One-Pot Synthesis of Some New s-Triazole Derivatives and Their Potential Application for Water Decontamination

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ABSTRACT: A rapid, efficient, and one-pot protocol has been developed for the synthesis of cyclized 2,6-dimethyl-5-substituted-thiazolo[3,2-b]-s-triazoles (3a–c) through the interaction of 5-methyl-1H-s-triazole-3-thiol (1) with aliphatic ketones (2a–d) in refluxing acetic acid in the presence of a catalytic amount of sulfuric acid (AcOH/H+) while with aromatic ketones (5a–d), a mixture of uncyclized 3-methyl-s-triazolylthioacetophenone derivatives (6a–d) and cyclized 6-aryl-2-methyl-thiazolo[3,2-b]-s-triazoles (7a–d) has been produced. With this catalytic system, inexpensive sulfuric acid was utilized as a catalyst, which prevented the production of poisonous and irritating halo carbonyl compounds. On the other hand, the interaction of s-triazole 1 with cyano compounds (9a,b) afforded the corresponding 6-amino-2-methyl-5-substituted-thiazolo[3,2-b]-s-triazoles (10a,b). Similarly, treatment of 4-amino-3-methyl-s-triazole-5-thiol (12) with aliphatic and aromatic ketones (2c and 5a–e) afforded directly 3-methyl-7H-s-triazolo[3,4-b]-1,3,4-thiadiazines (13a and 14a–e). Further, reaction of 12 with cyano compounds (9a,b) under the same reaction conditions yielded the corresponding 3-methyl-s-triazolo[3,4-b]-1,3,4-thiadiazole derivatives (15a,b). The reaction mechanism was studied, and the structures of all novel compounds were verified using spectroscopy and elemental analysis. Moreover, the potential application of the synthesized compounds toward heavy metal ions and inorganic anion removal from aqueous solution has been investigated. The removal effectiveness for metal ions reached up to 76.29%, while for inorganic anions it reached up to 100%, indicating that such synthesized compounds are promising adsorbents for water remediation.

INTRODUCTION

In recent years, s-triazoles and their fused heterocyclic derivatives have received much interest due to their effective medicinal importance. There are many marked drugs, such as triazolam, alprazolam, and etizolam, containing the s-triazole group.\(^1\)–\(^6\) In the past decade, several applications of heterocyclic compounds containing nitrogen atoms have been reported.\(^7\)–\(^10\) Biological activities; biomedical uses; and commercial applications such as dyes, insecticides, and herbicides of s-triazoles linked to heterocyclic rings have also been demonstrated.\(^11\)–\(^15\) Recently, derivatives carrying the s-triazole moiety possess a wide spectrum of chemotherapeutic activities including antiviral,\(^16\) antifungal,\(^17\),\(^18\) antihelminthic,\(^19\) antitumor,\(^20\)–\(^22\) antibacterial,\(^23\) anti-inflammatory,\(^24\)–\(^26\) antitubercular,\(^27\) analgesic,\(^28\),\(^29\) antipyretic,\(^30\),\(^31\) and anticancer activities.\(^32\) Indeed, some of these derivatives were actually active ingredients of drugs.\(^33\) Based on the literature survey, due to the amino and mercapto groups, which are prime nucleophilic sites for the synthesis of condensed heterocyclic rings, 4-amino-s-triazol-3-thiones were thought to be helpful tools for the synthesis of triazolothiadiazoles and triazolothiadiazinones.\(^34\),\(^35\) We found that s-triazolo[3,4-b]-1,3,4-thiadiazines and s-triazolo[3,4-b]-1,3,4-thiadiazoles can be synthesized by the treatment of 4-amino-5-substituted-3-mercaptop-s-triazoles with \(\alpha\)-haloketone compounds and acids, respectively, in the presence of polyphosphoric acid.\(^36\) On the other hand, several reported methods were available for the synthesis of triazolo[3,2-b]-s-triazoles, including alkylation of s-triazole-3-thiol with phenacyl halides, 1,2-dihaloethane, or chloroacetic acid and the cyclization of 3-allyl-s-triazole with iodine.\(^40\) Unfortunately, the synthesis of such s-triazolothiadiazines, s-triazolothiadiazoles, and thiazolo-s-triazoles required several steps, lengthy time, and the use of poisonous and irritating halo carbonyl chemicals with generally low yields.\(^41\) Our team successfully synthesized novel compounds containing s-triazole diamines.\(^34\),\(^35\)
moiety derivatives and demonstrated their efficiencies toward heavy metal removal from aqueous solution.41

Therefore, development of new s-triazole derivatives with the efficient ability to remove heavy metals and anion ions from water is strongly needed. As part of our ongoing research toward the development of variously critical substances,42−44 this work demonstrates the synthesis of novel derivatives of s-triazolo-thiadiazines, s-triazolo-thiadiazoles, and thiazolo-s-triazoles in a faster reaction time and with high reaction yields using the acetylated acetic acid method that we have previously applied.45,46 Additionally, we demonstrate potential applications of such derivatives toward metals and anion removal from aqueous solution.

■ RESULTS AND DISCUSSION

Chemistry. In the context of our ongoing study on preparation of heterocyclic compounds using the acetylated acetic acid method, in this study, we scrutinized the behavior of 5-methyl-1H-s-triazole-3-thiol (1) and 4-amino-5-methyl-4H-s-triazole-3-thiol (12) with various aliphatic and aromatic ketones, as well as cyano compounds having active methylene or a methyl group. Remarkably, the reaction of compound 1 with aliphatic ketones such as acetone, ethyl acetoacetate, acetylaceton, and benzoyleceton (2a−d) in boiling acetic acid for 5 h in the presence of an acidic catalyst of sulfuric acid directly afforded 5,6-disubstituted-2-methyl-thiazolo[3,2-b]-s-triazoles 3a−c or other possible isomeric products of 4,5-disubstituted-3-methyl-thiazolo[2,3-c]-s-triazoles 4a−c or a mixture of them. Thin-layer chromatography (TLC) revealed that the reaction produced only a single product (Scheme 1). Similarly, the reaction of compound 1 with aromatic ketones such as acetophenone, p-methylacetophenone, p-chloroacetophenone, and p-bromoacetophenone (5a−d) under the same reaction conditions gave uncyclized 3-methyl-s-triazolylthioacetophenone derivatives (6a−d) in excellent yield, while increasing the reflux time to 10 h afforded a mixture of uncyclized compounds 6a−d and cyclized 6-aryl-2-methyl-thiazolo[3,2-b]s-triazoles (7a−d) or 5-aryl-3-methyl-thiazolo[2,3-c]-s-triazoles (8a−d); this mixture was separated via column chromatography (Scheme 1).

