Synthesis of 2-aryl-6-nitro-4-(*vic*-triazol-1-yl)-1*H*-indoles from *E*-2,4,6-trinitrostilbenes*

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A method is developed for the preparation of 4-(*vic*-triazol-1-yl)indoles that involves replacement of the *ortho*-NO_2 group in *E*-2,4,6-trinitrostilbenes by an azido group, condensation of *E*-2-azido-4,6-dinitrostilbenes with acetylacetone, replacement of the second *ortho*-NO_2 group in the resulting stilbenes by N_3, and subsequent thermolysis of the azide into the target indole. The reactions of *E*-2-azido-4,6-dinitrostilbenes with cyclohexane-1,3-dione gave *E*-2-amino-4,6-dinitrostilbenes, which can be used for selective transformation of the *ortho*-NO_2 group into an amino group in *E*-2,4,6-trinitrostilbenes.

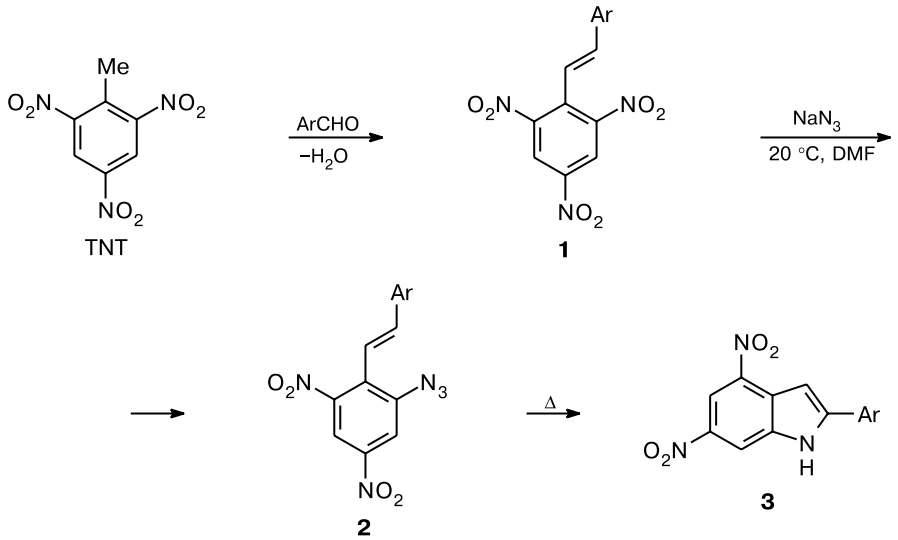
Key words: indoles, *E*-2,4,6-trinitrostilbenes, 2,4,6-trinitrotoluene, nucleophilic substitution of the nitro group, azides, 1,2,3-triazoles, 1,3-dipolar cycloaddition, intramolecular cyclization, diazo transfer.

The present work was performed as a part of the program on the study of chemistry of 2,4,6-trinitrotoluene (TNT) aimed at creating scientific fundamentals and technologies for its use as a multipurpose starting material.[1,2] *E*-2,4,6-Trinitrostilbenes **1** belong to the most accessible TNT derivatives; these can be prepared in high yields by condensation of TNT with aromatic aldehydes under the conditions of the Knoevenagel reaction (see Ref. 3 and references therein). In the framework of the aforementioned program, we are studying the transformations of *E*-2,4,6-trinitrostilbenes **1** in order to synthesize polyfunctional benzoannelated heterocycles based on them.

Earlier,[3—5] we have demonstrated that the *ortho*-NO_2 group in stilbenes **1** is regioselectively replaced under the action of anionic nucleophiles, which allowed the use of a β-arylvinyl fragment in an intramolecular cyclization. For instance, thermolysis of *E*-2-azido-4,6-dinitrostilbenes **2** obtained by the action of NaN_3 on stilbenes **1** gave 2-aryl-4,6-dinitroindoles **3** in high yields (see Ref. 3) (Scheme 1).

* Dedicated to Academician N. K. Kochetkov on the occasion of his 90th birthday.

Scheme 1



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The goal of the present work was to develop a method for the synthesis of a rare type of indoles with the 1,2,3-triazolyl substituent from stilbenes **1**.

