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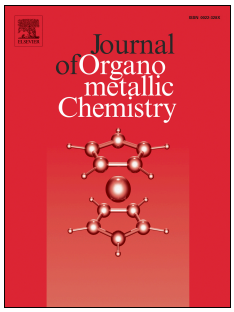

Antimony–lithium exchange reaction: Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles by triazolyllithium with electrophiles

Mizuki Yamada, Mio Matsumura, Masatoshi Kawahata, Yuki Murata, Naoki Kakusawa, Kentaro Yamaguchi, Shuji Yasuike

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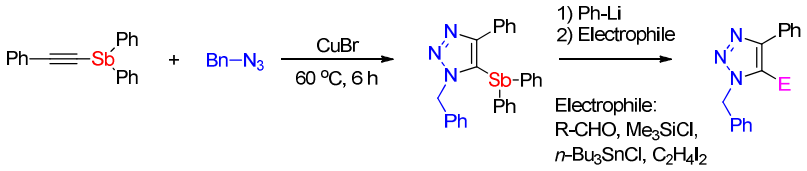
Graphical Abstract:



Note

Antimony–lithium exchange reaction: synthesis of 1,4,5-trisubstituted-1,2,3-triazoles by triazolyllithium with electrophiles

Mizuki Yamada,[a] Mio Matsumura,[a] Masatoshi Kawahata,[b] Yuki Murata,[a] Naoki Kakusawa,[c] Kentaro Yamaguchi,[b] Shuji Yasuike [a,*]

[a] *School of Pharmaceutical Sciences, Aichi Gakuin University, 1-100 Kusumoto-cho, Chikusa-ku, Nagoya 464-8650, Japan*

[b] *Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University, 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan*

[c] *Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan*

*Corresponding authors.

Address: School of Pharmaceutical Sciences, Aichi Gakuin University, 1-100 Kusumoto-cho, Chikusa-ku, Nagoya 464-8650, Japan

Tel: +81-52-757-6774

E-mail address: s-yasuik@dpc.agu.ac.jp (S. Yasuike)

ABSTRACT

Trisubstituted 5-stibano-1*H*-1,2,3-triazoles **3** was synthesized by the Cu-catalyzed [3+2] cycloaddition of ethynylstibane **1** with benzyl azide **2** in the presence of CuBr (5 mol%) under aerobic conditions. 5-Stibanotriazole **3** was treated with an equimolecular amount of phenyllithium (PhLi) in anhydrous THF under argon atmosphere at -78 °C. Subsequent treatment with various electrophiles formed 1,4,5-trisubstituted-1,2,3-triazoles **5** containing a benzyl moiety. This reaction is a novel example of an antimony (Sb) – lithium (Li) exchange reaction for the functionalization of heterocycles.

Keywords:

Antimony–lithium exchange reaction

5-Stibano-1,2,3-triazole

1,4,5-Trisubstituted-1,2,3-triazole

Phenyllithium

Cu-catalyzed azide-alkyne cycloaddition

Highlights:

5-Stibano-1,2,3-triazole was prepared by the regioselective CuAAC of ethynylstibane with benzyl azide.

Fully substituted 1,2,3-triazoles were prepared by the reaction of electrophiles with triazolyllithium.

This reaction is a novel example of an Sb-Li exchange reaction for the functionalization of heterocycles.

1. **Introduction**

1,2,3-Triazoles are important heterocycles, serving as key functional groups in many bioactive molecules and pharmaceuticals [1, 2]. Among these, 1,4,5-trisubstituted-1,2,3-triazoles have attracted interest as target molecules because of their use as reagents with biological activities. For instance, SST0287CL1 **I** [3] exhibits heat shock protein 90 inhibition, sulfur-containing triazole **II** [4] is a potential herbicide with antifungal activity, triazole **III** [5] behaves as a potent inhibitor of human aromatase, and triazole derivative having isoxazolyl **IV** [6] is a potent non-pseudo-substrate inhibitor of O^6-alkylguanine-DNA-methyltransferase (Fig. 1). Consequently, a general method for the synthesis of fully substituted 1,2,3-triazoles would be a valuable addition to existing synthetic strategies [7]. 1,4,5-Trisubstituted-1,2,3-triazoles have been synthesized *via* functionalization of 1,2,3-triazoles by exploiting the reactivity of substrates that possess heavier main-group elements such as Bi and Te at the C5-position. Fokin et al. reported the reaction of 5-bismuthano-1,2,3-triazoles with electrophiles such as acyl chlorides, diphosgene, sulfuryl chloride, and halogens to form the corresponding fully substituted 1,2,3-triazoles [8]. Stefani et al. have developed a derivatization protocol that exploits Sonogashira- and Suzuki-type cross-coupling reactions of 5-tellanyl-1,2,3-triazoles [9, 10]. In addition, they reported the Te-Li exchange reaction and functionalization of 5-(*n*-butyltellanyl)-1,4-diphenyl-1,2,3-triazole to afford 1,4,5-trisubstituted-1,2,3-triazoles [10]. Metal-lithium exchange reactions that generate organolithium compounds are very important strategies in organic synthesis, and it is well known that organometallic compounds containing heavier main-group elements such as Sn and Te are excellent precursors for metal-lithium exchange reactions [11-13]. Heteroatom-Li exchange reactions of group 15 elements such as Sb and Bi have been known for over 60 years [14-17]. However, their reactivities and synthetic efficiencies remain underexplored. Recently, Yamago et al. reported Sb- and Bi-metal exchange reactions of organoantimony and bismuth compounds, respectively, with organolithium, and their application to the synthesis of a functionalized polymer [18]. On the other hand, we recently reported the synthesis of 5-stibano-1,2,3-triazoles such as 1-benzyl-5-(di-*p*-tolylstibano)-4-phenyl-1,2,3-triazole by regioselective Cu-catalyzed azide-alkyne