The structures of all products were confirmed using Fourier-transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopies, in addition to mass spectroscopy. FTIR spectra of the isolated products indicated the presence of distinct absorption bands at wavenumbers of 2997−2849, 1608−1568, and 1485−1444 cm−1 for C−H aliphatic, C=O, and C=O vibration bonds, respectively (Figures S1−S3). While the FTIR spectra of compounds obtained from

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acetylacetone and benzylocetone showed absorption bands at 1655–1637 cm⁻¹ attributed to CO vibration bonds, in addition, compounds obtained from benzylocetone featured a C–H aromatic vibration band at 3068 cm⁻¹. The ¹H-NMR spectra of the isolated products showed a singlet signal at 2.47–2.58 and 2.54–2.66 ppm corresponding to the protons of the CH₃ group in thiazole and triazole rings, respectively (Figures S4–S6). The compound obtained from acetylacetone was characterized by a signal at 2.91 ppm for COCH₃. In addition, the isolated products from acetoacetone and benzylocetone showed signals at 6.56 and 7.53 ppm attributed to protons of CH₃ triazole and the S–CH₂–CO group, respectively (Figures S7 and S8). In addition, compound 3b showed two additional peaks at 190.32 and 29.32 ppm attributed to the C=O and COCH₃ groups, respectively (Figure S8). Furthermore, the predicted molecular ion peaks were observed in the mass spectra of the produced compounds, and the mass spectra of the compounds obtained from acetylacetone and benzylocetone showed molecular ion M⁺ peaks at m/z values of 195 and 257, respectively. All of these findings cannot be used to determine which isomers, 3ac and 4ac–c, are produced.

The regioselectivity of the cyclization step is strongly dependent on the difference in the electron density on the N-1 and N-4 atoms of the starting compound 1. We have reported that the electron density of the N-1 atom is higher than that on the N-4 atom. Consequently, cyclization should be performed on the N-1 atom, leading to the formation of the isomeric products 3ac–c rather than 4ac–c. In addition, the electronic energy calculations confirmed that the isomeric products 3ac–c are more stable than the other isomeric products 4ac–c (Table S1). It is worth noting that s-triazole 1 produced the same product 3a when treated with acetone or ethyl acetoacetate, which was confirmed by the lack of carbonyl and ethyl groups in FTIR (Figure S1) and NMR (Figures S4 and S7) spectra. This finding indicated the hydrolysis of the ester group, followed by decarboxylation, as shown in Scheme S1.

The FTIR spectra of compounds 6a–d showed absorption bands at 3100–3018, 2923–2853, 1595–1582, and 1486–1431 cm⁻¹ for C–H aromatic, C–H aliphatic, C=N, and C=O vibration bands, in addition to the appearance of the N–H and C=O absorption bands at 3355–3156 and 1713–1680 cm⁻¹, respectively (Figures S9–S12). The ¹H-NMR spectra of compounds 6a–d featured a singlet signal at 2.28–2.39 and 4.69–4.74 ppm attributed to protons of CH₂ triazole and the S–CH₂–CO group, respectively. Additionally, aromatic protons and NH peaks were found at 7.35–8.09 and 13.56–13.58 ppm, respectively, in the isolated products 6a–d (Figures S13–S16). The ¹³C-NMR spectra of compounds 6a, 6c, and 6d showed signals at 193.06–193.88, 157.68–157.89, 153.86–154.45, and 31.26–38.86 ppm, respectively, for C=O, two triazole C=N, and S–CH₂–CO groups, as well as the other carbons at the anticipated chemical shifts (Figures S17–S19). The mass spectra of isolated products 6a, 6b, and 6c showed the expected molecular ion peaks of 233 [M⁺], 247 [M⁺], and 267 [Cl³⁵, M⁺ + 1], respectively.

As we deduced before and according to the electronic energy calculations (Table S1), the cyclization reaction of compounds 6a–d should produce cyclized 6-aryl-2-methyl-thiazolo[3,2-b]-2-triazoles (7a–d) rather than 5-aryl-3-methyl-thiazolo[2,3-c]-2-triazoles (8a–d). The FTIR spectra of compounds 7a–d showed absorption bands at 3091–3027, 2989–2848, 1598–1540, and 1478–1445 cm⁻¹ for C–H aromatic, C–H aliphatic, C=N, and C=O vibration bands, respectively (Figures S20–S23). All compounds 7a–d lacked NH absorption bands. The ¹H-NMR spectra of isolated products 7a–d showed signals at 2.55–2.70 and 7.14–8.08 ppm attributed to protons of CH₃ triazole and C–H aromatic, respectively (Figures S24–S26). In addition, compound 7b showed a singlet CH₃ signal at 2.44 ppm. The mass spectra of isolated products 7b, 7c, and 7d showed the expected molecular ion peaks of 229.20 [M⁺], 249 [Cl³⁵, M⁺], 251 [Cl³⁷, M⁺], 293 [Br³⁷, M⁺], and 295 [Br³⁹, M⁺], respectively.

When s-triazole 1 reacted with cyano compounds such as ethyl cyanoacacetate, cyanoacacetamide, and malononitrite (9a–c), it afforded 6-amino-2-methyl-thiazolo[3,2-b]-2-triazoles 10a,b,
other possible isomeric products 4-amino-3-methyl-thiazolo-
[2,3-c]-s-triazole 11a,b, or a mixture of them. However, based
on TLC, the reaction gave only a single product (Scheme 2).
According to the electronic energy calculations (Table S1), the
reaction product should be the more stable 10a,b rather than
the other isomeric products 11a,b (Scheme 2). It is
recognizable that the cyano group (9c, R=CN) undergoes
hydrolysis to the amide derivative 10b.

