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Sulfur–Carbon Bond Formation through Ring-Opening of Triazolothiadiazole with Organometallics

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An efficient and convenient method was developed for the formation of *S*-substituted thiotriazoles through an unprecedented organometallic addition and subsequent ring-opening sequence of 3-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole. The method is applicable to a wide range of substrates containing different functional groups and furnishes excellent yields of the corresponding *N*-unsubstituted 3- or 5-alkyl, aryl, alkynyl and alkenyl sulfanyl-1,2,4-triazole products.

Introduction

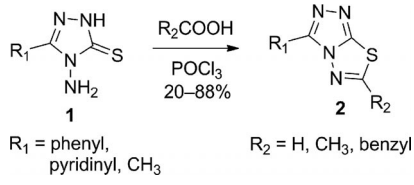
During the past decade, C–S bond formation reactions have received considerable attention. Their creation is challenging because thiols can dimerize or complex transition metals.[1] As a result, catalytic reactions involving organometallic reagents are seldom used compared to more versatile methods generating C–C, C–O, and C–N bonds.[2] Nevertheless, despite these drawbacks, methods leading to C–S bonds are becoming increasingly prevalent. Among them, metal-catalyzed reactions involving copper, palladium, rhodium, iron, and gold, are widely employed.[3]

Despite numerous efforts, limitations occur in heterocyclic series especially when an acidic proton is present. For example, when triazole nitrogen atoms are not substituted, access to such heterocycles is restricted to nucleophilic substitutions without involving any transition metals. Organometallic methods are, in this case, inefficient and useful electrophiles are limited to nitrobenzenes, halogenoalkyls, and propargylic acid.[4] It is therefore of great interest to develop efficient methods for the synthesis and functionalization of 1,2,4-triazoles, especially because several of its fellows are known to possess a wide range of biological activities, for example against cancer, tuberculosis, convulsion, inflammation, pain, depression, bacterial growth or ulcers.[5]

Interestingly, working with sulfur-containing heterocycles may provide unexpected results. Ethylene was accidentaly proved to be released during the cryogenic reaction of organolithium derivatives with imidazothiazolines. Although this method led to free-nitrogen 1,2,4-triazoles, its extrapolation to other Grignard reagents seemed uncertain. Improvements were, however, considered possible,[6] and we report herein unprecedented results in the pursuit of this objective.

Results and Discussion

In a continuation of our research programs on novel reactions of rare heterocycles, we focused on building a library of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole derivatives **2** (Scheme 1), which are readily available from the parent thiones **1** through a classical protocol.[7]



Scheme 1. Synthesis of starting material 3-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

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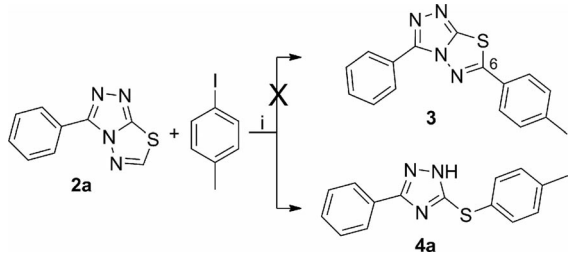
We first prepared **2a** as a model with which to examine CH activation.[8] To this end, we carried out a reaction with **2a** and *p*-iodotoluene in the presence of CuI (10 mol-%), phenanthroline, and *t*BuOK, however, only 3-phenyl-5-thioaryl-1*H*-1,2,4-triazole (**4a**) was isolated in very low yield (7%; Scheme 2). Because CH arylation of **2a** was not possible, irrespective of the conditions used, we decided to focus on increasing the yield in **4a**. By omitting phenanthroline from the reaction mixture, the reaction reached completion and the desired product **4a** was isolated in 90% yield; the 6-arylated derivative **3** was never detected.



Scheme 2. First reactions leading to 3-phenyl-5-thioaryl-1*H*-1,2,4-triazole (**4a**). *Reagents and conditions:* (i) *t*BuOK (2.5 equiv.), CuI (10 mol-%), DMF, argon, 36 h, 140 °C; Yield: 6% (with 0.1 equiv. phenanthroline) or 90% (without phenanthroline).

A survey of the literature did not reveal any reports of thiadiazole ring opening concomitant with the reaction of a halogenoaryl derivative under copper catalysis. The high yield and novelty of this tandem transformation, which seems to imply cyanide release, compelled us to investigate its scope and limitations as well as to seek a realistic mechanism. We report herein a novel and efficient protocol for the preparation of a collection of 5-thioether triazoles **4** from readily available [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles derivatives of type **2**.

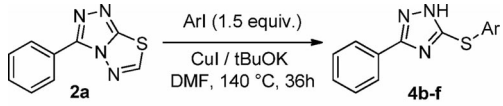
The use of the optimized reaction conditions [i.e., CuI (cat.), *t*BuOK, *N*,*N*-dimethylformamide (DMF), 140 °C] with **2a** and a series of aryl iodides (Table 1) led, in all cases, to the expected products **4**.

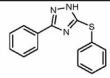
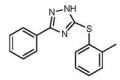
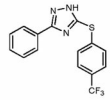
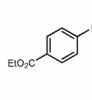
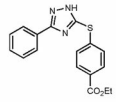
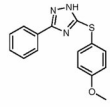
Reactions involving electron-rich or -deficient phenyl iodides proceeded smoothly and efficiently and afforded the desired products **4b**–**f** in excellent yields after 36 h. When the reaction was carried out under microwave irradiation, only degradation products were observed.

