Click Chemistry with 2-Ethynyl-4,5,6,7-tetrahydroindoles: Towards Functionalized Tetrahydroindole-Triazole Ensembles

Lyubov N. Sobenina,[a] Denis N. Tomilin,[a] Igor A. Ushakov,[a] Albina I. Mikhaleva,[a] J. Sh. Ma,[b] G. Yang,[b] Boris A. Trofimov*[a]

[a] A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, 1 Favorsky Str., 664033 Irkutsk, Russian Federation

[b] Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Photochemistry, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, P. R. of China
Fax +7(3952)419346; E-mail: boris_trofimov@irioch.irk.ru

Received: 02.12.2012; Accepted after revision: 11.01.2013

Abstract: 2-Ethynyl-4,5,6,7-tetrahydroindoles, readily available from 4,5,6,7-tetrahydroindoles and bromoacetylenes on K_2CO_3, when treated with sodium azide in DMSO, afford functionalized tetrahydroindole-triazoles ensembles. The reaction proceeds under mild conditions (room temperature) to give triazoles with acyl or ester moieties in quantitative yields.

Key words: click chemistry, cycloaddition, alkynes, sodium azide, triazoles

The triazole nucleus is one of the most important heterocyclic structures, and is frequently encountered in a number of natural products and medicines,[1] including antimicrobial,[2] anti-inflammatory, analgesic,[3] antitubercular,[4] antiviral,[5] anticancer,[6] anticonvulsant,[7] and antifungal[8] agents. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs, including H_1/H_2 histamine receptor blockers, CNS stimulants, antianxiety agents and sedatives.[9] Recently, some new 1,2,3-triazole derivatives have been reported to inhibit tumor proliferation, invasion, and metastasis.[10] Importantly, they are applied as antimycotics in drugs such as fluconazole, itraconazole, and voriconazole.[11] Triazoles are also used in several industrial fields, such as agrochemicals,[12] corrosion inhibitors,[13] dyes,[14] and optical brighteners.[15]

Further developments in the synthesis of triazoles is clearly of essential importance. Ensembles of triazoles with other heterocycles, particularly with pyrrole or indole rings, possess additional potential to act as promising biologically active compounds and components for high-tech materials. This is supported for instance by the observations that pyrrolyl- and indolyltriazoles have anticancer[6f] and antifungal[16] activities and also by the finding that pyrrolo-triazolophane ensembles are reported to act as receptors for the pyrophosphate anion.[17]

However, the development of synthetic strategies for the preparation of pyrrolyl- or indolyl-triazoles still represents a challenge and remains the subject of a steadily growing number of investigations.

Numerous synthetic methods for the preparation of 1,2,3-triazole derivatives have been developed.[18] Among them, Huisgen 1,3-dipolar cycloaddition between an alkyne and an azide ('click chemistry') is the classical and most extensively used method.[19] However, this method is not so widespread in the synthesis of triazole ensembles with pyrrole or indole rings because of the inaccessibility of starting ethynylpyrroles or ethynylindoles, especially those bearing electron-withdrawing substituents at the triple bond.

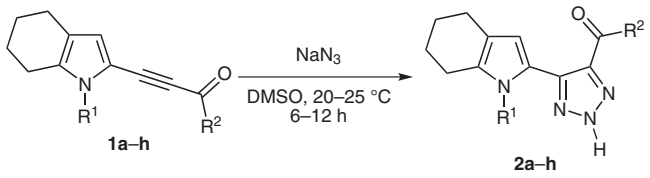
Recently, owing to the discovery of transition-metal- and solvent-free ethynylation of the pyrrole nucleus with electrophilic haloacetylenes on alumina[20] or other active surfaces,[21] 2-ethynylpyrroles, 2-ethynyl-4,5,6,7-tetrahydroindoles and 3-ethynylindoles having electron-withdrawing substituents, including acyl and ester moieties at the triple bond have become readily available. This new methodology has made 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynones **1a**–**d** and 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **1e**–**h** particularly accessible on a large-scale by using 4,5,6,7-tetrahydroindole[22] as starting material. Consequently, the reaction of these compounds with sodium azide might be considered as a short-cut to triazole-containing tetrahydroindole moieties.

These compounds, due to their easy aromatization, might be suitable intermediates for the synthesis of triazole derivatives with the indole function.

Herein, we disclose an efficient method for the synthesis of triazole derivatives with tetrahydroindole moieties. The method comprises the 1,3-dipolar cycloaddition of sodium azide to the C≡C bond of 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynones **1a**–**d** and 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **1e**–**h** (Scheme 1, Table 1).

