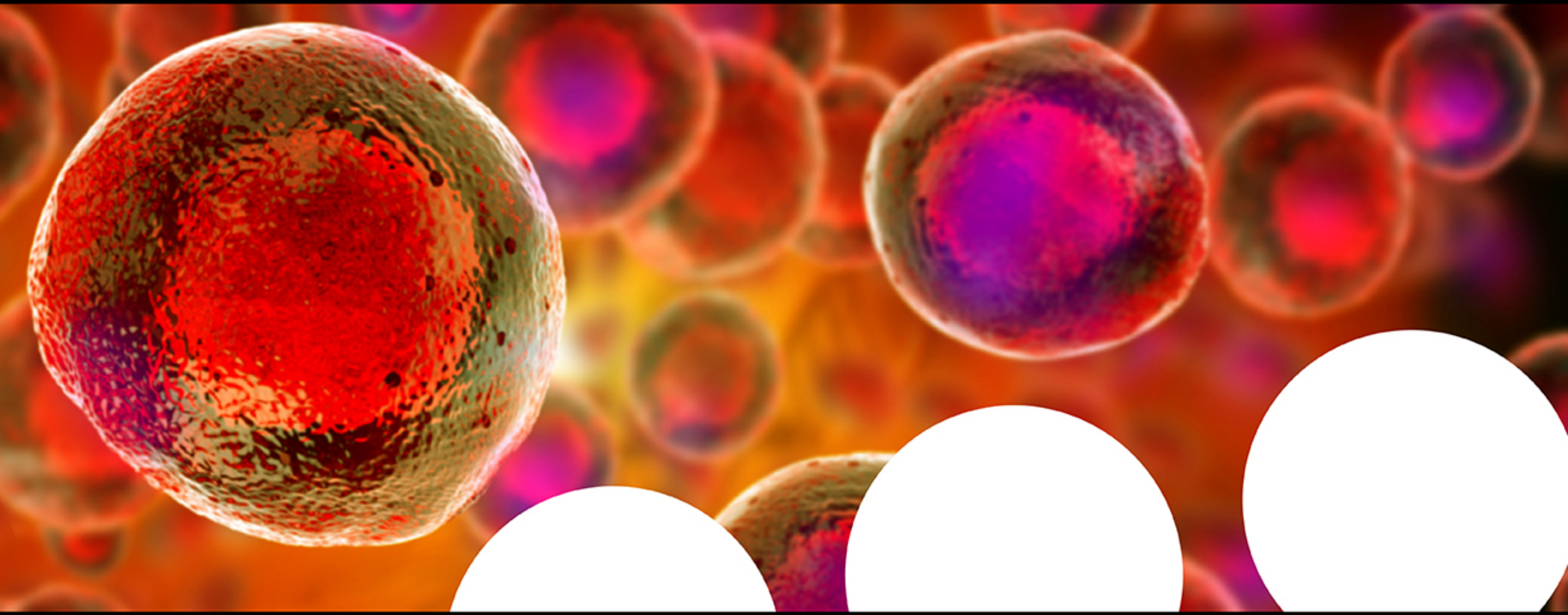

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Coupling of *N*-Tosylhydrazones with Tetrazoles: A Regioselective Synthesis of 2,5-Disubstituted-2*H*-Tetrazoles

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Herein we describe the C–N coupling reaction of *N*-tosylhydrazones with tetrazoles using thermic activation in the presence of different bases. The reactions proved to be highly regioselective to result in the corresponding 2,5-disubstituted-2*H*-tetrazoles as main products and 1,5-disubstituted-1*H*-tetrazoles as minor products. Owing to its mild conditions, the method enabled the use of a wide range of substrates.

Introduction

The interest in tetrazole derivatives has been rapidly increasing due to their wide range of applications in coordination and medicinal chemistry, as well as in the chemical industry.[1] Their broad biological application is primarily due to the fact that tetrazole, as a bioisostere of carboxylic acid functionalities, offers a preferable pharmacokinetic profile and a metabolically stable substitute for them.[2] Tetrazole derivatives have admirable biological, pharmaceutical and clinical applications as antibacterial, antifungal, anticancer, analgesic, anti-inflammatory, antidiabetic, anti-hyperlipidemic and antitubercular agents.[2] The medicinal importance of 2,5- and 1,5-disubstituated tetrazoles is outstanding in respect of more than twenty of their proved beneficial biological activities.[2] Disubstituted tetrazoles are drugs' active ingredients such as the antidepressant Amoten™, the third-generation cephalosporin antibiotic Cefobid™, the anticancer agent Lifoxitin™ and the broad spectrum antibiotic Cetazone™.[3] Polymer chemistry has also shown great interest toward tetrazoles. The synthesis of fluorescent single chain nanoparticles (SCNPs) is carried out via UV-light induced folding based on tetrazole chemistry.[4]

