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1,2,3-Triazole N(2)-chelated C–S coupling: Access to *ortho* methylthiolated 1,2,3-triazoles

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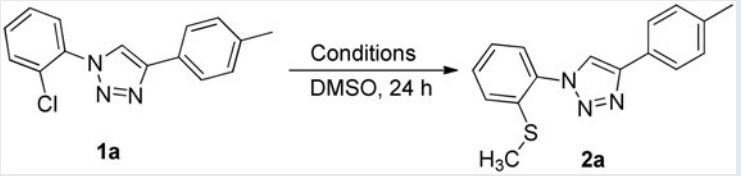
ABSTRACT

CuF_2-mediated selective C-S coupling of 1,4-disubstituted 1,2,3-triazole halides using the widely available DMSO as the methylthiolation reagent were achieved through the chelation of N(2) atom in triazole ring. The ortho- C-halogen bond in N(1) aryl was selectively coupled, while other C-halogen bonds remained, generating 1,4-disubstituted 1,2,3-triazoles bearing aryl methyl thioether fragment.

GRAPHICAL ABSTRACT



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KEYWORDS
CuF2-mediated; DMSO; methylthiolation; 1,2,3-triazoles

Introduction

Aryl methyl thioethers are commonly found in many pharmaceuticals and agrochemicals, especially in the field of some biology inhibitors such as monoamine oxidase A (MAO-A), cyclooxygenase-2 (COX-2), cytokine release, and etc (Figure 1).[1–6] In addition, they also act as important structural moieties[7–9] and vital intermediates,[10–16] which can be transformed into corresponding sulfoxides, thiols, and used for cross-couplings.

Consequently, broad efforts have been devoted in exploring efficient and facile accesses for the synthesis of aryl methyl thioethers.[17–21] Mostly, the classical accesses to aryl methyl sulfides usually depend on the combination of aryl lithiums with dimethyl disulfides[22] or nucleophilic aromatic substitution of aryl halides with thiolate anions, including sodium methylthiolate (NaSMe)[23] or (methylthio)trimethylsilanes (TMSSMe).[24] Inspiringly, the widely available dimethyl sulfoxide (DMSO) was found as an applicable methylthiolation reagent, which was highly valued then. In the early year of 2010, Qing group[25] explored CuF_2-mediated selective methylthiolation of aryl

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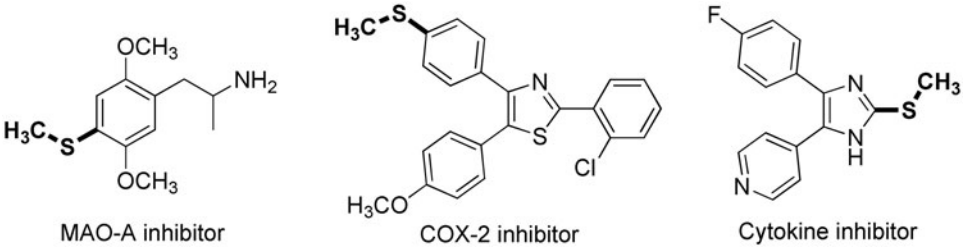


Figure 1. Examples of biology inhibitors.

C–H bonds with DMSO under the direction of 2-pyridyl. Thereafter, methylthiolation of aryl halides with DMSO was also reported by Cheng,[26] which was mediated by CuBr or CuI with excellent tolerance of functional group. Recently, Huang[27] reached copper-catalyzed ortho-thiomethylation of benzamides through 8-aminoquinoline-assisted C–H activation with dimethyl sulfoxide. Simultaneously, Tan group realized decarboxylative methylthiolation of aromatic carboxylate salts with DMSO.[28]

Meanwhile, from the breakthrough of Sharpless's highly efficient Cu-catalyzed cycloaddition reaction of terminal alkyne with azide, a large number of 1,2,3-triazoles have been constructed,[29–32] which were widely applied in many fields such as organic synthesis, materials, and biochemistry.[33–39] However, most methods still suffer from the synthesis of target with complicated structure as the corresponding functionalized alkyne and azide needed are unobtainable. As an alternative, the strategy of direct modification of 1,2,3-triazoles emerges as a powerful access for the construction of functionalized 1,2,3-triazoles. Kuang, Wu, Liu, Correa, Ackmann, and our groups respectively explored the modifications of 1,2,3-triazoles, mainly including C–C, C–N, and C–O couplings, generating functionalized molecules bearing biphenyl, nitryl, and ether fragment, which enormously enriched the kinds of 1,2,3-triazoles for various applications.[40–45]