The structure of **4c** was solved by single-crystal X-ray diffraction analysis. The ORTEP depiction in Figure 1 confirms that the aromatic part originating from the organometallic reagent is bonded to the sulfur atom. Crystalline cohesion is reinforced through an internal H bond (HN(1)–N(4) 2.845 Å) that leads to an infinite chain along the *c*-axis.[9]

Reasoning that the reaction proceeded through an nucleophilic organocopper species generated in situ, we then decided to investigate the effect of various organometallic compounds, i.e., Grignard reagents, at room temperature, and organolithium derivatives at low temperature, with substrate **2a**.

Table 1. Copper iodide-catalyzed reactions of triazolo-thiadiazole **2a** with aryl iodides.



Entry	ArI	3-Phenyl-5-thioaryl-triazole derivatives **4**[c]		Yield[a,b] (%)
1			**4b**	83
2			**4c**	98
3			**4d**	95
4			**4e**	67
5			**4f**	79

[a] Yield of isolated product after column chromatography on silica gel. [b] When the reaction was carried out under microwave irradiation, after 1 h only degradation products were observed. [c] The position of the NH group is based on the ORTEP diagram of **4c** (Figure 1).

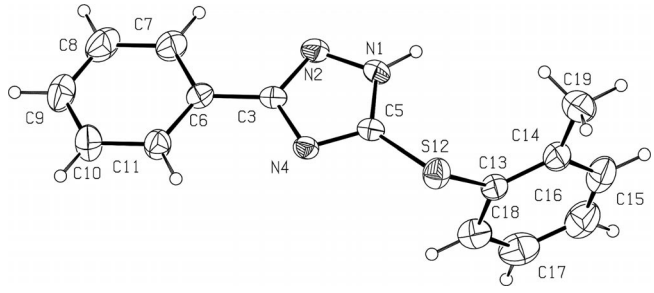
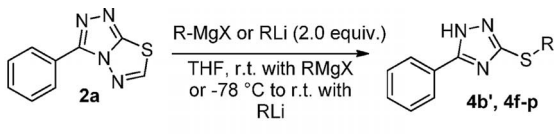


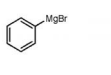
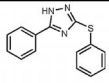
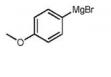
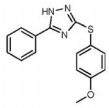
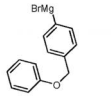
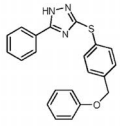
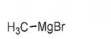
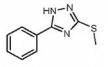
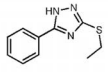
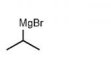
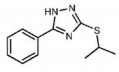
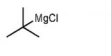
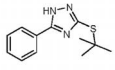
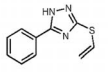
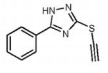
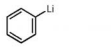
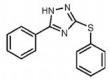
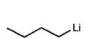
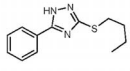
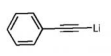
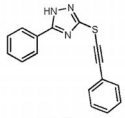
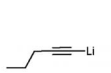
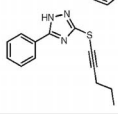
Figure 1. ORTEP diagram of **4c**.

Several functional groups were tolerated and the reaction afforded *S*-substituted thiotriazoles **4b′**–**p** in good to very good yields (Table 2). Vinyl and acetylenyl moieties were also good substrates (Table 2, entries 8, 12, 13), with the exception of **4m**, which was isolated but was too unstable to be stored (Table 2, entry 9). The use of phenylmagnesium bromine or phenyllithium led to the formation of **4b′** in yields similar to those obtained using cuprate formed in situ (Compare Table 2 entries 1 and 10 with Table 1, entry 1).[10] In all cases, condenstations of organometallics are achieved in less than 1 h.

The structure of **4b′** was solved by single-crystal X-ray diffraction. The given ORTEP representations confirm that the aromatic part originating from the organocuprate is bonded to the sulfur atom (Figure 2). Compound **4b′** crys-

Table 2. Reactions of triazolothiadiazole **2a** with Grignard reagents RMgX and organolithiums RLi.[a] (All reactions required 2 equiv. of organometallic reagent. A stoichiometric amount led to incomplete reactions).



Entry	RMgX[a] or RLi[b]	Time [min]	5-Phenyl-3-thioether triazole derivatives **4**[d]		Yield[c] (%)
1		30		**4b'**	83
2		30		**4f'**	82
3		60		**4g**	75
4		30		**4h**	93
5		30		**4i**	91
6		25		**4j**	98
7		25		**4k**	95
8		25		**4l**	94
9		25		**4m**	89
10		30		**4b'**	93
11		25		**4n**	84
12		25		**4o**	96
13		25		**4p**	97

[a] Argon atmosphere, conducted at room temp. [b] Argon atmosphere, conducted at –78 °C to room temp. [c] Yield of isolated product after column chromatography on silica gel. [d] The position of the NH group based on the ORTEP diagram of **4b′**.