Several methods are known for the formation of 1,5-diaryl tetrazoles, most of them are based on a [2+3] cycloaddition with an azide reagent.[1,5] In contrast, the synthesis of 2,5-disubstituted derivatives is significantly more challenging (summarized in Scheme 1).[1,5a] The first synthesis of 2,5-diphenyltetrazole, reported by Dimroth and Merzbach, involved the condensation reaction of phenyl azide and benzaldehyde-phenylhydrazone under basic conditions (i).[6] Other cyclization methods were also published: (ii) from *N*-arylsulfonylbenzhydrazidoyl chlorides and arylhydrazines in the presence of potassium carbonate;[7] (iii) azo coupling reaction of aldehyde phenylsulphonylhydrazones with arenediazonium ions;[8] (iv) 1,3-dipolar cycloaddition of lithium trimethylsilyldiazomethane with the methyl esters of carboxylic acids;[9] (v) silver-catalyzed [3+2]-cycloaddition of arenediazonium salts with trimethylsilyldiazomethane,[10] 2,2,2-trifluorodiazoethane[11] and α-diazocarbonyl compounds[12] and (vi) a novel one-pot preparation for the synthesis of 5-aryl-2-methyl- and benzyltetrazoles was carried out from aromatic aldehydes and alkylhydrazine, followed by the treatment with di-*t*-butyl azodicarboxylate and [bis(trifluoroacetoxy)iodo]benzene.[13] The most typical preparative method for the synthesis of 2,5-disubstituted tetrazoles includes alkylation of 5-substituted-1*H*-tetrazoles. However, these reactions result in mixtures of regioisomers which need to be separated by fractional crystallization or chromatography (Scheme 1(vii)).[1,5a,14] Alternatively, the Pd and Cu-catalyzed *N*-2-arylation of 5-substituted tetrazoles has been investigated, but proved to be limited to the use of *N*-metalated tetrazoles (metal=SnR_3 and Na) and diaryliodonium salts as coupling partners.[15] A direct coupling of N–H free tetrazoles with low toxic boronic acids in the presence of a catalytic amount of Cu_2O in O_2 atmosphere represents an alternative route for 2,5-disubstituted tetrazoles (Scheme 1(ix)).[16] A further synthetic method starts from 5-substituted tetrazoles for the cobalt-catalyzed intermolecular hydroamination reaction of nonactivated olefins (Scheme 1(x)).[17]

However, many of the reported methods suffer from one or more of the following drawbacks: (i) the application of toxic/ and explosive reagents, (ii) the use of uncommon starting materials (iii) troublesome preparation of starting materials, (iv) tedious workup and low yields, (v) toxic wastes such as organotin compounds, (vi) the use of expensive and toxic metal

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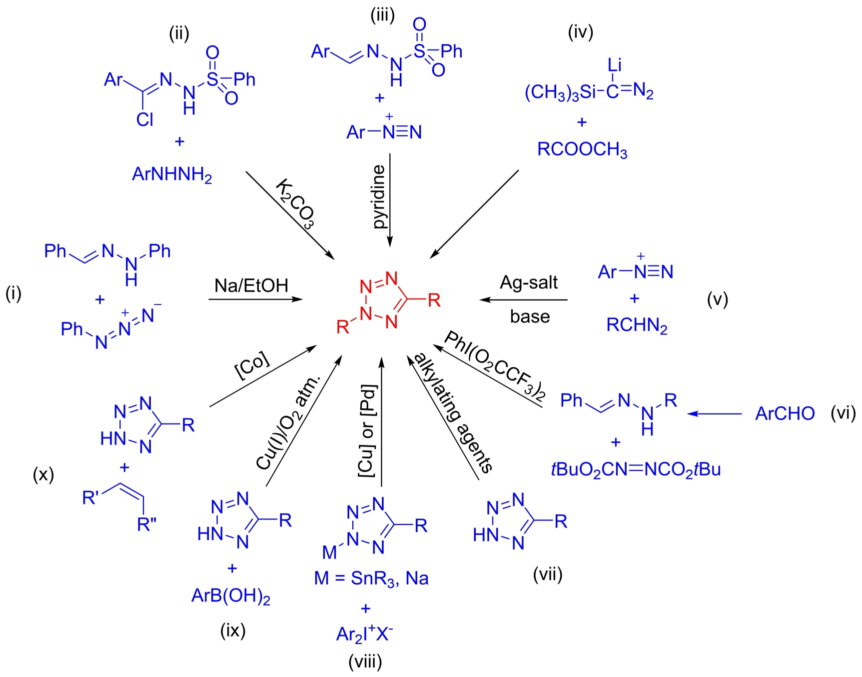
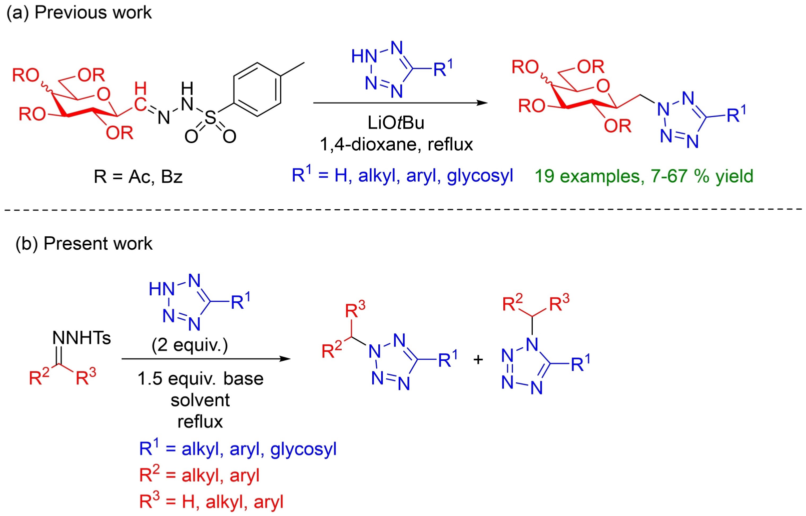


Scheme 1. Synthesis of 2,5-disubstituted tetrazoles.

catalysts. Thus, a mild and effective method is still required for the synthesis of 2,5-disubstituted tetrazoles.

