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Direct Synthesis of Thioethers from Carboxylates and Thiols Catalyzed by $FeCl_3$

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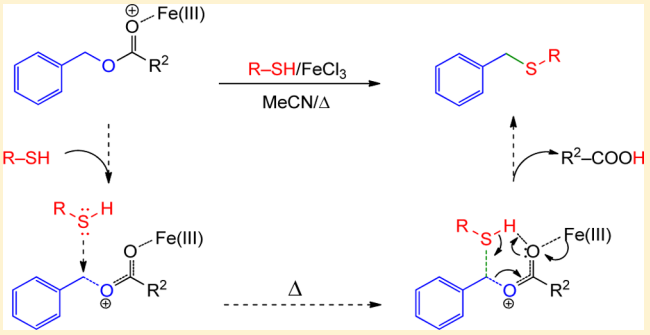
Supporting Information

ABSTRACT: A new and efficient method has been developed for the synthesis of thioethers from carboxylates and thiols. The reaction proceeds via a Fe(III)-catalyzed direct displacement of carboxylates from benzylic or allylic esters by heterocyclic thiols. Short reaction times, good to excellent yields of products, and few side reactions are the significant features of the new protocol.



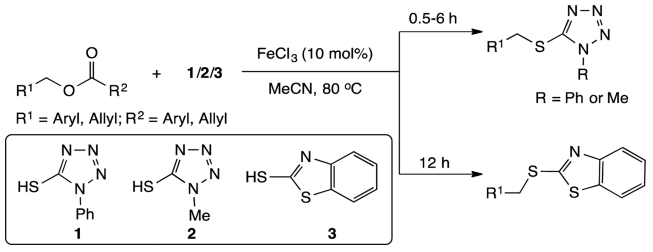
Organosulfur compounds are versatile intermediates for the synthesis of bioactive natural products and often possess significant pharmaceutical activities.[1,2] Among this class of compounds, thioethers[3] (e.g., Cephalosporin analogues), their derived sulfones[4] (e.g., Dapsone), and some sulfoxides[5] (e.g., Omeprazole, Armodafinil, and Ajoene) have been used extensively in human health care as well as in medicinal chemistry research.[3−5] All of these compounds have been prepared by several routes.[6] A wide range of thioethers and their derived sulfones are being used as synthons for the preparation of lead compounds and novel materials for human needs.[7]

In the past, several other methods have been employed for the synthesis of thioethers,[8] but these transformations required stoichiometric or near-stoichiometric amounts of catalyst. Although these techniques have shown great promise, in practice, they are characterized by various limitations such as tedious reaction procedures, contamination by side products, low yields, and expensive reagents and catalysts. These requirements render them commercially as well as ecologically untenable. Consequently, they are restricted from extensive industrial applications. To circumvent these problems, the development of more reliable and convenient procedures using readily accessible and inexpensive materials is a continuing goal. For example, in 2002, Hidai and co-workers[9] reported that ruthenium complexes catalyzed the direct synthesis of thioethers from propargyl alcohols and thiols. Recently, Wu et al.[10] reported that $Ga(OTf)_3$ also catalyzed the one-pot synthesis of thioethers from benzylic and allylic alcohols.

In the recent past, Fe-based catalysts have become a powerful tool in organic synthesis.[11] Interest in Fe(III)-catalyzed transformations has blossomed because of their environmentally benign characteristics, significant reactivity, and low cost. Furthermore, it is one of the most abundant metals in the Earth's crust. Metal-catalyzed C−O, C−S, C−C, and C−N bond formations have also gained much recent attention,[12] since they have vast potential in organic synthesis and material chemistry. In this connection, we wish to advance a simple and efficient Fe(III)-catalyzed protocol for the synthesis of thioethers.

As an extension of our previous work on the pivaloylation of alcohols[13a] and Fe(III)-catalyzed synthesis of esters,[13b] we herein report our recent work on the development of an inexpensive and efficient approach to the synthesis of thioethers. Direct displacement of carboxylates from benzyl or allyl esters by thiols has been achieved to generate the corresponding thioethers in the presence of anhydrous $FeCl_3$ in MeCN at 80 °C (Scheme 1).

Scheme 1. Direct Displacement of Benzylic and Allylic Carboxylates by Using Heterocyclic Thiols



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To optimize the required displacement of carboxylates with thiols, we selected the reaction of *p*-methoxybenzyl pivalate (**4**) with 1-phenyl-1*H*-tetrazole-5-thiol (**1**) as a model system. This transformation was evaluated under a variety of conditions to identify the optimum protocol, and the results are summarized in Table 1. These experiments demonstrated that the reaction

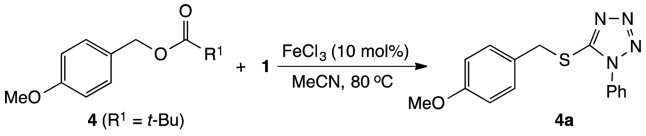
Table 1. Optimized Conditions for the Reaction of 1 with 4 To Give 4a[a]

entry	catalyst	conditions	time (h)	yield (%)
1	$FeCl_3$	MeCN/80 °C	1	96
2	$FeCl_3$	MeCN/25 °C	6	0
3	$FeCl_3$	H_2O/80 °C	6	trace
4	$FeCl_3{\cdot}6H_2O$	MeCN/80 °C	6	91
5	$Fe(OTf)_3$	MeCN/80 °C	1	96
6	$BiCl_3$	MeCN/80 °C	12	80
7	$AlCl_3$	MeCN/80 °C	12	68
8	none	MeCN/80 °C	6	00