Previously,[6—8] in our studies on sequential replacement of nitro groups in 1,3,5-trinitrobenzene (TNB) under the action of NH-azoles in the presence of inorganic bases, we have found that an N-azolyl substituent (1,2,3- and 1,2,4-triazolyl) is similar to the nitro group in activating effect in S_NAr reactions of the *meta*-NO_2 group.

The accumulated data altogether allowed us to choose two possible versions of the synthesis of the target 4-(*vic*-triazol-1-yl)indoles. The first version involves replacement of the *ortho*-NO_2 group in stilbenes **1** by a triazole to give 4,6-dinitro-2-(*vic*-triazol-1-yl)stilbenes **4** (Scheme 2, pathway *a*), replacement of the second *ortho*-NO_2 group in compound **4** under the action of NaN_3, and thermolysis of the resulting azide **5** into the target indole **6**.

However, NH-azoles (1,2,3- and 1,2,4-triazoles and benzotriazole) could not replace the nitro group in stilbenes **1**: no replacement occurred at moderate temperatures (20—60 °C) in dipolar aprotic solvents (DMF, *N*-methylpyrrolidone, DMSO, *etc.*) in the presence of inorganic bases, while an increase in the temperature (≥80 °C) resulted only in strong resinification.

The second version involves 1,3-dipolar cycloaddition of the *E*-2-azido-4,6-dinitrostilbenes **2** prepared earlier[3] to appropriate dipolarophiles (*e.g.*, 1,3-dicarbonyl compounds[9]) to give the corresponding 4,6-dinitro-2-(*vic*-1,2,3-triazol-1-yl)stilbenes **4** and their subsequent transformations.

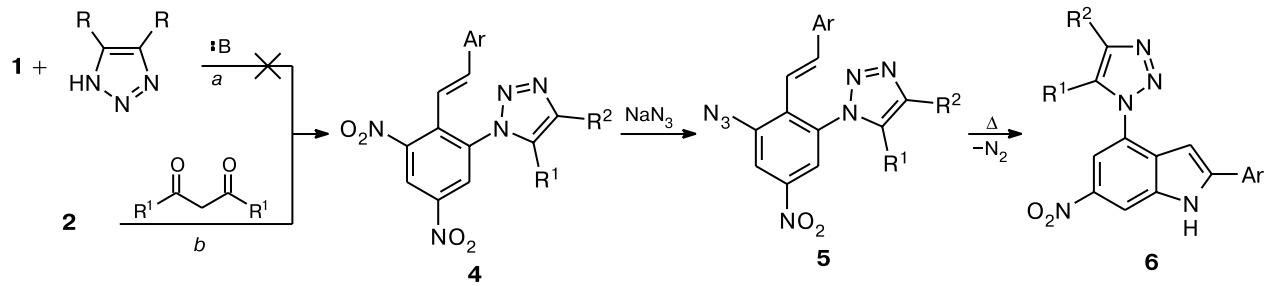
We studied the reactions of azides **2** with different types of dipolarophiles: vinyl ethers, 1,3-diketones, and diethyl acetylenedicarboxylate. An unambiguous reaction proved to occur only with acetylacetone (see Scheme 2, pathway *b*). Heating of equimolar amounts of *E*-2-azido-4,6-dinitrostilbenes **2a**—**c** with acetylacetone in EtOH in the presence of Et_3N gave *E*-6-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2,4-dinitrostilbenes **4a**—**c** in 40—75% yields (Scheme 3). As noted above, the N-triazolyl fragment is similar to the nitro group in the activating effect in S_NAr reactions of the *meta*-NO_2 group. Indeed, the nitro group in stilbenes **4a**—**c** is replaced under the action of NaN_3 under the same mild conditions as in stilbenes **1** (DMF, ~20 °C). The reaction is also regiospecific: only the *ortho*-NO_2 group is replaced to give *E*-6-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-azido-4-nitrostilbenes **5a**—**c** in 60—80% yields (see Scheme 3). According to ^1H NMR data, the reaction is unambiguous: in all cases, the reaction of NaN_3 with stilbenes **4a**—**c** yielded single products. The fact of replacement of the *ortho*-NO_2 group in stilbenes **4a**—**c** was proved by thermolysis of *ortho*-azidostilbenes **5a**—**c**: when heated in ethylene glycol at 160—180 °C, they liberated nitrogen to form the target indoles, namely, 4-(4-acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-aryl-6-nitro-1*H*-indoles **6a**—**c**, in high yields (see Scheme 3). Thus, we developed a novel method for the synthesis of 4-(*vic*-triazol-1-yl)indoles.

