ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 7, pp. 1091–1093. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © V.A. Glushkov, E.V. Vedernikova, M.S. Kotelev, E.V. Baigachev, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 7, pp. 1100–1102.

SHORT COMMUNICATIONS

Synthesis of 2-Aryl-5,5-dimethyl-5,6-dihydro-1,2,4-triazolo-[3,4-*a*]isoquinolinium Tetrafluoroborates

V. A. Glushkov[a], E. V. Vedernikova[b], M. S. Kotelev[b], and E. V. Baigacheva[a]

[a]*Institute of Chemical Engineering, Ural Division, Russian Academy of Sciences, Perm, 614013 Russia*
e-mail: glusha@nm.ru
[b]*Perm State University, Perm, Russia*

Received November 21, 2007

DOI: 10.1134/S1070428008070270

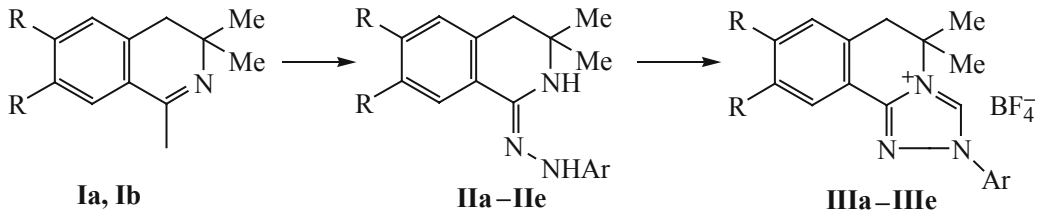
Recently the chemistry of N-heterocyclic carbenes made rapid progress, as seen from a large number of freshly published reviews [1–4] and a monograph [5]. In the modern organic synthesis the N-heterocyclic carbenes are used either directly [1, 2] or in complexes with transition and nontransition metals [3].

N-heterocyclic carbenes known now and their derivatives known now contain metal complexes based on salts of 1,2,4-triazole substituted with chiral functional groups [6] and of 1,2,4-triazole fused with pyrrolidine [7], oxazole [8], oxazine [9], morpholine [10], indeno[2,1-*b*]-morpholine [11], and also with indeno[1,2-*b*]pyrroline, naphtho[1,2-*b*]pyrroline, and naphtho[2,1-*b*]morpholine [2]. Yet the heterocyclic system of triazolo[3,4-*a*]isoquinoline was notused as a precursor of N-heterocyclic carbenes. The target of the present study was the preparation of 2-aryl-5,5-dimethyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinolinium salts and their 8,9-dimethoxy analogs as precursors N-heterocyclic carbenes. We chose for counterion the tetrafluoroborate anion since unlike chlorides and bromides 2-aryl-5,5-dimethyl-5,6-dihydro-1,2,4-triazolo-[3,4-*a*]isoquinolinium tetrafluoroborates were nonhydroscopic, heat-resistant, and formed well-developed crystals.

The developed method of preparation of the target compound consisted in the cyclization of amidrazones **IIa–IIe**, obtained via methylsulfanyl derivatives **Ia** and **Ib**, carried out in excess ethyl orthoformate in the presence of ammonium tetrafluoroborate.

Amidrazones **IIa–IIe** were obtained by heating 1-methylsulfanyl-3,4-dihydroisoquinolines **Ia** and **Ib** [12] with arylhydrazines in an argon atmosphere at ~170–180°C for 0.5–1 h. Compounds **IIa** and **IIb** have been isolated as yellow oily substances darkening in air and stable at room temperature for several days; amidrazone **IIe** can be stored at room temperature for 6 months without visible signs of decomposition . The attempts to isolate intermediate amidrazones **IIc** and **IId** in pure state failed due to their fast oxidation in air, therefore we further used them direct after the synthesis in the cyclization into the target compounds **IIIc** and **IIId**. Amidrazones **IIa–IIe** may exist in two tautomer forms but ^{1}H NMR spectra detect the form shown in the scheme as indicated by the downfield shift of the signal belonging to proton HC^8 [13].

