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Synthesis of (1-substituted 1,2,3-triazol-4-yl)-7-deazapurines

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A simple synthesis of 2-phenyl-6-(1-substituted 1,2,3-triazol-4-yl)- and 2,6-bis(1-phenyl 1,2,3-triazol-4-yl)-9-methyl-7-deazapurines from 2,6-dichloro-9-methyl-7-deazapurine has been developed.

Keywords: 7-deazapurine, pyrrolo[2,3-*d*]pyrimidine, Sonogashira reaction, Stille reaction, 1,2,3-triazole

INTRODUCTION

Deazapurine (pyrrolo[2,3-*d*]pyrimidine) [1] occupies an exclusive place, mainly due to its structural resemblance to biogenic purines. Many 7-deazapurine derivatives display a broad spectrum of biological activities, such as antimycobacterial [2], antimicrobial [3], inhibition of protein kinases [4–7] and dihydrofolate reductase [8], antagonist effects to receptors [9, 10] and cytostatic effect [11, 12]. Moreover, some conjugated 7-deazapurine derivatives exhibit strong fluorescence and are promising candidates as functional materials for optoelectronic applications [13]. Since the discovery of Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) by Sharpless [14] and Meldal [15], 1,4-disubstituted 1,2,3-triazole has also become an increasingly common motif in organic compounds possessing valuable properties. Various heterocycles containing an embedded 1,2,3-triazole moiety have found application in fields of bioconjugation [16], material science [17], chemical sensors [18], drug discovery [19] and related areas [20] including supramolecular chemistry [21]. However, triazolyl-7-deazapurines have received very little attention in the current literature. To the best of our knowledge, there are only few reports on the synthesis of 7-deazapurines containing 1,2,3-triazole fragment. The triazole moiety was mainly constructed on a pyrrole ring of 7-deazapurine [22], and only recently, the synthesis of several examples of 7-deazapurines with a triazole moiety at the pyrimidine ring has been published [23].

In this context and continuing our work dedicated to the development of efficient methods for the synthesis of functionalized pyrimidine [24] and fused pyrimidine heterocycles [25], we were interested in the synthesis of 7-deazapurine – 1,2,3-triazole conjugates as potential functional materials [26]. Herein, we present the synthesis of novel 6- and 2,6-bis(1-substituted 1,2,3-triazol-4-yl)-7-deazapurines.

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EXPERIMENTAL

Melting points were determined in open capillaries with a digital melting point IA9100 series apparatus (ThermoFischer Scientific). All reactions and purity of the synthesized compounds were monitored by TLC using Silica Gel 60 F_{254} aluminum plates (Merck). Visualization was accomplished by UV light. Column chromatography was performed using Silica Gel 60 (0.040–0.063 mm) (Merck). NMR spectra were recorded on a Bruker Ascend 400 spectrometer. ^{1}H NMR and ^{13}C NMR were referenced to residual solvent peaks. Infrared spectra (IR) were recorded on a FTIR spectrophotometer Spectrum BX II (Perkin Elmer). High Resolution Mass Spectrometry (HRMS) analyses were carried out on a Dual-ESI Q-TOF 6520 (Agilent Technologies) mass spectrometer.

Initial compound – 2,6-dichloro-9-methyl-7-deazapurine (**1**) – was synthesized according to the procedure described in [27]. Aryl azides R-N_3 were prepared according to the literature [28].

