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A Straightforward Synthesis of Alkyl 1*H*-Tetrazol-5-yl Thioethers via a One-pot Reaction of Aldehydes and 1*H*-Tetrazole-5-thiols Mediated by *N*-Tosylhydrazones

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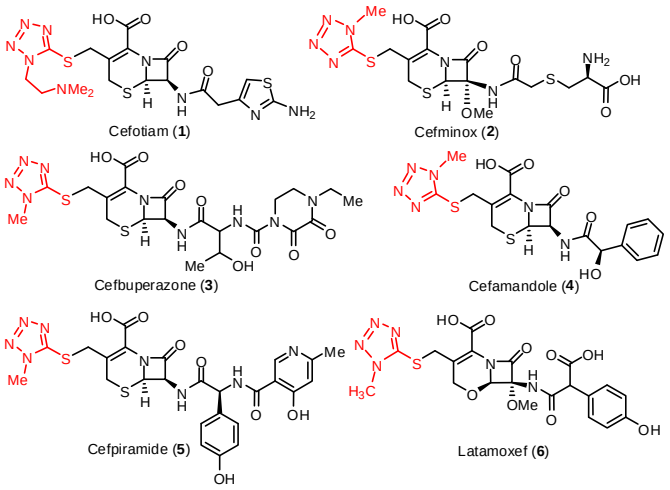
A straightforward approach for the synthesis of alkyl 1*H*-tetrazol-5-yl thioethers from aldehydes and 1*H*-tetrazole-5-thiol through a one-pot procedure is presented. Namely, the aldehydes were first condensed with *N*-tosylhydrazine to generate the *N*-tosylhydrazones, which were then reductively coupled *in situ* with 1*H*-tetrazole-5-thiols under metal-free conditions to afford the thioethers in high to excellent yields.

The 1*H*-tetrazol-5-yl thioether skeletons are key structural motifs in many bioactive compounds and drugs.[1] Typically, such units are frequently presented in a wide variety of clinically used antibiotics such as Cefotiam (**1**),[2] Cefminox (**2**),[3] Cefbuperazone (**3**),[4] Cefamandole (**4**),[5] Cefpiramide (**5**),[6] and Latamoxef (**6**)[7] (Scheme 1). More importantly, the alkyl 1*H*-tetrazol-5-yl thioethers are useful precursors or intermdediates in organic synthesis. For instance, they serve as precursors in Kocienski-modified Julia olefination which has been one of the most popularly used methods for the construction of internal olefins and shows unique advantage for the preparation of non-conjugated alkenes in high *E*-selectivity.[8] Therefore, development of efficient approaches for the synthesis of 1*H*-tetrazol-5-yl thioethers is of greatly attractive. Classical methods for the synthesis of alkyl 1*H*-tetrazol-5-yl thioethers have been relied mainly on the substitution reaction of an alkyl (pseudo)halide with a 1*H*-tetrazole-5-thiol under basic conditions,[9] and the Mitsunobu condensation between an alcohol and a 1*H*-tetrazole-5-thiol.[10] Although these protocols have been widely used due to high yield, broad functional group compatibility, and mild reaction conditions, a multistep procedure is essentially required when aldehydes or ketones are employed as starting materials.

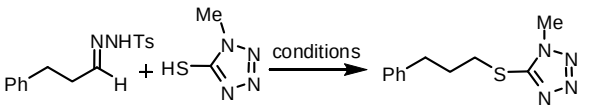


Scheme 1. Structures of some clinically used antibiotics.

Recently, a rapidly growing interest has been observed in the area of transition-metal-catalyzed and metal-free cross-coupling of *N*-tosylhydrazones.[11] The versatility of this reagent has been well demonstrated through the creation of various C–C bonds.[12] In addition, the formation of C–O,[13] C–N,[14] C–P,[15] C–S,[16] and N–N bonds[14b,c] has also been exemplified. Since *N*-tosylhydrazones are prepared through the condensation of aldehydes or ketones with *N*-tosylhydrazine, and moreover, aldehydes and ketones are abundant chemicals from nature and industry, these extensive contributions expand significantly the utilities of aldehyde and ketone compounds in organic synthesis.