In the above reports the regioselective couplings occurred only on C(4) aryl of the 1,4-disubstituted 1,2,3-triazoles as the N(3) atom was selectively chelated in the catalytic cycle. To my knowledge, the types were mainly limited in C–C, C–N, and C–O coupling, while the C–S bond formation has not been reported and there was scarcely no work focused on the N(1) aryl till now. Herein, we would like to demonstrate a process of C–S formation on the N(1) aryl, in which N(2) atom should be chelated in the in the active mediate revolved.

Results and discussion

In our initial study, 1-(2-chlorophenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole (**1a**) was chosen as model substrate for optimization of the reaction conditions. We investigated the effects of catalyst, oxide, and temperature respectively, as summarized in Table 1. No product of 1-(2-(methylthio)phenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole **2a** was obtained when the reaction was catalyzed by $Pd(OAc)_2$ (0.2 equiv.), using $K_2S_2O_8$ (2 equiv.) as the oxide, and DMSO as the thiomethylation reagent and solvent under 150 °C (Table 1, entry 1). The product was obtained if 0.2 equivalent of CuF_2 was applied to mediate the reaction, though the yield was low (Table 1, entry 2). When the amount of CuF_2 was increased

Table 1. Optimization of reaction conditions[a].

Entry	Additive (Equiv.)	Oxide (Equiv.)	Temp.	**2a** (%)[b]
1	$Pd(OAc)_2$ (0.2)	$K_2S_2O_8$ (2)	150 °C	0
2	CuF_2 (0.2)	$K_2S_2O_8$ (2)	150 °C	9
3	CuF_2 (4)	$K_2S_2O_8$ (2)	150 °C	19
4	CuF_2 (4)	$K_2S_2O_8$ (2)	140 °C	0
5	CuF_2 (4)	$K_2S_2O_8$ (2)	160 °C	20
6	CuF_2 (4)	$(NH_4)_2S_2O_8$ (2)	150 °C	46
7	CuF_2 (4)	Ag_2CO_3 (2)	150 °C	53
8	CuF_2 (4)	TBHP (2)	150 °C	88
9	CuF_2 (4)	O_2	150 °C	0
10	CuF_2 (4)	$Cu(OAc)_2$ (2)	150 °C	26
11	$Cu(OTf)_2$ (4)	TBHP (2)	150 °C	25
12	$CuBr_2$ (4)	TBHP (2)	100 °C	0
13	$CuCl_2$ (4)	TBHP (2)	90 °C	0
14	CuO (4)	TBHP (2)	110 °C	36
15	CuF_2 (3)	TBHP (2)	100 °C	66
16	CuF_2 (5)	TBHP (2)	100 °C	83