Because the ease of azide cyclization is governed by polarization of the acetylene, we anticipated that acetylenic ketones **1a**–**d** and acetylenic esters **1e**–**h** would be reactive enough towards sodium azide in spite of possible steric effects from the bulky tetrahydroindole substituents. As expected, these acetylenes easily reacted with sodium azide in dimethyl sulfoxide (DMSO) at room temperature

SYNTHESIS 2013, 45, 0678–0682
Advanced online publication: 01.02.2013
DOI: 10.1055/s-0032-1318149; Art ID: SS-2012-Z0842-OP



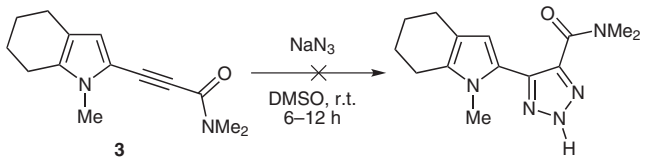
Scheme 1 Synthesis of triazole derivatives **2a**–**h** with tetrahydroindole moieties

Table 1 Synthesis of Triazole Derivatives **2a**–**h**

Pyrrole	R^1	R^2	Yield of **2a**–**h** (%)
1a, **2a**	H	Ph	95
1b, **2b**	Me	Ph	97
1c, **2c**	Bn	Ph	96
1d, **2d**	Vinyl	Ph	94
1e, **2e**	H	OEt	96
1f, **2f**	Me	OEt	94
1g, **2g**	Bn	OEt	97
1h, **2h**	Vinyl	OEt	92

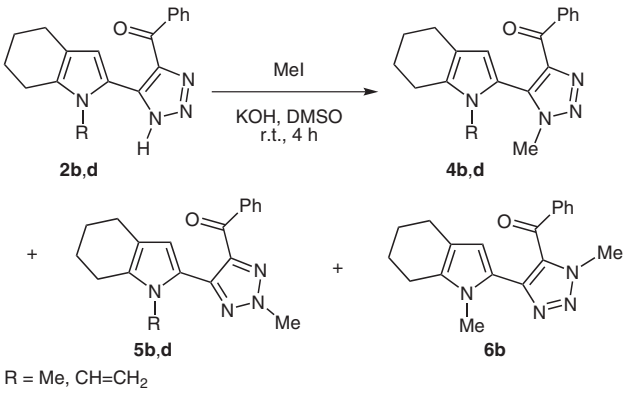
(6–12 h) to give the corresponding triazoles **2a**–**h** in essentially quantitative yield. Acetylenic ketones **1a**–**d** are more reactive towards sodium azide than acetylenic esters **1e**–**h**; the reaction time for the former was 6 hours while 12 hours were necessary for the preparation of triazoles containing the CO_2Et group.

Interestingly, the acetylenic amide **3** appears to be inactive in this cyclization (under analogous conditions), the starting compounds being recovered almost completely, a result that is in agreement with previous reports (Scheme 2).[19b]



Scheme 2 The reaction of acetylenic amide **3** with NaN_3

Triazoles **2b** and **2d** were alkylated with methyl iodide under basic conditions using the KOH/DMSO system to afford a mixture of two possible regioisomers: N-1 (**4b** and **4d**) and N-2 (**5b** and **5d**) substituted 1,2,3-triazoles in approximately 1:1 ratio (Scheme 3). In the case of triazole **2b**, traces of the third regioisomer, triazole **6b**, were detected in the reaction mixture.



Scheme 3 Alkylation of triazoles **2b** and **2d**

The structural assignment of these regioisomers was based on 2D ^1H-^{13}C HMBC, ^1H-^{15}N HMBC, and NOESY NMR experiments.

In conclusion, we have developed a short-cut to functionalized tetrahydroindole-triazole ensembles **2a**–**h** from available 2-ethynyltetrahydroindoles with electron-withdrawing substituents at the triple bond using 'click chemistry' (1,3-dipolar addition of azide anion to the triple bond). The synthesized compounds represent a new family of promising precursors for drug design and are potent building blocks for heterocyclic compounds and anion receptors; furthermore, the properties of the resulting compounds can be easily fine-tuned by changing their functionalities.

IR spectra were obtained with a Bruker Vertex 70 spectrometer (400–4000 cm^{-1}, KBr pellets). ^1H (400.1 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded with a Bruker DPX-400 instrument. The concerted application of ^1H-^1H 2D homonuclear experiments COSY and NOESY and also ^1H-^{13}C 2D heteronuclear experiments HSQC and HMBC were used to differentiate the carbon and proton resonances in all cases. TLC was carried out using TLC Silica gel 60 F254 plates. Elemental analyses were recorded with an EA FLASH 1112 Series (CHN Analyzer) instrument.