[a]Reaction conditions: Thiol **1** (1 equiv), ester **4** (1.1 equiv), catalyst (10 mol %), 2.5 mL of MeCN, 80 °C.

performed in MeCN using anhydrous $FeCl_3$ (10 mol %) at 80 °C gave superior results, affording 96% of product **4a** in 1 h (Scheme 2). This same reaction (Table 1) afforded almost

Scheme 2. Reaction of 1 with 4−9



equal yields of **4a** (>95%) in the presence of $Fe(OTf)_3$ (10 mol %, 1 h) and gave slightly diminished yields (91%) of the required product in the presence of $FeCl_3{\cdot}6H_2O$ (10 mol %, 6 h).

After initial refinement of the reaction conditions, we turned our attention to evaluating the leaving group characteristics of the different carboxylate groups. We studied a series of carboxylates in place of the pivalyloxy group in **4** and performed reactions with thiol **1** under the same reaction conditions (10 mol % $FeCl_3$/MeCN/Δ, 1 h). Indeed, we did not perceive any significant change in the reactivity of esters **5**, **6**, and **7** which contain acetyloxy, benzoyloxy, or *p*-methoxybenzoyloxy, respectively, as leaving groups. In each case, the reaction proceeded smoothly with thiol **1** under the optimized conditions to furnish similar yields of **4a** (>94%). However, the use of ester **8**, with *p*-nitrobenzoyloxy as the leaving group, afforded only moderate yields of **4a** (∼74%), and **9**, with *m*-nitrobenzoyloxy as the leaving group, did not give any product.

To further validate our method, we investigated the scope and limitations of this novel transformation (Table 2). In this study, we used different benzylic and allylic pivalates in combination with **1**. The benzylic esters with electron-donating groups (e.g., -OMe) at C-4 of the benzene ring afforded excellent yields in most instances. The benzylic esters with electron-withdrawing groups (e.g., $-NO_2$) at C-4 afforded moderate to good yields (Table 2). Impressively, polycyclic aromatic and heteroaromatic esters furnished stunning (>99%) yields of the thioether products within 30 min (Table 2) under our standard reaction conditions. The allylic esters also gave high yields as shown in Table 2. On the other hand, esters **28**, **30**, and **32** did not react with **1** to any appreciable extent under the optimized conditions. We suspect this may be due to the steric hindrance present in one or both of the reacting partners (ester or thiols) in these reactions.

To extend the substrate scope, we have employed three additional thiols: 1-methyl-1*H*-tetrazole-5-thiol (**2**), benzo[*d*]-thiazole-2-thiol (**3**), and pyridine-2-thiol, as nucleophiles in combination with various esters that were reacted with **1** (Table 3). In assessing the expected reactivity of the various thiols, **1** and **2** should exhibit very similar nucleophilicities, with **2** being slightly more nucleophilic. Additionally, Ph- substitution adjacent to the thiol in **1** should make it more hindered than **2**. Thus, one might expect that **2** would react with more esters since it is less influenced by these two limiting factors. Thiol **3**, while not sterically hindered, potentially suffers from resonance deactivation and should show reduced nucleophilicity. Finally, the more highly delocalized pyridine-2-thiol should be even less reactive.

In practice, thiol **1** reacted with a large number of esters, including those with electron-rich benzylic esters, such as **6** and **7**, and more hindered benzylic and allylic systems such as **16** and **27**. However, it failed to react with extended chain esters such as **28**, **30**, and **32**. Thiol **2** also reacted smoothly with a broad selection of esters. In contrast to **1**, however, **2** did not react with electron-rich esters such as **6** and **7** or hindered systems such as **16** and **27**, but did react with the three esters **28**, **30**, and **32**. The results with **16**, **27**, **28**, **30**, and **32** support our assumptions regarding the importance of steric and electronic factors in the reactivity. Thiol **2** would be expected to fail when steric hindrance is close to the reaction site, as in **16** and **27**, since the methyl group cannot rotate to avoid the steric interaction as phenyl can. For the chain-extended esters, the site bearing the ester leaving group is less congested and reaction occurs faster with the less hindered more nucleophilic thiol **2**. The importance of thiol nucleophilicity was further substantiated by examination of the remaining thiols. As expected, resonance deactivated **3** (Scheme 3) reacted with fewer esters under the optimized reaction conditions and afforded products in only moderate yields. Finally, the more highly delocalized thiol in pyridine-2-thiol did not react with any of the esters used in the current study. Hence, the nucleophilicity of the four thiols **1**, **2**, **3**, and pyridine-2-thiol is in the order **2** > **1** > **3** ≫ pyridine-2-thiol.

Sulfides are most commonly prepared by the Mitsunobu reaction of an alcohol with a thiol in the presence of excess diisopropyl azodicarboxylate and triphenylphosphine.[14] This route, however, generally leads to a higher impurity profile (requiring chromatographic purification) and lower yields of the desired product. In contrast, the only byproduct generated in the current method is pivalic acid, and it can be easily removed from the reaction mixture by washing with aq $NaHCO_3$. Thus, our new method affords these sulfides in higher yields and with greater purities than most of the previously reported methods.