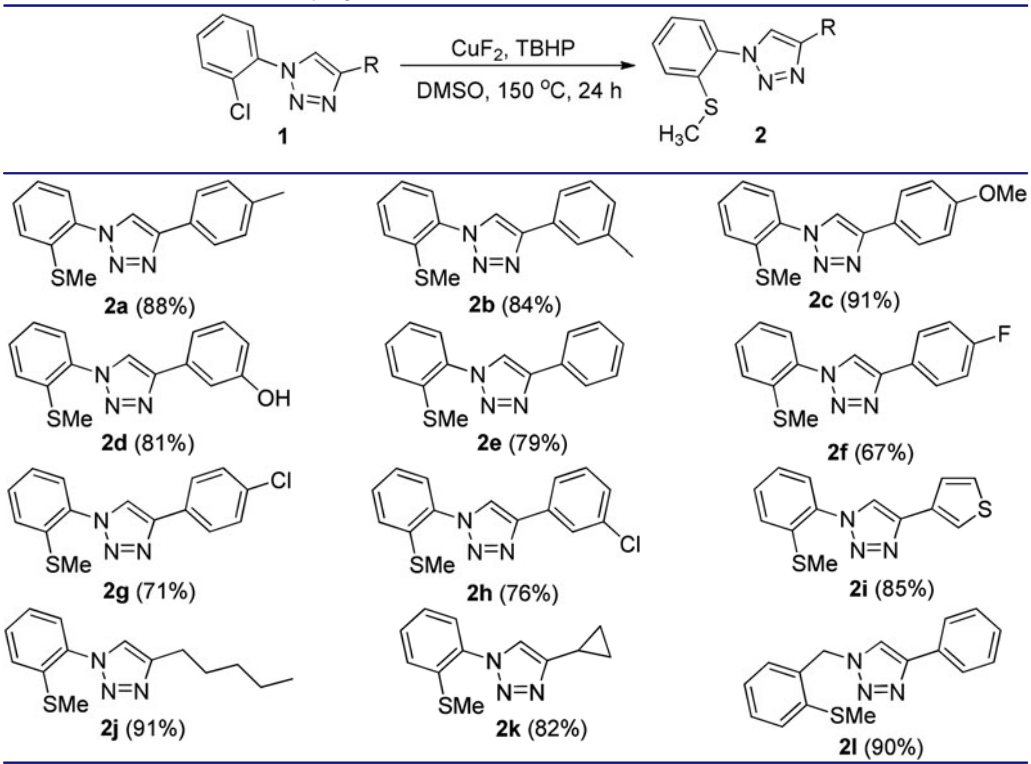
[a]The reaction conditions are as follows: 1,2,3-triazole chloride **1a** (0.3 mmol), additive, oxide (0.6 mmol), and DMSO (2 mL).
[b]Isolated yield.

to 4 equivalents, a better yield of 19% could be obtained (Table 1, entry 3). The reaction temperature has a distinct influence on this conversion as no product was detected when the temperature was decreased to 140 °C (Table 1, entry 4). Higher temperature seemed of no obvious use, as the yield was not increased when the reaction was conducted under 160 °C (Table 1, entry 5).

We then explored the influence of oxides and found that TBHP was the best choice, under which a satisfying yield of 88% could be obtained and others like $(NH_4)_2S_2O_8$, Ag_2CO_3, $Cu(OAc)_2$, and O_2 were comparatively inferior (Table 1, entries 6-10). Other cuprous salts such as $Cu(OTf)_2$, $CuBr_2$, $CuCl_2$, and CuO are not so efficient than CuF_2 to this reaction (Table 1, entries 11–14). The amount of CuF_2 screenings showed that 4 equivalent was superior as the yield decreased to 66% when we adjusted CuF_2 to 3 equivalent and more CuF_2 adding played no obvious positive role in the reaction (Table 1, entries 15–16). So, the best conditions for this transformation is CuF_2 (4 eq.), TBHP (2 eq.), and DMSO under 150 °C for 24 h (Table 1, entry 8).

With the optimized conditions in hand, the selective C–S coupling reactions were carried out with a range of 1, 4-disubstituted 1,2,3-triazole chloride **1** in DMSO, generating methylthiolation products with good to excellent yields. As shown in Table 2, the coupling reactions of 1,2,3-triazole substrates containing electron-donating group (such as $-CH_3$, –OH, $-OCH_3$) or electron-withdrawing group (such as –F, –Cl) on its C(4)-aryl could all go smoothly (Table 2, 2a–2h). It was observed that electron-donating substituents are beneficial to this C–S coupling, leading to higher yields, and some electron-withdrawing groups seemed unfavorable to this reaction (Table 2, 2a–2c vs 2f–2h). Moreover, hydroxyl active group was tolerated in the system and a good yield was

Table 2. N(2)-coordinated C-S coupling of 1,4-disubstituted 1,2,3-triazole chlorides[a,b].