The FTIR spectra of compounds 10a,b showed absorption
bands at 3439−3270, 2977−2850, 1682−1667, 1606−1567,
and 1499−1477 cm$^{-1}$ for NH$_2$, C−H aliphatic, C=O, C=N,
and C=C vibration bands, respectively (Figures S27 and S28).

$^1$H-NMR spectra of compounds 10a,b showed singlet
signals at $\delta = 2.43−2.53$ and 6.26−7.27 (exchange with
D$_2$O) ppm attributed to protons of CH$_3$ triazole and NH$_2$,
respectively (Figures S29 and S30). Additionally, the isolated
product from ethyl cyanoacetate 10a showed a triplet signal at
$\delta = 1.35−1.38$ ppm for CH$_2$CH$_3$ and a quadruple signal at $\delta =
4.31−4.35$ ppm for CH$_3$CH$_2$ (Figure S29), while product 10b
showed singlet signal at $\delta = 7.53$ ppm attributed to CONH$_2$. 

Scheme 3. Reaction of 4-Amino-5-methyl-4H-s-triazole-3-thiol (12) with Ketones and Cyano Compounds
Under the reaction conditions, we studied the behavior of 4-amino-5-methyl-4H-s-triazole-3-thiol (12) with aliphatic ketone (2c) and aromatic ketones (5a–e), which confirmed the formation of 7-benzoyl-3,6-dimethyl-s-triazolo[3,4-b]-1,3,4-thiadiazine (13a) and 3-methyl-7H-s-triazolo[3,4-b]-1,3,4-thiadiazines (14a–e), respectively (Scheme 3). The FTIR spectrum of compound 13a was characterized by several absorption bands at 3069, 2926, 1592, and 1467 cm⁻¹ for C–H aromatic, C–H aliphatic, C=O, C=O=C, and C=C vibrations, respectively (Figure S32), while the FTIR spectra of the products 14a–e featured several absorption bands at 3072–3030, 2985–2904, 1608–1537, and 1473–1448 cm⁻¹ for C–H aromatic, C–H aliphatic, C=O, and C=C vibrations, respectively (Figures S33–S37). In addition, compound 14e showed a specific OH absorption band at 3265 cm⁻¹ (Figure S37). The 1H-NMR spectra of compound 13a featured a series of singlet signals at 5.00, 2.50, and 2.30 ppm, which could be assigned to the C–H, triazole CH₃, and thiadiazine CH₃ groups, respectively, as well as the aromatic vibrations, respectively (Figure S32), while the FTIR spectra of compounds 14a–e featured several singlet signals at 3.95 and 3.90 ppm attributed to the C–H and CH₃ triazole groups, respectively (Figure S50 and S51). The mass spectra of isolated products 14a,b showed the expected molecular ion peaks of 154.10 [M⁺] and 197.22 [M⁺], respectively.

Proposed Mechanism. The proposed mechanism for formation of isolated products 3a–c and 7a–d, 10a,b, and 15a,b are summarized in Schemes S2–S4, respectively. For 3a–c and 7a–d, the s-triazole is initially oxidized to form the disulfide intermediate 16, which is followed by the nucleophilic attack of the enolate form of the ketone to give the S-alkylation intermediate 17. This formed intermediate then undergoes intramolecular cyclization to directly give the desired products 3a–c and 7a–d (Scheme S2). The mechanism for formation of 6-amino-2-methyl-thiazolo[3,2-b]-s-triazoles (10a,b) may proceed via the formed disulfide 16, followed by a nucleophilic attack by the imine form on the dimeric disulfide to give the carbonium ion 18, which then undergoes intramolecular cyclization to produce the cyclized imino structures 19. Protonation of 19 in the presence of an acid medium produces the cyclized carbonium ion 20, followed by deprotonation to yield the cyclized compound 10a,b (Scheme S3). On the other hand, formation of s-triazolo[3,4-b]-1,3,4-thiadiazoles (15a,b) can be illustrated by the nucleophilic attack of the amino group of the starting s-triazole (12) on the cyano group of the nitrile compound (9a–c) to form the uncyclized imines (21). The formed imine 21 then undergoes intramolecular cyclization with elimination of ammonia molecule to produce the cyclized products 15a,b (Scheme S4). It is notable that the ester group of compound 15 (R=C=COOEt) formed from 9a undergoes hydrolysis followed by decarboxylation to produce the product 15a (R₁=H). The cyano group of compound 14 (R₂=CN) derived from 9c also undergoes hydrolysis to produce 14b (R₂=CONH₂).