cycloaddition (CuAAC) of alkynylstibane with organic azides [19]. As a continuation of our studies on 1,2,3-triazoles containing an antimony group, we now report the synthesis of fully substituted 1,2,3-triazoles having benzyl moiety by the reaction of electrophiles with the key lithium intermediate **4** formed following an Sb-Li exchange reaction. This reaction constitutes a novel examples of an Sb-Li exchange reaction for the functionalization of heterocycle, and the reaction proceeds without impairing the benzyl position of the substrate.

Fig 1

2. Results and discussion

2.1 Synthesis and molecular structure of 1-benzyl-5-(diphenylstibano)-4-phenyl-1,2,3-triazole

Novel starting material **3** was prepared in 80% yield by the regioselective CuAAC of ethynylstibane **1** with benzyl azide **2**. The reaction proceeded in the presence of CuBr (5 mol%) at 60 °C under aerobic conditions, following a similar procedure previously reported by us (Scheme 1) [19]. The molecular structure of compound **3** was confirmed by their spectral techniques (^{1}H and ^{13}C NMR, MS). The regiochemistry of 5-stibanotriazole **3** was confirmed by single-crystal X-ray analysis (Fig. 2). Table 1 shows the selected bond lengths and angles. The central antimony atom exhibited trigonal pyramidal structure with Sb–C bond lengths ranging 2.148 Å and C–Sb–C angles between 96.07° and 99.13°. These bond lengths and angles were similar to Ph_3Sb (2.143-2.169 Å, 96.0-98.0°) [20]. The bond lengths and angles of the triazole ring also showed values similar to 1-benzyl-4-phenyl-1,2,3-triazole [21]. Moreover, the crystal structure revealed intramolecular π-π interaction. One phenyl ring on antimony atom and benzyl group adopt a parallel-displaced structure, with distances of 3.755 Å between the centroids of the two phenyl rings (Ph1-Ph2).

Scheme 1

Fig 2

Table 1

2.2 Antimony–lithium exchange reaction followed by trapping with electrophile

First, the optimal experimental conditions for the Sb-Li exchange reaction of **3** with organolithium reagents such as *n*-BuLi, *sec*-BuLi, MeLi, lithium diisopropylamide (LDA), lithium 2,2,6,6-tetramethylpiperidide (LiTMP), and PhLi were determined. The generation of lithium intermediate **4** was confirmed by the isolation of product **5a** upon quenching the reaction with iodomethane. The results including reaction conditions are summarized in Table 2. Several available organolithium reagents were screened at -78 °C in THF (entries 1-6). In terms of yield, PhLi was found to be the best reagent for this reaction, producing 86% of the expected product **5a**, and triphenylstibane as a by-product in 63% yield (entry 6). Other organolithium reagents were inefficient and afforded complex mixtures. The reaction was found to be sensitive to reaction temperature, with the reaction by PhLi at -20 °C and -40 °C giving inferior results. These reactions also gave complex mixtures including compounds in which the benzyl position was methylated (entries 7, 8). Thus, the optimum reaction conditions were determined to be as followed: 5-stibanotriazole **3** was treated with an equimolecular amount of PhLi in anhydrous THF under argon atmosphere at -78 °C. Subsequent quenching with iodomethane resulted in the formation of product **5a**.

Table 2

We next examined the scope of the functionalization of 5-stibano-1,2,3-triazole **3** *via* Sb-Li exchange reactions, followed by trapping of the lithium intermediate with various electrophiles. The results are summarized in Table 3. Compound **3** was treated with PhLi, and then trapped with aromatic aldehydes to afford the corresponding alcohols **5b-e** in good to excellent yields (entries 1-4). These reactions were sensitive to the electronic nature of the aryl groups, with electron-donating groups giving higher yields than that observed with electron-withdrawing groups. An alkyl aldehyde also gave the corresponding product **5f** in 73% yield (entry 5). Introduction of a heteroatom-containing substituent group at the 5-position of **3** was achieved smoothly by using chlorotrimethylsilane,

chlorotri-*n*-butyltin, and 1,2-diiodoethane as electrophiles (entries 6-8). It is known that benzylic lithium intermediates can be easily generated, and that they can undergo chemical modification in the presence of various electrophiles [22-24]. In the present reaction, the benzyl moiety in **3** and **5a-i** remained intact. Unfortunately, the reaction of intermediate **4** with acetophenone or *N*,*N*-dimethylformamide gave a complex mixture under these conditions (entries 9, 10).

