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Efficient synthesis of tetrazole hemiaminal silyl ethers *via* three-component hemiaminal silylation

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Abstract: An efficient route to construct 2,5-disubstituted tetrazole hemiaminal silyl ethers *via* one-pot three-component hemiaminal silylation of 5-substituted tetrazoles, aldehydes, and silyl triflates was developed. Diverse 2,5-disubstituted tetrazole hemiaminal silyl ethers were obtained with 37:63->99:1 regioisomeric ratios. The regioselectivities of this reaction were significantly affected by the steric hindrance and conjugation effects of substitutions on the 5-position of tetrazoles.

5-Substituted tetrazoles are valuable heterocycles in drug discovery as carboxylic acid isosteres, with similar acidities but higher lipophilicities and metabolic resistance.[1] As shown in Figure 1, **losartan** is a selective antagonist of the receptor for angiotensin II and has been in clinical use.[2] **Irbesartan** is also a drug for the treatment of hypertension.[3] However, some tetrazoles may exist as zwitterions,[1a,4] which can result in low permeability and consequently poor oral bioavailability. To address this issue, a prodrug approach to mask the tetrazole has been developed. The prodrug of **BMS-183920**, containing an esterase-sensitive hemiaminal ester moiety, exhibits improved bioavailability than 5-substituted tetrazole without hemiaminal ester moiety (Fig. 1).[5] Compared to the well-known prodrugs of carboxylic acids, the prodrugs of tetrazoles are less common.[6] Silyl ethers, the most widely used protecting groups for the alcohol, have been applied in the prodrug field. Representative examples include the silyl ether prodrug of **docetaxel**[7] and silyl ether prodrug of **gemcitabine**,[8] which are acid labile prodrugs (Fig. 1). Therefore, developing an efficient method to synthesize silyl ether prodrugs of 5-substituted tetrazoles would be highly desirable.

The substitution reaction of 5-substituted tetrazoles is the most common method for the synthesis of disubstituted tetrazoles.[1b] In the 5-substituted tetrazoles, there are two

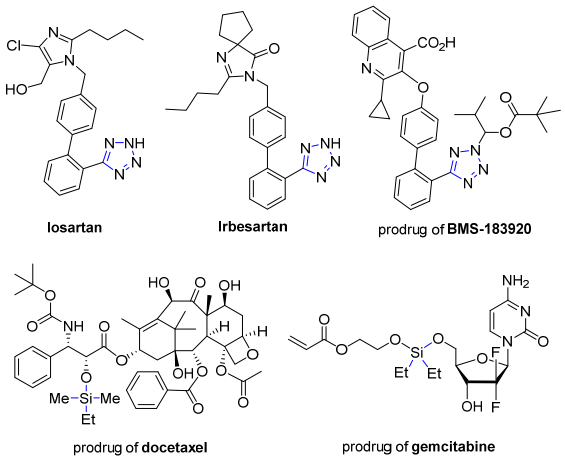
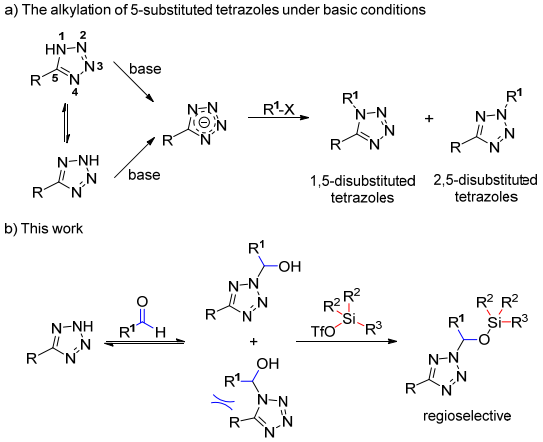


Fig. 1 Selected 5-substituted tetrazole drugs, tetrazole prodrug, and silyl ether prodrugs.

tautomeric states: 1*H*- and 2*H*-tautomers.[9] The tetrazole anion is generated after deprotonation under basic conditions,[1b] which reacts with halo hydrocarbon, usually affording a mixture of both 1,5- and 2,5-disubstituted tetrazoles (Scheme 1a).[10] Thus, searching for a highly regioselective method resulting in the formation of only one disubstituted tetrazole



Scheme 1 a) The alkylation of 5-substituted tetrazoles under basic condition; b) synthetic route to disubstituted tetrazole hemiaminal silyl ethers.