tallizes with two independent molecules that show a slight difference in the N(1)–C(5)–S(12)–C(13) torsion angle. These independent molecules are linked by two successive H bonds (HN(22)–N(4) 2.816 Å and N(21)–HN(2) 3.012 Å with N–H–N angles close to 170°) to form a tetramer.[9]

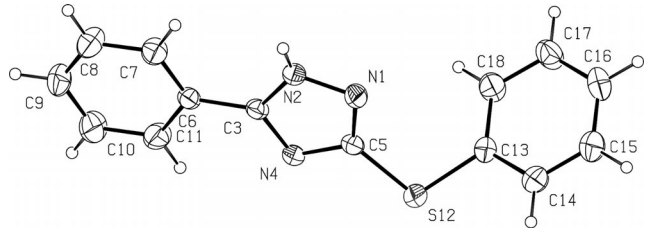
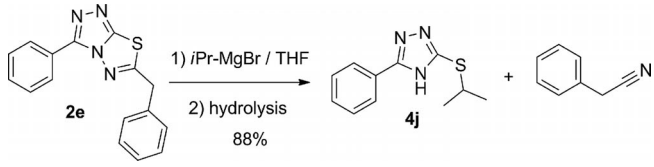


Figure 2. ORTEP diagram of **4b′**.

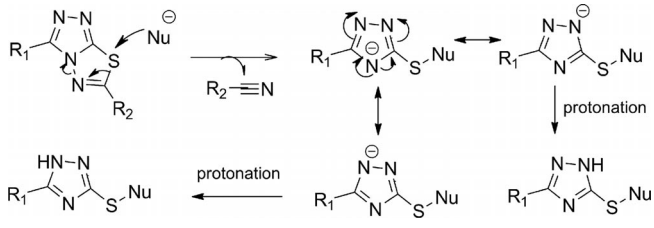
This novel method clearly represents an improvement over existing reactions because it furnishes unconventional aryl, vinyl, and acetylenyl sulfides[11] on unsubstituted nitrogen triazoles. The reaction occurs in a single step through cyanide ejection in situ,[12] irrespective of the organometallic compound used. In addition, the system is compatible with both small and large Grignard reagents.

To the best of our knowledge, this is the first example of the direct introduction of vinyl groups on the sulfur atom with a good yield; at present, these vinyl sulfides are only accessible from acetylenic thioethers.[13] To examine the cyanide moiety removal in more detail and to gain further insight into the mechanism, we reacted **2b** in the presence of *i*PrMgBr (Scheme 3). Ring opening was achieved as expected and the reaction provided a stoichiometric amount of benzylcyanide concomitant with **4j**.



Scheme 3. Examining nitrile elimination.

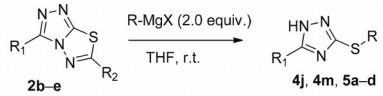
Based on of these results, we are now able to propose a plausible mechanism and explain the formation of *S*-substituted 5-thiotriazoles and 3-thiotriazoles (Scheme 4). A nucleophilic attack of the organometallic reagent on the sulfur atom initiates ring opening, leading to the elimination of the cyanide moiety. The desired products were obtained in different tautomeric forms of the 1,2,4-triazole ring after hydrolysis.



Scheme 4. Proposed mechanism for the formation of *S*-substituted thiotriazoles.

To complete the study, we explored the scope of this reaction. To our satisfaction, the reaction took place easily using a range of 3-substituted triazolothiadiazoles **2** (Table 3) and gave good yields in the presence of vinyl and isopropylmagnesium bromides. A methyl group at C(3) of **2** was well tolerated (entries 2 and 6) despite its mildly acidic character, whereas reactions with C(3)-substituted pyridinyl-triazolothiadiazole-specific optimization was required (entries 4 and 8). Access to the previously isolated (see above) compounds **4j** and **4m** from triazolothiadiazole **2d** (entries 3 and 7) is consistent with the proposed mechanism.

Table 3. Reactions of other triazolothiadiazoles with Grignard reagents, RMgX.



2b–e **4j, 4m, 5a–d**

Entry	Starting material	Time [min]	5-Phenyl-3-thioether triazole derivatives **4**[d]		Yield[a] (%)
1	**2b**: R_1 = Ph, R_2 = CH_2Ph	40		**4j**	88
2	**2c:** R_1 = Me, R_2 = H	35		**5a**	96
3	**2d:** R_1 = Ph, R_2 = Me	45		**4j**	86
4	**2e**: R_1 = Pyr, R_2 = H	70		**5b**	62[b]
5	**2b**: R_1 =:Ph, R_2 = CH_2Ph	40		**4m**	87
6	**2c**: R_1 = Me, R_2 = H	35		**5c**	92
7	**2d**: R_1 = Ph, R_2 = Me	45		**4m**	75
8	**2e**: R_1 = Pyr, R_2 = H	70		**5d**	63 [b,c]

[a] Yield of isolated product after column chromatography on silica gel. [b] Reaction carried out in a very high concentration.