It should be noted that the reactions of *ortho*-azidostilbenes **2a**—**c** with a cyclic 1,3-dicarbonyl compound (cyclohexane-1,3-dione) occur differently than with acetylacetone. Here, the azido group is replaced by an amino group rather than an N-*vic*-triazolyl fragment; *i.e.*, the azido group is formally reduced to give *E*-2-amino-4,6-dinitrostilbenes **7a**—**c** (see Scheme 3). Owing to the satisfactory yields of *ortho*-aminostilbenes **7** (45—85%), this process can be regarded as a two-step preparative method for selective transformation of the *ortho*-NO_2 group in *E*-2,4,6-trinitrostilbenes **1** into an amino group: first, the *ortho*-NO_2 group is replaced under the action of NaN_3 and then the azido group is transformed into an amino group in the reaction of *ortho*-azidostilbenes **2** with cyclohexane-1,3-dione.

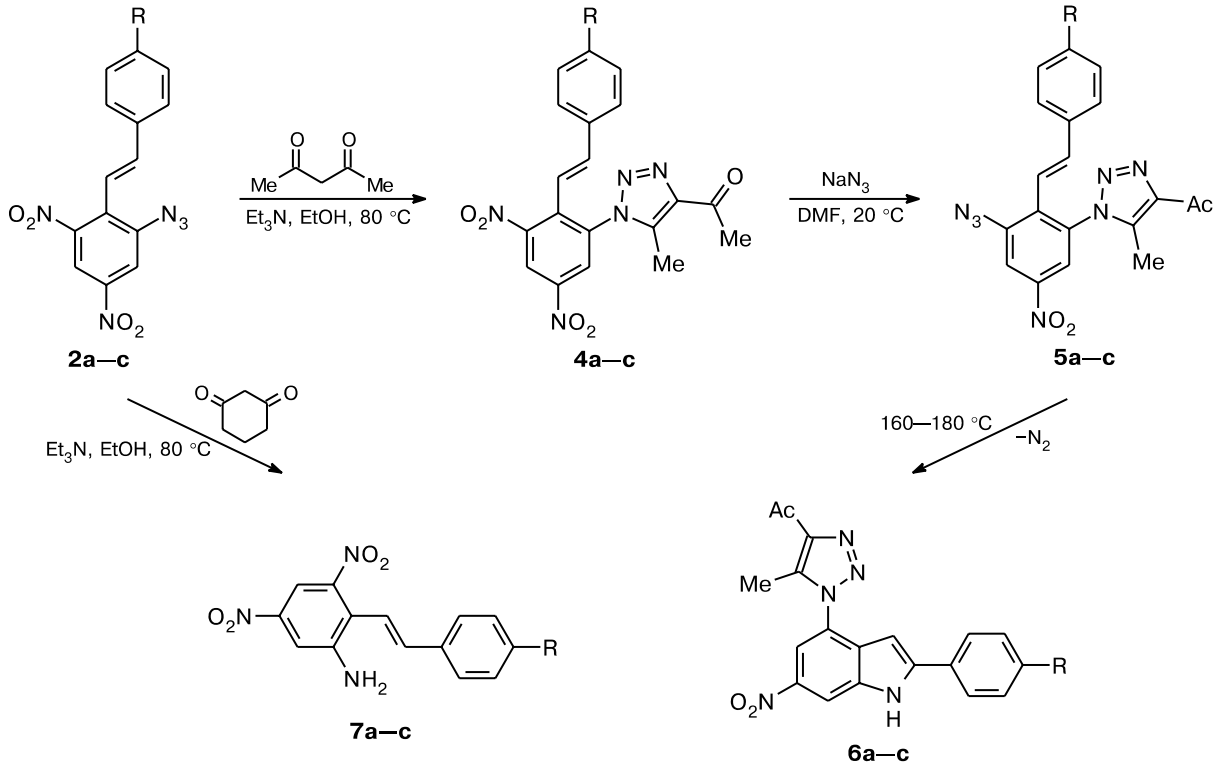
The formation of the amino group from the azido group in the presence of dipolarophiles containing a reactive methylene group (1,3-dicarbonyl compounds, benzyl cyanides, malononitrile, ethyl cyanoacetate, *etc.*) is well known[10] and suggests that diazo transfer occurs instead of 1,3-dipolar addition: a methylene compound is converted into a diazo derivative, and the azido group is transformed into an amino group (Scheme 4).