N-Tosylhydrazones have been established as versatile reagents for metal-catalyzed and metal-free coupling reactions to form carbon-carbon and carbon-heteroatom (e.g. C–O, C–S and C–N) bonds.[18] However, only a few metal-catalyzed (Cu,[19] Pd,[20] Rh[21]) coupling reactions have been reported between *N*-tosylhydrazones and amines or N-heterocycles, and only one catalyst-free reaction with a C–N coupling side product.[22]

Recently, a systematic study has begun in our research group aiming at the investigation of the applicability of anhydro-aldose-tosylhydrazones[23] in Pd-catalyzed and catalyst-free coupling reactions.[24] As part of this research work 5-alkyl and 5-aryl-2-glycopyranosylmethyl-2*H*-tetrazoles and 5-glycosyl-2-glycopyranosylmethyl-2*H*-tetrazoles have been synthesized from *O*-peracylated 2,6-anhydro-aldose tosylhydrazones (*C*-(β-D-glycopyranosyl)formaldehyde tosylhydrazones) in non-catalyzed coupling reactions with tetrazoles. These reactions proved to be highly regioselective and gave the corresponding, up-to-then unknown 2-β-D-glycopyranosylmethyl-2*H*-tetrazoles in 7–67% yields (Scheme 2(a)).[24e] Based on these preliminaries we decided to explore the capacity of *N*-tosylhydrazones to



Scheme 2. Coupling of *N*-tosylhydrazones with 5-substituted 1*H*-tetrazoles.

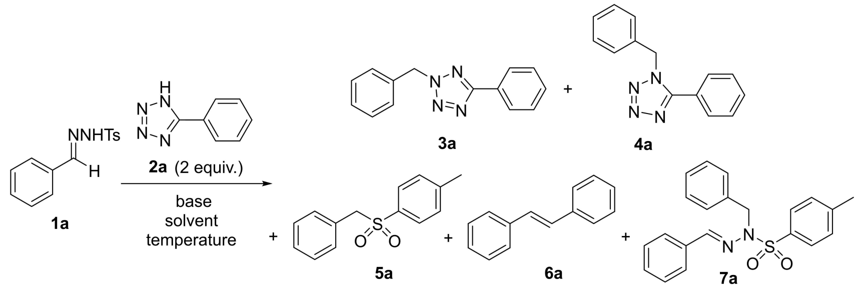
participate in non-catalyzed C–N coupling reactions with variously substituted tetrazoles. In this study, we report our success in achieving the coupling of *N*-tosylhydrazones with 5-substituted 1*H*-tetrazoles in the presence of LiO*t*Bu in dioxane providing a new regioselective synthesis of 2,5- and 1,5-disubstituted tetrazoles (Scheme 2(b)) in reasonable to good yields.

Results and Discussion

In our initial study, benzaldehyde tosylhydrazone **1a** and 5-phenyltetrazole **2a** were chosen as model substrates for the C(sp^3)–N bond forming process (Table 1). The reaction was first investigated with 2 equivalents of 5-phenyltetrazole and 1.5 equivalents of K_2CO_3 as base, in 1,4-dioxane at reflux temperature. This transformation resulted in a complex reaction mixture from which 2-benzyl-5-phenyl-2*H*-tetrazole **3a**[14d] (47%) and 1-benzyl-5-phenyl-2*H*-tetrazole **4a**[5b] (27%) were isolated as main products (entry 1). 1-(Benzylsulfonyl)-4-methylbenzene **5a**[25] and *N*-benzylated derivative **7a**[26] were also formed. Sulfone **5a** can be derived from the carbene insertion reaction into the sulfinate generated in the Bamford–Stevens reaction of tosylhydrazone **1a** while, **7a** can be formed by the carbene insertion to the tosylhydrazone NH group. To promote the formation of tetrazoles **3a** and **4a**, an extensive screening of various reaction parameters (concentration, solvent, base, temperature) was carried out. Using a sealed tube yielded **3a** in 36% yield. Homocoupling product, *trans*-stilbene **6a**[27] was also identified in the reaction mixture by ^{1}H-NMR (entry 2). Increasing the amount of K_2CO_3 (entries 3 and 4) did not improve the yields. Attempts to carry out the reaction in fluorobenzene or DMF also failed. The transformation in these solvents gave tetrazoles **3a** and **4a** with sulfone **5a** and stilbene **6a** by-products in low yields (entries 5–8). Although better results were achieved in toluene but the low solubility of tosylhydrazone **2a** required very dilute solutions (entries 9 and 10). After finding dioxane as the optimal solvent, different bases (Cs_2CO_3, K_3PO_4 and LiO*t*Bu) were tested (entries 11–19). Performing the transformation with Cs_2CO_3 provided moderate yields of **3a** (entries 11 and 12). The application of K_3PO_4 gave **3a** in moderate and **4a** in low yield (entry 13). The application of a sealed tube yielded tetrazole **3a** in moderate yield (entry 14). Next, 2-fold excess of tetrazole **2a** and 1.5-fold excess of LiO*t*Bu in 1,4-dioxane was employed at reflux temperature to give tetrazoles **3a** and **4a** in good and moderate yields, respectively (entry 15). Using a sealed tube or increasing the excess of LiO*t*Bu or tetrazole **2a** resulted in poorer yields (entries 16–19).

Optimal conditions for coupling of tosylhydrazone **1a** with 5-phenyl-1*H*-tetrazole **2a** required the use of 2-fold excess of tetrazole **2a** and 1.5-fold excess of LiO*t*Bu in 1,4-dioxane at reflux temperature. Under this protocol, the desired tetrazoles

Table 1. Optimization of the coupling reaction of benzaldehyde tosylhydrazone **1a** with 5-phenyltetrazole **2a**.