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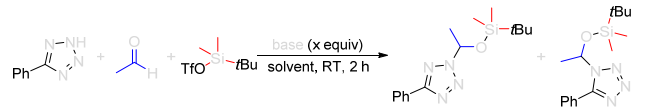
Electronic Supplementary Information (ESI) available: Experimental details and analytical data of the products. CCDC 1835497 (**4an**) and 1835498 (**5aa**) . For ESI and crystallographic data in CIF or other electronic format, See DOI: 10.1039/x0xx00000x

isomer is currently an intensely investigated research topic.[11] In 2016, Piotrowski and Kamlet group reported that the hemiaminals, formed by reversible addition of tetrazoles to aldehydes, could be trapped by an acyl group in a regioselective manner with excellent enantiomeric excess.[12] Considering that the silylation of alcohols is a powerful route for the construction of ethers, herein, we now report the three-component reaction of 5-substituted tetrazoles, aldehydes, and silyl triflates for the synthesis of disubstituted tetrazoles,[13] in which the tetrazole hemiaminals are trapped by the silyl triflates. Owing to the steric hindrance in 1,5-disubstituted tetrazole hemiaminals, the three-component hemiaminal silylation may generate 2,5-disubstituted tetrazole hemiaminal silyl ethers in a regioselective manner (Scheme 1b).

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a 4aa 5aa

Entry	Base	Solvent	x	1a/2a/3a	Yield[b] (4aa) (%)	4aa/5aa[c]
1	*i*Pr$_2$EtN	THF	3	1:1.5:1.5	11	73:27
2	*i*Pr$_2$EtN	CH_3CN	3	1:1.5:1.5	26	92:8
3	*i*Pr$_2$EtN	CH_3OH	3	1:1.5:1.5	NR	-
4	*i*Pr$_2$EtN	n-hexane	3	1:1.5:1.5	32	86:14
5	*i*Pr$_2$EtN	dioxane	3	1:1.5:1.5	59	95:5
6	*i*Pr$_2$EtN	toluene	3	1:1.5:1.5	56	72:28
7	*i*Pr$_2$EtN	Et_2O	3	1:1.5:1.5	67	79:21
8	*i*Pr$_2$EtN	CH_2Cl_2	3	1:1.5:1.5	92	96:4
9	Et_3N	CH_2Cl_2	3	1:1.5:1.5	6	-
10	Na_2CO_3	CH_2Cl_2	3	1:1.5:1.5	1	-
11	K_2CO_3	CH_2Cl_2	3	1:1.5:1.5	2	-
12	Cs_2CO_3	CH_2Cl_2	3	1:1.5:1.5	NR	-
13	*i*Pr$_2$EtN	CH_2Cl_2	1.5	1:1.5:1.5	97	>99:1
14	*i*Pr$_2$EtN	CH_2Cl_2	1.2	1:1.5:1.5	24	>99:1
15	*i*Pr$_2$EtN	CH_2Cl_2	1.5	1:1.5:1.2	58	67:33
16	*i*Pr$_2$EtN	CH_2Cl_2	1.5	1:1.5:1	28	58:42
17	*i*Pr$_2$EtN	CH_2Cl_2	1.5	1:1.4:1.5	99	>99:1
18	*i*Pr$_2$EtN	CH_2Cl_2	1.5	1:1:1.5	76	99:1

[a] Reaction conditions: **1a** (0.5 mmol), base (x equiv), and solvent (5 mL) were added in a test tube. Then, **2a** and **3a** were added at RT. [b] Isolated yield of **4aa** based on **1aa**. [c] Determined by ^{1}H NMR of the crude reaction mixture. NR = No Reaction.

Initially, 5-phenyl tetrazole **1a**, acetaldehyde **2a**, and *t*-butyldimethylsilyl triflate (TBSOTf) **3a** were selected as reactants (Table 1). When *i*Pr$_2$EtN was used as the base in THF, the desired disubstituted tetrazole hemiaminal silyl ethers (**4aa** and **5aa**) were obtained, in which the 2,5-disubstituted tetrazole hemiaminal silyl ether **4aa** was the major product (11% yield), along with the minor 1,5-disubstituted product **5aa** (entry 1). Then, in the presence of *i*Pr$_2$EtN, several solvents were evaluated, and CH_2Cl_2 was found to be the best to give tetrazole hemiaminal silyl ether **4aa** in 92% yield with 96:4 regioisomeric ratio (rr) (entries 2-8). Next, several bases were examined and *i*Pr$_2$EtN was still the better choice (entries 8-12). After that, the amount of *i*Pr$_2$EtN was investigated, and the use of 1.5 equiv of *i*Pr$_2$EtN could result in 97% yield for **4aa** (entries 8, 13-14). Furthermore, the ratio of reactants was evaluated, and the use of 1.4 equiv of **2a** and 1.5 equiv of **3a** could afford the disubstituted hemiaminal silyl ether **4aa** in 99% yield in a regioselective manner (entries 15-18). Thus, the optimal reaction conditions were 1.5 equiv of *i*Pr$_2$EtN, 1.4 equiv of aldehyde, and 1.5 equiv of TBSOTf in CH_2Cl_2 at RT (entry 17).