Stimulated by these pioneering works, we became interested in investigating the metal-free cross-coupling reaction of *N*-tosylhydrazones with 1*H*-tetrazole-5-thiols because this transformation would provide a more straightforward pathway for flexible accessing alkyl 1*H*-tetrazol-5-yl thioethers from aldehydes and ketones. The successful demonstration of this chemistry will be presented herein.

Table 1 Evaluation of the reaction conditions[a]



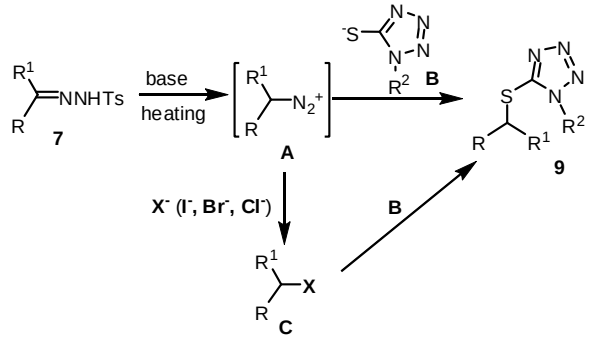
7a **8a** **9a**

Entry	Base	Solvent	Yield (%)[b]
1	K_2CO_3	dioxane	30
2	K_2CO_3	Toluene	–[c]
3	K_2CO_3	PhF	–[c]
4	K_2CO_3	MeCN	16
5	K_2CO_3	DME	21
6	K_2CO_3	THF	–[c]
7	Na_2CO_3	dioxane	–[c]
8	KOH	dioxane	27
9	NaOH	dioxane	28
10	Cs_2CO_3	dioxane	23
11	^{t}BuOK	dioxane	–[c]
12	K_3PO_4	dioxane	25
13	LiOH	dioxane	36
14	LiOH	dioxane	36[d]
15	LiOH	dioxane	46[e]
16	**LiOH**	**dioxane**	**68**[f]

[a] Unless otherwise noted, the reaction conditions were: *N*-Tosylhydrazone **7a** (0.8 mmol), tetrazole thiol **8a** (1.6 mmol), and base (2.4 mmol) in solvent (4 mL) at 110 °C for 2 h. [b] Isolated yield based on *N*-tosylhydrazone **7a**. [c] No desired product was isolated due to decomposition of **7a**. [d] 4.0 equiv of LiOH was used. [e] The molar ratio of **7a**/**8a** was 2:1 in the presence of 3.0 equiv of LiOH; isolated yield based on **8a**. [f] The molar ratio of **7a**/**8a** was 2:1 in the presence of 4.0 equiv of LiOH; isolated yield based on **8a**.

The evaluation on the feasibility of the transformation was carried out by using *N*-tosylhydrazone **7a** and commercially available 1-methyl-1*H*-tetrazole-5-thiol **8a** as the coupling partners (Table 1). Initial trial under the metal-free conditions showed that the reaction could proceed to give the desired product **9a**. However, the yield was rather low (30%, entry 1). Attempted improvement of the reaction efficiency by varying the solvents (entries 2–6) and bases (entries 7–13) was futile albeit the use of LiOH base led to a slightly increased yield (36%, entry 13). A further optimization of the molar ratio of **7a** to **8a** and the amount of base (entries 14–16) revealed that the yield of **9a** might be increased to 68% when the molar ratio of **7a** to **8a** was changed from 1:2 to 2:1 combined with the use of 4.0 equiv of LiOH base (entry 16).

By employing the conditions in entry 16 as the optimal ones, we examined the generality of the method. Unfortunately, only poor to moderate yields were obtained for a range of *N*-tosylhydrazones derived from different aliphatic aldehydes. These results indicate that the conditions optimized in this way are less general. In fact, a survey of literature revealed that for the metal-free cross-coupling of *N*-tosylhydrazones with heteroatom nucleophiles,[13-16] the *N*-tosylhydrazones derived from aliphatic aldehydes and ketones were much less investigated than those derived from aryl aldehydes or ketones. Moreover, it is also noted from the few available examples that the aliphatic *N*-tosylhydrazones usually displayed a lower reactivity to compare with the aromatic ones. These observations imply that methods for the coupling of *N*-tosylhydrazones derived from aliphatic aldehydes and ketones are neither general nor practical.



