Iodocyclization of *N*-(2-nitrophenyl)- and *N*-phenyl-*N′*-[2-(alk-1-enyl)phenyl]ethanimidamides

Rail R. Gataullin, Ivan S. Afon'kin,* Akhnaf A. Fatykhov, Leonid V. Spirikhin and Il'dus B. Abdrakhmanov

Institute of Organic Chemistry, Ufa Scientific Centre of the Russian Academy of Sciences, 450054 Ufa, Russian Federation. Fax: +7 3472 35 6066; e-mail: chemorg@anrb.ru

10.1070/MC2001v011n05ABEH001490

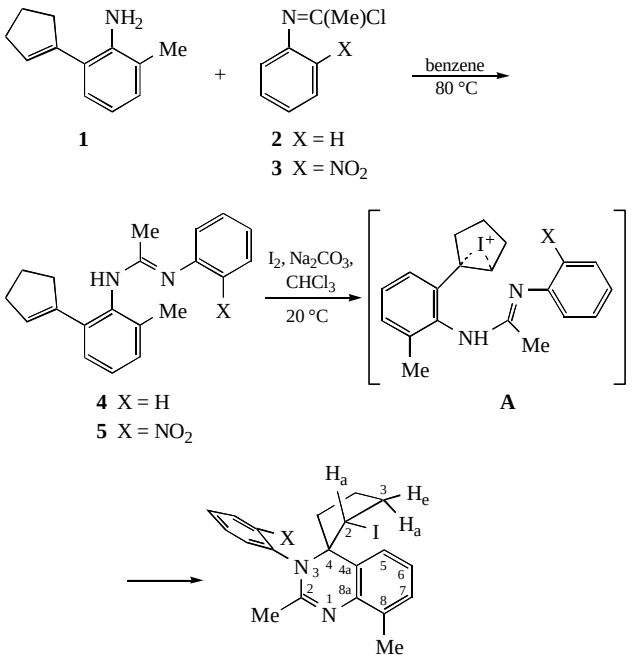
The action of iodine on *N*-(2-nitrophenyl)- or *N*-phenyl-*N′*-[2-(alk-1-enyl)phenyl]ethanimidamides obtained by the condensation of 2-(cyclopent-1-enyl)-6-methylaniline with *N*-(1-chloroethylidene)aniline or *N*-(1-chloroethylidene)-2-nitroaniline results in corresponding spiro(3,4-dihydroquinazoline)-4,1′-(2′-iodocyclopentane) in good yields, but the analoguous reaction with 4-methyl-2-(1-methylbut-1-enyl)aniline leads to an *N*-[(2,3-dihydro-1*H*-indol-1-yl)ethylidene]aniline derivative.

In the past few years, quinazolines and their 3,4-dihydro derivatives obtained from 2-aminomethylanilines[1,2] or by the addition of alkylisocyanates to 2-aminocinnamic acid esters[3] have attracted the attention of scientists due to their biological activities.

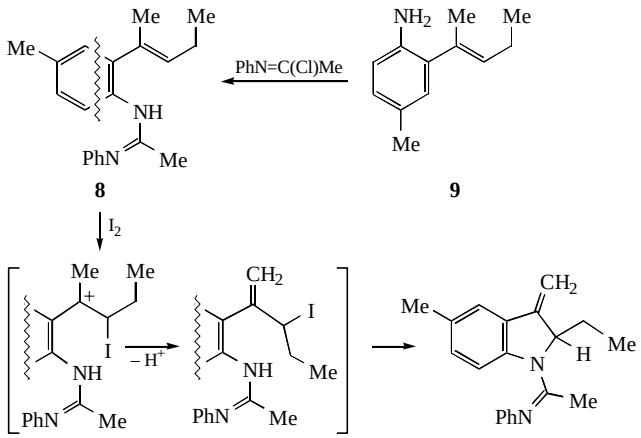
Continuing our work[4] on the heterocyclization of alkenylarylethanimidamides synthesised from 2-(alk-1-enyl)anilines, we now report on the interaction with I_2. Therefore, the condensation of 2-(cyclopent-1-enyl)-6-methylaniline **1**[5] with *N*-(1-chloroethylidene)aniline **2** or *N*-(1-chloroethylidene)-2-nitroaniline **3**[6] in benzene at 80 °C gave ethanimidamides **4**[6] or **5**† in high yield (Scheme 1). The interaction of ethanimidamides **4** and **5** with iodine lead to spiro(dihydroquinazoline)cyclopentane **6** or **7**. Using the Overhauser effect to determine the orientation of the H(2′) proton in the cyclopentane fragment of a model of **7** suggested that the reaction proceeds *via* the formation of onium complex A.

