (94%), amorphous mass. Found (%): C, 78.60; H, 8.53; N, 11.94. $C_{15}H_{20}N_2$. Calculated (%): C, 78.89; H, 8.83; N, 12.27. IR, ν/cm^{-1}: 3220 (NH). ^1H NMR ($CDCl_3$), δ: 1.4 (s, 3 H, Me); 1.9 (m, 2 H, CH_2); 2.0 (s, 3 H, Me); 2.3—2.7 (m, 4 H, 2 CH_2); 2.8 (s, 3 H, Me); 4.9 (s, 1 H, NH); 5.9 (s, 1 H, =CH); 6.9 (t, 1 H, H(6′), J = 7.5 Hz); 7.0 (d, 1 H, H(3′)); 7.1 (d, 1 H, H(5′)). ^{13}C NMR ($CDCl_3$), δ: 16.9 (C(2)); 18.1 (C(2′)Me); 23.7 (C(4″)); 27.7 (NMe); 33.2 (C(3″)); 35.5 (C(5″)); 121.1 (C(4′)); 126.1 (C(2″)); 129.2 (C(6′)); 127.9 (C(5′)); 128.2 (C(3′)); 142.1 (C(1″)); 147.8 (C(1′)); 155.2 (C(1)).

1-Phenylamino-1-[2′-methyl-6′-(cyclopent-1-enyl)phenyl-(*Z*)-imino]ethane (9). Yield 5.4 r (93%), amorphous mass. Found (%): C, 82.40; H, 7.31; N, 9.29. $C_{20}H_{22}N_2$. Calculated (%): C, 82.72; H, 7.63; N, 9.65. IR, ν/cm^{-1}: 3270 (NH). ^1H NMR ($CDCl_3$), δ: 1.6 (s, 3 H, Me); 1.7—2.7 (m, 6 H, 3 CH_2); 2.1 (s, 3 H, Me); 5.9 (s, 1 H, H(2″)); 6.7—7.4 (m, 8 H, Ar); 9.4 (br.s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 16.4 (C(2)); 18.2 (Me); 23.4 (C(4″)); 33.1 (C(3″)); 35.4 (C(5″)); 123.0, 125.4, 125.8, 126.3, 128.6, 128.8, 129.0, 130.3, 132.9, 133.3, 137.8, 140.6 (C(1″), C(2″), C arom.); 160.2 (C(1)).

Cyclization of amidines in PPA. A corresponding amidine **4**—**6** or **9** (2 mmol) was mixed with PPA (1.5 g) and heated at 150—160 °C for 4 h (the reaction course was monitored by GLC). The reaction mixture was cooled to 20 °C, and a concentrated solution of Na_2CO_3 was added to alkaline reaction. The product was extracted with ethyl acetate (3×10 mL). The extract was dried with Na_2SO_4 and concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (3 g) in $CHCl_3$ as an eluent.

4-Propyl-2,3,4,6-tetramethyl-3,4-dihydro-1,3-quinazoline (7). Yield 70%, R_f 0.4 (C_6H_6—MeOH, 19 : 1). Found (%): C, 77.93; H, 9.29; N, 11.85. $C_{15}H_{22}N_2$. Calculated (%): C, 78.22; H, 9.62; N, 12.16. ^1H NMR ($CDCl_3$), δ: 0.8 (t, 3 H, Me, J = 7.3 Hz); 1.3—1.9 (m, 4 H, 2 CH_2); 1.5, 2.2, 2.8, 2.9 (all s, each 3 H, Me); 6.7—6.9 (m, 3 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 13.9 (C(3′)); 17.5 (C(2′)); 21.0, 23.2, 28.7, 31.3 (4 Me); 43.2 (C(1′)); 61.2 (C(4)); 122.5 (C(8)); 124.6 (C(7)); 127.3 (C(4a)); 132.8 (C(6)); 138.9 (C(8a)); 156.4 (C(2)).

2,3,8-Trimethyl-4-spirocyclopentane-3,4-dihydro-1,3-quinazoline (8). Yield 70%, R_f 0.4 (C_6H_6—MeOH, 19 : 1). Found (%): C, 78.53; H, 8.69; N, 11.97. $C_{15}H_{20}N_2$. Calculated (%): C, 78.91; H, 8.82; N, 12.27. ^1H NMR ($CDCl_3$), δ: 1.5—2.3 (m, 8 H, 4 CH_2); 2.1, 2.3 (both s, each 3 H, Me); 2.9 (s, 3 H, MeN); 6.9—7.9 (m, 3 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 17.8 ($\underline{C}H_3C(2)$); 24.3 ($\underline{C}H_3C(8)$); 26.2 (C(3′), C(4′)); 32.7 (MeN); 40.8 (C(2′), C(5′)); 66.3 (C(4)); 121.6 (C(7)); 123.2 (C(5)); 128.8 (C(6)); 130.8 (C(8)); 131.6 (C(4a)); 139.8 (C(8a)); 156.4 (C(2)).

2,8-Dimethyl-3-phenyl-4-spirocyclopentane-3,4-dihydro-1,3-quinazoline (10). Yield 40%, R_f 0.35 (C_6H_6—MeOH, 19 : 1). Found (%): C, 82.31; H, 7.35; N, 9.22. $C_{20}H_{22}N_2$. Calculated (%): C, 82.72; H, 7.63; N, 9.65. ^1H NMR ($CDCl_3$), δ: 1.5—2.3 (m, 8 H, 4 CH_2); 1.9, 2.5 (both s, each 3 H, Me); 6.6—7.5 (m, 8 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 17.7 ($\underline{C}H_3C(2)$); 24.4 ($\underline{C}H_3C(8)$); 23.3 (C(3′), C(4′)); 38.3 (C(2′), C(5′)); 63.3 (C(4)); 105.6, 122.1, 123.2, 123.7, 125.0, 126.7, 129.7, 130.5, 134.3, 141.2 (C arom.); 154.8 (C(2)).

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