2-Chloro-9-methyl-6-[(trimethylsilyl)ethynyl]- (2) and 9-methyl-2,6-bis[(trimethylsilyl)ethynyl]-7-deaza-9*H*-purines (3)

To a mixture of compound **1** (400 mg, 1.98 mmol) $Pd(PPh_3)_2Cl_2$ (55 mg, 0.079 mmol), CuI (12 mg, 0.04 mmol) and PPh_3 (41 mg, 0.158 mmol) in Et_3N (13 mL) was heated to 60 °C under argon atmosphere and trimethylsilylacetylene (403 μL, 2.85 mmol) was added under stirring. The reaction mixture was stirred at 45–50 °C for 3 h under argon atmosphere, then poured into water and extracted with chloroform. The organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using chloroform as an eluent to give compounds **2** and **3**. Compound **2**: yield 396 mg (76%), m. p. = 131–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.33 (s, 9H, $Si(CH_3)_2$), 3.86 (s, 3H, NCH_3), 6.63 (d, 1H, *J* = 3.6 Hz, 7-H), 7.20 (d, 1H, *J* = 3.6 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 0.4, 31.4, 99.5, 100.2, 103.8, 119.1, 131.1, 143.0, 152.5, 153.2. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{12}H_{15}ClN_3Si$: 264.0718; found: 264.0725. Compound **3**: yield 19.4 mg (3%), m. p. = 109–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.30 [s, 9H, $Si(CH_3)_3$], 0.31 [s, 9H, $Si(CH_3)_3$], 3.88 (s, 3H, NCH_3), 6.63 (d, *J* = 3.5 Hz, 1H, 7-H), 7.26 (d, *J* = 3.5 Hz, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: –0.4, –0.3, 31.4, 91.6, 100.1, 100.2, 102.4, 103.4, 119.3, 131.6, 141.9, 144.7, 151.0. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{17}H_{24}N_3Si_2$: 326.1503; found: 326.1508.

2-Chloro-6-ethynyl-9-methyl-7-deaza-9*H*-purine (4)

To a solution of compound **2** (270 mg, 1.025 mmol) in methanol (10 ml) KF (93.5 mg, 1.23 mmol) was added. The reaction mixture was stirred at room temperature for 20–30 min and poured into water. The product was extracted with chloroform, the organic layer was dried with sodium sulfate, filtered and evaporated to dryness. The residue was purified by column chromatography using chloroform as an eluent to give 169 mg (86%) of compound **4**; m. p. = 166 °C dec. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.58 (s, 1H, ≡CH), 3.87 (s, 3H, NCH_3), 6.65 (d, 1H, *J* = 3.6 Hz, 7-H), 7.23 (d, 1H, *J* = 3.6 Hz, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 31.5, 79.1, 84.2, 100.0, 119.4, 131.5, 142.3, 152.6, 153.2. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_9H_7ClN_3$: 192.0323; found: 192.0328.

2,6-Bis(ethynyl)-9-methyl-7-deaza-9*H*-purine (5)

Compound **5** was synthesized from compound **3** using 2.5 equiv. KF according to the procedure described for the synthesis of compound **4**. Yield 98%, yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.09 (s, 1H, ≡CH), 3.53 (s, 1H, ≡CH), 3.90 (s, 3H, NCH_3), 6.67 (d, *J* = 3.5 Hz, 1H, 7-H), 7.31 (d, *J* = 3.5 Hz, 1H, 8-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 31.4, 73.9, 79.5, 82.6, 83.3, 100.0, 119.9, 132.2, 141.2, 144.0, 151.0. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{11}H_8N_3$: 182.0173; found: 182.0176.

6-(1-Aryl-1,2,3-triazol-4-yl)-2-chloro-9-methyl-7-deaza-9*H*-purines (6a–c). *General procedure*

To a solution of acetic acid (33 μL, 0.581 mmol) and ethyl(diizopropyl)amine (101 μL, 0.581 mmol) in dichloromethane (2 mL) the corresponding arylazide (1.11 mmol), compound **4** (100 mg, 0.523 mmol) and CuI (20 mg, 0.052 mmol) were added under argon atmosphere. The reaction mixture was stirred at room temperature under argon for 24 h, then poured into the 25% solution of aqueous ammonia and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude products **6a–c** were purified by column chromatography using chloroform/ethyl acetate as a gradient eluent.