Conclusions

A simple, efficient, practical, and convenient protocol has been developed for the synthesis of *S*-substituted thiotriazoles through the in situ generation of the cyanide compound and tandem ring-opening of triazolothiazole with various organometallic compounds including cuprates formed in situ, lithiated species, and a wide range of Grignard reagents. The direct introduction of alkyl, aryl, alkynes, and vinyl groups on the sulfur atom with high yield was achieved in only a few minutes by using organometallic reagents. A mechanism has been proposed that involves nucleophilic action of organometallic reagents onto the sulfur atom of the thiazolotriazole core. This unprecedented method could offer new perspectives for building triazole libraries and for access to nonclassical molecules.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX 250 MHz or 400 MHz spectrometer using $CDCl_3$ or [D_6]-DMSO. The chemical shifts are reported in parts per million (ppm, δ scale) and coupling constant (J) values are in Hertz [Hz]. The following abbreviations are used for multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet doublet), and ddd (doublet doublet doublet). For some compounds, only ^{13}C DEPT 135 spectra are described because we were unable to observe the Cq signals in ^{13}C NMR spectra even with high concentration of product or by changing the nature of the solvent. Melting points are uncorrected. IR absorption spectra were obtained with a Perkin–Elmer PARAGON 1000 PC spectrometer and values are reported in cm^{-1}. HRMS were recorded with a Bruker maXis mass spectrometer. The progress of the reactions were monitored by using TLC with silica gel plates (silica Merck 60 F254). Spots were visualized by UV light at 254 and 356 nm. Column chromatography was performed by using silica gel 60 (0.063–0.200 mm, Merck). Reactions requiring anhydrous conditions were performed under argon. All solvents were freshly distilled under argon prior to use. Petroleum ether (PE) had a boiling range of 45–65 °C. Chemicals were obtained from Aldrich and Acros organics. Microwave irradiation was carried out in sealed 2–5 mL vessels placed in a Biotage Initiator system using a standard absorbance level (300 W maximum power). The temperatures were externally measured by an IR probe, which gave the temperature on the surface of the vial. The reaction time was measured from the point at which the reaction mixture reached the stated temperature for temperature-controlled experiments. Pressure was measured by a non-invasive sensor integrated into the cavity lid.

Copper Iodide Catalysis with Aryl Iodides; General Procedure A: In a sealed tube, copper iodide (10 mol-%) was added under argon to a solution of **2a** (1.0 equiv., 0.50 mmol, 101.0 mg), aryl iodide (2.0 equiv., 1.00 mmol), and *t*BuOK (2.5 equiv., 1.25 mmol) in DMF (2 mL). The mixture was stirred at 140 °C for 48 h, then the crude material was evaporated under reduced pressure. The residue was dissolved in water (20 mL), and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers was dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc).

General Procedure B: In a 25 mL flask, RMgX (see Table 2; 2.0 equiv., 1.0 mmol, 2.5 M solution in THF) was added dropwise under argon at room temperature to a solution of **2a**–**e** (1.0 equiv., 0.5 mmol) in THF (5 mL), and the mixture was stirred for 25–60 min. At the end of the reaction, an aqueous solution of saturated NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc).

General Procedure C: In a 25 mL flask, *n*-BuLi (2.0 equiv., 1.0 mmol, 2.5 M in *n*-hexane) was added dropwise under argon at –78 °C to a solution of phenylethyne or propylethyne (2.0 equiv., 1.0 mmol) in THF (5 mL), and the mixture was stirred at –78 °C for 0.5 h. Compound **2a** (1.0 equiv., 0.5 mmol) was added and the reaction mixture was allowed to reach room temperature for 25 to 30 min. Upon completion, the reaction was quenched with aqueous saturated NH_4Cl (10 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc).

General Procedure D: In a 10 mL flask, isopropylmagnesium bromide or vinylmagnesium bromide (2.0 equiv., 1.0 mmol, 2.5 M solution in THF) was added dropwise under argon at room temperature to **2d** (1.0 equiv., 0.5 mmol), and the mixture was stirred for 70 min. At the end of the reaction, the mixture was quenched with aqueous saturated NH_4Cl (10 mL), and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (PE/EtOAc).

3-Phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (2a):[7c] ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.48 (s, 1 H), 8.27–8.20 (m, 2 H), 7.65–7.53 (m, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 157.1 (C_q), 155.1 (2 CH_{Ar}), 145.6 (2 CH_{Ar}), 130.7 (CH_{Ar}), 129.6 (C_q), 126.2 (C_q), 126.0 (CH) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_9H_6N_4S$ [M + H]$^+$ 203.03859; found 203.03876.

6-Benzyl-3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (2b):[7b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36–8.32 (m, 2 H), 7.60–7.33 (m, 8 H), 4.35 (s, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.7 (C_q), 154.9 (C_q), 146.3 (C_q), 134.2 (C_q), 130.3 (CH_{Ar}), 129.3 (2CH_{Ar}), 129.0 (2CH_{Ar}), 128.9 (2CH_{Ar}), 128.3 (CH_{Ar}), 126.4 (2CH_{Ar}), 125.6 (C_q), 38.6 (CH_2) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{16}H_{13}N_4S$ [M + H]$^+$ 293.08554; found 293.08591.

3-Methyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole: (2c).[7g,14] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 2.76 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.6 (C_q), 151.9 (CH), 144.7 (C_q), 10.3 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_4H_4N_4S$ [M + H]$^+$ 141.02294; found 141.02316.