Scheme 2. Proposed coupling of *N*-tosylhydrazones and 1*H*-tetrazole-5-thiols

According to the proposed mechanism in prior literature,[11b,16c] we reasoned that the sluggish reaction between aliphatic *N*-tosylhydrazones and 1*H*-tetrazole-5-thiols investigated herein should be resulted from the relatively low reactivity of both coupling partners. As shown in scheme 2, the thioether product **9** may be produced through the substitution of a diazo ion **A** with a tetrazole thioanion **B**. However, the diazo ion **A** generated from an aliphatic hydrazone **7** is less electrophilic than that formed from an aromatic one. On the other hand, the thioanion **B** generated from 1*H*-tetrazole-5-thiol **8** is considered to be a weak nucleophile as a result of the electron-withdrawing nature of tetrazole moiety.[17] Consequently, less effective reactions were observed.

Based on the above analysis, we reasoned that the reaction efficiency might be improved by means of the addition of a halogen anion X^- (X = I, Br, Cl) into the reaction system. Namely, with the presence of such an anion, the diazo ion **A** might be converted into the halogenoalkane **C**. Subsequently, the substitution reaction of **C** with tetrazole thioanion **B** should proceed smoothly to deliver the thioether **9** because such a transformation has been well demonstrated for the synthesis of thioethers.[9] Accordingly, we examined the effect of an array of halogen salts (Table 2). While the yields were somewhat decreased when several organic chloride and bromide salts were added (entries 1–3), the presence of a catalytic amount of ^{n}BuNI resulted in a slightly increased yield of **9a** (entry 4). The yield could be improved to 80% when 2.0 equiv of ^{n}BuNI was used (entry 5). These results suggest that the use of an appropriate iodide salt would be beneficial for the reaction. The assumption was further supported by a parallel comparison of different lithium halides. That is, LiI was much more effective than LiBr, giving **9a** in 88% yield (entries 6 vs. 7). In comparison, LiCl displayed a detrimental effect to the reaction (entry 8). A brief optimization of the molar equivalent of LiI showed that the use of 1.0 equiv of LiI was optimal, affording **9a** in almost equally high yield to that of the presence of 2.0 equiv of LiI (entries 6 *vs.* 9 and 10). We also evaluated the effect of the counter ions of I^-. The results showed that LiI afforded a better outcome than NaI and KI (entries 9 *vs.* 11 and 12). An examination on the effect of the molar equivalent of hydrazone (entries 9 *vs.* 13) revealed that the use of 2.0 equiv of **7a** was important since the by-products **10** and **11**[18] generated from the

homocoupling of **7a** were unavoidably formed under different conditions (Figure 1). Finally, the reaction could also be performed through a one-pot operation to afford the product **9a** in 91% yield (entry 14).

Table 2 Screening of the additives.[a]

Entry	Halogen salts (equiv)	Yield (%)[b]
1	$^{n}Bu_4NCl$ (0.2)	56
2	$^{n}Bu_3P(^{n}C_{16}H_{33})Br$ (0.2)	59
3	$Ph_3P(Me)Br$ (0.2)	58
4	$^{n}Bu_4NI$ (0.2)	73
5	$^{n}Bu_4NI$ (2)	80
6	LiI (2)	88
7	LiBr (2)	73
8	LiCl (2)	52
9	LiI (1)	87
10	LiI (0.5)	72
11	NaI (1)	80
12	KI (1)	64
13	LiI (1)	52[c]
14	**LiI (1)**	**91**[d]

[a] Unless otherwise noted, the reaction conditions were: *N*-Tosylhydrazone **7a** (1.6 mmol), tetrazole thiol **8a** (0.8 mmol), and LiOH (3.2 mmol) in dioxane (8 mL) at 110 °C for 4 h. [b] Isolated yield based on tetrazole **8a**. [c] 1.2 mmol of **7a** was used. [d] The reaction was performed via a one-pot operation.