Table 2 Substrate scope of aldehydes[a]

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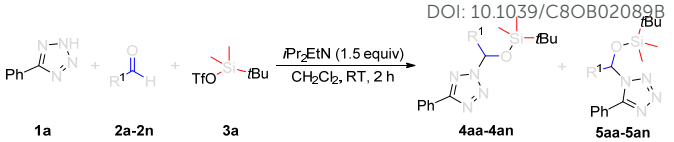
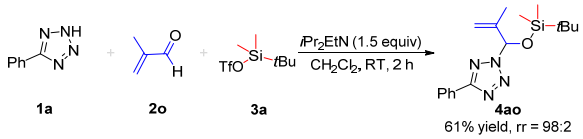


1a 2a-2n 3a 4aa-4an 5aa-5an

Entry	R^1	4	Yield[b] (4) (%)	rr (4/5)[c]
1		4aa	99	>99:1
2		4ab	96	98:2
3		4ac	97	99:1
4		4ad	93	95:5
5		4ae	91	99:1
6		4af	93	95:5
7		4ag	92	96:4
8		4ah	92	98:2
9		4ai	82	98:2
10		4aj	91	94:6
11		4ak	72	>99:1
12		4al	85	>99:1
13[d]		4am	71	98:2
14[d]		4an	48	94:6

[a] Unless otherwise noted, reaction conditions were: **1a** (0.2 mmol), **2** (1.4 equiv, 0.28 mmol), **3a** (1.5 equiv, 0.3 mmol), *i*Pr$_2$EtN (1.5 equiv, 0.3 mmol) in CH_2Cl_2 (2 mL) at RT. [b] Isolated yield of **4** based on **1a**. [c] The regioisomeric ratios (rr = **4**:**5**) were determined by ^{1}H NMR of the crude reaction mixtures. [d] Reaction was performed in $ClCH_2CH_2Cl$ at 50 °C.

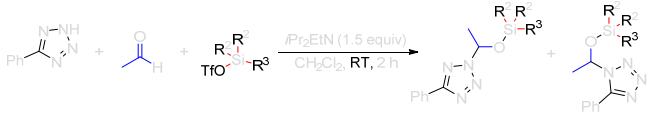
Under optimized reaction conditions (Table 1, entry 17), the substrate scope of the aldehydes was evaluated (Table 2). Various aliphatic aldehydes, such as straight-chain **2a**-**2e**, branched **2f**-**2h**, or cyclic aliphatic aldehyde **2i** were demonstrated to be suitable substrates, generating 2,5-disubstituted tetrazole hemiaminal silyl ethers **4aa**-**4ai** in high yields and excellent regioselectivities (entries 1-9). In the case of pent-4-enal **2j**, the 2,5-disubstituted adduct **4aj** was obtained in excellent results (entry 10). Upon using 2-phenylacetaldehyde **2k** and 3-phenylpropanal **2l**, the 2,5-disubstituted tetrazoles **4ak** and **4al** were generated in good results (entries 11-12). When benzaldehyde **2m** and 1-naphthaldehyde **2n** were employed, the 2,5-disubstituted tetrazole **4am**-**4an** could be generated by improving the reaction temperature to 50 °C (entries 13 and 14). When *α*,*β*-unsaturated aldehyde **2o** was used, the conjugated addition product was not observed, and the desired 2,5-disubstituted tetrazole **4ao** was given (Scheme 2).



1a 2o 3a 4ao
61% yield, rr = 98:2

Scheme 2 Silylation reaction of α,β-unsaturated aldehyde **2o**.