	Reaction conditions				Isolated yield				
Entry	Base [equiv.]	Solvent	T [°C]	Reaction time [h]	**3a**[14d]	**4a**[5b]	**5a**[25]	**6a**[27]	**7a**[26]
1	K_2CO_3 (1.5)	1,4-dioxane	101	18	47	27	3	–	+ [a]
2[b]	K_2CO_3 (1.5)	1,4-dioxane	101	22	36	–	–	36	+ [a]
3	K_2CO_3 (2)	1,4-dioxane	101	21	34	3	+ [a]	16	+ [a]
4	K_2CO_3 (3)	1,4-dioxane	101	21	+ [a]	4	+ [a]	68	+ [a]
5	K_2CO_3 (1.5)	fluorobenzene	85	21	23	+ [a]	+ [a]	–	61
6[b]	K_2CO_3 (1.5)	fluorobenzene	85	45	26	–	+	–	+ [a]
7	K_2CO_3 (1.5)	DMF	100	22	26	9	7	–	+ [a]
8	K_2CO_3 (1.5)	DMF	130	22	22	2	12	–	+ [a]
9[c]	K_2CO_3 (1.5)	toluene	111	120	30	–	–	–	–
10[d]	K_2CO_3 (1.5)	toluene	111	16	43	12	–	–	+ [a]
11	Cs_2CO_3 (1.5)	1,4-dioxane	101	22	36	+ [a]	14	–	+ [a]
12[b]	Cs_2CO_3 (1.5)	1,4-dioxane	101	22	35	–	–	16	+ [a]
13	K_3PO_4 (1.5)	1,4-dioxane	101	22	51	19	+ [a]	–	+ [a]
14[b]	K_3PO_4 (1.5)	1,4-dioxane	101	22	42	–	1	–	+ [a]
15	**LiO*t*Bu (1.5)**	**1,4-dioxane**	**101**	**24**	**73**	**25**	+ [a]	–	+ [a]
16[b]	LiO*t*Bu (1.5)	1,4-dioxane	101	18	39	–	2	30	–
17	LiO*t*Bu (2)	1,4-dioxane	101	5	34	18	+ [a]	–	+ [a]
18	LiO*t*Bu (3)	1,4-dioxane	101	5	12	5	+ [a]	–	+ [a]
19[e]	LiO*t*Bu (1.5)	1,4-dioxane	101	26	50	37	+ [a]	–	+ [a]

[a] Compounds were detected in the mixture. [b] Performed in a sealed tube. [c] Applying three-fold dilution (0.03 mmol/ml). [d] Applying four-fold dilution (0.015 mmol/ml). [e] Application of 3 equiv. of phenyltetrazole.

3 a and **4 a** were isolated in high overall yield (98 %, Table 1, entry 15) with high regioselectivity towards **3 a**.

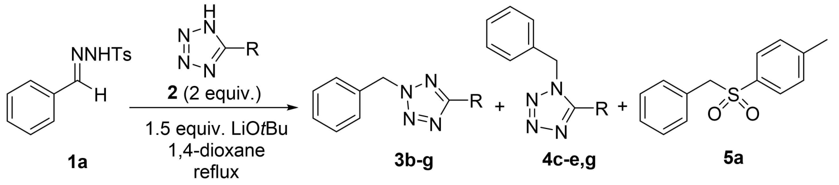
With the optimized conditions in hand, next the scope of the coupling reaction was studied by transforming benzaldehyde tosylhydrazone **1 a** with a variety of tetrazoles prepared in our lab earlier.[24e] As summarized in Table 2, the C–N coupling appeared to be general and regioselective, resulting in 2,5-disubstituted tetrazoles **3 b**–**g** as the main products with satisfactory to good yields and 1,5-disubstituted tetrazoles **4 c**–**e**, **g** with low yields. The couplings were found not to be significantly affected by the tetrazole substituents, gave more or less similar yields of the expected products. By-product sulfone **5 a** was also formed in some reactions (entries 1–3). Unfortunately, performing the reaction with 5-(4-methoxybenzyl)-1*H*-tetrazole gave a complex reaction mixture from which none of the desired products could be isolated (entry 7).

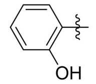
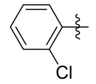
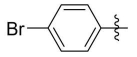
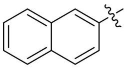
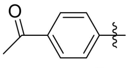
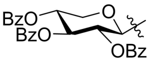
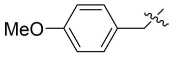
To broaden the scope of substrates, we further investigated the reaction with substituted benzaldehyde tosylhydrazones **1 b**–**j** and 2-phenylacetaldehyde tosylhydrazone **1 k** with 5-phenyltetrazole (Table 3). To this end the necessary *N*-tosylhydrazones **1** were synthesized with classical solution chemistry[28] and/or with a mechanochemical process[29] (see Supporting information for details). These couplings were found to be somehow affected by the substituents. Methyl (entry 1) and halogen (entries 2, 5–8) substituted tosylhydrazones gave better yields. However, in the presence of methoxy (entry 9) and the strong electron-withdrawing cyano and nitro groups (entries 3 and 4) lower yields were achieved. 2,5-Disubstituted tetrazoles **3 h**–**p** were isolated as main products in moderate to good yields (58–69 %) beside 1,5-disubstituted derivatives **4 h**–**p** (13–29 %) and sulfones (**5 h**, **i**, **l**, **m**, **o**) as side products. Nonetheless, the coupling reaction with aliphatic tosylhydrazone **1 k** resulted in the desired products **3 q** and **4 q** in very low yields (entry 10).