Table 3

At present, the mechanism of the Sb-Li exchange reaction is unclear. It is known that the reaction of organometallic compounds containing heavier main-group elements with organolithium reagents forms hypervalent ate complexes on the main-group atoms [25-29]. In previous work, we have reported the nucleophilic displacement of the ethynyl groups on ethynylstibanes with organolithium reagents [30-32]. The work showed that a more stable conjugated base is preferentially released in the ligand exchange reaction. It is known that calculated pK_a values of the C5-position of 1-methyl-1,2,3-triazole and benzene in DMSO are 27.8 [33] and 44.7 [34], respectively. In the present case, the triazolyl group may be released from hypervalent ate complex **A** in preference to the phenyl group based on PhLi to form triazolyllithium (Fig. 3). Indeed, this reaction gave triphenylstibane **6** as a by-product. We probed the mechanism of this Sb-Li exchange reaction by using ^{1}H- and ^{121}Sb-NMR spectroscopy at low temperature (-80 ^{o}C). However, the proposed intermediate species **A** and **4** could not be confirmed on the NMR time scale. These intermediates might be unstable and/or exist equilibrium with each other.

Fig 3

3. Conclusion

In summary, we have demonstrated the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles by the reaction of electrophiles with the key lithium intermediate **4**, formed following an Sb-Li exchange

reaction. The obtained compounds **5b-h** were first synthesis of trisubstituted 1,2,3-triazoles. Studies on the synthetic application of this reaction and a detailed investigation of the reaction mechanisms are in progress. Moreover, a screen for biological activity of the fully substituted 1,2,3-triazoles is currently underway in our laboratory.

4. Experimental

4.1. General

Melting points were measured on a Yanagimoto micro melting point hot-stage apparatus (MP-S3) and reported as uncorrected values. ^{1}H NMR (TMS: δ: 0.00 or CH_2Cl_2: 5.30 ppm as an internal standard) and ^{13}C NMR ($CDCl_3$: δ: 77.00 ppm as an internal standard) spectra were recorded on JEOL JNM-AL400 (400 MHz and 100 MHz) spectrometers in $CDCl_3$. Mass spectra were obtained on a JEOL JMP-DX300 instrument (70 eV, 300 μA). IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer and reported in terms of frequency of absorption (cm^{-1}). Only selected IR bands are reported. Chromatographic separations were carried out using Silica Gel 60N (Kanto Chemical Co., Inc.) under the solvent system stated. Thin-layer chromatography (TLC) was performed using Merck Pre-coated TLC plates (silica gel 60 F_{254}). Each electrophiles were purchased from Wako Pure Chemical Industries and Tokyo Chemical Industry Co., Ltd.

*4.2. Synthesis of 1-benzyl-5-(diphenylstibano)-4-phenyl-1H-1,2,3-triazole (**3**)*

CuBr (72 mg, 0.5 mmol, 5 mol%), (phenylethynyl)diphenylstibane (**1** : 3.77 g, 10 mmol), and benzyl azide (**2** : 1.33 g, 10 mmol) were dissolved in THF (40 mL). The reaction mixture was stirred for 6 h at 60 ºC. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and water (30 mL). The phases were separated and aqueous layer was extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed 5% aqueous ammonia and water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1), affording compound **3**.

Colorless prisms (4.08 g, 80 % yield), mp: 105-107 ºC (from *n*-hexane-CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.34 (2H, s), 6.78-6.81 (2H, m), 7.15-7.21 (10H, m), 7.24-7.28 (6H, m), 7.42-7.45 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.1 (t), 126.6 (s), 127.2 (d), 127.8 (d), 127.9 (d), 128.0 (d), 128.5

(d), 129.0 (d), 129.1 (d), 129.2 (d), 131.9 (s), 134.6 (s), 135.5 (s), 135.8 (d), 156.7 (s). LRMS (FAB) *m/z*: 510 ($[M+H]^+$, 100), 275 (22), 236 (15), 154 (17), 91 (53). HRMS: *m/z* $[M]^+$ calcd for $C_{27}H_{22}N_3Sb$: 509.0852. Found: 509.0850.

4.3. General procedure for Sb/Li exchange followed by trapping with electrophile

PhLi (0.46 mL, 0.5 mmol, 1.54 mol/L in diethyl ether) was added to a solution of 1-benzyl-5-(diphenylstibano)-4-phenyl-1*H*-1,2,3-triazole (**3** : 255 mg, 0.5 mmol) in THF (2 mL) at -78 ºC. After 15 min, electrophile (0.75 mmol) was added and stirred at -78 ºC. Then the reaction mixture was quenched with MeOH, diluted with CH_2Cl_2 (3 mL) and water (3 mL). The phases were separated and organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt) to give **5a**-**g**, **5i** (4 : 1), **5h** (6 : 1).