Screening of Contaminant Removal from Aqueous Solution. The removal efficiencies of different contaminants from aqueous solutions using the thiazolo-s-triazole (compounds 3a–c and 7a–d), s-triazolylthioacetophe (compounds 6a–d), 6-amino-thiazolo-s-triazole (compounds 10a and 10b), s-triazolo[3,4-b]-1,3,4-thiadiazines (compounds 13a and 14a–e), and s-triazolo[3,4-b]-1,3,4-thiadiazole (compounds 15a and 15b) derivatives in this work were studied. For instance, the contaminants under investigation were cadmium and lead ions as heavy metal ions, and the anions were fluoride, chloride, and sulfate. Batch adsorption tests were used in the adsorption studies to assess the efficacy of the produced compounds based on the s-triazole moiety. Residual contaminant concentration in the aqueous solution after 24 h of adsorption (Cᵣ) was estimated via the related analytical technique, which has been previously described, and the removal efficiency of the synthesized compounds was calculated using eq 1. Adsorption experiments are based either on the reported typical concentration in water or on the maximum contaminated level (MCL) in drinking water. For instance, 10 mg/L was selected as the initial fluoride concentration because its MCL in water is 1.5 mg/L according to WHO. In the case of fluoride, its content in groundwater in many areas has been observed to range from less than 1.0 mg/L to more than 35.0 mg/L. In addition, the initial concentrations of chloride and sulfate ions were the same as the MCL (250 mg/L). Furthermore, 10 mg/L lead (Pb²⁺) and cadmium ions (Cd²⁺) as the initial concentration was selected as wastewater contains 10–100 mg/L heavy metal ion contaminant. All of the experiments were performed at pH 5.5.
Heavy Metal Ion Removal. Heavy metal ions such as cadmium and lead are known to be toxic and presage a risk to living systems when released into the environment. While poisoning of water with lead ions causes reduced intelligence, renal failure, and increased risk of cardiovascular diseases, contamination with cadmium ions leads to chronic anemia and endocrine disruptor and interferes with calcium regulation in biological systems. Adsorption technique allows for fast, cost-effective, reusable, and selective elimination of pollutants from aqueous solutions using synthetic chemicals. The adsorption process is used in the purifying of water where the dissolved pollutants are transferred to the adsorbent surface. Moreover, most technologies used in water treatment cost from 10 to 200 US$/m^3, while the cost of the adsorption method ranges from 1 to 54.47 US$/m^3, which is lower than that of the bromo group. For instance, 26.49 and 21.03% removal of Pb$^{2+}$ and Cd$^{2+}$ was found using 7b, while 52.91 and 30.96% removal was observed using 7a, respectively. Although the removal efficiencies were decreased when bromo and chloro groups were in the para position, the efficacy of the chloro group was higher than that of the bromo group. For instance, 26.49 and 21.03% removal of Pb$^{2+}$ and Cd$^{2+}$ was found using 7c, while 7d shows 17.31 and 13.65% removal of Pb$^{2+}$ and Cd$^{2+}$, respectively.

Likewise, high removal efficiency was observed using 10b with 64.77 and 48.26% removal of Pb$^{2+}$ and Cd$^{2+}$, respectively, in comparison with 10a, where the removal of Pb$^{2+}$ and Cd$^{2+}$ was found to be 58.05 and 35.74%, respectively. The reason for this could be attributed to the presence of the –CONH$_2$ group (amide group) in 10b and –COOC$_2$H$_5$ (ester group) in 10a that enhances complex formation.

Besides, compounds 6a–d (s-triazolylthioacetophenone) displayed the highest efficiencies compared to compounds 7a–d and the same trend as in the presence or the absence of donating or withdrawing groups, as shown in Figure 2. This could be ascribed to a lack of –NH absorption bands in compounds 7a–d. For example, the highest value of removal was found in the case of the presence of the methoxy group in the para position against the absence of the donating group with 66.55, 60.29, 56.60, and 59.17% removal of Pb$^{2+}$ and Cd$^{2+}$, respectively. Also, low removal of heavy metal ions was obtained in the case of the presence of the withdrawing group in the para position. For example, the chloro group in the para position, 6c, demonstrated Pb$^{2+}$ and Cd$^{2+}$ capacities of 59.17 and 36.84%, respectively, while 57.05 and 33.21% removal of Pb$^{2+}$ and Cd$^{2+}$ was observed using 5d in the case of the absence of the bromo group in the para position.

Moreover, moderate to high capacities of Pb$^{2+}$ and Cd$^{2+}$ removal were observed using s-triazolo[3,4-b][1,3,4]-thiadiazines (13a and 14a–e) and s-triazolo[3,4-b]-1,3,4-thiadiazole (15a and 15b) derivatives. Figure 3 illustrates removal efficiencies of Pb$^{2+}$ in the order of 66.55, 60.29, 56.60, 54.47, 50.89, and 41.26% and for Cd$^{2+}$ as 50.24, 37.36, 32.36, 31.20, 30.61, and 26.85% using 13a, 14e, 14b, 14a, 14c, and 25579

![Figure 1](https://doi.org/10.1021/acsomega.1c03675)

**Figure 1.** Lead and cadmium ion removal using 1,3-thiazolo-s-triazole derivatives.

![Figure 2](https://doi.org/10.1021/acsomega.1c03675)

**Figure 2.** Lead and cadmium ion removal using s-triazolylthioacetophenone derivatives.
Although lead and cadmium have the same radius, the outer electron configuration of lead shows a higher capacity than those of cadmium ions. This could be explained in terms of the adsorption capacity being related to the ionic radius, the electron configurations, and ionic charges of the metal ions. Although lead and cadmium have the same ionic radius, the outer electron configuration of cadmium is $3d^9$, while for lead it is $6s^2$. Moreover, the ionic radius of cadmium was smaller than that of lead. Thus, lead ion easily forms a stable electron configuration of $6s^2$ when reacted with the compounds under study.

**Inorganic Anion Removal.** It is shown that the thiazolo-$s$-triazole, 3a–c, and 7a–d, $s$-triazolylthioacetophenone, 6a–d, 6-amino-thiazolo-$s$-triazole, 10a and 10b, $s$-triazolo-$3,4-b$-$1,3,4$-thiazidazole, 13a, 14a–e, and $s$-triazolo-$3,4-b$-$1,3,4$-thiadiazole, 15a and 15b derivatives have a potency for anionic contaminants from 1 to 94% removal for chloride, 6 to 100% removal for sulfate, and 9 to 100% for fluoride. Figure 4 demonstrates that the 1,3-thiazolo-$s$-triazoles produced by the reaction of $s$-triazole with aliphatic ketones (3a–c) have higher efficiencies than those with aromatic ketones (7a–d). For instance, 56.34, 92.62, and 79.67% removal of chloride; 10.65, 32.04, and 16.54% removal of sulfate; and 80.47, 100.00, and 85.64% removal of fluoride were obtained using 3a, 3b, and 3c, respectively. However, 7a, 7b, 7c, and 7d offered 12.61, 25.17, 3.02, and 0.86% removal of chloride; 8.46, 15.14, 6.51, and 2.56% removal of sulfate; and 29.46, 36.15, 14.20, and 9.02% removal of fluoride, respectively.