In contrast, the interaction of **8** with iodine obtained from amine **9**[7] and acetanilide lead to basic reaction product indoline **10** (Scheme 2). The following reaction mechanism is proposed. Carbocation **11** resulting from the reaction of iodine with **8** loses a proton to give amidine **12**. By intramolecular displacement of iodide, ion **12** cyclises to **10**.‡

The structure of all new compounds was determined by spectral methods and elemental analysis. In the ^{1}H NMR spectra of compounds **6** and **7**, a signal of the H(2′) proton is observed at 4.3 ppm as a double doublet with spin–spin coupling constants at 8.2–9.0 and 9.6–11.0 Hz. The high values of these constants support the



Scheme 1



Scheme 2

axial orientation of proton H(2′). The ^{13}C NMR spectra of compounds **6** and **7**, detected in the JMOD regime, show a peak in the

† *General methods.* ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz (with Me_4Si as an internal standard). IR spectra were measured on a UR-20 instrument. Mass spectra were measured on an MX 1320 mass spectrometer (EI, 70 eV). The purity of the reaction products was checked by TCL on Silufol UV-254 plates.

General procedure for the synthesis of N-*(2-cyclopent-1-en-1-yl-6-methylphenyl)*-N′-*(2-nitrophenyl)ethanimidamide* **5** *and* N-*{4-methyl-2-[(*E*)-1-methylbut-1-enyl]phenyl}*-N′-*phenylethanimidamide* **8**. The corresponding acetanilide (0.02 mol) was added slowly in small portions to a stirred cooled solution of phosphorus pentachloride (4.8 g, 0.023 mol) in chloroform or benzene (20 ml). After completion of reaction, a solution of alkenylaniline **1** or **9** (0.02 mol) in chloroform or benzene (10 ml) was added slowly. The resulting reaction mixture was refluxed for 2.5 h. After cooling, it was treated with a 10% sodium hydroxide solution, extracted with chloroform or benzene and dried ($MgSO_4$). The solvent was evaporated, and the crude residue was purified by column chromatography using silica gel to give ethanimidamide **5** or was extracted with hot hexane to give ethanimidamide **8**.

5: yield 91%, yellow glassy mass. ^{1}H NMR ($CDCl_3$) δ: 1.8–2.2 (m, 2H, CH_2), 2.3 (s, 3H, Me), 2.5 (s, 3H, Me), 2.7 (m, 2H, CH_2), 2.9 (m, 2H, CH_2), 6.2 (s, 1H, H-2″), 7.0–7.7 (m, 5H, Ar), 8.3 (d, 1H, H-6–$PhNO_2$, *J* 8.0 Hz), 9.7 (d, 1H, H-3–$PhNO_2$, *J* 6.5 Hz), 10.2 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 18.3 (C-2), 19.2 [C(2′)–Me], 23.3 [C(4″)], 33.3 [C(3″)], 35.1 [C(5″)], 120.4, 121.2, 122.3, 125.4, 126.1, 127.6, 128.0, 128.5, 128.6, 134.7, 135.7, 137.8, 141.7, 145.6 [C_{Ar}, C(1″), C(2″)], 151.4 [C(1)]. IR, ν/cm^{-1}: 3270 (NH). Found (%): C, 71.28; H, 6.32; N, 12.11. Calc. for $C_{20}H_{21}N_3O_2$ (%): C, 71.62; H, 6.71; N, 12.53.

8: yield 95%, R_f 0.2 (C_6H_6–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 1.0 (t, 3H, Me, *J* 7.5 Hz), 1.9 (m, 2H, CH_2), 2.0, 2.1, 2.4 (3s, 3×3H, 3Me), 5.6 (t, H-3′, *J* 6.9 Hz), 7.0 (s, 1H, H-3), 7.1–7.4 (m, 7H, Ar), 7.6 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 13.9, 17.0, 20.4, 24.3 (4Me), 22.3 [C(3′)], 121.1 [C(6)], 127.9 [C(5)], 128.5 [C(2′)], 130.7 [C(3)], 132.1 [C(2)], 133.2 [C(4)], 133.4 [C(1′)], 145.2 [C(1)], 151.1 (N=C–N), 122.4, 127.7, 128.5, 130.7 (C–Ph). IR, ν/cm^{-1}: 3230 (NH). Found (%): C, 82.00; H, 8.07; N, 9.34. Calc. for $C_{20}H_{24}N_2$ (%): C, 82.15; H, 8.27; N, 9.58.

aliphatic region, a quaternary carbon atom C(4) peak is observed at 71.5 ppm and a cyclopentane C(2′) peak, at 34.0 and 35.9 ppm.