In conclusion, we have developed a convenient and efficient method for the conversion of benzyl and allyl pivalate (acetate and some benzoate) esters to sulfides by treatment with catalytic anhydrous $FeCl_3$ in MeCN at 80 °C. The reaction proceeds in high yield for activated benzyl and allyl pivalates as

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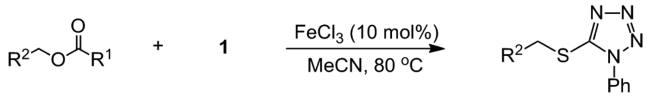
Table 2. Reaction of Different Esters with thiol 1 in the Presence of $FeCl_3$ in MeCN at 80 °C



Entry	Ester	Product, Yield, Time (h)
1	**5** (R^1 = Me, R^2 = 4-MeO-Ph)	**4a**, 95%, 1 h
2	**6** (R^1 = Ph, R^2 = 4-MeO-Ph)	**4a**, 95%, 1 h
3	**7** (R^1 = 4-MeO-Ph, R^2 = 4-MeO-Ph)	**4a**, 94%, 1 h
4	**8** (R^1 = 4-NO_2-Ph, R^2 = 4-MeO-Ph)	**4a**, 74%, 6 h
5	**9** (R^1 = 3-NO_2-Ph, R^2 = 4-MeO-Ph)	**4a**, 00%, 6 h
6	**10** (R^1 = *t*-Bu, R^2 = 4-Et-Ph)	**10a**, 94%, 4 h
7	**11** (R^1 = *t*-Bu, R^2 = 4-Pr-Ph)	**11a**, 95%, 4 h
8	**12** (R^1 = *t*-Bu, R^2 = 4-NO_2-Ph)	**12a**, 84%, 6 h
9	**13** (R^1 = *t*-Bu, R^2 = 3-NO_2-Ph)	**13a**, 92%, 6 h
10	**14**	**14a**, 96%, 1 h
11	**15**	**15a**, 88%, 3 h
12	**16** (R = Piv)	**16a**, 97%, 1 h
13	**17** (R = Ac)	**16a**, 95%, 1 h
15	**18** (X = O; R = Piv)	**18a**, 99%, 0.5 h
16	**19** (X = O; R = Ac)	**18a**, 99%, 0.5 h
17	**20** (X = S, R = Piv)	**20a**, 99%, 0.5 h
18	**21** (X = S; R = Ac)	**20a**, 99%, 0.5 h
19	**22**	**22a**, 99%, 0.5 h
20	**23** (R^1 = Piv, R^2 = Ph)	**23a**, 96%, 1 h
21	**24** (R^1 = Piv, R^2 = 4-OMe-Ph)	**24a**, 99%, 0.5 h
22	**25**	**25a**, 98%, 0.5 h
23	**26**	**26a**, 98%, 0.5 h
24	**27**	**27a**, 92%, 6 h
25	**28** (R = Piv)	No Reaction, 6 h
26	**29** (R = Ac)	No Reaction, 6 h
27	**30** (R = Piv)	No Reaction, 6 h
28	**31** (R = Ac)	No Reaction, 6 h
29	**32**	No Reaction, 6 h

well as substrates incorporating polycyclic aromatic and heteroaromatic rings. The conversion is rapid (generally ≤6 h) and generates the target sulfides with fewer side reactions than are observed by other approaches. The level of success in the reaction is somewhat dependent on the nucleophilicity of the sulfide nucleophile and the steric hindrance in proximity to the ester leaving group. It was also found that nitro substitution on the benzoate esters diminished the yields in the reaction. Nevertheless, the direct carboxylate-to-thioether conversion constitutes a powerful method for the high yield synthesis of a wide range of thioethers. These compounds are widely distributed in many commercial drugs, and thus, the current method could have broad applications in the synthesis of natural products and medicinal agents.

EXPERIMENTAL SECTION

General Procedure. The reaction was carried out by simple addition of the heterocyclic thiol (1.1 mmol) to the solution of ester (1.0 mmol) in MeCN (2.5 mL) in a 10 mL round-bottomed flask followed by the catalyst [$FeCl_3$, 16 mg (10 mol %)]. The reaction mixture was stirred at 80 °C and monitored by TLC. Upon completion, the crude mixture was diluted with EtOAc (5 mL) and washed with saturated aq $NaHCO_3$ (5 mL). The aqueous phase was extracted with EtOAc (1 × 10 mL), and the combined organic layers were dried over Na_2SO_4. The mixture was then concentrated under vacuum to yield the corresponding product. Purification of the final products, when necessary, was performed by chromatography through a short column of silica gel using hexane/EtOAc as the mobile phase.

5-(4-Methoxybenzylthio)-1-phenyl-1*H*-tetrazole[10] (4a, Scheme 2). Yield: 283 mg (95%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (m, 5H), 7.29 (d, 2H, J = 8.0 Hz), 6.78 (d, 2H, J = 8.0 Hz), 4.56 (s, 2H), 3.76 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 159.4, 153.9, 133.6, 130.5 (2C), 130.0, 129.7 (2C), 127.0, 123.7 (2C), 114.2 (2C), 55.2, 37.3; IR: 2933, 2837, 1730, 1608, 1508, 1246, 1032, 761 cm^{-1}; MS (ESI): m/z 321 (M + Na).