1-Phenyl-3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynones **1a**–**d** and ethyl 3-(4,5,6,7-tetrahydroindol-2-yl)-2-propynoates **1e**–**h** were prepared from pyrroles and benzoylbromoacetylene and ethyl bromopropynoate, correspondingly, according to previous reports.[20,21]

Synthesis of Triazoles 2a–h; General Procedure

NaN_3 (75 mg, 1.15 mmol) was carefully stirred in DMSO (20 mL) for 10–15 min, then 2-ethynyl-4,5,6,7-tetrahydriondole **1a**–**h** (1.15 mmol) in DMSO (20 mL) was added and the reaction mixture was stirred for 6–12 h at r.t. (until TLC showed no traces of starting acetylene). The reaction mixture was diluted with H_2O (150 mL) and neutralized with 10% acetic acid. After 10 min, the formed residue was filtered off and washed with H_2O to give pure product.

Phenyl [5-(4,5,6,7-Tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazol-4-yl]methanone (2a)

Yield: 0.319 g (95%); light-brown solid; mp 234–236 °C.

IR (KBr): 3457, 3317, 3280, 3060, 2922, 2845, 1631, 1588, 1536, 1462, 1401, 1305, 1251, 1182, 1145, 1057, 982, 953, 896, 793, 748, 698, 523, 467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.55 (br s, 1 H, N-H), 8.24–8.23 (m, 2 H, *o*-PhH), 7.61–7.57 (m, 1 H, *p*-PhH), 7.52–7.48 (m, 2 H, *m*-PhH), 6.56 (d, *J* = 2.0 Hz, 1 H, H-3), 2.72–2.69 (m, 2 H, CH_2-7),

2.56–2.54 (m, 2 H, CH_2-4), 1.85–1.83 (m, 2 H, CH_2-6), 1.78–1.76 (m, 2 H, CH_2-5).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.9, 138.4, 138.1, 137.4, 132.9, 131.0, 130.5, 128.3, 119.3, 116.1, 110.6, 23.4, 23.0, 22.9, 22.7.

Anal. Calcd. for $C_{17}H_{16}N_4O$: C, 69.85; H, 5.52; N, 19.17. Found: C, 70.02; H, 5.40; N, 19.02.

Phenyl [5-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazol-4-yl]methanone (2b)
Yield: 0.341 g (97%); yellow solid; mp 108–110 °C.

IR (KBr): 3457, 3130, 2929, 2846, 1642, 1534, 1450, 1390, 1315, 1276, 1173, 1142, 980, 902, 803, 753, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.95 (br s, 1 H, N-H), 8.16–8.14 (m, 2 H, *o*-PhH), 7.59–7.56 (m, 1 H, *p*-PhH), 7.48–7.45 (m, 2 H, *m*-PhH), 6.40 (s, 1 H, H-3), 3.44 (s, 3 H, NMe), 2.56–2.54 (m, 2 H, CH_2-7), 2.51–2.49 (m, 2 H, CH_2-4), 1.84–1.82 (m, 2 H, CH_2-5), 1.73–1.71 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 150.4, 141.3, 137.4, 133.1, 132.9, 130.4, 128.3, 118.1, 117.5, 111.5, 31.6, 23.5, 23.1, 23.0, 22.3.

Anal. Calcd. for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.25; H, 5.76; N, 18.46.

Phenyl [5-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazol-4-yl]methanone (2c)
Yield: 0.422 g (96%); yellow solid; mp 58–60 °C.

IR (KBr): 3482, 3094, 2927, 2847, 1653, 1599, 1541, 1447, 1399, 1277, 1141, 985, 905, 801, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.73 (br s, 1 H, N-H), 8.04–8.02 (m, 2 H, *o*-PhH), 7.57–7.55 (m, 1 H, *p*-PhH), 7.44–7.42 (m, 2 H, *m*-PhH), 7.23–7.19 (m, 3 H, *m*,*p*-PhH-CH_2), 6.86–6.84 (m, 2 H, *o*-PhHCH_2), 6.56 (s, 1 H, H-3), 5.20 (s, 2 H, CH_2Ph), 2.53–2.51 (m, 2 H, CH_2-7), 2.46–2.44 (m, 2 H, CH_2-4), 1.79–1.77 (m, 2 H, CH_2-5), 1.73–1.71 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 141.5, 138.6, 137.3, 133.03, 133.0, 132.6, 130.4, 128.5, 128.2, 126.9, 125.9, 118.5, 118.2, 112.7, 47.8, 23.4, 23.1, 22.9, 22.2.