The structure of compound **10** is supported by elemental analysis and spectral data. In the ^{1}H NMR spectrum, non-equivalent alkene protons are observed at 5.2 and 5.5 ppm as two one-proton singlets, (spin–spin coupling constant is 0–2 Hz[8]). A peak corresponding to the H(2) proton is observed as a double doublet at 4.2 ppm (J_1 5.9 Hz, J_2 11.3 Hz). The two-proton multiplet peaks of the methylene group appear at 1.3–1.9 ppm and a three-proton triplet of the methyl group at 0.6 ppm (J 7.3 Hz) corresponds to the ethyl fragment. Moreover, two three-proton singlet peaks at 2.2 and 2.5 ppm correspond to the other two methyl groups. The ^{13}C NMR data support this structure. In the aliphatic region, the five peaks observed are correlated using the method of a pulse sequence of *J*-modulated spin echo. Three of these signals correspond to carbon atoms of methyl groups, one to a methylene carbon atom of ethyl group, and that at low field (73.6 ppm) to the carbon atom C(2). There are 13 aromatic and olefinic peaks, where the carbon atom of the amidine group resonates at 155.0 ppm. The calculations on increments of substituents testify that these signals correspond to the given structure. The mass spectrum of compound **10** showed the presence of a molecular ion at *m*/*z* 290, as expected.

Thus, the reaction path of the iodocyclization of *N*-[2-(alk-1-enyl)phenyl]ethanimidamides depends on the nature of alkenyl radical; thus, the derivatives of *N*-[2-(cyclopent-1-enyl)phenyl]-ethanimidamide gave corresponding spiro(3,4-dihydroquinazoline)-4,1′-(2′-iodocyclopentane), but *N*-phenyl-*N′*-[2-(1-methylbut-1-enyl)phenyl]ethanimidamide gave an *N*-[(2,3-dihydro-1*H*-indol-1-yl)ethylidene]aniline derivative.

‡ *General procedure for the synthesis of spiro(2,8-dimethyl-3-phenyl-3,4-dihydroquinazoline)-4,1′-(2′-iodocyclopentane)* **6**, *spiro[2,8-dimethyl-3-(2-nitrophenyl)-3,4-dihydroquinazoline]-4,1′-(2′-iodocyclopentane)* ***7*** *and* N-*[(2-ethyl-5-methyl-3-methylene-2,3-dihydro-1*H*-indol-1-yl)ethylidene]aniline* **10**. A mixture of ethanimidamide **4**, **5** or **8** (1 mmol), iodine (0.51 g, 2 mmol) and sodium carbonate (1.1 g, 10 mmol) in chloroform (7 ml) was stirred for 24 h at 20 °C. The progress of the reaction was monitored by TLC (CCl_4 as an eluent). The reaction mixture was diluted with chloroform (30 ml), washed with a sodium thiosulfate solution (2×30 ml) and then with water (10 ml). The combined organic phases were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography using silica gel (eluent: C_6H_6–EtOAc, 4:1) to give product **6**; the recrystallization from benzene gave product **7**; column chromatography using silica gel (eluent: C_6H_6–MeOH, 15:1) gave product **10**.

6: yield 93%, amorphous solid, R_f 0.5 (C_6H_6–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 1.2–2.3 (m, 6H, 3CH_2), 2.0, 2.5 (2s, 2×3H, 2Me), 4.3 (dd, 1H, H-2′, J_1 9.0 Hz, J_2 9.6 Hz), 6.8–7.5 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$) δ: 17.8, 24.8 (2Me), 23.2 [C(4′)], 32.8 [C(5′)], 34.0 [C(2′)], 38.2 [C(3′)], 71.5 [C(4)], 123.2, 125.2, 126.6, 128.3, 128.7, 130.1, 130.7, 130.8, 138.6, 138.9 (C_{Ar}), 155.8 [C(2)]. Found (%): C, 57.39; H, 4.76; I, 29.99; N, 6.34. Calc. for $C_{20}H_{21}IN_2$ (%): C, 57.70; H, 5.09; I, 30.48; N, 6.73.