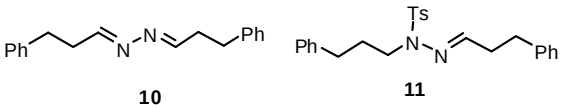
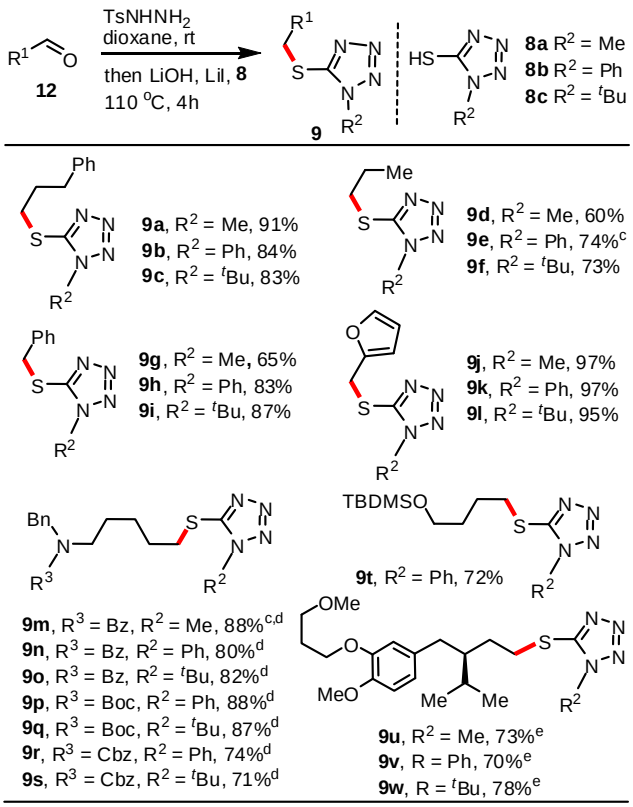


Figure 1. By-products generated in the reaction system.

Thus, an exhaustive screening of various parameters enabled us to define the high yielding conditions for a straightforward and high yielding synthesis of alkyl tetrazol-5-yl thioethers from the aldehydes and 1*H*-tetrazole-5-thiols, which are 2:2:1 of aldehyde to *N*-tosylhydrazone to 1*H*-tetrazole-5-thiol, 4.0 equiv of LiOH, and 1.0 equiv of LiI in dioxane at 110 °C. To evaluate the generality of this protocol, an array of aldehydes **12** and 1*H*-tetrazole-5-thiols **8** were examined through the one-pot procedure. The results showed that the method exhibited good compatibility to a wide variety of aldehydes. As summarized in Table 3, the simply substituted aliphatic aldehydes reacted smoothly with various commercially affordable 1*H*-tetrazole-5-thiols **8a**–**c** to give the thioethers **9a**–**9f** in high yields. In addition, an aromatic and a heteroaromatic aldehyde were also well tolerated, giving **9g**–**9l** in high to excellent yields. Most significantly, an array of aliphatic aldehydes modified by various functional groups such as Bz (**9m**–**9o**), Boc (**9p** and **9q**), and Cbz (**9r** and **9s**) protected amino groups, as well as TBDMS (**9t**) protected hydroxy group were also viable substrates under the optimized reaction conditions. The broad compatibility to a variety of functional groups would be an important advantage of the method because it provides additional opportunities for further modification of the coupled products through the orthogonal transformation of latent amino/alcohol and thioether functionalities. Finally, the method can be applied for the efficient synthesis of thioethers **9u**–**9w**, which were synthesized previously by us[19] through the conventional multistep procedure and used as the key intermediate for the synthesis of Aliskiren, a novel marketed drug for the treatment of hypertensive disease. It should be mentioned that while the protocol exhibits a broad generality to aldehydes, a brief examination showed that ketones were less effective substrates under the conditions.