6-Methyl-3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (2d):[15] ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27–8.18 (m, 2 H), 7.66–7.49 (m, 3 H), 2.80 (s, 3 H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 167.4 (C_q), 155.5 (C_q), 145.4 (C_q), 130.6 (CH_{Ar}), 129.5 (2CH_{Ar}), 126.1 (2CH_{Ar}), 126.0 (C_q), 18.5 (CH_3) ppm.

3-(4-Pyridyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (2e):[16] ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 9.56 (s, 1 H), 8.88–8.77 (m, 2 H), 8.20–8.10 (m, 2 H) ppm. ^{13}C NMR (63 MHz, [D$_6$]DMSO): δ = 159.5 (CH), 157.8 (C_q), 152.6 (2CH_{Ar}), 145.1 (C_q), 134.3 (C_q), 121.2 (2CH_{Ar}) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_8H_6N_5S$ [M + H]$^+$ 204.03384; found 204.03438.

3-Phenyl-5-(*p*-tolylthio)-1*H*-1,2,4-triazole (4a): Compound **4a** was obtained as a white solid in 90% yield by following General Procedure A. R_f = 0.61 (PE/EtOAc, 6:4); m.p. 125–127 °C. IR (ATR diamond): $\tilde{\nu}$ = 3075, 2978, 2920, 2850, 2783, 1557, 1491, 1260, 1142, 1019, 976, 806, 775, 687, 634 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.54 (br. s, 1 H), 7.86 (d, *J* = 6.8 Hz, 2 H), 7.40–7.28 (m, 5 H), 7.02 (d, *J* = 8.0 Hz, 2 H), 2.23 (s, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 132.9 (2 CH_{Ar}), 130.3 (2 CH_{Ar}), 130.0 (CH_{Ar}), 128.7 (2 CH_{Ar}), 126.5 (2 CH_{Ar}), 21.1 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{15}H_{13}N_3S$ [M + H]$^+$ 268.09029; found 268.09061.

3-Phenyl-5-(phenylthio)-1*H*-1,2,4-triazole (4b): Compound **4b** was obtained as a white solid in 83% (General Procedure A), 83% (General Procedure B), and 93% (General Procedure C). R_f = 0.61 (PE/EtOAc, 6:4); m.p. 125–127 °C. IR (ATR diamond): $\tilde{\nu}$ = 3061, 2917, 2782, 1556, 1488, 1465, 1417, 1327, 1271, 1258, 1004, 778, 704, 682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.19 (br. s, 1 H), 7.91 (d, *J* = 6.6 Hz, 2 H), 7.53–7.45 (m, 2 H), 7.43–7.32 (m, 3 H), 7.31–7.22 (m, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 132.2 (CH_{Ar}), 130.2 (CH_{Ar}), 129.5 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 128.6 (CH_{Ar}), 126.5 (3 CH_{Ar}) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{14}H_{11}N_3S$ [M + H]$^+$ 254.07464; found 254.07492.

3-Phenyl-5-(*o*-tolylthio)-1*H*-1,2,4-triazole (4c): Compound **4c** was obtained as a white solid in 98% yield (General Procedure A). R_f = 0.61 (PE/EtOAc, 6:4); m.p. 159–161 °C. IR (ATR diamond): $\tilde{\nu}$= 3049, 2916, 2849, 2712, 1509, 1441, 1393, 1321, 1258, 1158, 1072, 1024, 971, 787, 728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.95 (br. s, 1 H), 7.89 (d, *J* = 7.1 Hz, 2 H), 7.44 (d, *J* = 7.7 Hz, 1 H), 7.41–7.30 (m, 3 H), 7.22–7.04 (m, 3 H), 2.39 (s, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 133.8 (CH_{Ar}), 131.0 (CH_{Ar}), 130.0 (CH_{Ar}), 129.3 (CH_{Ar}), 128.7 (2 CH_{Ar}), 127.0 (CH_{Ar}), 126.5 (2 CH_{Ar}), 20.7 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{15}H_{13}N_3S$ [M + H]$^+$ 268.09029; found 268.09059.

3-Phenyl-5-{[4-(trifluoromethyl)phenyl]thio}-1*H*-1,2,4-triazole (4d): Compound **4d** was obtained as a white solid in 95% yield (General Procedure A). R_f = 0.61 (PE/EtOAc, 6:4); m.p. 161–163 °C. IR (ATR diamond): $\tilde{\nu}$ = 3049, 2916, 2851, 2782, 1605, 1459, 1400, 1326, 1259, 1154, 1101, 1063, 981, 828, 692. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.53 (br. s, 1 H), 7.88 (d, *J* = 7.5 Hz, 2 H), 7.55–7.41 (m, 5 H), 7.41–7.32 (m, 2 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.8 (CH_{Ar}), 130.1 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 126.5 (2 CH_{Ar}), 125.9 (q, $^3J_{CH-F}$ = 4.0 Hz, 2 CH) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{15}H_{10}F_3N_3S$ [M + H]$^+$ 322.06202; found 322.06221.