2-Chloro-9-methyl-6-(1-phenyl-1,2,3-triazol-4-yl)-7-deaza-9*H*-purine (6a)

Yield 71%, m. p. = 210–213 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.92 (s, 3H, NCH_3), 7.28 (d, *J* = 3.5 Hz, 1H, 7-H),), 7.49 (d, *J* = 3.5 Hz, 1H, 8-H), 7.91–7.51 (m, 5H, Ph), 8.90 (s, 1H, CH). ^{13}C NMR (101 MHz, $CDCl_3$), δ, ppm: 31.4, 102.6, 113.6, 120.5, 122.6, 129.2, 129.9, 131.0, 136.7, 147.5, 149.9, 153.2, 153.6. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{15}H_{12}ClN_6$: 311.0806; found: 311.0733.

6-(1-Benzyl-1,2,3-triazol-4-yl)-2-chloro-9-methyl-7-deaza-9*H*-purine (6b)

Yield 70%, m. p. = 180 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.35 (s, 2H, CH_2), 3.81, (s, 3H, NCH_3), 7.18 (d, 1H, *J* = 3.5 Hz, 7-H), 7.35–7.45 (m, 5H, Ph), 7.67 (d, 1H, *J* = 3.6 Hz, 8-H), 9.05 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 31.6, 53.7, 101.5, 113.1, 126.8, 128.6, 128.8, 129.3, 133.1, 136.2, 146.1, 150.2, 152.5, 153.3. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{16}H_{14}ClN_6$: 325.0963; found: 325.0968.

2-Chloro-9-methyl-6-[1-(2-methylbenzyl)-1,2,3-triazol-4-yl)-7-deaza-9*H*-purine (6c)

Yield 88%, m. p. = 191–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.33 (s, 3H, CH_3), 3.88 (s, 3H, NCH_3), 5.65 (s, 2H, CH_2), 7.20–7.34 (m, 5H, Ph, 7-H), 7.44 (d, *J* = 3.5 Hz, 1H, 8-H), 8.21 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 19.0, 31.4, 52.7, 102.6, 113.4, 124.4, 126.8, 129.5, 130.0, 130.8, 131.2, 131.8, 137.1, 147.1, 150.3, 153.1, 153.5. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{17}H_{16}ClN_6$: 339.1119; found: 339.1116.

2,6-Bis(1-phenyl-1,2,3-triazol-1-yl)-9-methyl-7-deaza-9*H*-purine (7)

Compound **7** was synthesized from compound **5** using a double amount of phenylazide according to the general procedure described for the synthesis of compounds **6a–c**. Yield 65%, m. p. = 152 °C dec. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 4.02 (s, 3H, NCH_3), 7.34 (d, *J* = 3.5 Hz, 1H, 7-H), 7.56 (m, 7H, Ph, 8-H), 9.07 (s, 1H, CH), 8.79 (s, 1H, CH), 7.92 (dd, *J* = 12.7, 5.0 Hz, 4H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 31.3, 102.4, 113.9, 120.6, 120.8, 122.3, 122.5, 128.9, 129.0, 129.8, 129.9, 131.1, 136.9, 137.1, 148.6, 148.6, 149.1, 151.5, 152.8. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{23}H_{18}N_9$: 420.1680; found: 420.1697.

9-Methyl-2-phenyl-6-(1-phenyl-1,2,3-triazol-4-yl)-7-deaza-9*H*-purine (8a)