Salts **IIIa–IIIe** are colorless or light-yellow (**IIIb** and **IIIe**) crystalline substances soluble in DMF, DMSO,



I, R = H (**a**), OMe (**b**); **II, III**, Ar = Ph, R = H (**a**), OMe (**b**); Ar = 4-FC_6H_4, R = H (**c**), OMe (**d**); Ar = 4-$NO_2C_6H_4$, R = H (**e**).

sparingly soluble in ethanol, chloroform insoluble in ethyl acatete, toluene, hexane, and water. Their structure was confirmed by elemental analysis, IR and ^{1}H NMR spectra. 2-Aryl-5,5-dimethyl-8,9-di-R-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinolinium tetrafluoroborates **IIIa–IIIe** we plan to use further as precursors of N-heterocyclic carbenes of new structural type. It is evident that the *gem*-dimethyl fragment of the isoquinoline system in these compounds operates as a spatially hindering function indispensable for increasing the stability of the N-heterocyclic carbenes.

3,3-Dimethyl-1-phenylhydrazono-1,2,3,4-tetrahydroisoquinoline (IIa) was obtained by heating 10 mmol of methylsulfanylisoquinoline **Ia** with 10 mmol of phenylhydrazine in an argon atmosphere at ~170–180°C for 30 min. Yield 2.09 g (82%), yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 s (6H, $2CH_3$), 2.81 s (2H, C^4H_2), 5.24 br.s (1H, N^2H), 6.09 br.s (1H, ArNH), 6.82 m (1H, H_{arom}), 7.03 d.d (2H, $H^{6',2'}$, ^3J 6.6, ^4J 1.2 Hz), 7.09–7.41 m (5H, H_{arom}), 8.19 m (1H, H^8).

3,3-Dimethyl-6,7-dimethoxy-1-phenylhydrazono-1,2,3,4-tetrahydroisoquinoline (IIb) was similarly obtained from methylsulfanylisoquinoline **Ib** and phenylhydrazine. Yield 2.36 g (75%), yellow oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 s (6H, $2CH_3$), 2.76 s (2H, C^4H_2), 3.88 s (6H, $2OCH_3$), 5.25 br.s (1H, N^2H), 5.86 br.s (1H, ArNH), 6.60 d (1H, H_{arom}), 6.81 m (1H, $H^{4'}$), 6.99 d (1H, H_{arom}), 7.15 C (1H, H^5), 7.21 m (2H, H_{arom}), 7.72 C (1H, H^8).

3,3-Dimethyl-1-(4-nitrophenylhydrazono)-1,2,3,4-tetrahydroisoquinoline (IIe) was obtained by boiling 10 mmol of thioether **Ia** with 10 mmol of *p*-nitrophenylhydrazine in 60 ml of ethanol for 12 h. Yield 1.35 g (45%), dark-violet crystals, mp 186–187°C (from ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 s (6H, $2CH_3$), 2.82 C (2H, C^4H_2), 6.23 br.s (1H, N^2H), 7.05 d (2H, $H^{6',2'}$), 7.15 d (1H, H^5), 7.28 m (2H, $H^{6,7}$), 8.00 d (1H, $H^{3',5'}$), 8.00 d (1H, $H^{6,7}$), 8.10 d (1H, H^8), 9.46 br.s (1H, ArNH).

2-Aryl-5,5-dimethyl-8,9-di-R-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinolinium tetrafluoroborates IIIa–IIIe. *General procedure.* Into a flask filled with argon equipped with a reflux condenser cooled by an air flow was charged 10 mmol of thioether **Ia** or **Ib** and 10 mmol of an appropriate arylhydrazine, and the mixture was heated to 170–180°C for 30–40 min, then it was cooled, a triple excess of ethyl orthoformate was added to the melt, and 1–2 drops of formic acid as catalyst, and the reaction mixture was boiled for 20–30 min. To the resulting mixture 12 mmol of ammonium tetrafluoroborate was added, 15–20 ml of acetonitrile was poured (to dissolve the inorganic salt), the mixture was boiled for 10 min more, and then acetonitrile was distilled off in a vacuum on a water bath. The residue was diluted with a little ethyl acetate, the precipitated crystals of salts **IIIa–IIIe** were filtered off and recrystallized from methanol.