Table 3 Substrate scope of silyl triflates[a]



1a 2a 3a-3d 4 5

Entry	3	R^2/R^3	4	Yield[b] (4) (%)	rr (4:5)[c]
1	3a	Me/*t*Bu	4aa	99	>99:1
2	3b	Me/Me	4ap	40	96:4
3	3c	Et/Et	4aq	71	93:7
4	3d	*i*Pr/*i*Pr	4ar	92	99:1

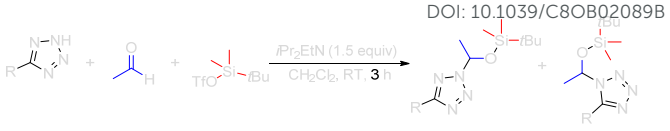
[a] Reaction conditions were: **1a** (0.2 mmol), **2a** (1.4 equiv, 0.28 mmol), **3** (1.5 equiv, 0.3 mmol), iPr$_2$EtN (1.5 equiv, 0.3 mmol) in CH_2Cl_2 (2 mL) at RT. [b] Isolated yield of **4** based on **1a**. [c] The regioisomeric ratios (rr = **4**:**5**) were determined by ^{1}H NMR of the crude reaction mixtures.

Then, different silyl triflates were explored in this three-component hemiaminal silylation reaction (Table 3). When TMSOTf **3b** was used, high conversion of tetrazole **1a** was detected, while the 2,5-disubstituted tetrazole **4ap** was isolated only in 40% yield, which indicated that the TMS derived disubstituted tetrazole **4ap** was unstable during the purification step. As for TESOTf **3c** and TIPSOTf **3d**, the reactions proceeded well with high regioselectivities, giving 2,5-disubstituted tetrazole **4aq** (71% yield) and **4ar** (92% yield), respectively.

Subsequently, the substrate scope of 5-substituted tetrazoles was evaluated (Table 4). When 5-(*m*-tolyl)-tetrazole **1b** and 5-(4-bromophenyl)-tetrazole **1c** were used, the 2,5-disubstituted tetrazoles **4ba** and **4ca** were obtained in good regioselectivities (entries 2-3). Then, a variety of tetrazoles with alkyl substitutions on the 5-position were investigated. By comparing 5-methyl tetrazole **1d**, 5-cyclopropyl-tetrazole **1e**, and 5-(*tert*-butyl)-tetrazole **1f**, it was found that the steric hindrance of alkyl substitutions on the 5-position of tetrazoles significantly influenced the regioselectivity, and larger steric hindrance substitution was beneficial to the 2,5-disubstutitued tetrazole product (entries 4-6). When (*E*)-5-styryl-tetrazole **1g** and 5-alkenyl tetrazoles **1h**-**1i** were evaluated, the desired 2,5-disubstituted tetrazole products **4ga**-**4ia** were produced in good regioselectivities, which indicated that 5-alkenyl tetrazoles with a C=C double bond conjugated with tetrazole ring were in favor of 2,5-disubstituted hemiaminal tetrazole products remarkably (entries 7-9). When 5-benzyl tetrazole **1j** was examined at RT or -40 °C, 2,5-disubstituted tetrazole **4ja** and 1,5-disubstituted tetrazole **5ja** were obtained in different regioisomeric ratios, which showed that the 2,5-disubstituted tetrazole **4ja** might be the thermodynamic product and 1,5-disubstituted tetrazole **5ja** might be the kinetic product (entries 10 and 11). In addition, 5-benzhydryl-tetrazole **1k**, 5-(benzylthio)-tetrazole **1l**, and ethyl 2-(2*H*-tetrazol-5-yl)acetate **1m** were also evaluated, and different 2,5-disubstituted tetrazoles **4ka**-**4ma** could also be obtained (entries 12-14).

As shown in Figure 2, the structure of 2,5-disubstituted tetrazole hemiaminal silyl ether **4an** was determined by the single-crystal X-ray diffraction analysis. Meanwhile, the structure of 1,5-disubstituted tetrazole hemiaminal silyl ether

Table 4 Substrate scope of 5-substituted tetrazoles[a]