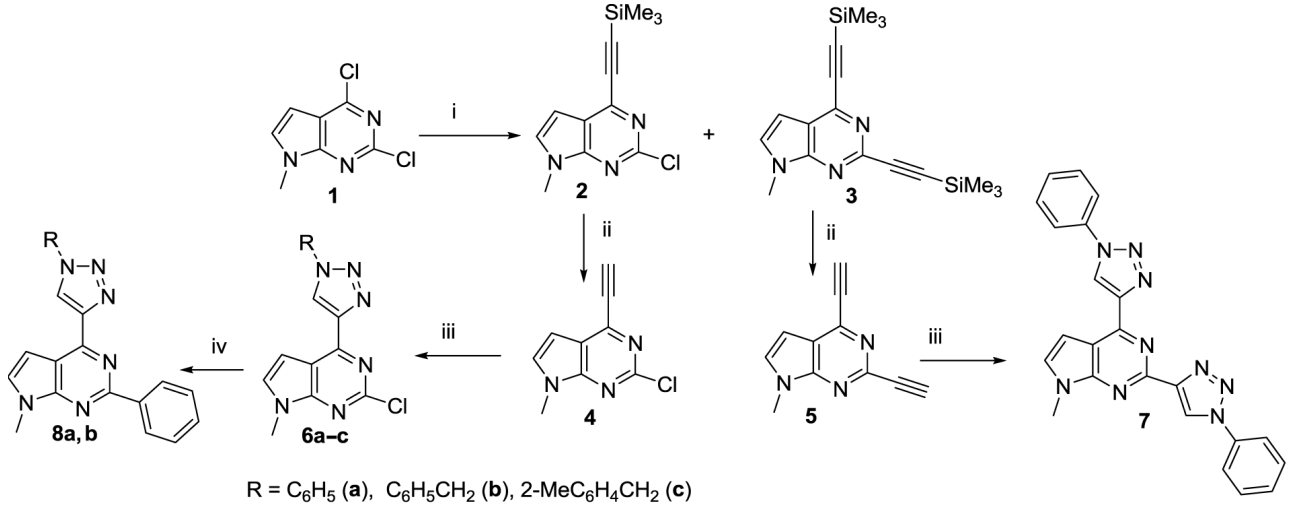
Compound **6a** (75 mg, 0.241 mmol), $Pd(PPh_3)_2Cl_2$ (16.8 mg, 0.024 mmol), $AsPh_3$ (29.5 mg, 0.096 mmol), dioxane (2 ml) and tributyl(phenyl)stannane (197 μL, 0.603 mmol) were placed in a screw-cap vial equipped with a magnetic stir bar. The vial was purged with argon and the reaction mixture was stirred vigorously at 120 °C for 70 h under argon atmosphere. After cooling to room temperature, the reaction mixture was poured into water and extracted with chloroform. The organic layer was dried over Na_2SO_4, filtered, and chloroform was removed under reduced pressure. The residue was purified by column chromatography using chloroform as an eluent to give 83.9 mg (99%) of compound **8a**, m. p = 164–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.98 (s, 3H, NCH_3), 7.29 (d, *J* = 2.9 Hz, 1H, 7-H), 7.38–7.66 (m, 7H, Ph, 8-H), 7.92 (dd, *J* = 7.5, 1.2 Hz, 2H, Ph), 8.65 (dd, *J* = 8.3, 1.3 Hz, 2H, Ph), 9.00 (s, 1H, CH). ^{13}C NMR ($CDCl_3$), δ, ppm: 31.0, 102.1, 113.2, 120.7, 122.2, 128.1, 128.4, 129.0, 129.7, 129.9, 130.7, 137.0, 138.6, 147.9, 148.9, 153.2, 157.4. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{21}H_{17}N_6$: 353.1509; found: 353.1512.

6-(1-Benzyl-1,2,3-triazol-4-yl)-9-methyl-2-phenyl-7-deaza-9*H*-purine (8b)

Compound **8b** was synthesized from compound **6b** according to the procedure described for the synthesis of compound **8a**. Yield 89%, m. p. = 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 3.94 (s, 3H, NCH_3), 5.66 (s, 2H, CH_2), 7.23 (d, 1H, *J* = 3.6 Hz, 7-H), 7.36–7.53 (m, 9H, Ph, 8-H), 8.46 (s, 1H, CH), 8.59 (d, 2H, *J* = 7.2, Ph). ^{13}C NMR (100 MHz, $CDCl_3$), δ, ppm: 30.9, 54.3, 101.9, 113.0, 115.4, 124.1, 127.9, 128.1, 128.3, 129.2, 129.5, 130.5, 134.5, 138.8, 148.2, 148.8, 153.1, 157.3. HRMS (ESI), m/z $[M+H]^+$: calculated for $C_{22}H_{19}N_6$: 367.1117; found: 367.1116.