Coupling reactions were also extended to aldehyde tosylhydrazones **1 b** and **1 d** and tetrazoles **2 b** and **2 c** (Table 4). Reactions of 4-methylbenzaldehyde **1 b** and 4-cyanobenzaldehyde tosylhydrazone **1 d** with 5-(2-hydroxyphenyl) tetrazole **2 b** and 5-(2-chlorophenyl) tetrazole **2 c** resulted regioselectively in the corresponding coupled products **3 r**–**u** and **4 s** with various yields (entries 1–4). In one case, the sulfone **5 s** was also detected in the reaction mixture (entry 2).

Next, the coupling reactions of ketone tosylhydrazones **8** were examined. Applying the optimized conditions for the reaction of acetophenone tosylhydrazone **8 a** and phenyl tetrazole **2 a** resulted in the desired coupled products **9 a** and **10 a** in low yields beside 87 % conversion (Table 5, entry 1). To get higher yields and total conversion we started a new optimization process. Performing the reaction in a sealed tube provided tetrazoles **9 a** and **10 a** in similar yields and the *N*-benzylated product **12 a** in 29 % beside 89 % conversion (entry 2). Using longer reaction time and a sealed tube resulted in total conversion, but lower yields (entry 3). The application of 3 equiv. of tetrazole and longer reaction time gave low yields, as well (entry 4). The use of microwave activation significantly reduced the reaction time but had no effect on the yields of tetrazoles **9 a** and **10 a** (entry 5). Using K_3PO_4, K_2CO_3 and Cs_2CO_3 as base did not improve the yields (entries 6–8). In the case of the latter, the main product of the reaction was the sulfone

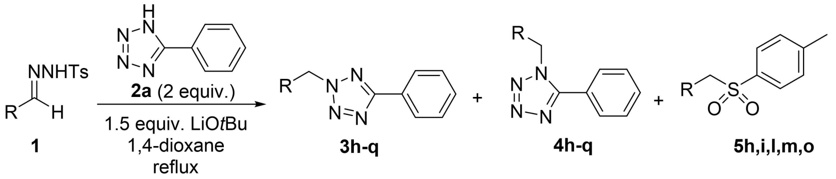
Table 2. Reactions of benzaldehyde tosylhydrazone **1 a** with 5-aryltetrazoles **2**.

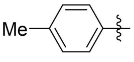
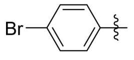
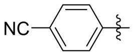
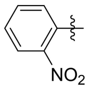
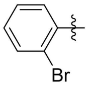
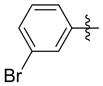
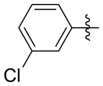
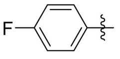
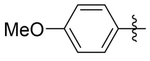
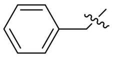


Entry	Tetrazole	R	Reaction time [h]		Isolated yield [%] 3	 4	 5 a[25]
1	**2 b**		25	**b**	58	–	+[a]
2	**2 c**		28	**c**	54	39	+[a]
3	**2 d**		22	**d**	38[14e]	10[14e]	+[a]
4	**2 e**		26	**e**	67	19	–
5	**2 f**		43	**f**	18	–	–
6	**2 g**		43	**g**	31	8	–
7	**2 h**		28		complex reaction mixture		

[a] Compound was detected in the mixture.

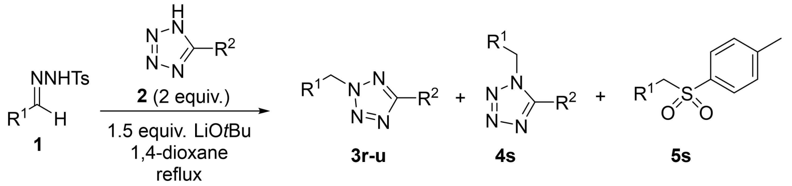
Table 3. Reactions of aldehyde tosylhydrazones **1** with 5-phenyltetrazole **2a**.

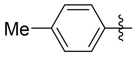
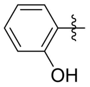
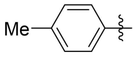
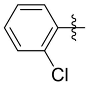
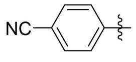
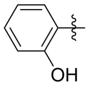
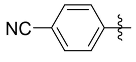
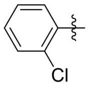


Entry	TsH	R	Reaction time [h]		Isolated yield [%]		
					3	4	5
1	**1b**		24	**h**	58[14d]	22	+[a][38]
2	**1c**		21	**i**	61[14d]	17	+[a][38]
3	**1d**		21	**j**	47	25	–
4	**1e**		21	**k**	48	13	–
5	**1f**		4.5	**l**	58	15	+[a][38]
6	**1g**		4.5	**m**	67	25	+[a][38]
7	**1h**		4.5	**n**	69	18	–
8	**1i**		25	**o**	69[14d]	29	+[a][25]
9	**1j**		21	**p**	37[14d]	21	–
10	**1k**		24	**q**	+[a]	3[39]	–

[a] Compound was detected in the mixture.