5-(4-Ethylbenzylthio)-1-phenyl-1*H*-tetrazole (10a, Table 2). Yield: 140 mg (94%), 0.5 mmol reaction; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 5H), 7.32 (d, 2H, J = 8.0 Hz), 7.15 (d, 2H, J = 8.0 Hz), 4.60 (s, 2H), 2.62 (q, 2H, J = 7.4 Hz), 1.21 (t, 3H, J = 7.4 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.9, 144.3, 133.5, 132.2, 129.9, 129.6 (2C), 129.1 (2C), 128.2 (2C), 123.7 (2C), 37.4, 29.6, 15.4; IR: 2962, 2853, 1724, 1499, 1385, 1238, 1082, 760 cm^{-1}; MS (ESI): m/z 319 (M + Na); HRMS: m/z Calcd: 319.0988 ($C_{16}H_{16}N_4S$ + Na); Found: 319.1008.

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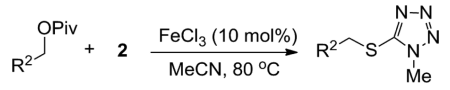
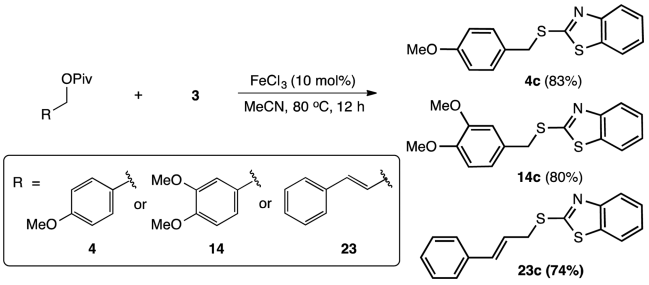
Table 3. Reaction of 2 with Different Esters in the Presence of $FeCl_3$ in MeCN at 80 °C



Entry	R^2	Product, Yield, Time (h)
1	**4**	**4b** (R = 4-MeO), 98%, 1 h
2	**10**	No Reaction, 6 h
3	**11**	No Reaction, 6 h
4	**12**	No Reaction, 6 h
5	**13**	No Reaction, 6 h
6	**15**	**15b** (R = 2,4-diMe), 90%, 6 h
7	**16**	No Reaction, 6 h
8	**17**	No Reaction, 6 h
9	**18**	**18b** (X = O), 100%, 0.5 h
10	**20**	**20b** (X = S), 100%, 0.5 h
11	**22**	**22b**, 99%, 0.5 h
12	**23**	**23b** (R = Ph), 95%, 1 h
13	**24**	**24b** (R = 4-MeO-Ph), 99%, 0.5 h
14	**25**	**25b** (R = Ph), 96%, 1 h
15	**26**	**26b**, 98%, 1 h
16	**28**	**28b**, 98%, 0.5 h
17	**30**	**30b**, 99%, 1 h
18	**32**	**32b**; 96%, 2 h

Scheme 3. Reaction of Thiol 3 with Esters 4, 14, and 23



1-Phenyl-5-(4-propylbenzylthio)-1*H*-tetrazole (11a, Table 2). Yield: 148 mg (95%), 0.5 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 5H), 7.32 (d, 2H, J = 8.0 Hz), 7.12 (d, 2H, J = 8.0 Hz), 4.60 (s, 2H), 2.56 (t, 2H, J = 7.6 Hz), 1.6 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.9, 142.8, 133.6, 132.2, 130.0, 129.6 (2C), 129.0 (2C), 128.8 (2C), 123.7 (2C), 37.6, 37.4, 24.3, 13.7; IR: 2960, 2851, 1720, 1499, 1385, 1239, 1081, 760 cm^{-1}; MS (ESI): m/z 333 (M + Na); HRMS: m/z Calcd: 333.1144 ($C_{17}H_{18}N_4S$ + Na); Found: 333.1162.

5-(4-Nitrobenzylthio)-1-phenyl-1*H*-tetrazole (12a, Table 2). Yield: 263 mg (84%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 2H, J = 8.9 Hz), 7.60 (m, 5H), 7.53 (d, 2H, J = 8.9 Hz), 5.20 (s, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.4, 151.4, 143.1, 132.9, 130.9, 129.9 (2C), 128.2 (2C), 124.5, 124.4, 123.7 (2C), 64.7; IR: 2927, 1605, 1483, 1351, 1229, 770 cm^{-1}; MS (ESI): m/z 314 (M + H); HRMS: m/z Calcd: 314.0706 ($C_{14}H_{11}N_5O_2S$ + H); Found: 314.0729.

5-(3-Nitrobenzylthio)-1-phenyl-1*H*-tetrazole (13a, Table 2). Yield: 144 mg (92%), 0.5 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.15 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 7.4 Hz), 7.59 (m, 5H), 7.53 (t, 1H, J = 8.0 Hz), 4.83 (s, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 152.2, 132.9, 132.6, 130.8 (2C), 129.9 (3C), 129.3, 124.3 (2C), 122.2, 121.4, 63.7; IR: 2921, 1595, 1498, 1350, 1234, 762 cm^{-1}; MS (ESI): m/z 314 (M + H); HRMS: m/z Calcd: 314.0706 ($C_{14}H_{11}N_5O_2S$ + H); Found: 314.0729.

5-(3,4-Dimethoxybenzylthio)-1-phenyl-1*H*-tetrazole (14a, Table 2). Yield: 158 mg (96%), 0.5 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.48 (m, 5H), 6.95 (dd, 1H, J = 8.0, 2.1 Hz), 6.94 (m, 1H), 6.79 (d, 1H, J = 7.7 Hz), 4.59 (s, 2H), 3.86 (s, 3H), 3.86 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.7, 149.0, 148.8, 133.4, 129.9, 129.5 (2C), 127.4, 123.6 (2C), 121.5, 112.0, 111.0, 55.7 (2C), 37.6; IR: 2934, 2836, 1706, 1596, 1337, 1264, 1026, 762 cm^{-1}; MS (ESI): m/z 351 (M + Na); HRMS: m/z Calcd: 351.0886 ($C_{16}H_{16}N_4O_2S$ + Na); Found: 351.0903.