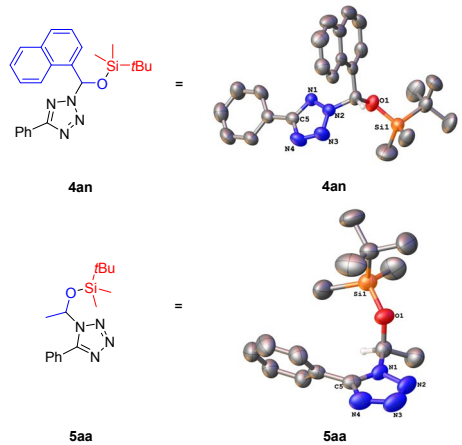


1 2a 3a 4 5

Entry	1	R	4	Yield[b] (4) (%)	rr (4:5)[c]
1[d]	1a	Ph	4aa	99	>99:1
2[d]	1b	3-MeC_6H_4	4ba	98	>99:1
3[d]	1c	4-BrC_6H_4	4ca	64	81:19
4	1d	Me	4da	27	52:48
5	1e		4ea	35	65:35
6	1f		4fa	29	>99:1
7	1g		4ga	69	81:19
8	1h		4ha	90	96:4
9	1i		4ia	91	95:5
10	1j		4ja	48	82:18
11[e]	1j		4ja	12	37:63
12	1k		4ka	55	91:9
13	1l		4la	56	66:34
14	1m		4ma	51	80:20

[a] Unless otherwise noted, reaction conditions were: **1** (0.2 mmol), **2a** (1.4 equiv, 0.28 mmol), **3a** (1.5 equiv, 0.3 mmol), iPr$_2$EtN (1.5 equiv, 0.3 mmol) in CH_2Cl_2 (2 mL) at RT for 3 h. [b] Isolated yield of **4** based on **1**. [c] The rr values were determined by ^{1}H NMR of the crude reaction mixtures. [d] Reaction time: 2 h. [e] At -40 °C.

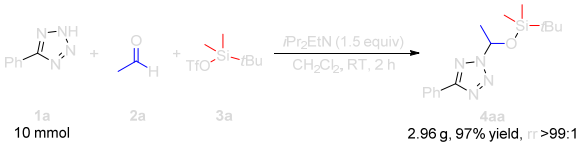
Fig. 2 X-ray structures of 2,5-disubstituted tetrazole **4an** and 1,5-disbstituted tetrazole **5aa**.



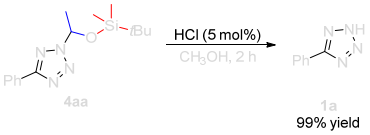
5aa was also confirmed by the single-crystal X-ray diffraction analysis.

To demonstrate the synthetic utility of the current methodology, the gram-scale synthesis of 2,5-disubstituted tetrazole hemiaminal silyl ether **4aa** was carried out (Scheme 3). By treatment of 10 mmol of 5-phenyl tetrazole **1a** in the presence of iPr$_2$EtN, the one-pot three-component hemiaminal silylation reaction of 5-phenyl tetrazole **1a**, acetaldehyde **2a**,

Scheme 3 Gram-scale synthesis of 2,5-disubstituted tetrazole **4aa**.



and TBSOTf **3a** proceeded well at RT for 2 h, giving the desired 2,5-disubstituted tetrazole hemiaminal silyl ether **4aa** in 2.96 g without any loss of yield and regioselectivity.



Scheme 4 The release of 5-phenyl tetrazole **1a** from 2,5-disubstituted tetrazole hemiaminal silyl ether **4aa**.

Considering that silyl ether prodrugs are acid labile and release the corresponding drugs under acid conditions, the release experiment of 5-substituted tetrazole from 2,5-disubstituted tetrazole hemiaminal silyl ether was performed (Scheme 4). In the presence of 5 mol% of HCl solution in CH_3OH for 2 h, the 2,5-disubstituted tetrazole hemiaminal silyl ether **4aa** was consumed completely, affording 5-phenyl tetrazole **1a** in 99% yield.

Conclusions

We have reported an efficient route to construct 2,5-disubstituted tetrazole hemiaminal silyl ethers *via* one-pot three-component hemiaminal silylation reaction of 5-substituted tetrazoles, aldehydes, and silyl triflates. With iPr$_2$EtN as the base, a variety of 2,5-disubstituted tetrazole hemiaminal silyl ethers were afforded in moderate to good yields and 37:62->99:1 regioisomeric ratios. The regioselectivities of this three-component hemiaminal silylation were significantly affected by the steric hindrance and conjugation effects of substitutions on the 5-position of tetrazoles. Furthermore, the three-component hemiaminal silylation reaction could be performed on a gram-scale, delivering the desired disubstituted tetrazole in excellent results. In addition, the 5-phenyl tetrazole could be released totally under acid atmosphere from the 2,5-disubstituted tetrazole hemiaminal silyl ether.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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