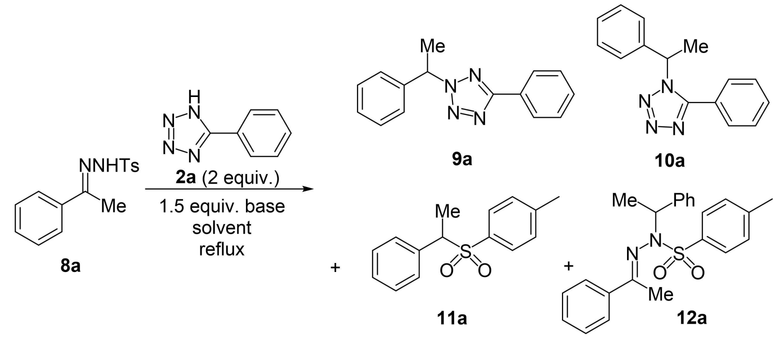
Table 4. Reactions of aldehyde tosylhydrazones **1** with 5-aryltetrazoles **2**.



Entry	TsH	Tetrazole	R^1	R^2	Reaction time [h]		Isolated yield [%]		
							3	4	5
1	**1b**	**2b**			25	**r**	14	–	–
2	**1b**	**2c**			25	**s**	28	19	+[a][38]
3	**1d**	**2b**			25	**t**	26	–	–
4	**1d**	**2c**			25	**u**	49	–	–

[a] Compound was detected in the mixture.

Table 5. Reactions of acetophenone tosylhydrazone **8a** with 5-phenyltetrazole **2a**.



Entry	Solvent	Base	Reaction time [h]	Conv. [%]	Isolated yield [%] **9a**[14d]	**10a**	**11a**[40]	**12a**[26]
1	1,4-dioxane	LiO*t*Bu	24	87	30[a]	14[a]	–	+[b]
2[c]	1,4-dioxane	LiO*t*Bu	24	89	43[a]	14[a]	–	29[a]
3[c]	1,4-dioxane	LiO*t*Bu	48	100	18	9	–	30
4[d]	1,4-dioxane	LiO*t*Bu	48	100	24	17	+[b]	–
5[e]	1,4-dioxane	LiO*t*Bu	15 min	100	27	15	+[b]	+[b]
6	1,4-dioxane	K_3PO_4	48	100	21	16	+[b]	–
7	1,4-dioxane	K_2CO_3	48	100	22	–	–	–
8	1,4-dioxane	Cs_2CO_3	48	100	+[b]	+[b]	14	+[b]
9	DMF	LiO*t*Bu	48	100	20	10	+[b]	+[b]
10	fluorobenzene	LiO*t*Bu	48	61	11[a]	29[a]	–	9[a]
11	toluene	LiO*t*Bu	48	100	49	24	+[b]	–
12[c]	toluene	LiO*t*Bu	48	89	27[a]	43[a]	–	+[b]
13[e]	toluene	LiO*t*Bu	2	100	18	39	5	19

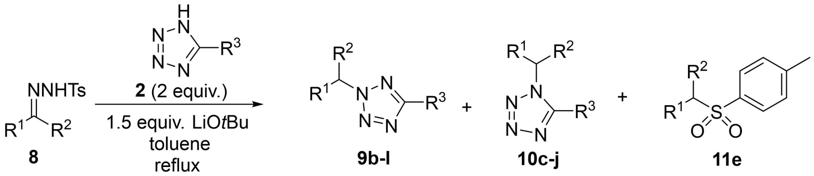
[a] Yield was corrected with the conversion. [b] Compound was detected in the mixture. [c] Performed in a sealed tube. [d] Application of 3 equiv. of tetrazole. [e] Microwave activation.

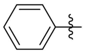
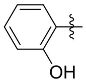
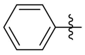
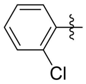
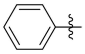
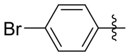
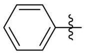
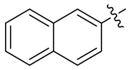
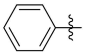
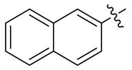
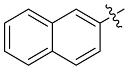
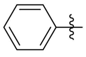
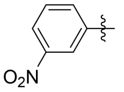
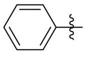
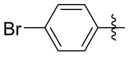
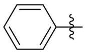
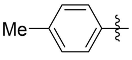
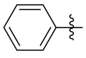
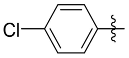
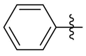
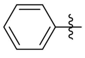
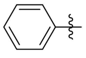
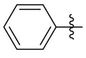
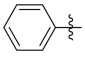
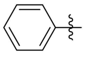
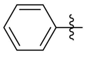
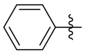
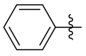
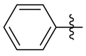
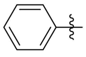
derivative **11a** (entry 8). After finding LiO*t*Bu as the optimal base, different solvents (DMF, fluorobenzene and toluene) were tested (entries 9–13). The best yields were achieved in toluene (entries 11–13). The ratio of regioisomers was significantly influenced by the way the transformation was performed. Contrary to previous results, the main product of the reactions carried out in a sealed tube or with microwave activation was the 1,5-disubstituted isomer **10a** (entries 12 and 13).

Finally, the scope of the reactions of ketone tosylhydrazones **8** (prepared by solution reactions[28] and/or with a mechanochemical method[29] (see Supporting information for details)) with tetrazoles **2** was studied and results are listed in Table 6. It seems obvious from the outcome of the couplings that ketone tosylhydrazones **8** react less smoothly than aldehyde tosylhydrazones **1**, require longer reaction time and result in lower yields. Otherwise, the regioselectivity of the reactions is also unclear, since 1,5-disubstituted tetrazoles **10** are the main products in some cases (entries 2–5 and 10). In one case sulfone **11e** was also detected in the reaction mixture (entry 4). Acetophenone type derivatives gave somehow acceptable yields of tetrazoles **9** and **10** (entries 1–10), while benzophenone **8h** and acetone tosylhydrazone **8g** gave complex reaction mixtures from which the coupled products could not be isolated in pure state (entries 11–14).