5-(2,4-Dimethylbenzylthio)-1-phenyl-1*H*-tetrazole (15a, Table 2). Yield: 260 mg (88%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (m, 5H), 7.25 (d, 1H, J = 6.7 Hz), 6.98 (m, 2H), 4.63 (s, 2H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.0, 138.4, 136.9, 131.4, 130.3, 129.9 (2C), 129.6 (3C), 127.0, 123.6 (2C), 35.7, 21.0, 19.0; IR: 2922, 2854, 1731, 1595, 1499, 1384, 1235, 761 cm^{-1}; MS (ESI): m/z 319 (M + Na); HRMS: m/z Calcd: 319.0988 ($C_{16}H_{16}N_4S$ + Na); Found: 319.1008.

1-Phenyl-5-(1-phenylethylthio)-1*H*-tetrazole[10] (16a, Table 2). Yield: 274 mg (97%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.42 (m, 5H), 7.39 (m, 2H), 7.35–7.26 (m, 2H), 5.20 (q, 1H, J = 6.8 Hz), 1.89 (d, 3H, J = 6.8 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.4, 140.7, 133.5, 129.9, 129.5 (2C), 128.7 (2C), 128.1, 127.1 (2C), 123.9 (2C), 47.8, 22.1; IR: 2973, 2867, 1596, 1497, 1385, 1222, 1087, 762 cm^{-1}; MS (ESI): m/z 305 (M + Na).

5-(Furan-2-ylmethylthio)-1-phenyl-1*H*-tetrazole[10] (18a, Table 2). Yield: 256 mg (99%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, 2H, J = 7.9 Hz), 7.60–7.47 (m, 3H), 7.44 (m, 1H), 6.61 (d, 1H, J = 3.2 Hz), 6.39 (m, 1H), 5.55 (s, 2H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.4, 143.5, 142.8, 130.1 (2C),

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129.7, 129.1, 123.7 (2C), 110.7, 109.7, 44.1; IR: 2923, 2852, 1729, 1596, 1499, 1219, 772 cm^{-1}; MS (ESI): m/z 281 (M + Na).

1-Phenyl-5-(thiophen-2-ylmethylthio)-1*H*-tetrazole[10] (20a, Table 2). Yield: 136 mg (99%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 5H), 7.22 (dd, 1H, J = 5.0, 1.1 Hz), 7.11 (d, 1H, J = 3.5 Hz), 6.92 (dd, 1H, J = 3.5, 1.1 Hz), 4.86 (s, 2H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.4, 137.2, 133.4, 130.1, 129.7 (2C), 128.1, 127.0, 126.2, 123.7 (2C), 32.2; IR: 2927, 2850, 1733, 1595, 1497, 771 cm^{-1}; MS (ESI): m/z 297 (M + Na), 292 (M + NH_4).

5-(Naphthalen-1-ylmethylthio)-1-phenyl-1*H*-tetrazole (22a, Table 2). Yield: 157 mg (99%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, 1H, J = 8.5 Hz), 7.87 (dd, 1H, J = 7.3, 1.4 Hz), 7.82 (d, 1H, J = 8.2 Hz), 7.62 (d, 1H, J = 7.0 Hz), 7.57−7.49 (m, 2H), 7.46 (m, 5H), 7.41 (d, 1H, J = 8.4 Hz), 5.13 (s, 2H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 154.1, 133.9, 133.5, 131.2, 130.3, 130.0, 129.6 (2C), 129.3, 128.9, 128.5, 126.7, 126.1, 125.4, 123.7 (2C), 123.2, 35.6; IR: 2924, 2852, 1745, 1499, 1386, 1234, 762 cm^{-1}; MS (ESI): m/z 319 (M + H); HRMS: m/z Calcd: 319.1012 ($C_{18}H_{14}N_4S$ + H); Found: 319.1026.

5-(Cinnamylthio)-1-phenyl-1*H*-tetrazole[10] (23a, Table 2). Yield: 141 mg (96%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (m, 5H), 7.36 (d, 2H, J = 7.4 Hz), 7.30 (t, 2H, J = 7.3 Hz), 7.24 (t, 1H, J = 6.7 Hz), 6.72 (d, 1H, J = 15.5 Hz), 6.35 (m, 1H), 4.2 (d, 2H, J = 7.4 Hz); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.6, 135.9, 135.1, 133.5, 130.0, 129.7 (2C), 128.5 (2C), 128.0, 126.5 (2C), 123.8 (2C), 122.3, 35.8; IR: 2973, 2873, 1728, 1599, 1479, 1281, 1151, 965, 744 cm^{-1}; MS (ESI): m/z 317 (M + Na).