*4.3.1. 1-Benzyl-5-methyl-4-phenyl-1H-1,2,3-triazole (**5a**) [35]*

Colorless plates (107 mg, 86% yield), mp 92-93 ºC (from *n*-hexane-CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.33 (3H, s), 5.55 (2H, s), 7.20 (2H, d, *J* = 5.9 Hz), 7.29-7.38 (4H, m), 7.44 (2H, t, *J* = 7.6 Hz), 7.69 (2H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.2 (q), 52.0 (t), 127.08 (d), 127.11 (d), 127.6 (d), 128.3 (d), 128.6 (d), 129.0 (d), 129.1 (s), 131.6 (s), 134.8 (s), 145.0 (s). LRMS (EI) *m/z* : 249 (M^+, 100), 220 (16), 130 (100), 115 (15), 104 (62), 83 (80), 77 (23), 65 (20), 63 (15). HRMS: *m/z* $[M]^+$ calcd for $C_{16}H_{15}N_3$: 249.1266. Found: 249.1252.

*4.3.2. (1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)(4-methoxyphenyl)methanol (**5b**)*

Colorless needles (158 mg, 85% yield), mp 165-168 ºC (from CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.12 (1H, d, *J* = 4.9 Hz), 3.78 (3H, s), 5.30 (1H, d, *J* = 15.1 Hz), 5.46 (1H, d, *J* = 15.1 Hz), 6.27 (1H, d, *J* = 4.9 Hz), 6.76 (2H, d, *J* = 8.3 Hz), 7.02-7.10 (4H, m), 7.17-7.25 (3H, m), 7.32-7.39 (3H, m), 7.57 (2H, dd, *J* = 2.0, 7.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.9 (t), 55.3 (q), 65.2 (d), 114.0 (d), 127.1 (d), 127.8 (d), 127.9 (d), 128.15 (d), 128.24 (d), 128.5 (d), 128.7 (d), 130.7 (s), 131.4 (s), 134.1 (s), 135.2 (s), 146.1 (s), 159.2 (s). FTIR (KBr) : 3188 cm^{-1}. LRMS (EI) *m/z* : 371 (M^+, 56), 355 (10), 236 (22), 207 (16), 149 (70), 130 (50), 91 (100), 77 (17), 65 (11). HRMS: *m/z* $[M]^+$ calcd for $C_{23}H_{21}N_3O_2$: 371.1634. Found: 371.1631.

*4.3.3. (1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)(p-tolyl)methanol (**5c**)*

Colorless needles (151 mg, 85% yield), mp 140-142 ºC (from *n*-hexane-CH_2Cl_2). ^{1}H NMR (400

MHz, $CDCl_3$) δ: 2.31 (3H, s), 3.27 (1H, br), 5.25 (1H, d, J = 15.1 Hz), 5.43 (1H, d, J = 15.1 Hz), 6.29 (1H, s), 7.00-7.08 (6H, m), 7.15-7.23 (3H, m), 7.30-7.38 (3H, m), 7.55-7.60 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.0 (q), 52.8 (t), 65.3 (d), 125.7 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.5 (d), 128.7 (d), 129.3 (d), 130.7 (s), 134.1 (s), 135.1 (s), 136.4 (s), 137.7 (s), 146.1 (s). FTIR (KBr) : 3231 cm^{-1}. LRMS (EI) *m/z* : 355 (M^+, 92), 327 (12), 236 (61), 207 (23), 206 (15), 133 (70), 121 (22), 105 (21), 91 (100), 83 (22), 65 (15). HRMS: *m/z* $[M]^+$ calcd for $C_{23}H_{21}N_3O$: 355.1685. Found: 355.1689.

*4.3.4. (1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)(4-bromophenyl)methanol (**5d**)*

Colorless needles (147 mg, 70% yield), mp 152-153 ºC (from *n*-hexane-CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.31 (1H, br), 5.26 (1H, d, J = 15.2 Hz), 5.40 (1H, d, J = 15.2 Hz), 6.26 (1H, s), 6.90-6.98 (4H, m), 7.10-7.23 (3H, m), 7.23-7.26 (2H, m), 7.30-7.35 (3H, m), 7.45-7.52 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.9 (t), 64.7 (d), 121.8 (s), 127.5 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.7 (d), 130.3 (s), 131.5 (d), 133.8 (s), 134.7 (s), 138.5 (s), 146.1 (s). FTIR (KBr) : 3211 cm^{-1}. LRMS (EI) *m/z* : 419 (M^+, 40), 300 (38), 221 (30), 197 (35), 185 (18), 178 (10), 116 (12), 91 (100), 77 (33), 65 (20). HRMS: *m/z* $[M]^+$ calcd for $C_{22}H_{18}BrN_3O$: 419.0633. Found: 419.0629.