5,5-dimethyl-2-phenyl-5,6-dihydro-1,2,4-triazolo-[3,4-*a*]isoquinolinium tetrafluoroborate (IIIa). Yield 0.9 g (25%), mp 237–239°C. IR spectrum, ν, cm^{-1}: 1668, 1612, 1596 (C=C), 1572, 1536, 1492 (C=C), 1340, 1288, 1252, 1228, 1196, 1180, 1160, 1048, 1104, 1070, 1026, 976, 924, 876, 846. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.68 s (6H, $2CH_3$), 3.34 s (2H, C^6H_2), 7.54–7.77 m (6H, H_{arom}), 8.04 d.d (2H, $H^{6',2'}$, ^3J 8, ^4J 1.2 Hz), 8.12 d.d (1H, $C^{10}H$, ^3J 8, ^4J 1.8 Hz), 10.97 C (1H, =CH). Found, %: C 59.28; H 4.93; N 11.81. $C_{18}H_{18}N_3^+ \cdot BF_4^-$. Calculated, %: C 59.53; H 4.99; N 11.57.

5,5-dimethyl-8,9-dimethoxy-2-phenyl-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinolinium tetrafluoroborate (IIIb). Yield 0.8 g (19%), mp 269–271°C, light-yellow crystals. IR spectrum, ν, cm^{-1}: 1596 (C=C), 1538, 1494 (C=C), 1348, 1288, 1256 [ν_{as}(C–O–C)], 1224, 1196, 1168, 1084 [ν_s(C–O–C)], 868. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.69 s (6H, $2CH_3$), 3.26 s 2H, C^6H_2), 3.90 s (3H, OCH_3), 3.91 s (3H, OCH_3), 7.15 s (1H, C^7H), 7.55 s (1H, $C^{10}H$), 7.66 m (1H, $H^{4'}$), 7.74 m (2H, $H^{3',5'}$), 8.05 d.d (2H, $H^{2',6'}$, ^3J 8, ^4J 1.5 Hz), 10.88 s (1H, =CH). Found, %: C 56.67; H 5.20; N 9.85. $C_{20}H_{22}N_3O_2^+ \cdot BF_4^-$. Calculated, %: C 56.76; H 5.24; N 9.93.

5,5-dimethyl-2-(4-fluorophenyl)-5,6-dihydro-1,2,4-triazolo[3,4-*a*]-isoquinolinium tetrafluoroborate (IIIc). Yield 1.4 g (32%), mp 270–272°C. IR spectrum, ν, cm^{-1}: 1596 (C=C), 1572, 1538, 1508 (C=C), 1344, 1302, 1252, 1194, 1164, 1064, 976, 844. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.71 s (6H, $2CH_3$), 3.38 s (1H, C^6H_2), 7.57–7.75 m ($2H_{arom}$), 7.73 t ($1H_{arom}$, J 7.8 Hz), 8.15 d (1H, H^{10}, J 7.8 Hz), 8.35 d (2H, $H^{2',6'}$, ^3J 9.3 Hz), 8.61 d (2H, $H^{3',5'}$, ^3J 9.3 Hz), 11.18 s (1H, =CH). Found, %: C 57.00; H 4.29; N 10.93. $C_{18}H_{17}FN^+_3 \cdot BF_4^-$. Calculated, %: C 56.72; H 4.49; N 11.02.

5,5-dimethyl-8,9-dimethoxy-2-(4-fluorophenyl)-5,6-dihydro-1,2,4-triazolo[3,4-*a*]-isoquinolinium tetrafluoroborate (IIId). Yield 0.7 g (16%), mp 236–238°C. IR spectrum, ν, cm^{-1}: 1608 (C=C), 1576, 1540, 1502 (C=C), 1468, 1356, 1288, 1260 [ν_{as}(C–O–C)], 1228, 1192, 1166, 1068 [ν_s(C–O–C)], 984, 976, 916, 872,

860, 848, 816. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.71 s (6H, $2CH_3$), 3.41 s (1H, C^6H_2), 3.92 s (6H, $2OCH_3$), 7.19 s (1H, C^7H), 7.57 s (1H, $C^{10}H$), 7.65 d.d (2H, $H^{2',6'}$, ^3J 8.4, ^4J 2.1 Hz), 8.15 m (2H, $H^{3',5'}$), 10.93 s (1H, =CH). Found, %: C 54.51; H 4.73; N 9.46. $C_{20}H_{21}FN_3O^+_2 \cdot BF_4^-$. Calculated, %: C 54.44; H 4.80; N 9.52.