Moreover, a range of chloride, sulfate, and fluoride removal from 19.29 to 33.74%, 94.09 to 100.00%, and 61.13 to 100.00%, respectively, was found using 6a, 6b, 6c, and 6d as illustrated in Figure 5. Regardless of the formation of the fused ring, as indicated in 6a–d and 7a–d, it is clear that the donating group in the para position has higher efficiency for inorganic anions and in heavy metal ions than the withdrawing group in the para position. Also, the bromo group in the para position decreases the capacity of anion removal compared to the chloro group. This could be attributed to the larger size of bromine than chlorine. For example, 21.25 and 19.29% using 6c and 6d and 3.02 and 0.86% using 7c and 7d for chloride were obtained. Likewise, 6c and 6d show 80.26 and 61.13% removal of fluoride, and 14.20 and 9.02% using 7c and 7d.

The reason for the high removal efficiency of fluoride compared to chloride could be attributed to the small size of fluoride in comparison to chlorine. The presence of two $-NH_2$ groups enhances anion removal from aqueous solution compared to one $-NH_2$ group as presented in 10b and 10a. For example, 18.70, 36.28, and 100% removal of chloride, sulfate, and fluoride were obtained using 10a, while 10b shows 21.84, 37.14, and 100% removal for chloride, sulfate, and fluoride, respectively. Even though 14a–d compounds have the same donating and withdrawing functional groups as 7a–d, their removal capacities were found to be higher. This could be attributed to the fused ring of the six-membered ring having higher efficiency than five-membered rings. Thus, 88.27, 90.34, 68.12, and 5.45% removal of chloride; 88.27, 90.34, 68.12, and 5.45% removal of sulfate; and 88.27, 90.34, 68.12, and 5.45% removal of fluoride were obtained using 14a, 14b, 14c, and 14d, respectively, as shown in Figure 6. In addition, high capacities using 13a and 14e were acquired with 75.84 and 63.31% removal of fluoride, 94.14 and 93.69% removal of chloride, and 91.46 and 90.77% removal of sulfate. Furthermore, the acetamide group increases the removal percentage of inorganic anion contaminants. Therefore, the removal of fluoride, chloride, and sulfate with 100.00, 94.35,
interactions led to the high affinity of inorganic anions (e.g., fluoride, chloride, and sulfate) towards metal ions and the compounds under investigation. Consequently, elucidation of the removal mechanism of lead ions and fluoride using representative compounds under investigation (6b and 10b) is demonstrated in Figures S52 and S53. Figure S52 shows that the intensity of −NH and −C═O functional groups of 6b decreased in the case of interaction either with lead or fluoride ions. Also, when 10b reacted with fluoride or lead ions, it led to a decrease in the bands of −NH₃ and −C═O functional groups, as shown in Figure S53. Therefore, it is worth mentioning that the nitrogen and/or oxygen atoms of the s-triazole moiety act as donor ligands, and the unpaired electrons of oxygen and/or nitrogen atoms could create coordination bonds with M²⁺ ions leading to mononucelating ligand structures, as shown in Figure 7. The results are in agreement with those reported in the literature.54

**CONCLUSIONS**

In summary, we have developed an efficient and a one-pot protocol for the synthesis of 2,6-dimethyl-5-substituted-thiazolo[3,2-b]-s-triazoles (3a–c), 3-methyl-s-triazolylthioacetophenone derivatives (6a–d), cyclized 6-aryl-2-methyl-thiazolo[3,2-b]-s-triazoles (7a–d), and 6-amino-2-methyl-5-substituted-thiazolo[3,2-b]-s-triazoles (10a,b) through the interaction of 5-methyl-1H-s-triazole-3-thiol (1) with aliphatic and aromatic ketones and cyano compounds in refluxing acetic acid in the presence of a catalytic amount of sulfuric acid (AcOH/H⁺). Similarly, we studied the behavior of 4-amino-3-methyl-s-triazolylthioacetophenone derivatives produced using aromatic ketones and cyano compounds to produce 3-methyl-7H-s-triazolo[3,4-b]-1,3,4-thiadiazines (13a and 14a–e) and 3-methyl-s-triazolo[3,4-b]-1,3,4-thiadiazole derivatives (15a,b). The present work shows the highest removal of lead with 45.59, 76.29, 63.53, 64.77, 66.55, and 60.40% and cadmium with 29.75, 52.39, 47.26, 48.26, 50.24, and 40.19% using 3b, 5b, 6b, 10b, 13a, and 14b, respectively. Also, the thiazolo-s-triazole derivatives produced using aromatic ketones exhibited higher efficiencies for heavy metal ion removal compared to those produced using aliphatic amines. In addition, the isolated intermediate compounds of s-triazolylthioacetophenone present high removal of lead and cadmium ions in comparison to thiazolo-s-triazole derivatives. For example, 76.29% removal of lead was found using 5b, while 6b shows 63.53% removal of lead ions. Furthermore, the methoxy group in the para position as the donating group shows a higher value of removal than

and 81.34%, respectively, was obtained using 15b. However, 15a demonstrates 96.48, 20.90, and 29.09% removal of fluoride, chloride, and sulfate, respectively.

**Contaminant Removal Mechanism.** The synthesized compounds based on the s-triazole derivatives’ moieties have a powerful effect for anionic contaminant (i.e., chloride, sulfate, and fluoride) removal up to 100% but up to 76% for cationic contaminants’ removal such as cadmium and lead. Thus, different adsorption processes may be discussed in terms of the physicochemical properties of the s-triazole derivatives, and thus the adsorption mechanism could be hypothesized. To explain this property, two aspects should be considered. First, the contaminant species at the studied pH and second the surface composition of the synthesized compounds may undergo a protonation reaction at the studied pH value. Therefore, high anion removal and low-to-moderate efficiencies for heavy metal ion removal were observed due to the presence of protons that induce the competitive adsorption reaction of proton ions for the existing adsorption sites. Another possibility is the production of protonated triazolium salts when the s-triazole heterocycle derivatives exist in an acidic medium.53 In this case, electrostatic attraction interactions led to the high affinity between inorganic anions and the synthesized triazole derivative compounds. But there is low attraction toward metal ions and the compounds under investigation. Consequently, elucidation of the removal mechanism of lead ions and fluoride using representative compounds under investigation (6b and 10b) is demonstrated in Figures S52 and S53. Figure S52 shows that the intensity of −NH and −C═O functional groups of 6b decreased in the case of interaction either with lead or fluoride ions. Also, when 10b reacted with fluoride or lead ions, it led to a decrease in the bands of −NH₃ and −C═O functional groups, as shown in Figure S53. Therefore, it is worth mentioning that the nitrogen and/or oxygen atoms of the s-triazole moiety act as donor ligands, and the unpaired electrons of oxygen and/or nitrogen atoms could create coordination bonds with M²⁺ ions leading to mono- or multinucleating ligand structures, as shown in Figure 7. The results are in agreement with those reported in the literature.54