Ethyl 4-[(3-Phenyl-1*H*-1,2,4-triazol-5-yl)thio]benzoate (4e): Compound **4e** was obtained as a white solid in 67% yield (General Procedure A). R_f = 0.50 (PE/EtOAc, 6:4); m.p. 108–110 °C. IR (ATR diamond): $\tilde{\nu}$= 3052, 2968, 2850, 2723, 1719, 1593, 1459, 1399, 1286, 1276, 1257, 1176, 1123, 1016, 981, 848, 705, 685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.82 (br. s, 1 H), 7.98–7.83 (m, 4 H), 7.46–7.33 (m, 5 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.6 (CH_{Ar}), 130.2 (2 CH_{Ar}), 129.4 (CH_{Ar}), 128.9 (2 CH_{Ar}), 126.5 (3 CH_{Ar}), 61.2 (CH_2), 14.2 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{17}H_{15}N_3O_2S$ [M + H]$^+$ 326.09577; found 326.09581.

5-[(4-Methoxyphenyl)thio]-3-phenyl-1*H*-1,2,4-triazole (4f): Compound **4f** was obtained as a white solid in 79% yield (General Procedure A) and 82% yield (General Procedure B). R_f = 0.42 (PE/EtOAc, 6:4); m.p. 142–144 °C. IR (ATR diamond): $\tilde{\nu}$= 3068, 2916, 2842, 2664, 1719, 1590, 1493, 1467, 1341, 1246, 1183, 1175, 1022, 976, 825, 728, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.32 (br. s, 1 H), 8.00–7.87 (m, 2 H), 7.61–7.51 (m, 2 H), 7.36–7.41 (m, 3 H), 6.93–6.79 (m, 2 H), 3.77 (s, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 135.8 (2 CH_{Ar}), 129.9 (CH_{Ar}), 128.7 (2 CH_{Ar}), 126.4 (2 CH_{Ar}), 115.3 (2 CH_{Ar}), 55.4 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{15}H_{13}N_3OS$ [M + H]$^+$ 284.08521; found 284.08532.

3-{[4-(Phenoxymethyl)phenyl]thio}-5-phenyl-1*H*-1,2,4-triazole (4g): Compound **4g** was obtained as a viscous liquid in 75% yield (General Procedure B). R_f = 0.46 (PE/EtOAc, 6:4). IR (ATR diamond): $\tilde{\nu}$= 3063, 2928, 2865, 1588, 1476, 1462, 1324, 1224, 1141, 1072, 1023, 777, 728, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.63 (br. s, 1 H), 7.92–7.81 (m, 2 H), 7.37–7.22 (m, 8 H), 7.11–7.04 (m, 2 H), 6.99 (dt, *J* = 7.9, 1.3 Hz, 1 H), 6.76 (ddd, *J* = 8.4, 2.4, 1.1 Hz, 1 H), 4.86 (s, 2 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.2 (CH_{Ar}), 130.2 (CH_{Ar}), 128.8 (2 CH_{Ar}), 128.5 (2 CH_{Ar}), 128.0 (CH_{Ar}), 127.5 (2 CH_{Ar}), 126.5 (2 CH_{Ar}), 124.1 (CH_{Ar}), 117.8 (CH_{Ar}), 115.0 (CH_{Ar}), 70.0 (CH_2) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{21}H_{17}N_3OS$ [M + H]$^+$ 360.11651; found 360.11665.

3-(Methylthio)-5-phenyl-1*H*-1,2,4-triazole (4h):[17] Compound **4h** was obtained as a white solid in 93% yield (General Procedure B). R_f = 0.42 (PE/EtOAc, 6:4); m.p. 160–162 °C. IR (ATR diamond): $\tilde{\nu}$= 2974, 2840, 2773, 2649, 1548, 1463, 1338, 1267, 1139, 1027, 976, 780, 726, 692 cm^{-1}. ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 14.28 (br. s, 1 H), 8.04–7.91 (m, 2 H), 7.60–7.40 (m, 3 H), 2.63 (s, 3

H) ppm. ^{13}C DEPT NMR (63 MHz, [D$_6$]DMSO): δ = 129.8 (CH_{Ar}), 128.5 (2 CH_{Ar}), 126.0 (2 CH_{Ar}), 14.7 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_9H_9N_3S$ [M + H]$^+$ 192.05899; found 192.05929.

3-(Ethylthio)-5-phenyl-1*H*-1,2,4-triazole (4i):[17a] Compound **4i** was obtained as a white solid in 91% yield (General Procedure B). R_f = 0.46 (PE/EtOAc, 6:4); m.p. 85–87 °C. IR (ATR diamond): ṽ= 3068, 2978, 2848, 2776, 1556, 1463, 1335, 1263, 1143, 1027, 977, 726, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.31 (br. s, 1 H), 8.03–7.89 (m, 2 H), 7.45–7.31 (m, 3 H), 3.16 (q, *J* = 7.3 Hz, 2 H), 1.36 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.0 (CH_{Ar}), 128.8 (2 CH_{Ar}), 126.5 (2 CH_{Ar}), 27.3 (CH_2), 14.9 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{10}H_{11}N_3S$ [M + H]$^+$ 206.07464; found 206.07486.