Anal. Calcd. for $C_{24}H_{22}N_4O$: C, 75.37; H, 5.80; N, 14.65. Found: C, 75.75; H, 5.92; N, 14.25.

Phenyl [5-(1-Vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazol-4-yl]methanone (2d)
Yield: 0.344 g (94%); yellow solid; mp 132–134 °C.

IR (KBr): 3481, 3092, 3055, 2930, 2849, 1633, 1599, 1561, 1457, 1424, 1286, 1251, 1168, 1142, 993, 902, 802, 748, 691 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.30 (br s, 1 H, N-H), 8.07–8.05 (m, 2 H, *o*-PhH), 7.56–7.54 (m, 1 H, *p*-PhH), 7.43–7.41 (m, 2 H, *m*-PhH), 6.67 (dd, *J* = 8.7, 16.0 Hz, 1 H, NCH), 6.51 (s, 1 H, H-3), 4.77 (d, *J* = 8.7 Hz, 1 H, CH=CH_2), 4.75 (d, *J* = 16.0 Hz, 1 H, CH=CH_2), 2.59–2.57 (m, 2 H, CH_2-7), 2.50–2.48 (m, 2 H, CH_2-4), 1.79–1.77 (m, 2 H, CH_2-5), 1.72–1.70 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.1, 141.3, 138.3, 137.3, 133.1, 132.6, 130.8, 130.4, 128.2, 119.9, 117.2, 114.4, 105.9, 23.7, 23.3, 23.1, 23.0.

Anal. Calcd. for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.48; H, 5.55; N, 17.79.

Ethyl 5-(4,5,6,7-Tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazole-4-carboxylate (2e)
Yield: 0.287 g (96%); light-brown solid; mp 182–184 °C.

IR (KBr): 3302, 3125, 3082, 2929, 2846, 1690, 1612, 1557, 1479, 1414, 1352, 1304, 1251, 1138, 999, 841, 785, 686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.07 (br s, 1 H, N-H of triazole), 11.01 (s, 1 H, N-H of pyrrole), 6.62 (d, *J* = 2.1 Hz, 1 H, H-3), 4.39 (q, *J* = 7.2 Hz, 2 H, OCH_2), 2.65–2.63 (m, 2 H, CH_2-7), 2.48–2.46 (m, 2 H, CH_2-4), 1.83–1.81 (m, 2 H, CH_2-6), 1.72–1.70 (m, 2 H, CH_2-5), 1.33 (t, *J* = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 136.8, 131.4, 130.1, 119.7, 115.5, 109.8, 61.7, 23.6, 23.1, 23.0, 22.7, 14.1.

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 60.04; H, 6.42; N, 21.29.

Ethyl 5-(1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazole-4-carboxylate (2f)
Yield: 0.296 g (94%); yellow solid; mp 44–46 °C.

IR (KBr): 3432, 3184, 3159, 2930, 2847, 1725, 1611, 1553, 1445, 1382, 1294, 1236, 1129, 1027, 838, 787, 643 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.07 (br s, 1 H, N-H), 6.46 (s, 1 H, H-3), 4.38 (q, *J* = 7.1 Hz, 2 H, OCH_2), 3.47 (s, 3 H, NMe), 2.56–2.54 (m, 2 H, CH_2-7), 2.51–2.50 (m, 2 H, CH_2-4), 1.84–1.82 (m, 2 H, CH_2-6), 1.73–1.71 (m, 2 H, CH_2-5), 1.35 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.2, 139.1, 134.2, 132.3, 117.8, 117.7, 111.8, 61.4, 31.6, 23.6, 23.2, 23.1, 22.4, 14.2.

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.68; H, 6.65; N, 20.05.

Ethyl 5-(1-Benzyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazole-4-carboxylate (2g)
Yield: 0.390 g (97%); yellow solid; mp 52–54 °C.