Such a process is characteristic of those substrates in which an aromatic azido group is bound to a strongly electron-deficient aromatic ring (*e.g.*, some azidotriazines, azidopyrimidines, picryl azide, *etc.*[10]). Among 1,3-dicarbonyl compounds, cyclic diketones are more prone to

Scheme 2

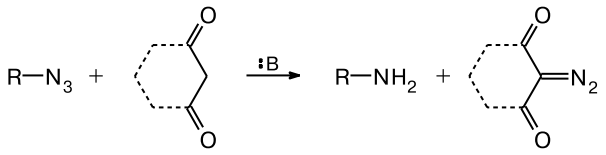


Scheme 3



R = H (**a**), Cl (**b**), OMe (**c**)

Scheme 4



diazo transfer than their acyclic analogs,[11,12] which was observed in our case.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AM-300 instruments, respectively. Chemical shifts are referenced to Me_4Si. Mass spectra (EI, 70 eV) were recorded on an MS-30 instrument (Kratos). Melting points were determined on a Boetius hot stage (heating rate 4 deg min^{-1}).

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2,4-dinitrostilbenes 4 (general procedure). Triethylamine (5 mmol) was added to a solution of *E*-2-azido-4,6-dinitrostilbene **2** [3] (10 mmol) and acetylacetone (10 mmol) in EtOH (20 mL). The mixture was refluxed for 3 to 4 h (TLC) and then cooled. The precipitate that formed was filtered off and recrystallized from MeCN—EtOH (1 : 1).

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2,4-dinitrostilbene (4a). The yield was 57%, m.p. 135—137 °C. Found (%): C, 57.79; H, 3.62; N, 17.86. $C_{19}H_{15}N_5O_5$. Calculated (%): C, 58.01; H, 3.84; N, 17.80. ^{1}H NMR (DMSO-d_6), δ: 9.10, 8.92 (both s, 1 H each, $C_6H_2(NO_2)_2$); 7.41—7.29 (m, 5 H, Ph); 7.12, 6.26 (both d, 1 H each, CH, $^3J_{trans}$ = 15.7 Hz); 2.62, 2.42 (both s, 3 H each, Me). MS, *m/z*: 393 $[M]^+$.

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-4′-chloro-2,4-dinitrostilbene (4b). The yield was 41%, m.p. 167—169 °C. Found (%): C, 53.25; H, 3.12; Cl, 8.07; N, 16.49. $C_{19}H_{14}ClN_5O_5$. Calculated (%): C, 53.34; H, 3.30; Cl, 8.29; N, 16.37. ^{1}H NMR ($CDCl_3$), δ: 8.28, 8.01 (both s, 1 H each, $C_6H_2(NO_2)_2$); 7.30, 7.19 (both d, 2 H each, C_6H_4Cl, ^3J = 6.7 Hz); 6.67—6.54 (m, 2 H, CH=CH); 2.76, 2.38 (both s, 3 H each, Me). MS, *m/z*: 427 $[M]^+$.

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-4′-methoxy-2,4-dinitrostilbene (4c). The yield was 73%, m.p. 177—178 °C. Found (%): C, 56.52; H, 3.77; N, 16.23. $C_{20}H_{17}N_5O_6$. Calculated (%): C, 56.74; H, 4.05; N, 16.54. ^{1}H NMR (DMSO-d_6), δ: 9.09, 8.89 (both s, 1 H each, $C_6H_2(NO_2)_2$); 7.30 (d, 2 H, C_6H_4OMe, ^3J = 7.1 Hz); 6.98—6.87 (m, 3 H, C_6H_4OMe + CH); 6.18 (d, 1 H, CH, $^3J_{trans}$ = 15.5 Hz); 3.79 (s, 3 H, OMe); 2.64, 2.41 (both s, 3 H each, Me). MS, *m/z*: 423 $[M]^+$.