2,5- and 1,5-disubstituted tetrazoles were identified by their analytical and spectral data, and in the case of known compounds, by comparison with reported ^1H NMR data. The regioisomers **3** and **4**, synthesized from aldehyde tosylhydrazones, were differentiated by the characteristically distinct chemical shifts of the benzyl CH_2 group attached to the tetrazole N-1 atom in the ^1H NMR spectra. These CH_2 signals for 2,5-disubstituted tetrazoles **3** are in the range of 5.77–5.96 ppm, while for 1,5-disubstituted tetrazoles **4** they are between 5.28–5.69 ppm, which show good correlation with literature data (δ 5.73–5.92 ppm[14d] for 2,5- and 5.42–5.68 ppm[5b] for 1,5-disubstituted tetrazoles). Regioisomers **3** and **4** showed quite different ^{13}C NMR spectral data for C-5 of the tetrazole ring. Signals for C-5 appear in the range of 165.4–165.8 ppm for 2,5-disubstituted tetrazoles **3**, and between 154.9–155.1 ppm for 1,5-disubstituted tetrazoles **4**. These correlate well with literature data (δ 164.2–165.5 ppm[14d] for 2,5- and 152.7–155.4 ppm[5b] for 1,5-disubstituted derivatives). The regioisomers **9** and **10**, derived from couplings of ketone tosylhydrazones, showed characteristic signals for CH attached to the tetrazole ring. This CH hydrogen resonates in the range of 6.08–6.28 ppm for 2,5- **9** and 5.26–5.83 ppm for 1,5-isomers **10**. Resonances for this CH carbon appear between 62.7–64.3 ppm for 2,5- **9** and are shifted to 57.9–59.1 ppm in 1,5-disubstituted tetrazoles **10**. These data are in good correlation with literature values: CH protons around 5.96–6.60 ppm in the ^1H NMR and CH carbons between 57.5–63.6 ppm in the ^{13}C NMR spectra of 2,5-disubstituted tetrazoles.[14c–e,41] Regioisomers **9** and **10** showed quite different ^{13}C NMR spectral data for C-5 of the tetrazole ring. Signals for C-5 appear in the range of 163.3–165.5 ppm for 2,5-disubstituted tetrazoles **9**, and around 152.3–154.6 ppm for 1,5-disubstituted tetrazoles **10**. These data are in good correlation

Table 6. Coupling of ketone tosylhydrazones **8** with 5-aryltetrazoles **2**.



Entry	TsH	Tetrazole	R¹	R²	R³	Reaction time [day]	Conv. [%]		Isolated yield [%]		
									9	**10**	**11**
1	**8a**	**2b**		Me		2	100	**b**	25	–	–
2	**8a**	**2c**		Me		2	100	**c**	25	37	–
3	**8a**	**2d**		Me		2	100	**d**	24	26	–
4	**8a**	**2e**		Me		2	100	**e**	13	17	+[a][40]
5[b]	**8a**	**2e**		Me		2	100	**e**	5	37	–
6	**8b**	**2a**		Me		2	100	**f**	30	+[a]	–
7	**8c**	**2a**		Me		2	100	**g**	40	28	–
8	**8d**	**2a**		Me		2	100	**h**	61	20	–
9	**8e**	**2a**		Me		2	100	**i**	30[41]	21	–
10	**8f**	**2a**		Me		2	100	**j**	23	44	–
11[c]	**8h**	**2a**				2	73	**k**	+[a][14d]	–	–
12	**8h**	**2a**				5	100	**k**	+[a][14d]	–	–
13[c,d]	**8h**	**2a**				3	60	**k**	+[a][14d]	–	–
14[c]	**8g**	**2a**	Me	Me		4	100	**l**	3[14e]	–	–

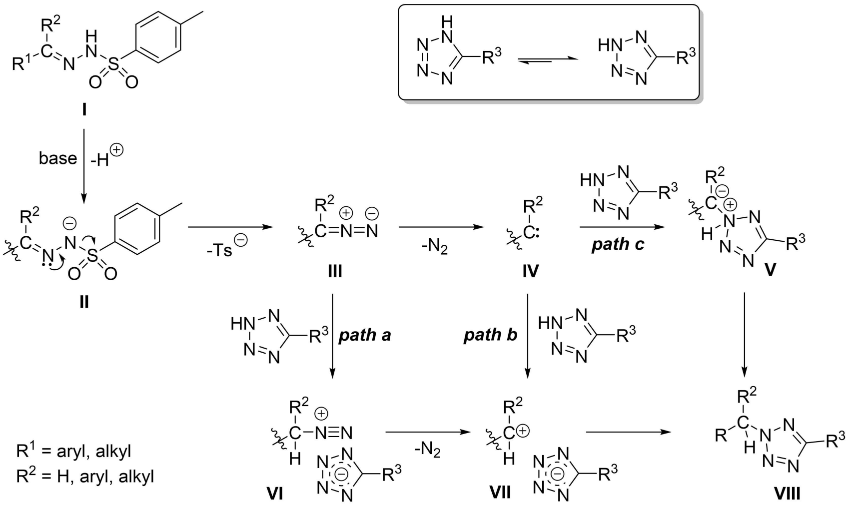
[a] Compound was detected in the mixture. [b] Performed in a sealed tube. [c] Solvent: 1,4-dioxane. [d] Base: K_3PO_4.

with the literature data which are 164.0–165.3 ppm for 2,5-disubstituted derivatives.[14c–e,41]