IR (KBr): 3435, 3200, 3137, 2927, 2849, 1725, 1608, 1539, 1448, 1406, 1294, 1185, 1122, 1039, 787, 729, 700, 640 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.39 (br s, 1 H, NH), 7.21–7.14 (m, 3 H, *m*,*p*-PhH), 6.84–6.82 (m, 2 H, *o*-PhH), 6.63 (s, 1 H, H-3), 5.19 (s, 2 H, CH_2Ph), 4.36 (q, *J* = 7.1 Hz, 2 H, OCH_2), 2.56–2.54 (m, 2 H, CH_2-7), 2.44–2.42 (m, 2 H, CH_2-4), 1.78–1.76 (m, 2 H, CH_2-6), 1.73–1.71 (m, 2 H, CH_2-5), 1.33 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 141.0, 138.8, 134.9, 132.5, 128.6, 127.0, 126.0, 118.5, 118.2, 112.9, 61.6, 47.9, 23.6, 23.2, 23.1, 22.4, 14.2.

Anal. Calcd. for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.21; H, 6.27; N, 15.61.

Ethyl 5-(1-Vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-3*H*-1,2,3-triazole-4-carboxylate (2h)
Yield: 0.303 g (92%); yellow oil.

IR (KBr): 3432, 3239, 3131, 2931, 2850, 1728, 1642, 1558, 1436, 1382, 1293, 1235, 1193, 1134, 1016, 869, 792 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.77 (br s, 1 H, NH), 6.78 (dd, *J* = 8.9, 16.0 Hz, 1 H, NCH), 6.51 (s, 1 H, H-3), 4.82 (d, *J* = 8.9 Hz, 1 H, CH=CH_2), 4.78 (d, *J* = 16.0 Hz, 1 H, CH=CH_2), 4.36 (q, *J* = 7.1 Hz, 2 H, OCH_2), 2.66–2.64 (m, 2 H, CH_2-7), 2.53–2.51 (m, 2 H, CH_2-4), 1.82–1.80 (m, 2 H, CH_2-5), 1.74–1.73 (m, 2 H, CH_2-6), 1.33 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 138.1, 134.6, 131.7, 130.8, 119.5, 117.0, 114.1, 104.6, 61.3, 23.8, 23.2, 22.9, 22.8, 13.9.

Anal. Calcd. for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57. Found: C, 62.78; H, 6.52; N, 19.78.

[1-Methyl-5-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1*H*-1,2,3-triazol-4-yl](phenyl)methanone (4b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.26 (m, 2 H, *o*-PhH), 7.53–7.52 (m, 1 H, *p*-PhH), 7.50–7.48 (m, 2 H, *m*-PhH), 6.06 (s, 1 H, H-3), 4.00 (s, 3 H, N-Me of triazole), 3.20 (s, 3 H, N-Me of pyrrole), 2.56–2.54 (m, 2 H, CH_2-7), 2.50–2.48 (m, 2 H, CH_2-4), 1.84–1.82 (m, 2 H, CH_2-5), 1.73–1.71 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.3 (CO), 144.0 (C-4 of triazole), 138.9 (*p*-Ph), 137.3 (*i*-Ph), 134.9 (C-5 of triazole), 132.5 (C-5), 130.5 (*o*-Ph), 128.1 (*m*-Ph), 118.2 (C-4), 114.9 (C-2), 110.7 (C-3), 35.3 (N-Me of triazole), 31.0 (N-Me of pyrrole), 23.5, 23.2, 23.0, 22.2 (CH_2-4,5,6,7).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –233.9 (NMe of pyrrole), –141.2 (NMe of triazole), –19.0 (N of triazole).

[2-Methyl-5-(1-methyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2*H*-1,2,3-triazol-4-yl](phenyl)methanone (5b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.99 (m, 2 H, *o*-PhH), 7.53–7.51 (m, 1 H, *p*-PhH), 7.50–7.48 (m, 2 H, *m*-PhH), 6.53 (s, 1 H, H-3), 4.21 (s, 3 H, N-Me of triazole), 3.50 (s, 3 H, N-Me of pyrrole), 2.62–2.60 (m, 2 H, CH_2-7), 2.48–2.46 (m, 2 H, CH_2-4), 1.84–1.82 (m, 2 H, CH_2-5), 1.73–1.71 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.1 (CO), 143.5 (C-5 of triazole), 142.1 (C-4 of triazole), 137.7 (*i*-Ph), 132.8 (*p*-Ph), 131.7 (C-5), 130.2 (*o*-Ph), 128.1 (*m*-Ph), 119.8 (C-2), 117.5 (C-4), 111.4 (C-3), 42.2 (N-Me of triazole), 31.7 (N-Me of pyrrole), 23.3, 23.1, 23.0, 22.1 (CH_2-4,5,6,7).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –237.0 (NMe of pyrrole), –136.9 (NMe of triazole), –54.6, –44.2 (N of triazole).