5,5-dimethyl-2-(4-nitrophenyl)-5,6-dihydro-1,2,4-triazolo[3,4-*a*]isoquinolinium tetrafluoroborate (IIIe). Yield 0.4 g (10%), mp > 300°C. IR spectrum, ν, cm^{-1}: 1604 (C=C), 1520, 1348, 1292, 1244, 1194, 1076, 1032, 976, 860. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.71 s (6H, $2CH_3$), 3.38 s (1H, C^6H_2), 7.62 m (2H, $H^{7,8}$), 7.73 t (1H, H^9, ^3J 8 Hz), 8.16 d (1H, H^{10}), 8.35 d (2H, $H^{2',6'}$, ^3J 9 Hz), 8.61 d (2H, $H^{3'5'}$, ^3J 9 Hz), 11.18 C (1H, =CH). Found, %: C 52.20; H 3.82; N 13.75. $C_{18}H_{17}N_4O^+_2 \cdot BF^-_4$. Calculated, %: C 52.96; H 4.20; N 13.73.

IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury Plus 300 (300 MHz), internal reference HMDS. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol plates, eluent chloroform–acetone, 10:1, development with 0.5% chloranil solution in toluene or in iodine vapor. Elemental analysis was carried out on analyzer Leco CHNS-932. Melting points were measured on a PTP device and were reported without corrections.

The study was carried out under a financial support of the Russian Foundation for Basic Research (grant no. 07-03-96033–Ural).

REFERENCES

1. Nair, V., Bindu, S., and Sreekumar, V., *Angew Chem. Int. Ed.,* 2004, vol. 43, p. 5130.
2. Marion, N., Diez-Gonsбlez, S., and Nolan, S.P., *Angew Chem. Int. Ed*., 2007, vol. 46, p. 2988.
3. Herrmann, W.A., *Angew Chem. Int. Ed.,* 2002, vol. 41, p. 1290.
4. Korotkikh, N.I., Shvaika, O.P., Raenko, G.F., Kiselyov, A.V., Knishevitsky, A.V., Cowley, A.H., Jones, J.N., and Macdonald, C.L.B., *ARKIVOC*, 2005, vol. *viii,* p. 10.
5. *N-Heterocyclic Carbenes in Synthesis*, Nolan, S.P., Ed., New York: Wiley and Sons, 2006.
6. Enders, D. and Balensiefer, T., *Ass. Chem. Res*., 2004, vol. 37, p. 534.
7. Sohn, S. and Bode, J.W., *Angew Chem., Int. Ed.,* 2006, vol. 45, p. 6021.
8. Enders, D., Niemeier, O., and Raabe, G., *Synlett*., 2006, p. 2431.
9. Cйsar, V., Bellemin-Laponnaz, S., and Gade, L.H., *Chem. Soc. Rev.,* 2004, vol. 33, p. 619.
10. Wadamoto, M., Philips, E.M., Reynolds, T.E., and Scheidt, K.A., *J. Am. Chem. Soc.,* 2007, vol. 129, p. 10098.
11. De Alaniz, J.R., Rovis, T. *J. Am. Chem. Soc.,* 2005, vol. 127, p. 6284; Takikawa, H., and Suzuki, K., *Org. Lett.,* 2007, vol. 9, p. 2713.
12. Aleksandrov, B.B., Glushkov, V.A., Glushkova, E.N., Gorbunov, A.A., Shklyaev, V.S., and Shklyaev, Yu.V., *Khim. Geterotsikl. Soedin.,* 1994, p. 511.
13. Shklyaev, Yu.V., Glushkov, V.A., Belogub, N.B., and Misyura, I.L., *Khim. Geterotsikl. Soedin.,* 1996, p. 800.