RESULTS AND DISCUSSION

Synthesis of the title compounds can be achieved by the Cu(I)-catalyzed cycloaddition reaction of azides with terminal alkynes. For the introduction of alkynyl groups onto aromatic or heteroaromatic scaffolds the Sonogashira cross-coupling is one of the most straightforward methods [29]. Therefore, for the synthesis of the required ethynyl-7-deazapurines, the Sonogashira coupling of 2,6-dichloro-7-deazapurine (**1**) was attempted. Compound **1** reacted with a slight excess of trimethylsilylethyne in triethylamine under gentle heating (45–50 °C) in the presence of bis(triphenylphosphine) palladium chloride $[Pd(PPh_3)_2Cl_2]$ as a catalyst to give a mixture of mono and double cross-coupling products **2** and **3** (Scheme).



Scheme. Reagents and conditions: i is trimethylsilylethyne, $Pd(PPh_3)_2Cl_2$, CuI, Ph_3P, Et_3N, 45–50 °C, 3 h. argon; ii is KF, MeOH, rt, 20–30 min.; iii is R-N_3, CuI, DIPEA, AcOH, CH_2Cl_2, rt, 24 h, argon; iv is tributyl(phenyl)stannane, $Pd(PPh_3)_2Cl_2$, $AsPh_3$, dioxane, 120 °C, 70 h, argon

The main reaction product appeared to be 2-chloro-6-(trimethylsilyl)ethynyl-7-deazapurine (**2**). It was obtained in 76% yield, while 2,6-bis(trimethylsilylethynyl)-7-deazapurine (**3**) was isolated in 3% yield. The Sonogashira coupling of 2,6-dichloro-7-deazapurine first occurs at position 6 of deazapurine. The evidence of such regioselectivity is supported by our earlier investigations on the Sonogashira reaction of compound **1** with arylethynes [30]. In order to increase the yield of bis[(trimethylsilyl)ethynyl] derivative **3** higher reaction temperature and prolonged reaction time was applied, however, only formation of tars was observed. Increase of the amount of trimethylsilylethyne up to 2.5 equiv. also did not have any effect on the yield of compound **3**. In all experiments compound **3** was formed as a minor product and its yield did not exceed 3%. Attempts to synthesize compound **3** by the Stille reaction of compound **1** with tributyl(ethynyl) stannane did not give satisfactory results: at room temperature compound **1** did not react with ethynyltributylstannane, while at higher temperatures the tarry reaction mixture was formed and no product could be isolated. Removal of a trimethylsilyl group in compounds **2** and **3** was carried out with KF in methanol at room temperature to give 2-chloro-6-ethynyl- (**4**) and 2,6-bis(ethynyl)-7-deazapurines **5** in 86% and 98% yields, respectively. Further, compound **4** was subjected to the CuAAC reaction with phenyl- and benzyl azides using CuI/DIPEA/AcOH as a catalyst system to afford 2-chloro-9-methyl-6-(1-substituted 1,2,3-triazol-4-yl)-7-deazapurines **6a–c** in 70–88% yield. By analogy, the CuAAC reaction of compound **5** with the double amount of phenyl azide furnished 2,6-bis(1-phenyl-1,2,3-triazol-4-yl)-9-methyl-7-deazapurine (**7**) in 65% yield.