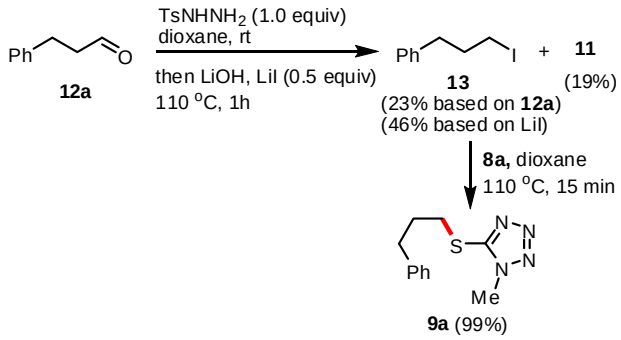
Table 3 Substrate scope.[a,b]



[a] Reaction conditions: aldehyde **12** (1.6 mmol), $TsNHNH_2$ (1.6 mmol), 1*H*-tetrazole-5-thiols **8** (0.8 mmol), LiOH (3.2 mmol), and LiI (0.8 mmol) in dioxane (8 mL) at 110 °C for 4 h. [b] Isolated yield based on **8**. [c] The yield was determined by ^{1}H-NMR analysis due to the contamination of a small amount of inseparable side-product. [d] Aldehyde **12** (1 mmol), $TsNHNH_2$ (1 mmol), **8** (0.5 mmol), LiOH (2 mmol), and LiI (0.5 mmol) in dioxane (5 mL) at 110 °C for 4 h. [e] Aldehyde **12** (0.8 mmol), $TsNHNH_2$ (0.8 mmol), **8** (0.4 mmol), LiOH (1.6 mmol), and LiI (0.4 mmol) in dioxane (4 mL) at 110 °C for 4 h.

To confirm the concrete role played by LiI additive, we carried out some control experiments (Scheme 3). Treatment of aldehyde **12a** under the otherwise conditions identical to the optimized conditions bust just with the absence of 1*H*-tetrazole-5-thiol **8a** produced 1-iodo-3-phenylpropane **13** in 23% yield (46% based on LiI) and the homo-coupled by-product **11** (see Figure 1) in 19% yield. In addition to the two major products, several other minor products were also observed by the TLC monitoring; however, their structures and contents were not determination due to the difficulty of separation. The reaction of **13** with 1*H*-tetrazole-5-thiol **8a** proceeded very rapidly within 15 min to give thioether **9a** in quantitative yield. These results suggest that in good agreement with the proposed mechanism (Scheme 2), the addition of LiI could help

to improve the synthetic efficiency of alkyl tetrazol-5-yl thioethers through the formation of a more reactive iodoalkane intermediate.



Scheme 3. Control experiments

Conclusions

As a summary, we have established a straightforward method that allows for a one-pot synthesis of alkyl 1*H*-tetrazol-5-yl thioethers from aldehydes through the metal-free reductive coupling of *in situ* generated *N*-tosylhydrazones with 1*H*-tetrazole-5-thiols. In addition, the method exhibits a broad generality for a wide variety of aldehydes and various 1*H*-tetrazole-5-thiols. Most significantly, various aliphatic aldehydes including those decorated by *N*- and *O*-containing functionalities were viable substrates under the reaction conditions. As a result, the methodology would find practical applications owing to the great importance of alkyl 1*H*-tetrazol-5-yl thioethers either as key structural motif in pharmaceuticals or as important precursors in synthetic organic chemistry. The use of this method for an improved synthesis of Aliskiren is currently underway in our lab.

Experimental Section

General procedure for the one-pot synthesis of 9

A mixture of aldehyde **12** (1.6 mmol, 2.0 equiv) and $TsNHNH_2$ (1.6 mmol, 2.0 equiv) in dioxane (5.0 mL) was stirred at rt for 0.5 h under argon atmosphere. Then, LiOH (3.2 mmol, 4.0 equiv), **8** (0.8 mmol, 1.0 equiv), LiI (0.8 mmol, 1.0 equiv), and dioxane (3.0 mL) were recharged *in situ* to the reaction vessel. The resulting mixture was then stirred vigorously at 110 °C for 4 h under argon atmosphere. After the completion of the reaction as monitored by TLC, the mixture was cooled to room temperature and diluted with CH_2Cl_2 (20 mL). The mixture was filtered through a celite pad to remove the insoluble materials, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel by using a mixed solvent of EtOAc and petroleum ether as eluent to afford product **9**.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Details of experimental procedures, characterization data, and copies of NMR spectra. See DOI: 10.1039/b000000x/

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Table of Contents

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