[1-Methyl-5-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-1*H*-1,2,3-triazol-4-yl](phenyl)methanone (4d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20–8.18 (m, 2 H, *o*-PhH), 7.53–7.51 (m, 1 H, *p*-PhH), 7.44–7.42 (m, 2 H, *m*-PhH), 6.52 (dd, *J* = 9.0, 15.9 Hz, 1 H, NCH), 6.19 (s, 1 H, H-3), 4.59 (d, *J* = 9.0 Hz, 1 H, CH=CH_2), 4.53 (d, *J* = 15.9 Hz, 1 H, CH=CH_2), 3.98 (s, 3 H, N-Me), 2.64–2.62 (m, 2 H, CH_2-7), 2.51–2.49 (m, 2 H, CH_2-4), 1.83–1.81 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.2 (CO), 144.3 (C-4 of triazole), 137.2 (*i*-Ph), 135.1 (C-5 of triazole), 132.9 (*p*-Ph), 132.2 (C-5), 130.5 (*o*-Ph), 129.9 (*C*H=CH_2), 128.2 (*m*-Ph), 119.9 (C-4), 114.2 (C-2), 114.0 (C-3), 104.2 (CH=*C*H_2), 35.3 (NMe), 23.5, 23.1, 23.0, 22.9 (CH_2-4,5,6,7).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –213.0 (N of pyrrole), –141.8 (NMe of triazole), –19.6 (N of triazole).

[2-Methyl-5-(1-vinyl-4,5,6,7-tetrahydro-1*H*-indol-2-yl)-2*H*-1,2,3-triazol-4-yl](phenyl)methanone (5d)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.99 (m, 2 H, *o*-PhH), 7.53–7.51 (m, 2 H, *m*-PhH), 7.44–7.42 (m, 1 H, *p*-PhH), 6.81 (dd, *J* = 9.0, 15.9 Hz, 1 H, NCH), 6.45 (s, 1 H, H-3), 4.79 (d, *J* = 15.9 Hz, 1 H, CH=CH_2), 4.68 (d, *J* = 9.0 Hz, 1 H, CH=CH_2), 4.26 (s, 3 H, N-Me), 2.63–2.61 (m, 2 H, CH_2-7), 2.49–2.47 (m, 2 H, CH_2-4), 1.83–1.81 (m, 2 H, CH_2-5), 1.74–1.72 (m, 2 H, CH_2-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.8 (CO), 143.3 (C-5 of triazole), 142.7 (C-4 of triazole), 137.4 (*i*-Ph), 132.9 (*p*-Ph), 131.3 (*C*H=CH_2), 131.2 (C-5), 130.2 (*o*-Ph), 128.2 (*m*-Ph), 119.6 (C-2), 119.4 (C-4), 113.4 (C-3), 104.0 (CH=*C*H_2), 42.4 (NMe), 23.4, 23.2, 23.0, 22.9 (CH_2-4,5,6,7).

^{15}N NMR (40 MHz, $CDCl_3$): δ = –214.9 (N of pyrrole), –136.3 (NMe of triazole), –52.1, –44.2 (N of triazole).

Acknowledgment

The authors thank Presidium of RAS (project No. 5.9.1) for the support of this research. This work was also carried out under financial support of the leading scientific schools by the President of the Russian Federation (Grant NSh-1550.2012).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Kharb, R.; Sharma, P. Ch.; Yar, M. Sh. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1. (b) Singhal, N.; Sharma, P. K.; Dudhe, R.; Kumar, N. *J. Chem. Pharm. Res.* **2011**, *3*, 126.

(2) (a) Bektaş, H.; Karaali, N.; Sahin, D.; Demirbaş, A.; Karaoglu, S. A.; Demirbaş, N. *Molecules* **2010**, *15*, 2427. (b) Sumangala, V.; Poojary, B.; Chidananda, N.; Fernandes, J.; Kumari, N. S. *Arch. Pharmacal. Res.* **2010**, *33*, 1911. (c) Pereira, D.; Fernandes, P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 510.

(3) (a) Savini, L.; Massarelli, P.; Chiasserini, L.; Pellerano, C.; Bruni, G. *Farmaco* **1994**, *49*, 633. (b) Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6057. (c) Ram, J. S. *Rasayan J. Chem.* **2009**, *2*, 706. (d) Rajasekaran, A.; Rajagopal, K. A. *Acta Pharm.* **2009**, *59*, 355.