**CONCLUSIONS**

In summary, we have developed an efficient and a one-pot protocol for the synthesis of 2,6-dimethyl-5-substituted-thiazolo[3,2-b]-s-triazoles (3a–c), 3-methyl-s-triazolylthioacetophenone derivatives (6a–d), cyclized 6-aryl-2-methyl-thiazolo[3,2-b]-s-triazoles (7a–d), and 6-amino-2-methyl-5-substituted-thiazolo[3,2-b]-s-triazoles (10a,b) through the interaction of 5-methyl-1H-s-triazole-3-thiol (1) with aliphatic and aromatic ketones and cyano compounds in refluxing acetic acid in the presence of a catalytic amount of sulfuric acid (AcOH/H⁺). Similarly, we studied the behavior of 4-amino-3-methyl-s-triazolylthioacetophenone derivatives produced using aromatic ketones and cyano compounds to produce 3-methyl-7H-s-triazolo[3,4-b]-1,3,4-thiadiazines (13a and 14a–e) and 3-methyl-s-triazolo[3,4-b]-1,3,4-thiadiazole derivatives (15a,b). The present work shows the highest removal of lead with 45.59, 76.29, 63.53, 64.77, 66.55, and 60.40% and cadmium with 29.75, 52.39, 47.26, 48.26, 50.24, and 40.19% using 3b, 5b, 6b, 10b, 13a, and 14b, respectively. Also, the thiazolo-s-triazole derivatives produced using aromatic ketones exhibited higher efficiencies for heavy metal ion removal compared to those produced using aliphatic amines. In addition, the isolated intermediate compounds of s-triazolylthioacetophenone present high removal of lead and cadmium ions in comparison to thiazolo-s-triazole derivatives. For example, 76.29% removal of lead was found using 5b, while 6b shows 63.53% removal of lead ions. Furthermore, the methoxy group in the para position as the donating group shows a higher value of removal than
chloro or bromo groups in the para position. For instance, 6b and 6c demonstrate 47.26 and 21.03% removal of lead, respectively. Hence, the adsorption capacity of lead was higher than that of cadmium due to its larger ionic radius. Moreover, 3b, 5b, 10a, 10b, and 14b offer 100% removal of fluoride. Also, 92.62, 33.74, 25.17, 21.84, 94.14, and 94.35% removal of chloride and 32.04, 100, 15.14, 37.14, 91.46, and 81.34% removal of sulfate were obtained using 3b, 5b, 6b, 10b, 13a, and 14b. As indicated, the synthesized compounds based on s-triazole moieties show high efficiency for anions as well as cations. The possible mechanism of heavy metal ion removal could be attributed to coordination bond formation between the nitrogen or the oxygen atom with the metal ion to form a stable complex. Also, electrostatic interaction between inorganic anions and the compounds under investigation is the predominant explanation for anion removal from aqueous solution. Thus, further studies on the chemical formula of the formed complex should be performed using elemental analysis, and the optimum conditions of removal of both anionic and cationic contaminants simultaneously must be identified.

## EXPERIMENTAL SECTION

### Materials

Thiosemicarbazide, ethyl cyanoacetate, and malononitrile were purchased from Prolabo, Paris. 2-Chloroacetoephene and p-bromoacetoephene were purchased from Fluka, and p-methylacetoephene from Riedel-de Haen ag. Ethyl acetoacetate was purchased from Aldrich and benzoylacetoephene from Sigma. Acetylacetone and glacial acetic acid were purchased from Sigma-Aldrich and glacial acetic acid from Fluka. Sodium chloride (NaCl), sodium sulfate (Na2SO4), sodium fluoride (NaF), lead chloride (PbCl2), cadmium chloride (CdCl2), dithizone, chloroform (CHCl3), potassium cyanide (KCN), and hydroxylamine hydrochloride (NH2Cl-H2O) were purchased from Sigma-Aldrich, Germany. All solutions were prepared with Milli-Q water and filtered using a 0.22 μm Nylon membrane filter.

### Synthetic Procedures

The general procedure for the synthesis of 2,6-dimethyl-5-substituted-1,3-thiazolo[3,2-b]-s-triazole (3a–c), 3-methyl-s-triazolylthioacetoephene derivates (6a–d), 2-methyl-6-aryl-1,3-thiazolo[3,2-b]-s-triazole (7a–d), and 6-amino-2-methyl-1,3-thiazolo[3,2-b]-s-triazole-5-carboxylate (10a,b) is as follows. Briefly, 5-methyl-1H-s-triazole-3-thiol (1, 0.008 mol) was added to a solution of aliphatic ketones (2a–c, 0.008 mol), aromatic ketones 5a–d (0.008 mol), or cyano compounds (9a,b, 0.008 mol) in glacial acetic acid (20 mL) with a catalytic amount of conc. H2SO4. Then, the mixture was refluxed for 5 h. After cooling to room temperature, the reaction mixture was diluted with H2O (10 mL) and neutralized with NH3 solution. The obtained crude product was collected by filtration, washed with H2O and crystallized from the appropriate solvent to give the desired products 3a–c, 6a–d, 7a–d, or 10a,b in good yield.