(*E*)-5-(3-(4-Methoxyphenyl)allylthio)-1-phenyl-1*H*-tetrazole[10] (24a, Table 2). Yield: 160 mg (99%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (m, 5H), 7.30 (d, 2H, J = 8.9 Hz), 6.82 (d, 2H, J = 8.9 Hz), 6.65 (d, 1H, J = 15.9 Hz), 6.20 (m, 1H), 4.19 (d, 2H, J = 7.4 Hz), 3.80 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 159.5, 151.7, 134.6, 133.6, 130.0, 129.6 (2C), 128.7, 127.7 (2C), 123.8 (2C), 119.9, 113.9 (2C), 55.2, 36.1; IR: 2924, 2852, 1725, 1603, 1507, 1386, 1550, 1032, 760 cm^{-1}; MS (ESI): m/z 325 (M + H), 347 (M + Na).

(*E*)-5-(2-Methyl-3-phenylallylthio)-1-phenyl-1*H*-tetrazole (25a, Table 2). Yield: 152 mg (98%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.60−7.53 (m, 5H), 7.32 (m, 2H), 7.23 (m, 3H), 6.63 (s, 1H), 4.22 (d, 2H, J = 0.9 Hz), 1.97 (d, 3H, J = 1.4 Hz); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.9, 136.7, 133.6, 131.4, 130.5, 130.0, 129.6 (2C), 128.7 (2C), 128.1 (2C), 126.8, 123.8 (2C), 43.6, 16.9; IR: 2921, 2852, 1736, 1595, 1497, 1385, 1237, 757 cm^{-1}; MS (ESI): m/z 309 (M + H); HRMS: m/z Calcd: 309.1168 ($C_{17}H_{16}N_4S$ + H); Found: 309.1193.

5-((2*E*,4*E*)-Hexa-2,4-dienylthio)-1-phenyl-1*H*-tetrazole (26a, Table 2). Yield: 253 mg (98%), 1.0 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (m, 5H), 6.32 (m, 1H), 5.99 (m, 1H), 5.79−5.63 (m, 2H) 4.05 (d, 2H, J = 7.6 Hz), 1.74 (d, 3H, J = 6.6 Hz); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.8, 135.7, 131.4, 130.1, 130.05, 129.8, 129.7 (2C), 123.8 (2C), 122.7, 29.6, 18.1; IR: 2963, 2855, 1724, 1597, 1388, 1242, 1016, 760 cm^{-1}; MS (ESI): m/z 281 (M + Na); HRMS: m/z Calcd: 281.0831 ($C_{13}H_{14}N_4S$ + Na); Found: 281.0842.

5-(Cyclohex-2-enylthio)-1-phenyl-1*H*-tetrazole[10] (27a, Table 2). Yield: 251 mg (92%), 1.0 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61−7.51 (m, 5H), 5.96 (m, 1H), 5.84 (m, 1H), 4.75 (m, 1H), 2.23−2.02 (m, 1H), 2.12−2.02 (m, 3H), 1.85−1.66 (m, 2H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 154.1, 133.7, 133.0, 129.9, 129.7 (2C), 124.8, 123.9 (2C), 44.7, 29.0, 24.8, 19.1; IR: 2923, 2854, 1729, 1595, 1498, 1385, 1239, 758 cm^{-1}; MS (ESI): m/z 281 (M + Na).

5-(4-Methoxybenzylthio)-1-methyl-1*H*-tetrazole (4b, Table 3). Yield: 232 mg (98%), 1.0 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (d, 2H, J = 8.7 Hz), 6.88 (d, 2H, J = 8.7 Hz), 5.39 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 163.9, 159.7, 130.2 (2C), 125.4, 114.0 (2C), 55.1, 50.9, 34.6; IR: 2921, 2832, 1611, 1511, 1366, 1210, 1028, 747 cm^{-1}; MS (ESI): m/z 259 (M + Na); HRMS: m/z Calcd: 259.0624 ($C_{10}H_{12}N_4OS$ + Na); Found: 259.0642.

5-(2,4-Dimethylbenzylthio)-1-methyl-1*H*-tetrazole (15b, Table 3). Yield: 106 mg (90%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 1H, J = 7.5 Hz), 7.15 (d, 1H, J = 7.8 Hz), 6.94 (d, 1H, J = 7.5 Hz), 4.53 (s, 2H), 3.78 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H); ^{13}C {^1H} NMR (75 MHz): δ 153.6, 138.3, 136.6, 131.4, 129.9, 129.9, 126.9, 35.9, 33.2, 20.9, 18.9; IR: 2923, 2853, 1736, 1502, 1461, 1386, 1278, 1170, 1027, 699 cm^{-1}; MS (ESI): m/z 257 (M + Na); HRMS: m/z Calcd: 257.0831 ($C_{11}H_{14}N_4S$ + Na); Found: 257.0850.

5-(Furan-2-ylmethylthio)-1-methyl-1*H*-tetrazole (18b, Table 3). Yield: 99 mg (100%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (dd, 1H, J = 1.6, 1.0 Hz), 6.30 (m, 2H), 4.56 (s, 2H), 3.85 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 164.0, 148.5, 142.9, 110.8, 109.7, 34.0, 30.4; IR: 2923, 2793, 1721, 1504, 1353, 1039, 174 cm^{-1}; MS (ESI): m/z 219 (M + Na); HRMS: m/z Calcd: 219.0311 ($C_7H_8N_4OS$ + Na); Found: 219. 0322.

1-Methyl-5-(thiophen-2-ylmethylthio)-1*H*-tetrazole (20b, Table 3). Yield: 105 mg (100%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 1H, J = 5.2 Hz), 7.27 (d, 1H, J = 3.2 Hz), 6.98 (t, 1H, J = 3.2 Hz), 5.62 (s, 2H), 3.88 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 163.7, 134.3, 128.8, 126.9, 126.8, 45.6, 34.6; IR: 3104, 2945, 1730, 1611, 1454, 1360, 1308, 1193, 1090, 772 cm^{-1}; MS (ESI): m/z 235 (M + Na); HRMS: m/z Calcd: 235.0083 ($C_7H_8N_4S_2$ + Na); Found: 235.0102.