***E*-2-Amino-4,6-dinitrostilbenes 8 (general procedure).** Triethylamine (5 mmol) was added to a solution of 2-azido-4,6-dinitrostilbene **2** (10 mmol) and cyclohexane-1,3-dione (10 mmol) in EtOH (50 mL). The mixture was refluxed for 5 h (TLC) and cooled. The precipitate that formed was filtered off.

2-Amino-4,6-dinitrostilbene (7a). The yield was 46%, m.p. 124—125 °C. Found (%): C, 58.57; H, 3.94; N, 14.37. $C_{14}H_{11}N_3O_4$. Calculated (%): C, 58.95; H, 3.89; N, 14.73.

^{1}H NMR (DMSO-d_6), δ: 7.79—7.74 (m, 2 H, $C_6H_2(NO_2)_2$); 7.62—7.56 (m, 2 H, Ph); 7.47—7.32 (m, 3 H, Ph); 7.13, 6.82 (both d, 1 H each, =CH, $^3J_{trans}$ = 16.3 Hz); 6.44 (s, 2 H, NH_2). MS, *m/z*: 285 $[M]^+$.

2-Amino-4′-chloro-4,6-dinitrostilbene (7b). The yield was 73%, m.p. 140—141 °C. Found (%): C, 52.69; H, 2.86; Cl, 10.84; N, 12.93. $C_{14}H_{10}ClN_3O_4$. Calculated (%): C, 52.60; H, 3.15; Cl, 11.09; N, 13.14. ^{1}H NMR (DMSO-d_6), δ: 7.79—7.76 (m, 2 H, $C_6H_2(NO_2)_2$); 7.64 (d, 2 H, C_6H_4Cl, ^3J = 6.9 Hz); 7.47 (d, 2 H, C_6H_4Cl, ^3J = 6.7 Hz); 7.14 (d, 1 H, CH, $^3J_{trans}$ = 16.2 Hz); 6.79 (d, 1 H, CH, $^3J_{trans}$ = 16.3 Hz); 6.46 (s, 2 H, NH_2). MS, *m/z*: 319 $[M]^+$.

2-Amino-4′-methoxy-4,6-dinitrostilbene (7c). The yield was 83%, m.p. 129—131 °C. Found (%): C, 56.88; H, 4.36; N, 13.07. $C_{15}H_{13}N_3O_5$. Calculated (%): C, 57.14; H, 4.16; N, 13.33. ^{1}H NMR (DMSO-d_6), δ: 7.78—7.74 (m, 2 H, $C_6H_2(NO_2)_2$); 7.55 (d, 2 H, C_6H_4OMe, ^3J = 6.9 Hz); 7.02—6.90 (m, 3 H, C_6H_4OMe + CH); 6.7 (d, 1 H, CH, $^3J_{trans}$ = 16.7 Hz); 6.37 (s, 2 H, NH_2); 3.79 (s, 3 H, OMe). MS, *m/z*: 315 $[M]^+$.

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-azido-4-nitrostilbenes 5 (general procedure). Sodium azide (0.31 g, 4.8 mmol) was added to a stirred solution of compound **4** (4 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature for 4 h (TLC) and then poured into cold water. The precipitate that formed was filtered off and recrystallized from MeCN.

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-azido-4-nitrostilbene (5a). The yield was 60%, m.p. 165—167 °C (decomp.). Found (%): C, 58.42; H, 3.60; N, 24.61. $C_{19}H_{15}N_7O_3$. Calculated (%): C, 58.61; H, 3.88; N, 25.18. ^{1}H NMR (DMSO-d_6), δ: 8.39, 8.32 (both s, 1 H each, $C_6H_2(NO_2)_2$); 7.41—7.30 (m, 5 H, Ph); 6.79—7.76 (m, 2 H, CH=CH); 2.63, 2.37 (both s, 3 H each, Me). MS, *m/z*: 361 $[M]^+ - N_2$.