The general procedure for the synthesis of 3-methyl-6,7-disubstituted-7H-s-triazolo[3,4-b]-1,3,4-thiadiazoles (13a and 14a–d) and 3-methyl-6-substituted-s-triazolo[3,4-b][1,3,4]-thiadiazoles (15a,b) is as follows. Briefly, 4-amino-5-methyl-4H-s-triazole-3-thiol (12, 0.008 mol) was added to a solution of ketones (2c, 5a–e, 0.008 mol) or cyano compounds (9a,b, 0.008 mol) in glacial acetic acid (20 mL) with a catalytic amount of conc. H2SO4. Then, the mixture was refluxed for 3 h. After cooling to room temperature, the reaction mixture was diluted with H2O (10 mL) and neutralized with NH3 solution. The obtained crude product was collected by filtration, washed with H2O, and crystallized from the appropriate solvent to give the desired products 13a, 14a–d, or 15a,b in excellent yield.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03675.

Reaction mechanisms, synthetic procedures, electronic energy calculations, and spectral data of the synthetic compounds and adsorption experiments and mechanisms of the synthetic compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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### REFERENCES

1. Karegoudar, P.; Prasad, D. J.; Ashok, M.; Mahalinga, M.; Poojary, B.; Holla, B. S. Synthesis, antimicrobial and anti-inflammatory activities of some 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazoles and 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines bearing tri-chlorophenyl moiety. Eur. J. Med. Chem. 2008, 43, 808–815.
2. Ishoor, A. M.; Kalluraya, B.; Shetty, P. Synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1,2,4-triazoles. Eur. J. Med. Chem. 2009, 44, 3784–3787.
3. Padmavathi, V.; Thiveni, P.; Reddy, G. S.; Deepthi, D. Synthesis and antimicrobial activity of novel sulfonyl-linked bis heterocycles. Eur. J. Med. Chem. 2008, 43, 917–924.
4. Amir, M.; Kumar, H.; Javed, S. A. Condensed bridgehead nitrogen heterocyclic system: Synthesis and pharmacological activities of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole derivatives of ibuprofen and biphenyl-4-xyloxy acetic acid. Eur. J. Med. Chem. 2008, 43, 2056–2066.
5. Sztanke, K.; Tuzimski, T.; Rzymowska, J.; Pasternak, K.; Szerszen, M. Synthesis, determination of the lipophilicity, anticancer and antimicrobial properties of some fused 1,2,4-triazole derivatives. Eur. J. Med. Chem. 2008, 43, 404–419.
N-methyl-1,3,4-thiadiazol-2-amine and 4-methyl-2H-1,2,4-triazole: Coban, T.; Can-Eke, B. Synthesis and antioxidant properties of novel N-methyl-1,3,4-thiadiazol-2-amine and 4-methyl-2H-1,2,4-triazole-3(4H)-thione derivatives of benzimidazole class. *Bioorg. Med. Chem. 2008*, 16, 4294–4303.

Mohamed, M. G.; Ahmed, M. M.; Du, W. T.; Kuo, S. W. 2021. Meso/microporous carbons from conjugated hyper-crosslinked polymers based on tetraphenylethene for high-performance CO2 capture and supercapacitor. *Molecules 2021*, 26, No. 738.

Danko, M.; Mosnáček, J.; Kuo, S. W.; Lukić, I. Crosslinking of polystyrene film by di-(4-dibenzoyle peroxy) ether synthesized or formed in situ using visible light-induced photo-oxidation of 4,4′-oxydibenzil. *J. Photochem. Photobiol., A 2020*, 403, No. 112849.

Mohamed, M. G.; Atayde, E. C., Jr.; Matsagar, B. M.; Na, J.; Yamauchi, Y.; Wu, K. C. W.; Kuo, S. W. Construction hierarchically mesoporous/microporous materials based on block copolymer and covalent organic framework. *J. Taiwan Inst. Chem. Eng. 2020*, 112, 180–192.

Mohamed, M. G.; Meng, T. S.; Kuo, S. W. Intrinsic watersoluble benzoxazine-functionalized cyclooctadiene and its formation of inclusion complex with polymer. *Polymer 2021*, 226, No. 123827.

Holla, B. S.; Aliherali, P. M.; Shivananda, M. K. New 4-[1-(aryl)methylidene]-amino-3-(4-pyridyl)-5-mercapto-4H-1,2,4-triazole-derivatives as antibacterial agents: synthesis, biological evaluation and molecular docking study. *Med. Chem. Commun. 2015*, 6, 1104–1116.

Ahmidi, F.; Ghayahbashi, M. R.; Shariizadef, M.; Alipourie, E.; Ostad, S. N.; Vosooghi, A.; Amini, M.; et al. Synthesis and evaluation of anti-inflammatory and analgesic activities of new 1,2,4-triazole derivatives. *Med. Chem. 2014*, 11, 69–76.

Radwan, A. A.; Alazani, F. K.; Al-Agamy, M. H. 1, 3, 4-Thiadiazole and 1, 2, 4-triazole-3(4H)-thione bearing salicylate moiety: synthesis and evaluation as anti-Candida albicans. *Braz. J. Pharm. Sci. 2017*, 53, 1–12.

Siddiqui, A. A.; Mishra, R.; Kumar, R.; Rashid, M.; Khaidem, S. Synthesis, spectral characterization, and pharmacological screening of some 3-(1-{aryl}-methylidene)-amino-3-[4-(pyridyl)]-5-mercapto-4H-1,2,4-triazole derivatives. *J. Pharm. BioAllied Sci. 2010*, 2, 109–112.

Saremi, K.; Rad, S. K.; Tayeby, F.; Abdulla, M. A.; Karimian, H.; Majid, N. A. 2021. Progastroprotective activity of a novel Schiff base derived dibromo substituted compound against ethanol-induced acute gastric lesions in rats. *BMJ Pharmacol. Toxicol. 2019*, 20, No. 13.

Kaur, R.; Dwivedi, A. R.; Kumar, B.; Kumar, V. Recent Developments on 1,2,4-Triazole Nucleus in Anticancer Compounds: A Review. *Anticancer Agents Med. Chem. 2016*, 16, 465–489.

Kharb, R.; Sharma, P. C.; Yar, M. S. Pharmacological significance of triazole scaffold. *J. Enzyme Inhib. Med. Chem. 2011*, 26, 1–21.