1-Methyl-5-(naphthalen-1-ylmethylthio)-1*H*-tetrazole (22b, Table 3). Yield: 127 mg (99%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 1H, J = 8.2 Hz), 7.89 (d, 1H, J = 8.1 Hz), 7.83 (d, 1H, J = 8.2 Hz), 7.59 (td, 1H, J = 8.1, 1.4 Hz), 7.54 (m, 2H), 7.39 (td, 1H, J = 8.1 Hz), 5.02 (s, 2H), 3.70 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.6, 133.7, 130.8, 130.5, 129.2, 128.9, 128.1, 126.6, 126.0, 125.2, 123.0, 35.7, 33.1; IR: 3051, 3011, 2926, 2853, 1736, 1596, 1511, 1467, 1389, 1227, 1170, 1020, 778 cm^{-1}; MS (ESI): m/z 257 (M + H); HRMS: m/z Calcd: 257.0855 ($C_{13}H_{12}N_4S$ + H); Found: 257.0869.

5-(Cinnamylthio)-1-methyl-1*H*-tetrazole (23b, Table 3). Yield: 111 mg (95%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30 (m, 5H), 6.66 (d, 1H, J = 15.6 Hz), 6.33 (p, 1H, J = 15.6, 7.5 Hz), 4.16 (dd, 2H, J = 7.5, 0.7 Hz), 3.91 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.5, 135.8, 134.9, 128.5 (2C), 128.0, 126.4 (2C), 122.4, 35.9, 33.3; IR: 3028, 2927, 1734, 1597, 1450, 1389, 1279, 1230, 1171, 967, 752 cm^{-1}; MS (ESI): m/z 233 (M + H); HRMS: m/z Calcd: 233.0855 ($C_{11}H_{12}N_4S$ + H); Found: 233.0863.

(*E*)-5-(3-(4-Methoxyphenyl)allylthio)-1-methyl-1*H*-tetrazole (24b, Table 3). Yield: 130 mg (99%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, 2H, J = 8.7 Hz), 6.83 (d, 2H, J = 8.7 Hz), 6.60 (d, 1H, J = 15.5 Hz), 6.18 (p, 1H, J = 15.5, 7.6 Hz), 4.13 (dd, 2H, J = 7.6, 1.0 Hz), 3.91 (s, 3H), 3.80 (s, 3H); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 159.5, 153.7, 134.5, 128.6, 127.7 (2C), 119.9, 113.9 (2C), 55.4, 36.3, 33.4; IR: 2924, 2852, 1725, 1507, 1386, 1250, 1032, 760 cm^{-1}; MS (ESI): m/z 285 (M + Na); HRMS: m/z Calcd: 285.0781 ($C_{12}H_{14}N_4OS$ + Na); Found: 285.0803.

(*E*)-1-Methyl-5-(2-methyl-3-phenylallylthio)-1H-tetrazole (25b, Table 3). Yield: 118 mg (96%), 0.5 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (t, 2H, J = 7.4 Hz), 7.23 (tt, 1H, J = 7.4, 1.2 Hz), 7.21 (d, 2H, J = 7.4 Hz), 6.54 (s, 1H), 4.13 (s, 2H), 3.93 (s, 3H), 2.01 (d, 3H, J = 1.3 Hz); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.7, 136.6, 131.5, 130.4, 128.7 (2C), 128.1 (2C), 126.9, 43.9, 33.4, 16.7; IR: 3059, 3021, 2949, 2792, 1598, 1513, 1354, 1219, 1171, 1037, 757 cm^{-1}; MS (ESI): m/z 247 (M + H); HRMS: m/z Calcd: 247.1012 ($C_{12}H_{14}N_4S$ + H); Found: 247.1017.

5-((2*E*,4*E*)-Hexa-2,4-dienylthio)-1-methyl-1*H*-tetrazole (26b, Table 3). Yield: 192 mg (98%), 1.0 mmol reaction scale; ^1H NMR (300 MHz, $CDCl_3$): δ 6.24 (q, 1H, J = 14.9, 10.4 Hz), 5.98 (t, 1H, J = 14.9 Hz), 5.69 (m, 2H), 4.00 (d, 2H, J = 7.5 Hz), 3.90 (s, 3H), 1.72 (d, 3H, J = 6.7 Hz); ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ 153.7, 135.5, 131.5, 130.0, 122.8, 35.9, 33.4, 18.1; IR: 2926, 1719, 1473, 1391, 1220, 1022, 772 cm^{-1}; MS (ESI): m/z 219 (M + Na); HRMS: m/z Calcd: 219.0675 ($C_8H_{12}N_4S$ + Na); Found: 219.0688.