*4.3.5. (1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)[4-(trifluoromethyl)phenyl]methanol (**5e**)*

Colorless needles (129 mg, 63% yield), mp 138-140 ºC (from *n*-hexane-CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.57 (1H, br), 5.34 (1H, d, J = 15.1 Hz), 5.45 (1H, d, J = 15.1 Hz), 6.36 (1H, s), 6.90 (2H, d, J = 7.3 Hz), 7.10-7.17 (3H, m), 7.21 (2H, d, J = 7.8 Hz), 7.36-7.40 (5H, m), 7.53-7.56 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.9 (t), 64.6 (d), 123.9 (s), 125.2 (d), 126.1 (d), 127.5 (d), 128.0 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.8 (d), 129.9 (s), 130.1 (s), 133.8 (s), 134.5 (s), 143.3 (s), 146.2 (s). FTIR (KBr) : 3155 cm^{-1}. LRMS (EI) *m/z* : 409 (M^+, 28), 369 (10), 290 (60), 135 (15), 91 (100). HRMS: *m/z* $[M]^+$ calcd for $C_{23}H_{18}F_3N_3O$: 409.1402. Found: 409.1411.

*4.3.6. 1-(1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)-2-methylpropan-1-ol (**5f**)*

Colorless plates (112 mg, 73% yield), mp 144.5-145.5 ºC (from *n*-hexane-CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.31 (3H, d, J = 6.9 Hz), 0.97 (3H, d, J = 6.9 Hz), 1.85-1.95 (1H, m), 3.47 (1H, br), 4.61 (1H, d, J = 9.6 Hz), 5.56 (1H, d, J = 15.5 Hz), 5.64 (1H, d, J = 15.5 Hz), 7.21 (2H, dd, J = 1.6, 7.9 Hz), 7.27-7.40 (6H, m), 7.64 (2H, dd, J = 1.6, 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7 (q), 19.5 (q), 32.8 (d), 52.8 (t), 70.6 (d), 127.3 (d), 128.05 (d), 128.13 (d), 128.5 (d), 128.7 (d), 128.8 (d),

131.2 (s), 134.6 (s), 135.7 (s), 145.7 (s). FTIR (KBr) : 3204 cm^{-1}. LRMS (EI) *m/z* : 307 (M^+, 65), 188 (100), 129 (10), 104 (20), 91 (98), 83 (40), 65 (20). HRMS: *m/z* $[M]^+$ calcd for $C_{19}H_{21}N_3O$: 307.1685. Found: 307.1679.

*4.3.7. 1-Benzyl-4-phenyl-5-(trimethylsilyl)-1H-1,2,3-triazole (**5g**)*

Colorless prisms (108 mg, 70% yield), mp 105-106 ºC (from *n*-hexane-CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.030 (9H, s), 5.75 (2H, s), 7.04 (2H, d, *J* = 6.8 Hz), 7.29-7.50 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: -0.34 (q), 54.0 (t), 126.4 (d), 127.96 (d), 127.98 (d), 128.3 (d), 128.8 (d), 129.8 (d), 131.3 (s), 133.1 (s), 136.3 (s), 156.5 (s). LRMS (EI) *m/z* : 307 (M^+, 65), 279 (98), 180 (20), 179 (11), 149 (16), 118 (11), 91 (100), 83 (92), 73 (45), 65 (24). HRMS: *m/z* $[M]^+$ calcd for $C_{18}H_{21}N_3Si$: 307.1505. Found: 307.1507.

*4.3.8. 1-Benzyl-4-phenyl-5-(tributylstannyl)-1H-1,2,3-triazole (**5h**)*

Colorless oil (194 mg, 74% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.73-0.84 (15H, m), 1.06-1.24 (12H, m), 5.67 (2H, s), 7.02 (2H, d, *J* = 6.6 Hz), 7.28-7.46 (6H, m), 7.52 (2H, dd, *J* = 1.6, 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 10.8 (t), 13.5 (q), 27.0 (t), 28.6 (t), 54.3 (t), 126.3 (d), 128.01 (d), 128.03 (d), 128.2 (d), 128.8 (d), 132.0 (s), 133.3 (s), 136.6 (s), 157.1 (s). LRMS (FAB) *m/z*: 526 ($[M+H]^+$, 100), 524 (75), 468 (13), 466 (10), 179 (16), 177 (15), 119 (15), 91 (40), 85 (16). HRMS: *m/z* $[M]^+$ calcd for $C_{27}H_{39}N_3Sn$: 525.2166. Found: 525.2161.