3-(Isopropylthio)-5-phenyl-1*H*-1,2,4-triazole (4j): Compound **4j** was obtained as a white solid by following General Procedure B, in 98% yield (from **2a**), 86% yield (from **2c**), and 88% yield (from **2e**). R_f = 0.46 (PE/EtOAc, 6:4); m.p. 128–130 °C. IR (ATR diamond): ṽ= 3073, 2926, 2864, 1556, 1460, 1442, 1460, 1328, 1240, 1154, 1055, 1019, 980, 783, 726, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.79 (br. s, 1 H), 8.06–7.92 (m, 2 H), 7.44–7.34 (m, 3 H), 3.84–3.75 (m, 1 H), 1.38 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.0 (CH_{Ar}), 128.8 (2 CH_{Ar}), 126.6 (2 CH_{Ar}), 38.9 (CH), 23.5 (2 CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{11}H_{13}N_3S$ [M + H]$^+$ 220.09029; found 220.09059.

3-(*tert*-Butylthio)-5-phenyl-1*H*-1,2,4-triazole (4k): Compound **4k** was obtained as a white solid in 95% yield (General Procedure B). R_f = 0.60 (PE/EtOAc, 6:4); m.p. 139–141 °C. IR (ATR diamond): ṽ= 2988, 2967, 2921, 2858, 2773, 2652, 1557, 1465, 1415, 1342, 1258, 1221, 1160, 1143, 975, 927, 906, 782, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.06 (br. s, 1 H), 8.13–8.03 (m, 2 H), 7.43–7.33 (m, 3 H), 1.44 (s, 9 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 129.9 (CH_{Ar}), 128.7 (2 CH_{Ar}), 126.6 (2 CH_{Ar}), 31.2 (3 CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{12}H_{15}N_3S$ [M + H]$^+$ 234.10594; found 234.10637.

5-Phenyl-3-(vinylthio)-1*H*-1,2,4-triazole (4l):[18] Compound **4l** was obtained as a white solid by following General Procedure B, in 94% yield (from **2a**), 75% yield (from **2c**), and 87% yield (from **2e**). R_f = 0.46 (PE/EtOAc, 6:4); m.p. 181–183 °C. IR (ATR diamond): ṽ= 3076, 2928, 2859, 1590, 1556, 1442, 1328, 1259, 1138, 1071, 1025, 981, 906, 780, 724, 705, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.66 (br. s, 1 H), 7.99–7.89 (m, 2 H), 7.46–7.36 (m, 3 H), 6.85 (dd, *J* = 16.9, 9.7 Hz, 1 H), 5.53 (d, *J* = 16.9 Hz, 1 H), 5.46 (d, *J* = 9.7 Hz, 1 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.5 (CH_{Ar}), 128.9 (2 CH_{Ar}), 127.3 (CH), 126.5 (2 CH_{Ar}), 117.8 (CH_2) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{10}H_9N_3S$ [M + H]$^+$ 204.05899; found 204.05934.

3-(Ethynylthio)-5-phenyl-1*H*-1,2,4-triazole (4m): Compound **4m** was obtained as a brown solid in 89% yield (General Procedure B). R_f = 0.38 (PE/EtOAc, 6:4); m.p. 87–89 °C. This product was not very stable and was only characterized by ^{1}H NMR analysis. IR (ATR diamond): ṽ= 3127, 3104, 2922, 1555, 1467, 1455, 1441, 1324, 1276, 1134, 1068, 977, 846, 789, 965, 757, 696, 683 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.94 (br. s, 1 H), 7.98–7.72 (m, 2 H), 7.52–7.44 (m, 3 H), 3.31 (s, 1 H) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{10}H_7N_3S$ [M + H]$^+$ 202.04334; found 202.04351.

3-(*n*-Butylthio)-5-phenyl-1*H*-1,2,4-triazole (4n): Compound **4n** was obtained as a white solid in 84% yield (General Procedure C). R_f = 0.58 (PE/EtOAc, 6:4); m.p. 83–85 °C. IR (ATR diamond): ṽ= 3059, 2922, 2857, 2789, 1552, 1465, 1418, 1335, 1265, 1139, 1008, 980, 922, 853, 775, 720, 685 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.00 (br. s, 1 H), 8.06–7.89 (m, 2 H), 7.48–7.29 (m, 3 H), 3.23–3.07 (m, 2 H), 1.70–1.42 (m, 2 H), 1.50–1.31 (m, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.0 (CH_{Ar}), 128.8 (2 CH_{Ar}), 126.5 (2 CH_{Ar}), 32.7 (CH_2), 31.6 (CH_2), 21.7 (CH_2), 13.5 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{12}H_{15}N_3S$ [M + H]$^+$ 234.10594; found 234.10643.

5-Phenyl-3-[(phenylethynyl)thio]-1*H*-1,2,4-triazole (4o): Compound **4o** was obtained as a white solid in 96% yield (General Procedure C). R_f = 0.56 (PE/EtOAc, 6:4); m.p. 148–150 °C. IR (ATR diamond): ṽ= 2992, 2921, 1863, 1796, 1560, 1464, 1328, 1286, 1274, 1146, 1008, 837, 775, 754, 718, 686 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 14.27 (br. s, 1 H), 7.87–7.75 (m, 2 H), 7.42–7.30 (m, 3 H), 7.24–7.18 (m, 1 H), 7.15–7.08 (m, 4 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 132.0 (2 CH_{Ar}), 130.6 (CH_{Ar}), 129.3 (CH_{Ar}), 128.8 (2 CH_{Ar}), 128.2 (2 CH_{Ar}), 126.5 (2 CH_{Ar}) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{16}H_{11}N_3S$ [M + H]$^+$ 278.07464; found 278.07514.