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1-Methyl-5-((2*E*,4*E*)-5-phenylpenta-2,4-dienylthio)-1*H*-tetrazole (28b, Table 3). Yield: 253 mg (98%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41−7.28 (m, 5H), 6.71 (dd, 1H, J = 15.6, 10.5 Hz), 6.56 (d, 1H, J = 15.6 Hz), 6.47 (dd, 1H, J = 15.6, 10.5 Hz), 5.92 (p, 1H, J = 15.6, 7.6 Hz), 4.08 (dd, 2H, J = 7.6, 0.6 Hz), 3.92 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.6, 136.7, 135.5, 133.9, 128.6 (2C), 127.8, 127.2, 126.4 (2C), 126.1, 35.9, 29.6; IR: 2924, 2853, 1721, 1451, 1389, 1171, 1076, 755, 697 cm^{-1}; MS (ESI): m/z 281 (M + Na); HRMS: m/z Calcd: 281.0831 ($C_{13}H_{14}N_4S$ + Na); Found: 281.0849.

(*E*)-1-Methyl-5-(3-(naphthalen-1-yl)allylthio)-1*H*-tetrazole (30b, Table 3). Yield: 140 mg (99%), 0.5 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 1H, J = 8.4 Hz), 7.82 (d, 1H, J = 8.7 Hz), 7.77 (d, 1H, J = 8.4 Hz), 7.54−7.46 (m, 4H), 7.42 (t, 1H, J = 7.9 Hz), 6.32 (p, 1H, J = 7.4 Hz), 4.27 (dd, 2H, J = 7.4, 1.0 Hz), 3.92 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.4, 133.5, 133.3, 132.2, 130.8, 128.3 (2C), 126.1, 125.7, 125.4, 125.3, 123.8, 123.4, 36.0, 33.3; IR: 3052, 2925, 2854, 1741, 1591, 1465, 1390, 1228, 1170, 966, 778 cm^{-1}; MS (ESI): m/z 305 (M + Na); HRMS: m/z Calcd: 305.0831 ($C_{15}H_{14}N_4S$ + Na); Found: 305.0846.

(*E*)-5-(3,7-Dimethylocta-2,6-dienylthio)-1-methyl-1*H*-tetrazole (32b, Table 3). Yield: 242 mg (96%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.38 (td, 1H, J = 8.0, 1.3 Hz), 5.03 (tt, 1H, J = 6.7, 1.3 Hz), 3.98 (d, 2H, J = 8.0 Hz), 3.90 (s, 3H), 2.05 (m, 4H), 1.71 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.2, 143.1, 131.9, 123.4, 116.9, 39.4, 33.4, 31.7, 26.2, 25.6, 17.7, 16.2; IR: 2965, 2924, 2855, 1728, 1663, 1449, 1385, 1277, 1228, 1170, 770 cm^{-1}; MS (ESI): m/z 253 (M + H); HRMS: m/z Calcd: 253.1481 ($C_{12}H_{20}N_4S$ + H); Found: 253.1497.

2-(4-Methoxybenzylthio)benzo[*d*]thiazole[10] (4c, Scheme 3). Yield: 238 mg (83%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (dd, 1H, J = 7.1, 1.7 Hz), 7.23 (m, 4H), 7.07 (dd, 1H, J = 7.1, 1.7 Hz), 6.82 (d, 2H, J = 8.5 Hz), 5.59 (s, 2H), 3.75 (s, 3H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 189.9, 159.1, 141.3, 128.5 (2C), 127.5, 126.8 (2C), 126.3, 124.7, 121.2, 114.2, 113.0, 55.2, 48.9; IR: 2925, 1679, 1511, 1366, 1254, 1026, 741 cm^{-1}; MS (ESI): m/z 288 (M + H).

2-(3,4-Dimethoxybenzylthio)benzo[*d*]thiazole (14c, Scheme 3). Yield: 253 mg (80%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 1H, J = 8.1 Hz), 7.72 (d, 1H, J = 7.7 Hz), 7.45−7.25 (m, 2H), 7.07 (d, 1H, J = 8.3 Hz), 6.83 (dd, 2H, J = 8.3, 6.6 Hz), 4.54 (s, 2H), 3.77 (s, 6H); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 153.0, 148.9, 148.6, 135.2, 128.4, 127.0, 126.0, 124.2, 121.4 (2C), 120.9, 112.2, 111.1, 55.8, 55.8, 37.7; IR: 3003, 2964, 2933, 2841, 1703, 1588, 1460, 1421, 1260, 1025, 761 cm^{-1}; MS (ESI): m/z 340 (M + Na); HRMS: m/z Calcd: 340.0436 ($C_{16}H_{15}NO_2S_2$ + Na); Found: 340.0443.

2-(Cinnamylthio)benzo[*d*]thiazole (23c, Scheme 3). Yield: 210 mg (74%), 1.0 mmol reaction scale; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, 1H, J = 8.1 Hz), 7.76 (d, 1H, J = 7.9 Hz), 7.50−7.17 (m, 7H), 6.68 (t, 1H, J = 15.8 Hz), 6.43−6.21 (m, 1H), 4.16 (d, 2H, J = 7.3 Hz); ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.1, 153.1, 136.2, 134.2, 133.5, 128.5 (2C), 127.8, 126.5, 126.4, 125.9, 124.2, 123.4, 121.4, 120.9, 36.0; IR: 3028, 2967, 2929, 1726, 1458, 1426, 1280, 1152, 995, 751 cm^{-1}; MS (ESI): m/z 284 (M + H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02143.

NMR, IR, and mass spectral data of all compounds; ^{1}H and ^{13}CNMR copies of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

§This paper is dedicated to the memory to our late mentor Dr. Yenamandra Venkateswarlu, who passed away on July 17, 2013.

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In the version published October 30, 2015 the ^{13}C $\{^{1}H\}$ NMR data for compound **15b** was missing; the correct version reposted later on October 30, 2015.

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