A plausible reaction mechanism for this transformation is illustrated in Scheme 3. This is identical with our former reported mechanism for anhydro-aldose tosylhydrazones.[24e] It is well known that *N*-tosylhydrazones undergo thermal decomposition in the presence of base through the Bamford–Stevens reaction to generate diazo compounds **III**. Subsequent reaction of **III** with the tetrazole could produce 2,5-disubstituted 2*H*-tetrazole **VIII** through diazonium **VI** or carbocation **VII** intermediates (*path a*). Carbocation **VII** could be formed via carbene **IV** (*path b*), as well. Finally, carbene **IV** may directly be inserted into the NH bond of the tetrazole that may result in the corresponding C–N coupled product **VIII** *via* intermediate **V** by proton migration (*path c*). The regioselective formation of the 2-substituted-2*H*-tetrazoles **VIII** may be explained by steric effects of the tetrazole 5-substituent on paths *a* and *b* while on path *c* the preponderance of the 2*H*-tautomer facilitated by the presence of the 5-substituent may be the reason for the selectivity.[42]

Conclusion

We have utilized aldehyde and ketone tosylhydrazones for alkylation of 5-substituted tetrazoles in a catalyst-free coupling reaction under mild conditions to give 2,5- and 1,5-disubstituted tetrazoles. The reaction proved to be regioselective, resulted in 2,5-disubstituted tetrazoles as the main products with aldehyde tosylhydrazones. In addition, this protocol also



Scheme 3. Proposed mechanistic rationale for the coupling reactions (reported earlier for anhydro-aldose tosylhydrazones[24e]).

exhibits excellent functional group compatibility. Consequently, this protocol represents a facile, universally applicable and regioselective synthesis of 2,5-disubstituted tetrazoles from aldehyde tosylhydrazones. On the other hand, coupling of ketone tosylhydrazones proved to be less effective giving lower yields and sometimes 1,5-disubstituted products as the main products.

Experimental Section

General Experimental Methods

Optical rotations were determined with a Perkin–Elmer 241 polarimeter at room temperature. NMR spectra were recorded with Bruker AM Avance DRX 360 MHz (360/90 MHz for ^{1}H/^{13}C) or Bruker AM Avance I 400 MHz (400/100 MHz for ^{1}H/^{13}C) or Bruker AM Avance II 500 MHz (500/125 MHz for ^{1}H/^{13}C) spectrometers. Chemical shifts are referenced to TMS as the internal reference (^{1}H), or to the residual solvent signals (^{13}C). The assignments of the ^{1}H and ^{13}C NMR signals of compounds **3g**, **n** and **4g**, **n** were performed by their COSY (**3g**, **n** and **4g**, **n**), HSQC (**3g**, **n** and **4g**, **n**), HMBC (**3g**, **n** and **4g**, **n**) spectra. Mass spectra were recorded with maXis II UHR ESI-QTOF MS (Bruker Daltonik, Bremen, Germany) instruments in positive ion mode with electrospray ionization technique or Thermo LTQ XL (Thermo Electron Corp., San Jose, CA, USA) mass spectrometers operated in a full scan positive ion ESI mode. TLC was performed on DCAlurolle Kieselgel 60 F254 (Merck). TLC plates were visualized under UV light, and by gentle heating (generally no spray reagent was used but, if more intense charring was necessary, the plate was sprayed with the following solution: abs. EtOH (95 mL), cc. H_2SO_4 (5 mL), anisaldehyde (1 mL)). For column chromatography Kieselgel 60 (Merck, particle size (0.063–0.200 mm) was applied. 1,4-Dioxane was distilled from sodium benzophenone ketyl and stored over sodium wires.

General procedure I for the synthesis of 2,5-disubstituted-2*H*-tetrazoles 3 and 1,5-disubstituted-1*H*-tetrazoles 4

The corresponding 5-substituted-1*H*-tetrazole **2** (2 mmol) was dissolved in 1,4-dioxane (6 mL) in a three-neck round-bottom flask, LiO*t*Bu (1.5 mmol) was added and the suspension was stirred and heated to reflux. Then, the corresponding tosylhydrazone **1** (1 mmol) was dissolved in 1,4-dioxane (6 mL) and added dropvise in 15 min. When TLC indicated complete consumption of the starting compound (1 day), the mixture was cooled and the insoluble material filtered off and washed with 1,4-dioxane. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (gradient elution with acetone–hexane = 1:15 to 1:2 or EtOAc–hexane = 1:8 to 1:2).

For the characterization of 2,5-disubstituted-2*H*-tetrazoles **3** and 1,5-disubstituted-1*H*-tetrazoles **4** see Supporting Information.

General procedure II for the synthesis of 2,5-disubstituted-2*H*-tetrazoles 9 and 1,5-disubstituted-1*H*-tetrazoles 10

The corresponding 5-substituted-1*H*-tetrazole **2** (2 mmol) was dissolved in toluene (6 mL) in a three-neck round-bottom flask, LiO*t*Bu (1.5 mmol) was added and the suspension was stirred and heated to reflux. Then, the corresponding tosylhydrazone **8** (1 mmol) was dissolved in toluene (14 mL) and added dropvise in 15 min. When TLC indicated complete consumption of the starting compound (2 days), the mixture was cooled and the insoluble material filtered off and washed with 1,4-dioxane. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (gradient elution with acetone–hexane 1:15 to 1:2 or EtOAc–hexane = 1:8 to 1:2).

For the characterization of 2,5-disubstituted-2*H*-tetrazoles **9** and 1,5-disubstituted-1*H*-tetrazoles **10** see Supporting Information.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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