El-Mahdy, A. F. M.; El-Shrief, H. A. H.; Zohein, Z. A.; Kuo, Sh-W. A Convenient One-Pot and Rapid Microwave-Assisted Synthesis of Biologically Active s-Triazole [3, 4-b][1, 3, 4] Thiaizidine and s-Triazolo [3, 4-b][1, 3, 4] Thiaizidine Nanoarchitectonics. *J. Nanosci. Nanotechnol. 2020*, 20, 2917–2929.

Shawali, A. S.; Zeid, I. F.; Abdellakder, M. H.; El-Sherbini, A. M.; et al. Synthesis, Acidity Constants and Tautomeric Structure of 7-Arylhydrazono[1,2,4]Triazolo[3,4-h][1,3,4]thiazidines in Ground and Excited States. *J. Chin. Chem. Soc. 2001*, 48, 65–72.

El-Dawy, M. A.; Omar, A. M. M. E.; Ismail, A. M.; Hazzaa, A. A. B. Potential Broad Spectrum Anthelmintics IV: Design, Synthesis, and Antiparasitic Screening of Certain 3,6-Disubstituted (7H) s-Triazolo-[1,2-a][1,3,4]thiadiazine Derivatives. *J. Pharm. Sci. A 1983*, 72, 45–50.

Heravi, M. M.; Rahimizadeh, M.; Seyf, M.; Davoodnia, A.; Ghassemzadeh, M. Bicyclic compounds derived from 4-amino-3-mercaptop-1,2,4-triazoles: Facile routes to 1,2,4-triazolo[3,4-b][1,3,4]thiazidines and 1,2,4-triazolo[3,4-b][1,3,4]thiazidines. *Phosphorus Sulfur Relat. Elem. 2000*, 167, 211–217.

Eweiss, N.; Bahajaj, A. Synthesis of heterocycles. Part VII Synthesis of 2- and 3-[4H]-1,2,4-triazolo[3,4-b][1,3,4]thiazidines and 1,2,4-triazolo[3,4-b][1,3,4]thiazidines. *Phosphorus Sulfur Relat. Elem. 2014*, 189, 157–179.

Hoizen, Z. A.; El-Mahdy, A. F. M.; Abo Marked, A.; Ali, L. S. A.; El-Shrief, A. H. Synthesis of Schiff and Mannich bases of new s-triazolyl derivatives and their potential applications for removal of heavy metals from aqueous solution and as antimicrobial agents. *RSC Adv. 2020*, 10, 20184–20194.
(42) El-Mahdy, A. F. M.; E-Sherief, H. A. H. An Efficient and Rapid Intramolecular Cyclization of a Quadruple Mannich Reaction for One-Pot Synthesis of Pentaazaphenalenes and Their Antimicrobial Activities. RSC Adv. 2016, 6, 92134−92143.

(43) El-Mahdy, A. F. M.; Mohamed, O. S.; El-Sherief, H. A. H.; Hozien, Z. A. An Efficient One-Pot Synthesis of Benzo[1,4]Thiazines, Benzo[1,3]Thiazoles and Benzo[1,5]Thiazepines. Curr. Org. Synth. 2017, 14, 604−611.

(44) El-Mahdy, A. F. M.; El-Sherief, H. A. H.; Hozien, Z. A. Convenient One-Pot Four-Component Synthesis of 6,8-Disubstituted-5,6,7,8-Tetrahydropyrimido[4,5-d]Pyrimidin-4(3H)-Ones via a Triple Mannich Reaction. Aust. J. Chem. 2019, 72, 542.

(45) El-Sherief, H. A. H.; Hozien, Z. A.; El-Mahdy, A. F. M.; Sarhan, A. A. O. Novel Method for the Synthesis of s-Triazolo[3,4-b][1,3,4]thiadiazines. Synthesis 2010, 2636−2642.

(46) Hozien, Z. A.; El-Mahdy, A. F. M.; El-Sherief, H. A. H.; Sarhan, A. A. O. One pot synthesis and reactions of novel 5-amino[1,3]-thiazolo[3,2-b][1,2,4]triazoles. ARKIVOC 2011, 2011, 71−84.

(47) Markeb, A. A.; Alonso, A.; Sánchez, A.; Font, X. Adsorption process of fluoride from drinking water with magnetic core-shell Ce-Ti@Fe3O4 and Ce-Ti oxide nanoparticles. Sci. Total Environ. 2017, 598, 949−958.

(48) Markeb, A. A.; Ordosgoitia, L. A.; Alonso, A.; Sanchez, A.; Font, X. Novel magnetic core−shell Ce−Ti@Fe3O4 nanoparticles as an adsorbent for water contaminants removal. RSC Adv. 2016, 6, 56913−56917.

(49) Ali, H.; Khan, E.; Sajad, M. A. Phytoremediation of heavy metals concepts and applications. Chemosphere 2013, 91, 869−881.

(50) Dotto, G. L.; McKay, G. Current scenario and challenges in adsorption for water treatment. J. Environ. Chem. Eng. 2020, 8, No. 103988.

(51) Mokadem, Z.; Mekki, S.; Saiti-Besbes, S.; Agusti, G.; Elaissari, A.; Derdour, A. Triazole containing magnetic core-silica shell nanoparticles for Pb2+, Cu2+ and Zn2+ removal. Arab. J. Chem. 2017, 10, 1039−1051.

(52) Zhu, L.; Zhang, L.; Tang, Y. Synthesis of Montmorillonite/Poly(acrylic acid-co-2-acrylamido-2-methyl-1-propane sulfonic acid) Superabsorbent Composite and the Study of its Adsorption. Bull. Korean Chem. Soc. 2012, 33, 1669−1674.

(53) Dehaen, W.; Bakulev, V. A. Chemistry of 1,2,3-Triazoles; Topics in Heterocyclic Chemistry; Springer, 2015; Vol. 40, p 384.

(54) Badruddoza, A. Z. M.; Tay, A. S. H.; Tan, P. Y.; Hidajat, K.; Uddin, M. S. Carboxymethyl-6-cyclodextrin conjugated magnetic nanoparticles as nano-adsorbents for removal of copper ions: Synthesis and adsorption studies. J. Hazard. Mater. 2011, 185, 1177−1186.