*4.3.9. 1-Benzyl-5-iodo-4-phenyl-1H-1,2,3-triazole (**5i**) [36]*

Colorless prisms (170 mg, 94% yield). mp 95-96 °C (from *n*-hexane-CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ : 5.68 (2H, s), 7.30-7.48 (8H, m), 7.94 (2H, d, *J* = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 54.4 (t), 76.4 (s), 127.4 (d), 127.8 (d), 128.5 (d), 128.5 (d), 128.6 (d), 128.9 (d), 130.2 (s), 134.3 (s), 150.2 (s). LRMS (EI) *m/z*: 361 (M^+, 13), 234 (22), 206 (95), 179 (27), 115 (11), 91 (100), 65 (14). HRMS: *m/z* $[M]^+$ calcd for $C_{15}H_{12}IN_3$: 361.0076. Found: 361.0084.

4.4. X-Ray Crystallographic data

The X-ray diffraction measurements of compound **3** was carried out using Bruker D8 VENTURE CCD area-detector diffractometer using CuKα radiation (λ = 1.54178 Å). The structure was solved by SHELXT [37] followed by successive refinements using the full-matrix least-squares method on F^2 using SHELXL-2014 [38]. All the non-hydrogen atoms were refined anisotropically, whereas the hydrogen atoms were refined isotropically.

Crystal data of **3**

$C_{27}H_{22}N_3Sb$, M = 510.22, Monoclinic, a = 13.3913(14), b = 10.9832(12), c = 15.1619(17) Å, β = 99.913(3)°, V = 2196.7(4) Å^3, Space group $P2_1/n$, Z = 4, D_{calc} = 1.543 Mg/m^3. Crystal size 0.20 x 0.20 x 0.02 mm^3, θ_{max} = 79.061°, 21970 reflections measured, 4515 unique (R_{int} = 0.0486), μ = 10.099 mm^{-1}. The final R_1 and wR_2 were 0.0349 and 0.1014 ($I > 2\sigma(I)$), for 280 parameters. CCDC 1506003.

Acknowledgments

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Supplementary data

Supplementary data related to this article can be found at http://

References and notes

[1] P. Thirumurugan, D. Matosiuk, K. Jozwiak, Chem. Rev. 113 (2013) 4905-4979.

[2] S.G. Agalave, S.R. Maujan, V.S. Pore, Chem. Asian. J. 6 (2011) 2696-2718.

[3] M. Taddei, S. Ferrini, L. Ginnotti, M. Corsi, F. Manetti, G. Giannini, L. Vesci, F.M. Milazzo, D. Alloatti, M.B. Guglielmi, M. Castorina, M.L. Cervoni, M. Barbarino, R. Foderà, V. Carollo, C. Pisano, S. Armaroli, W. Cabri, J. Med. Chem. 57 (2014) 2258-2274.

[4] Y. Morzherin, P.E. Prokhorova, D.A. Musikhin, T.V. Glukhareva, Z. Fan, Pure Appl. Chem. 83 (2011) 715-722.

[5] J. McNulty, K. Keskar, D.J. Crankshaw, A.C. Holloway, Bioorg. Med. Chem. Lett. 24 (2014) 4586-4589.

[6] C. Wang, D. Abegg, D.G. Hoch, A. Adibekian, Angew. Chem. Int. Ed. 55 (2016) 2911-2915.

[7] L. Ackermann, H.K. Potukuchi, Org. Biomol. Chem. 8 (2010) 4503-4513.

[8] B.T. Worrell, S.P. Ellery, V.V. Fokin, Angew. Chem. Int. Ed. 52 (2013) 13037-13041.

[9] H.A. Stefani, S.N.S. Vasconcelos, F. Manarin, D.M. Leal, F.B. Souza, L.S. Madureira, J. Zukerman-Schpector, M.N. Eberlin, M.N. Godoi, R.S. Galaverna, Eur. J. Org. Chem. (2013) 3780-3785.

[10] H.A. Stefani, N.C.S. Silva, S.N.S. Vasconcelos, F. Manarin, F.B. Souza, Tetrahedron Lett. 54 (2013) 2809-2812.

[11] A. Orita, J. Otera, in: H. Yamamoto, K. Oshima (Eds.), Main Group Metals in Organic Synthesis, vol. 2, Wiley-VCH, Weinheim, 2004, pp. 621-720 (Chapter 12).

[12] C. Rim, D.Y. Son, Arkivoc (2006) 265-291.

[13] N. Petragnani, H.A. Stefani, Tellurium in Organic Synthesis, 2nd ed. Academic Press: London, 2007.

[14] H. Gilman, H.L. Yale, J. Am. Chem. Soc. 72 (1950) 8-10.

[15] G. Wittig, A. Maercker, J. Organomet. Chem. 8 (1967) 491-494.

[16] F. Steinseifer, T. Kauffmann, Angew. Chem. Int. Ed. Engl. 19 (1980) 723-724.

[17] H. Suzuki, T. Murafuji, J. Chem. Soc. Chem. Commun. (1992) 1143-1144.

[18] E. Kayahara, H. Yamada, S. Yamago, Chem. Eur. J. 17 (2011) 5272-5280.