(4) (a) Singh, B. K.; Yadav, A. K.; Kumar, B.; Gaikwad, A.; Sinha, S. K.; Chaturvedi, V.; Tripathi, R. P. *Carbohydr. Res.* **2008**, *343*, 1153. (b) Wilkinson, B. L.; Long, H.; Sim, E.; Fairbanks, A. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6265. (c) Boechat, N.; Ferreira, V. F.; Ferreira, S. B.; de Lourdes, G.; Ferreira, M.; de C da Silva, F.; Bastos, M. M.; Dos, S.; Costa, M.; Lourenço, M. C.; Pinto, A. C.; Krettli, A. U.; Aguiar, A. C.; Teixeira, B. M.; da Silva, N. V.; Martins, P. R.; Bezerra, F. A.; Camilo, A. L.; da Silva, G. P.; Costa, C. C. *J. Med. Chem.* **2011**, *54*, 5988.

(5) (a) Zhou, L.; Amer, A.; Korn, M.; Burda, R.; Balzarini, J.; De Clercq, E.; Kern, E. R.; Torrence, P. F. *Antiviral Chem. Chemother.* **2005**, *16*, 375. (b) Jordão, A. K.; Afonso, P. P.; Ferreira, V. F.; de Souza, M. C.; Almeida, M. C.; Beltrame, C. O.; Paiva, D. P.; Wardell, S. M.; Wardell, J. L.; Tiekink, E. R.; Damaso, C. R.; Cunha, A. C. *Eur. J. Med. Chem.* **2009**, *44*, 3777. (c) Pérez-Castro, I.; Caamaño, O.; Fernández, F.; García, M. D.; López, C.; de Clercq, E. *ARKIVOC* **2010**, *(iii)*, 152.

(6) (a) Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. *Eur. J. Med. Chem.* **2002**, *37*, 511. (b) Holla, B. S.; Veerendra, B.; Shivananda, M. K.; Poojary, B. *Eur. J. Med. Chem.* **2003**, *38*, 759. (c) Reddy, D. M.; Srinivas, J.; Chashoo, G.; Saxena, A. K.; Kumar, H. M. S. *Eur. J. Med. Chem.* **2011**, *46*, 1983. (d) Singh, P.; Raj, R.; Kumar, V.; Mahajan, M. P.; Bedi, P. M.; Kaur, T.; Saxena, A. K. *Eur. J. Med. Chem.* **2012**, *47*, 594. (e) Li, X.; Lin, Y.; Yuan, Y.; Liu, K.; Qian, X. *Tetrahedron* **2011**, *67*, 2299. (f) Kumar, D.; Narayanam, M. K.; Chang, K.-H.; Shah, K. *Chem. Biol. Drug Des.* **2011**, *77*, 182.

(7) Kaur, H.; Kumar, S.; Lata, S.; Saxena, K. K.; Kumar, A. *Eur. J. Med. Chem.* DOI: 10.1016/j.ejmech.2010.07.047.

(8) (a) Aher, N. G.; Pore, V. S.; Mishra, N. N.; Kumar, A.; Shukla, P. K.; Sharma, A.; Bhat, M. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759. (b) Wei, J.-J.; Jin, L.; Wan, K.; Zhou, Ch.-He. *Bull. Korean Chem. Soc.* **2011**, *32*, 229. (c) Sangshetti, J. N.; Lokwani, D. K.; Sarkate, A. P.; Shinde, D. B. *Chem. Biol. Drug Des.* **2011**, *78*, 800. (d) Morzherin, Y.; Prokhorova, P. E.; Musikhin, D. A.; Glukhareva, T. V.; Fan, Z. *Pure Appl. Chem.* **2011**, *83*, 715. (e) Shalini, K.; Kumar, N.; Drabu, S.; Sharma, P. K. *Beilstein J. Org. Chem.* **2011**, *7*, 668. (f) Wang, X. L.; Wan, K.; Zhou, C. H. *Eur. J. Med. Chem.* **2010**, *45*, 4631.

(9) Schreier, E. *Helv. Chim. Acta* **1976**, *59*, 585.

(10) Dong, H.-S.; Wei, K.; Wang, Q.-L.; Quan, B.; Zhang, Z.-Y. *J. Chin. Chem. Soc.* **2000**, *47*, 343.

(11) (a) *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck Co. Inc: White House Station, NJ, **1996**. (b) Haber, J. *Cas. Lek. Cesk.* **2001**, *140*, 596.