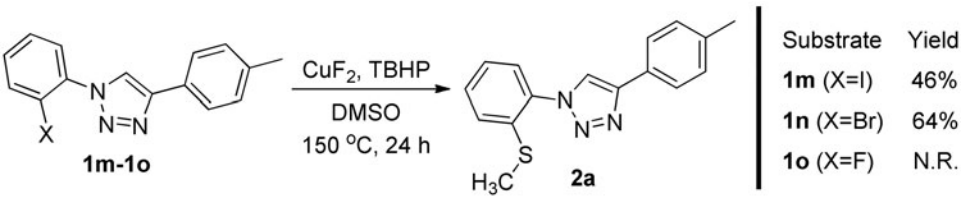


[a]Reaction conditions: 1,4-disubstituted 1,2,3-triazole chloride **1** (0.3 mmol), CuF_2 (1.2 mmol), TBHP (0.6 mmol), and DMSO (2 mL) were mixed and stirred at 150 °C for 24h.
[b]Isolated yield.

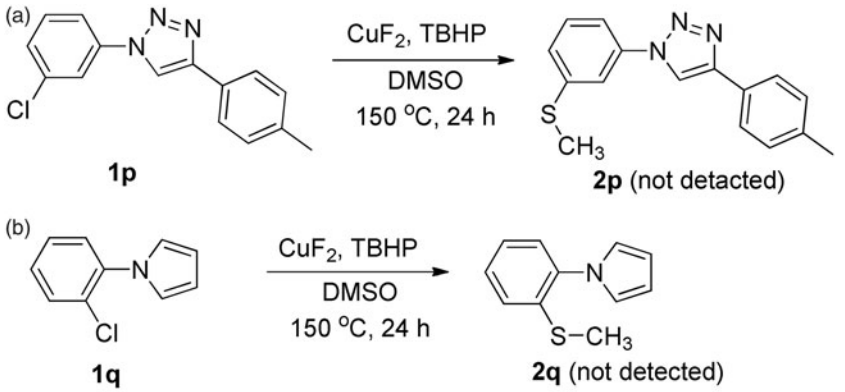
generated (Table 2, 2d). It is worth to be noted that substituent of -Cl on *meta*- or *para*- position of C(4)-aryl in the substrates was found to be perfectly compatible, which was probably owing to the effect of N(2) coordination of the 1,2,3-triazole ring (Table 2, 2g-2h). Except 1,4-diaryl 1,2,3-triazoles, molecules with 4-thienyl, 4-pentyl, 4-cyclopropyl, and 1-benzyl group can serve as the substrates, and good to excellent yields were obtained (Table 2, 2i–2l).

We then explored the coupling reactions of other C–X bonds (X = I, Br, and F) by using 1-(2-halophenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole (Scheme 1, 1m–1o) as the substrates. Obviously as shown in Scheme 1, good and excellent yields were obtained from the triazole iodide and bromide respectively (**1m**, **1n**). While no methylthiolation molecule was observed when the triazole fluoride was chosen for the coupling, which may be due to the high stability of C–F bond (**1o**).

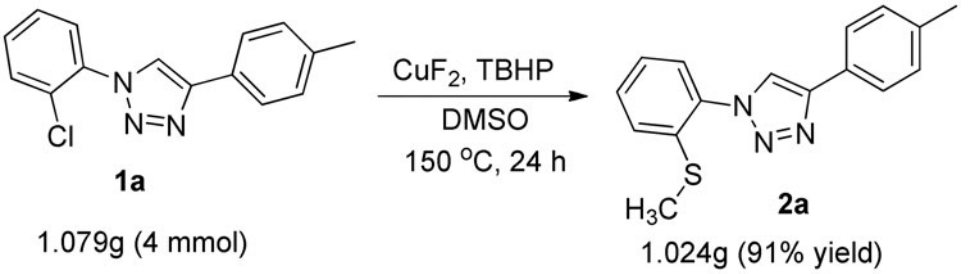
To evaluate the N(2) coordination role of the 1,2,3-triazole ring furtherly, we carried out the reaction of 1-(3-chlorophenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole **1p** and 1-(2-chlorophenyl)-1*H*-pyrrole **1p**, in which no directing effect could occur on the C–Cl bond (Scheme 2). After the reaction was conducted under standard conditions, no target molecules were detected, which explained that the N(2) coordination of the 1,2,3-triazole ring should play an important role in this methylthiolation process.



Scheme 1. Reactions of other triazole halides.