[19] M. Yamada, M. Matsumura, Y. Uchida, M. Kawahata, Y. Murata, N. Kakusawa, K. Yamaguchi, S. Yasuike, Beilstein J. Org. Chem. 12 (2016) 1309-1313.

[20] E.A. Adams, J.W. Kolis, W.T. Pennington, Acta Cryst. C46 (1990) 917-919.

[21] M. Gupta, M. Gupta, S. Paul, R. Kant, V.K. Gupta, Monatsh Chem. 146 (2015) 143-148.

[22] K. Kobayashi, T. Uneda, K. Takada, H. Tanaka, T. Kitamura, O. Morikawa, H. Konishi, J. Org. Chem. 62 (1997) 664-668.

[23] M. Hage, C.A. Ogle, T.L. Rathman, J.L. Hubbard, Main Group Met. Chem. 21 (1998) 777-782.

[24] G. Fraenkel, J.H. Duncan, K. Martin, J. Wang, J. Am. Chem. Soc. 121 (1999) 10538-10544.

[25] H.J. Reich, N.H. Phillips, J. Am. Chem. Soc. 108 (1986) 2102-2103.

[26] H.J. Reich, D.P. Green, N.H. Phillips, J.P. Borst, I.L. Reich, Phosphorus Sulfur Silicon Relat. Elem. 67 (1992) 83-97.

[27] L. Engman, D. Stern, Organometallics 12 (1993) 1445-1448.

[28] H.J. Reich, B.Ö. Gudmundsson, D.P. Green. M.J. Bevan, I.L. Reich, Helv. Chim. Acta 85 (2002) 3748-3772.

[29] H.J. Reich, M.J. Bevan, B.Ö. Gudmundsson, C.L. Puckett, Angew. Chem. Int. Ed. 41 (2002) 3436-3439.

[30] N. Kakusawa, T. Ikeda, A. Osada, J. Kurita. T. Tsuchiya, Synlett (2000) 1503-1505.

[31] S. Okajima, S. Yasuike, N. Kakusawa, A. Osada, K. Yamaguchi, H. Seki, J. Kurita, J. Organomet. Chem. 656 (2002) 234-242.

[32] S. Yasuike, Y. Kishi, S. Kawara, K. Yamaguchi, J. Kurita, J. Organomet. Chem. 691 (2006) 2213-2220.

[33] V.E. Matulis, Y.S. Halauko, O.A. Ivashkevich, P.N. Gaponik, J. Mol. Struct. (THEOCHEM) 909 (2009) 19-24.

[34] K. Shen, Y. Fu, J.-N. Li, L. Liu, Q.-X. Guo, Tetrahedron 63 (2007) 1568-1576.

[35] M.M. Majireck, S.M. Weinreb, J. Org. Chem. 71 (2006) 8680-8683.

[36] M. Juríček, K. Stout, P.H.J. Kouwer, A.E. Rowan, Org. Lett. 13 (2011) 3494-3497.

[37] G.M. Sheldrick, Acta Cryst. A71 (2015) 3-8.

[38] G.M. Sheldrick, Acta Cryst. C71 (2015) 3-8.

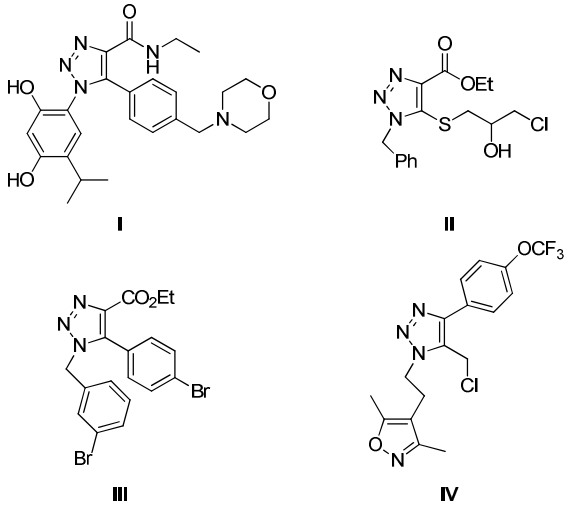
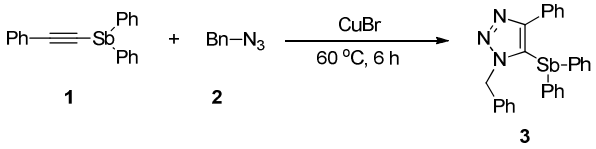


Fig. 1. Biologically active 1,4,5-trisubstituted-1,2,3-triazoles.



1 2 3

Scheme 1. Synthesis of 5-stibano-1,2,3-triazole **3**.