7: yield 95%, mp 125–127 °C, R_f 0.4 (C_6H_6–EtOAc, 2:1). ^{1}H NMR ($CDCl_3$) δ: 1.3–2.3 (m, 6H, 3CH_2), 2.0 (s, 3H, Me), 2.5 (s, 3H, Me), 4.3 (dd, 1H, H-2′, J_1 8.2 Hz, J_2 11.0 Hz), 6.7–7.9 (m, 7H, Ar). ^{13}C NMR ($CDCl_3$) δ: 17.5 [C(8′)H_3], 23.1 [C(4′)], 24.9 [C(2′)H_3], 31.6 [C(5′)], 33.1 [C(3′)], 35.9 [C(2′)], 71.5 [C(4)], 120.6 [C(7)], 123.6 [C(5)], 124.3 [C(6)], 125.9 [C(8)], 128.4 [C(4a)], 129.8 [C(8a)], 132.2, 133.1, 133.2, 139.6, 148.6 (C_{Ar}), 153.0 [C(2)]. Found (%): C, 51.69; H, 4.16; I, 27.06; N, 8.84. Calc. for $C_{20}H_{20}IN_3O_2$ (%): C, 52.07; H, 4.57; I, 27.51; N, 9.11.

10: yield 62%, mp 94–96 °C (Et_2O). ^{1}H NMR ($CDCl_3$) δ: 0.6 (t, 3H, Me, J 7.29 Hz), 1.3–1.9 (m, 2H, CH_2), 2,27, 2.40 (s, 3H, Me), 4.2 (dd, 1H, H-2′, J_1 5.90 Hz, J_2 11.34 Hz), 5.2 (s, 1H, H_2C=), 5.5 (s, 1H, H_2C=), 7.1–7.6 (m, 8H, Ar). ^{13}C NMR ($CDCl_3$) δ: 10.1, 20.5, 25.1 (3Me), 25.0 (CH_2), 73.6 [C(2′)], 115.5 (H_2C=C), 125.7, 126.0, 127.0, 128.1, 128.3, 129.1, 130.1, 134.6, 136.1, 142.7, 145.3, 155.0 (H_2C=*C*, C_{Ar}, N–C=N). MS, *m*/*z*: 290 $[M]^+$, 275 $[M - Me]^+$, 261 $[M - Et]^+$, 77 $[M - Ph]^+$. Found (%): C, 82.31; H, 7.25; N, 9.21. Calc. for $C_{12}H_{17}N$ (%); C, 82.72; H, 7.64; N, 9.65.

References

1 M. A. Arozome, T. Kondo and Y. Watanabe, *J. Org. Chem*., 1993, **58**, 310.

2 V. A. Savel'ev and V. A. Loskutov, *Khim. Geterotsikl. Soedin.*, 1991, 791 [*Chem. Heterocycl. Compd*. (*Engl. Transl.*), 1991, **27**, 621].

3 P. Molina, E. Aller and A. Lorenzo, *Synthesis*, 1998, 283.

4 R. R. Gataullin, T. V. Kazhanova, F. F. Minnigulov, A. A. Fatykhov, L. V. Spirikhin and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 1789 (*Russ. Chem. Bull*., 2000, **49**, 1769).

5 R. R. Gataullin, I. S. Afon'kin, I. V. Pavlova, I. B. Abdrakhmanov and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 398 (*Russ. Chem. Bull*., 1999, **48**, 396).

6 R. R. Gataullin, I. S. Afon'kin, I. B. Abdrakhmanov and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 522 (*Russ. Chem. Bull*., 2001, **50**, 545).

7 R. R. Gataullin, I. S. Afon'kin, A. A. Fatykhov, L. V. Spirihin, E. V. Tal'vinskiy and I. B. Abdrakhmanov, *Izv. Akad. Nauk, Ser. Khim*., 2001, 633 (*Russ. Chem. Bull*., 2001, **50**, 659).

8 B. I. Ionin, B. A. Ershov and A. I. Kol'tsov, *YaMR-spektroskopiya v organicheskoi khimii* (*NMR Spectroscopy in Organic Chemistry*), Khimiya, Leningrad, 1983 (in Russian).

Received: 28th June 2001; Com. 01/1816