Scheme 2. Experiments of testing the N(2) coordination role.



Scheme 3. Gram scale experiment.

To test the scalability of the current method, the gram scale reaction of 1-(2-chlorophenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole **1a** (4.0 mmol, 1.079 g) as the starting materials was carried out under the standard conditions, and the product **2a** was isolated in 91% yield (Scheme 3).

Conclusion

In conclusion, we have demonstrated the CuF-mediated regioselective C–S coupling of 1, 4-disubstituted 1,2,3-triazole halides, using DMSO as a methylthiolation source, in which the *ortho*- C–X (X = Cl, Br, I) bond in N(1) aryl can be selectively aryloxylated while other C–X bonds remained, owing to the coordination of the N(2) atom in the

1,2,3-triazole ring. The obtained products contain two important structures of 1,2,3-triazole and aryl methyl thioether, which may serve as meaningful molecules in the future.

Experimental

^{1}H and ^{13}C NMR spectra were recorded with a Bruker ACF400 spectrometer (400 MHz) in $CDCl_3$ with TMS as an internal standard. All reactions were monitored by TLC analysis with HuanghaiGF 254 silica gel-coated plates. Column chromatography was conducted using 300 to 400 mesh silica gel at medium pressure. Infrared spectra were recorded on the Bruker Vertex Series FTIR (KBr) and were reported in reciprocal centimeters (cm^{-1}). Melting points were obtained using the Büchi melting point apparatus and were uncorrected. HRMS spectra were recorded on the Waters Micromass Premier Q-TOF spectrometer.

General procedures

1, 4-Disubstited 1,2,3-triazole halide **1** (0.3 mmol), CuF_2 (1.2 mmol), *t*-butylhydroperoxide (TBHP) (0.6 mmol), and DMSO (2 mL) were added to a 15 mL pressure tube. Then the tube was sealed with a teflon screwcap and stirred at 150 °C for 24 h. After consumption of 1, 4-Disubstited 1,2,3-triazole halide **1** monitored by TLC analysis, the mixture was added with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (3 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude product. Purification by column chromatography on silica gel afforded the desired product **2**.

Spectral data for the selected compounds

Compound 2a:

Yellow solid; mp 90–92 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.51–7.47 (m, 2H), 7.43 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.7 Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.59, 138.13, 135.49, 135.07, 130.18, 129.53, 127.50, 127.47, 126.72, 125.91, 125.76, 121.22, 21.30, 15.93; IR (KBr): 3404,2919, 1474, 1229, 1032, 815,749 cm^{-1}; HRMS Calcd for $[C_{16}H_{16}N_3S]^+$: 282.1059, Found: 282.1057.

Compound 2c:

Light yellow solid; mp 125–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.87 – 7.83 (m, 2H), 7.51–7.45 (m, 2H), 7.42 (dd, J = 8.3, 1.3 Hz, 1H), 7.35–7.29 (m, 1H), 7.01–6.97 (m, 2H), 3.85 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.68, 147.35, 135.52, 135.06, 130.13, 127.50, 127.15, 126.67, 125.88, 123.05, 120.73, 114.26, 55.29, 15.95; IR (KBr): 3123, 2967, 2924, 1612, 1476, 1439, 1253, 1176, 1028, 836, 797, 788, 536 cm^{-1}; HRMS Calcd for $[C_{16}H_{16}N_3OS]^+$: 298.1009, Found: 298.1011.

Compound 2i:

Dark brown solid; mp 76–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.77 (dd, $J = 3.0$, 1.2 Hz, 1H), 7.52 (dd, $J = 5.0$, 1.2 Hz, 1H), 7.48–7.44 (m, 2H), 7.44–7.41 (m, 1H), 7.41–7.39 (m, 1H), 7.31 (ddd, $J = 8.0$, 7.3, 1.5 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.62, 135.29, 135.10, 131.48, 130.20, 127.42, 126.65, 126.31, 125.84, 125.83, 121.34, 15.86; IR (KBr): 3429, 3091,2921,1586, 1481, 1429, 1043, 803, 757, 620 cm^{-1}; HRMS Calcd for $[C_{13}H_{12}N_3S_2]^+$: 274.0467, Found: 274.0471.

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