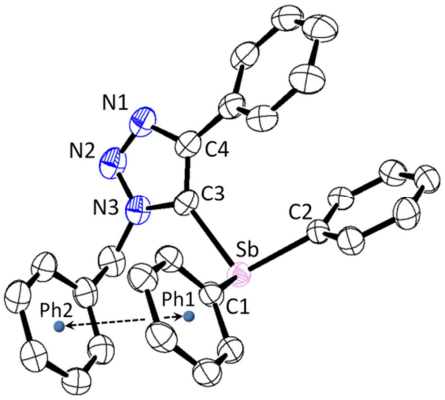
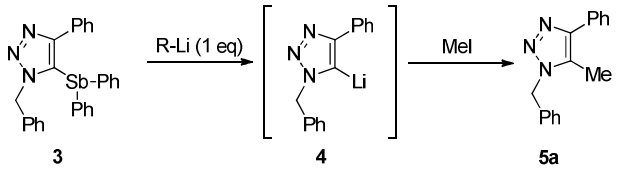


Fig. 2. ORTEP drawing of compound **3** with 50% probability. All hydrogen atoms are omitted for clarity.

Table 1. Selected bond lengths (Å) and bond angles (°) for **3**.

Bond lengths	
Sb–C1	2.148(4)
Sb–C2	2.148(4)
Sb–C3	2.148(4)
C3–C4	1.394(6)
C4–N1	1.364(5)
N1–N2	1.321(6)
N2–N3	1.331(5)
N3–C3	1.370(5)
Bond angles	
C1–Sb–C2	98.47(14)
C1–Sb–C3	99.13(15)
C2–Sb–C3	96.07(14)
C3–C4–N1	109.4(4)
C4–N1–N2	108.2(4)
N1–N2–N3	107.8(3)
N2–N3–C3	112.1(4)
N3–C3–C4	102.5(3)

Table 2. Antimony–lithium exchange reaction.[a,b]



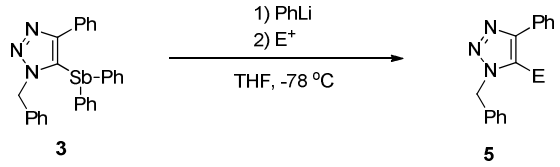
3 4 5a

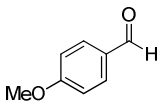
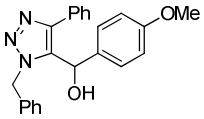
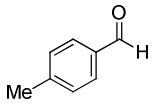
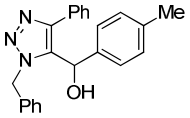
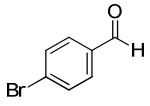
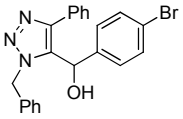
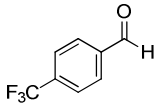
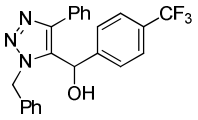
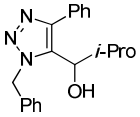
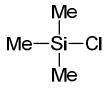
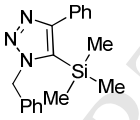
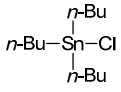
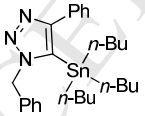
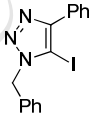
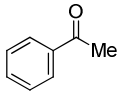
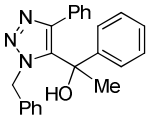
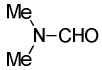
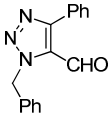
Entry	RLi	Temp.	Lithiation (min)	Yield (%)
1	*n*-BuLi	-78 °C	20	0
2	*sec*-BuLi	-78 °C	20	0
3	MeLi	-78 °C	20	0
4	LDA	-78 °C	15	0
5	LiTMP	-78 °C	30	0
6	PhLi	-78 °C	20	86
7	PhLi	-40 °C	10	12
8	PhLi	-20 °C	10	0

[a] Reaction conditions: **3** (0.5 mmol), RLi (0.5 mmol), MeI (0.75 mmol).

[b] Isolated yield.

Table 3. Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles **5**.[a, b]



Entry	Electrophile	Product	Yield (%)
1			**5b**: 85
2			**5c**: 85
3			**5d**: 70
4			**5e**: 63
5			**5f**: 73
6			**5g**: 70
7			**5h**: 74
8			**5i**: 94
9			**5j**: 0
10			**5k**: 0

[a] Reaction conditions: **3** (0.5 mmol), PhLi (0.5 mmol), Electrophile (0.75 mmol).

[b] Isolated yield.

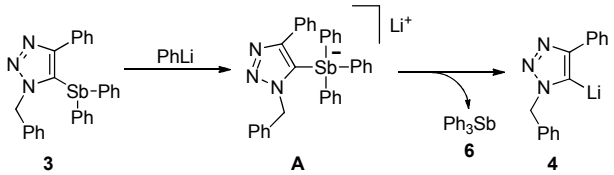


Fig. 3. Generation of triazolyllithium **4**.

Highlights:

5-Stibano-1,2,3-triazole was prepared by the regioselective CuAAC of ethynylstibane with benzyl azide.

Fully substituted 1,2,3-triazoles were prepared by the reaction of electrophiles with triazolyllithium.

This reaction is a novel example of an Sb-Li exchange reaction for the functionalization of heterocycles.