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-azido-4′-chloro-4-nitrostilbene (5b). The yield was 66%, m.p. 101—103 °C. Found (%): C, 53.81; H, 3.03; Cl, 7.96; N, 22.84. $C_{19}H_{14}ClN_7O_3$. Calculated (%): C, 53.85; H, 3.33; Cl, 8.37; N, 23.13. ^{1}H NMR (DMSO-d_6), δ: 8.40, 8.31 (both s, 1 H each, $C_6H_2(NO_2)_2$); 7.40—7.34 (m, 2 H, C_6H_4Cl); 6.73—7.69 (m, 2 H, CH=CH); 2.67, 2.38 (both s, 3 H each, Me). MS, *m/z*: 395 $[M]^+ - N_2$.

6-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-azido-4′-methoxy-4-nitrostilbene (5c). The yield was 81%, m.p. 190—193 °C (decomp.). Found (%): C, 57.20; H, 3.89; N, 23.50. $C_{20}H_{17}N_7O_4$. Calculated (%): C, 57.28; H, 4.09; N, 23.38. ^{1}H NMR (DMSO-d_6), δ: 8.35, 8.29 (both s, 1 H each, $C_6H_2(NO_2)_2$); 7.29, 6.93 (both d, 2 H each, C_6H_4OMe, ^3J = 7.0 Hz); 6.65, 6.52 (both d, 1 H each, =CH, $^3J_{trans}$ = 16.4 Hz); 3.77 (s, 3 H, OMe); 2.68, 2.32 (both s, 3 H each, Me). MS, *m/z*: 391 $[M]^+ - N_2$.

4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-aryl-6-nitro-1*H*-indoles 6 (general procedure). A stirred suspension of azide **5** (0.5 g) in ethylene glycol (30 mL) was heated to 160—180 °C and kept at this temperature until nitrogen ceased to evolve (~30 min). The mixture was poured into ice and the precipitate that formed was filtered off and recrystallized from MeCN.

4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-6-nitro-2-phenyl-1*H*-indole (6a). The yield was 73%, m.p. 295—297 °C. Found (%): C, 62.87; H, 3.92; N, 19.02. $C_{19}H_{15}N_5O_3$. Calculated (%): C, 63.15; H, 4.18; N, 19.38. ^{1}H NMR (DMSO-d_6), δ: 12.83 (s, 1 H, NH); 8.52, 8.18 (both s, 1 H each, $C_6H_2(NO_2)$); 8.02—7.96 (m, 2 H, Ph); 7.60—7.42 (m, 3 H, Ph); 6.97 (s, 1 H, CH); 2.72, 2.50 (both s, 3 H each, Me). MS, *m/z*: 361 $[M]^+$.

4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-(4-chlorophenyl)-6-nitro-1*H*-indole (6b). The yield was 68%, m.p. 217—219 °C. Found (%): C, 57.43; H, 3.64; Cl, 9.11; N, 17.52. $C_{19}H_{14}ClN_5O_3$. Calculated (%): C, 57.66; H, 3.57; Cl, 8.96; N, 17.69. ^{1}H NMR (DMSO-d_6), δ: 12.90 (s, 1 H, NH); 8.51, 8.17 (both s, 1 H each, $C_6H_2(NO_2)$); 8.03, 7.62 (both d, 2 H each, C_6H_4Cl, ^3J = 6.7 Hz); 7.01 (s, 1 H, CH); 2.72, 2.50 (both s, 3 H each, Me). MS, *m/z*: 395 $[M]^+$.

4-(4-Acetyl-5-methyl-1*H*-1,2,3-triazol-1-yl)-2-(4-methoxyphenyl)-6-nitro-1*H*-indole (6c). The yield was 83%, m.p. 137—139 °C. Found (%): C, 61.12; H, 4.50; N, 17.81. $C_{20}H_{17}N_5O_4$. Calculated (%): C, 61.38; H, 4.38; N, 17.89. ^{1}H NMR (DMSO-d_6), δ: 12.73 (s, 1 H, NH); 8.48, 8.11 (both s, 1 H each, $C_6H_2(NO_2)$); 7.93, 7.11 (both d, 2 H each, C_6H_4OMe, ^3J = 6.7 Hz); 6.82 (s, 1 H, CH); 3.83 (s, 3 H, OMe); 2.70, 2.50 (both s, 3 H each, Me). MS, *m/z*: 391 $[M]^+$.

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