(12) (a) Mothes-Wagner, U.; Reitze, H. K.; Seitz, K. A. *Exp. Appl. Acarol.* **1990**, *8*, 27. (b) Pechacek, J. T. US Patent 6015826 A, **1998**; *Chem. Abstr.* **2000**, *132*, 89499. (c) Jacobson, R. M.; Mulvihill, M. J.; Liu, Ch.; Liu, X. US Patent 6258751, **2001**; *Chem. Abstr.* **2001**, *134*, 42133.

(13) (a) Quraishi, M. A.; Danish, J. *J. Am. Oil Chem. Soc.* **2000**, *77*, 1107. (b) Quraishi, M. A.; Sardar, R. *Corrosion* **2002**, *58*, 748.

(14) (a) Khanmohammadi, H.; Erfantalab, M. *Spectrochim. Acta, Part A* **2012**, *86*, 39. (b) Smith, N. W.; Alonso, A.; Brown, C. M.; Dzyuba, S. V. *Biochem. Biophys. Res. Commun.* **2010**, *391*, 1455.

(15) Guenther, D.; Nestler, H. J.; Roesher, G.; Schinzel, E. Ger. Pat. 615164, **1980**; *Chem. Abstr.* **1980**, *93*, 73786.

(16) (a) Bijev, A. T.; Prodanova, P. *Chem. Heterocycl. Compd.* **2007**, *43*, 306. (b) Padmavathi, V.; Nagendra, Mohan. A. V.; Thriveni, P.; Shazia, A. *Eur. J. Med. Chem.* **2009**, *44*, 2313.

(17) Sessler, J. L.; Cai, J.; Gong, H.-Y.; Yang, X.; Arambula, J. F.; Hay, B. P. *J. Am. Chem. Soc.* **2010**, *132*, 14058.

(18) (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786. (b) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526. (c) Barluenga, J.; Valdés, C.; Beltrán, G.; Escribano, M.; Aznar, F. *Angew. Chem. Int. Ed.* **2006**, *45*, 6893. (d) Jiang, Y.; Kuang, C.; Yang, Q. *Synthesis* **2010**, 4256. (e) Kolarovič, A.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 2613.

(19) (a) Journet, M.; Cai, D.; Kowal, J. J.; Larsen, R. D. *Tetrahedron Lett.* **2001**, *42*, 9117. (b) Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077. (c) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (d) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225. (e) Li, J.; Wang, D.; Zhang, Y.; Li, J.; Chen, B. *Org. Lett.* **2009**, *11*, 3024. (f) Wu, L.-Y.; Xie, Y.-X.; Chen, Z.-S.; Niu, Y.-N.; Liang, Y.-M. *Synlett* **2009**, 1453. (g) Zhang, W.; Kuang, C.; Yang, Q. *Synthesis* **2010**, 283.

(20) (a) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513. (b) Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A.; Elokhina, V. N.; Voronov, V. K.; Trofimov, B. A. *Synthesis* **2004**, 2736. (c) Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I.; Ushakov, I. A.; Vasil'tsov, A. M.; Ivanov, A. V.; Trofimov, B. A. *Tetrahedron Lett.* **2006**, *47*, 7139. (d) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Demenev, A. P.; Mikhaleva, A. I.; Ushakov, I. A.; Vakul'skaya, T. I.; Petrova, O. V. *Russ. J. Org. Chem.* **2006**, *42*, 1348. (e) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Ushakov, I. A.; Petrova, O. V.; Tarasova, O. A.; Volkova, K. A.; Mikhaleva, A. I. *Synthesis* **2007**, 447. (f) Trofimov, B. A.; Sobenina, L. N.; Demenev, A. P.; Stepanova, Z. V.; Petrova, O. V.; Ushakov, I. A.; Mikhaleva, A. I. *Tetrahedron Lett.* **2007**, *48*, 4661.

(21) (a) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Vakul'skaya, T. I.; Kazheva, O. N.; Aleksandrov, G. G.; Dyachenko, O. A.; Mikhaleva, A. I. *Tetrahedron* **2008**, *64*, 5541. (b) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Petrova, O. V.; Ushakov, I. A.; Mikhaleva, A. I. *Tetrahedron Lett.* **2008**, *49*, 3946.

(22) (a) Trofimov, B. A.; Mikhaleva, A. I. *N-Vinylpyrroles*; Nauka: Novosibirsk, **1984**. (b) Trofimov, B. A. In *Advances in Heterocyclic Chemistry*; Vol. 51; Academic Press: New York, **1990**, 177. (c) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Yu.; Ryapolov, O. A.; Platonov, V. B. Russian Patent RU 2297410, **2006**; *Chem. Abstr.* **2008**, *146*, 462130.