3-(Pent-1-yn-1-ylthio)-5-phenyl-1*H*-1,2,4-triazole (4p): Compound **4p** was obtained as a white solid in 97% yield (General Procedure C). R_f = 0.60 (PE/EtOAc, 6:4); m.p. 122–124 °C. IR (ATR diamond): ṽ= 3129, 3069, 2930, 2868, 2797, 1558, 1464, 1407, 1329, 1283, 1272, 1140, 1008, 878, 828, 776, 720, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.78 (br. s, 1 H), 8.01–7.87 (m, 2 H), 7.49–7.32 (m, 3 H), 2.08–2.01 (m, 2 H), 1.47–1.29 (m, 2 H), 0.86 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C DEPT NMR (101 MHz, $CDCl_3$): δ = 130.5 (CH_{Ar}), 128.9 (2 CH_{Ar}), 126.5 (2 CH_{Ar}), 22.0 (CH_2), 21.6 (CH_2), 13.4 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{13}H_{13}N_3S$ [M + H]$^+$ 244.09029; found 244.09076.

3-(Isopropylthio)-5-methyl-1*H*-1,2,4-triazole (5a): Compound **5a** was obtained as a yellow solid in 96% yield (General Procedure B). R_f = 0.33 (PE/EtOAc, 6:4); m.p. 70–72 °C. IR (ATR diamond): ṽ= 3156, 3026, 2927, 2864, 2654, 1765, 1588, 1435, 1376, 1322, 1268, 1242, 1156, 1060, 883, 703, 641 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.83 (br. s, 1 H), 3.77–3.67 (m, 1 H), 2.56 (s, 3 H), 1.38 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.5 (C_q), 156.0 (C_q), 38.3 (CH), 23.5 (2CH_3), 12.6 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_6H_{11}N_3S$ [M + H]$^+$ 158.07464; found 158.07509.

3-(Isopropylthio)-5-pyridinyl-1*H*-1,2,4-triazole (5b): Compound **5b** was obtained as a white solid in 10% yield (General Procedure B) and 62% yield (General Procedure D). R_f = 0.23 (PE/EtOAc, 3:7); m.p. 157–159 °C. IR (ATR diamond): ṽ= 3396, 2962, 2494, 1846, 1613, 1427, 1337, 1308, 1240, 1009, 991, 836, 746, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.87 (br. s, 1 H), 8.75 (d, *J* = 6.1 Hz, 2 H), 8.08 (d, *J* = 6.2 Hz, 2 H), 3.80–3.92 (m, 1 H), 1.45 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.3 (C_q), 153.8 (C_q), 149.5 (2CH_{Ar}), 138.9 (C_q), 120.9 (2CH_{Ar}), 39.5 (CH), 23.5 (2CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_{10}H_{12}N_4S$ [M + H]$^+$ 221.08554; found 221.08610.

5-Methyl-3-(vinylthio)-1*H*-1,2,4-triazole (5c):[13b] Compound **5c** was obtained as a white solid in 92% yield (General Procedure B). R_f = 0.58 (PE/EtOAc, 6:4); m.p. 133–135 °C. IR (ATR diamond): ṽ= 3156, 3028, 2927, 2873, 2802, 2655, 1712, 1588, 1427, 1372, 1329, 1266, 1059, 955, 888, 864, 728, 713, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.36 (br. s, 1 H), 6.79 (dd, *J* = 16.8, 9.7 Hz, 1 H), 5.52 (d, *J* = 16.8 Hz, 1 H), 5.46 (d, *J* = 9.7 Hz, 1 H), 2.55 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.4 (C_q), 155.6 (C_q), 127.7 (CH), 117.1 (CH_2), 12.4 (CH_3) ppm. HRMS (EI-MS): *m*/*z* calcd. for $C_5H_7N_3S$ [M + H]$^+$ 142.04334; found 142.04366.

3-(Vinylthio)-5-pyridinyl-1*H*-1,2,4-triazole (5d): Compound **5d** was obtained as a white solid in 7% yield (General Procedure B) and

in 63% yield (General Procedure D). R_f = 0.16 (PE/EtOAc, 3:7); m.p. 160–162 °C. IR (ATR diamond): ṽ= 3031, 2452, 1873, 1612, 1427, 1333, 1301, 1009, 968, 836, 750, 707, 980, 678 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 13.71 (br. s, 1 H), 8.75 (d, J = 6.2 Hz, 2 H), 8.08 (d, J = 6.2 Hz, 2 H), 6.85 (dd, J = 16.8, 9.6 Hz, 1 H), 5.60 (d, J = 16.8 Hz, 1 H), 5.55 (d, J = 9.6 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.6 (C_q), 153.1 (C_q), 149.4 ($2CH_{Ar}$), 138.6 (C_q), 126.5 (CH), 121.0 ($2CH_{Ar}$), 118.7 (CH_2) ppm. HRMS (EI-MS): *m/z* calcd. for $C_9H_8N_4S$ $[M + H]^+$ 205.05424; found 205.05488.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C and ^{13}C DEPT NMR spectra for all compounds.

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[9] CCDC-961576 (for **4c**) and -961577 (for **4b′**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] ^1H NMR spectra of compounds **4b** and **4b′** as well as of their mixture in $CDCl_3$ are similar.

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