Further, the arylation reaction of 7-deazapurines **6** was studied. Taking into consideration advantages of the Suzuki coupling over other palladium-catalyzed cross-coupling reactions [31] the synthesis of compounds **8** by the reaction of compound **6a** with phenylboronic acid under the Suzuki coupling conditions was investigated. However, in contrast to our earlier obtained results on the synthesis of 2,6-diaryl-7-deazapurines [13a, b] the 2-chlorine group in compounds **6** appeared to be unreactive in the Suzuki coupling with phenylboronic acid. For example, employment of different catalyst systems [$Pd(PPh_3)_4/K_3PO_4$; $Pd(OAc)_2$/tricyclohexylphosphonium tetrafluoroborate/K_3PO_4; $Pd(OAc)_2$/2-(dicyclohexylphosphino)biphenyl/K_3PO_4], solvents (dioxane, N,N-dimethylacetamide) and different reaction temperatures did not give positive results. The desired product **8a** was formed in a negligible amount or the reaction did not take place at all. Only heating of compound **6a** with 2.5 equivalents of phenylboronic acid for 2 hours in dioxane at 180 °C under microwave irradiation in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% 2-(dicyclohexylphosphino)biphenyl, and 3 equiv. K_3PO_4 furnished compound **8a** in low 36% yield. Consequently, in order to develop a method for the synthesis of 2-aryl-6-(1,2,3-triazol-4-yl)-7-deazapurines (**8**) the Stille coupling was studied. After a brief optimization we found the reaction conditions leading to the formation of 2-aryl-7-deazapurines **8** in high yields. Compounds **6a, b** reacted with tributyl(phenyl)stannane in dioxane at 120 °C in the presence of $Pd(PPh_3)_2Cl_2/AsPh_3$ as a catalyst system to give 2-phenyl derivatives **8a, b** in excellent 99% and 89% yields, respectively. It is worth mentioning that at least 10 mol% $Pd(PPh_3)_2Cl_2$ as a catalyst should be used to produce cross-coupling products **8** in high yields.

CONCLUSIONS

In summary, novel (1-substituted 1,2,3-triazol-4-yl)-7-deazapurines have been successfully synthesized and characterized. The proposed protocol includes the Sonogashira coupling of 2,6-dichloro-9-methyl-7-deazapurine with (trimethylsilyl)ethyne, the removal of a trimethylsilyl group and the subsequent CuAAC reaction of the obtained alkynyl-7-deazapurines with phenyl and benzyl azides. The synthesis of 2-phenyl-6-(1,2,3-triazol-4-yl)-7-deazapurines was accomplished by the Stille cross-coupling reaction of 2-chloro-6-(1,2,3-triazol-4-yl)-7-deazapurines with tributyl(phenyl) stannane in the presence of $Pd(PPh_3)_2Cl_2/AsPh_3$ as a catalyst system. The results presented here may find use in pharmaceutical and materials research programs.

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(1-PAKEISTŲ 1,2,3-TRIAZOL-4-IL)-7-DEAZAPURINŲ SINTEZĖ

S a n t r a u k a

Pradiniu junginiu naudojant 2,6-dichlor-9-metil-7-deazapuriną susintetinti nauji (1-pakeisti 1,2,3-triazol-4-il)-9-metil-7-deazapurinai. Pasiūlytas sintezės kelias susideda iš 2,6-dichlor-9-metil-7-deazapurino Sonogashira reakcijos su (trimetilsilil)etinu, (trimetilsilil)grupės pašalinimo ir gautų etinil-7-deazapurinų CuAAC reakcijų su fenil- ir benzilazidais. 2-Fenil-6-(1,2,3-triazol-4-il)-7-deazapurinai susintetinti 2-chlor-6-(1-pakeistų 1,2,3-triazol-4-yl)-7-deazapurinų Stille kryžminio jungimo reakcija su tributil(fenil)stananu, naudojant katalitinę sistemą $Pd(PPh_3)_2Cl_2/AsPh_3$.