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Communication

Multicomponent Reactions

Convergent Three-Component Tetrazole Synthesis

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Abstract: A microwave-accelerated, simple, and efficient method for the construction of the 1,5-tetrazole scaffold was developed. It comprises a multicomponent reaction of an amine, a carboxylic acid derivative, and an azide source. On the basis of the availability of the archetypical starting materials, this method provided very versatile synthetic access to 1,5-disubstituted tetrazoles. The usefulness of this method was demonstrated in the synthesis of biologically important fused tetrazole scaffolds and the marketed drug cilostazol.

Introduction

The tetrazole motif is an important synthetic scaffold that is widely used in medicine, biochemistry, pharmacology, and materials; for example, this structure is found in explosives, photography and photoimaging chemicals, rocket propellants, polymers, gas generators, and agrochemicals.[1] The first tetrazole synthesis was reported in 1885.[2] Since then, a plethora of examples have been reported, the vast majority of which rely on the use of nitriles, heterocumulenes, amides, thioamides, imidoyl chlorides, ketones, amines, and alkenes as the starting materials.[3] The increasing importance of 1,5-disubstituted tetrazoles in different applications, including as bioactive agents;[1c] drugs such as cilostazol, pentylenetetrazole, and latamoxef; and *cis*-amide bond isosteres in peptides, has propelled the need for efficient synthetic methods. Direct access to diverse 1,5-disubstituted tetrazoles is mainly possible from amides and thioamides.[4] Other methods include the use of ketones and oximes with suitable azide sources or amidrazones with N_2O_4 or HNO_2[5] Recently, various methods were developed for the synthesis of 1,5-disubstituted tetrazoles from amides.[3a] These methods mainly use chlorinating agents to form imidoyl chlorides, and this is then followed by the addition of an azide source to give the disubstituted tetrazoles. However, the limited availability of diverse amides as starting materials compels an additional step for amide synthesis from carbonyl compounds such as acids and acetyl chlorides. Moreover, direct amide bond formation from unactivated acids is challenging, and thus, multistep sequential syntheses are often the result.[6] Direct amide formation requires basic conditions, whereas tetrazole formation is favored under acidic conditions through the formation of the imidoyl chloride, which make a one-pot synthesis of tetrazoles difficult. Also, a one-pot reaction for the synthesis of tetrazoles from amides is challenging, as hydrogen chloride formed in the chlorination step can have deleterious effects on acid-sensitive functionalities.[7] Reported methods for tetrazole formation from amides face major drawbacks, including the use of an excess amount of toxic, volatile, and highly explosive HN_3 (30 equiv.), long reaction time (2 days),[8] racemization of the product,[9] and the use of Mitsunobu reaction conditions, which require expensive reagents, long reaction times, and tedious workup procedures and furthermore provide the product in low yields.[10] The use of an excess amount of base to trap the HCl generated in the reaction[7] in addition to an excess amount of NaN_3 increases the chances of toxic hydrazoic acid formation.[11] Moreover, the majority of methods use less preferable solvents such as DMF.[11,12] The $SiCl_4/NaN_3$ combination was reported for the one-step synthesis of tetrazoles from amides, but the major drawbacks of this method are the requirement for anhydrous and inert conditions, long reaction times (50 h), and limited reported diversity.[13] Thus, the development of a straightforward, easy, safe, efficient, fast, diverse, and general method for the formation of tetrazoles from unactivated carbonyl compounds with the use of fewer equivalents of azide and with a simple workup procedure is warranted.

We foresaw that the accelerating effect of microwaves could potentially lead to a multicomponent reaction (MCR) of tetrazoles among suitable carbonyl compounds, amines, and azides with a chlorinating agent. We hypothesized that, in situ amide formation from amines and carbonyl compounds followed by imidoyl chloride formation and finally tetrazole formation by azide addition would be possible in a one-pot three-component reaction (3CR). Careful choice of a suitable chlorinating reagent could trigger carbonyl activation for both amide and imidoyl chloride formation as the key step of the reaction.

Results and Discussion

To test this hypothesis, optimization of the reaction was performed with hydrocinnamoyl chloride, benzylamine, and trimethylsilyl (TMS) azide as starting materials with different chlorinating reagents, solvents, temperatures, microwave conditions,

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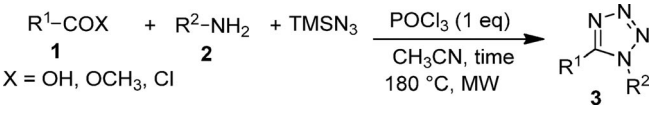
and reaction times. Initial screening was performed at room temperature and by using conventional heating. We screened different reagents such as HCl, $AlCl_3$, $(COCl)_2$, and $SOCl_2$ at room temperature or by heating and with the use of different solvents, including CH_3CN, DMF, THF, and 2,6-lutidine, but we did not get the expected product. The reactions mostly ended up in amide formation, and even with heating at reflux for 3 days in the presence of an excess amount HCl, the product was not formed. We shifted to $POCl_3$, which is a safer alternative to phosgene and easier to handle than PCl_5. Encouragingly, we found a trace amount of product formation with $POCl_3$ at room temperature after a long reaction time (3 days; see Table S1, Supporting Information). An increase in the temperature led to a slight enhancement in the reaction conversion, but the reaction still gave the amide as the major product. The use of a base to reduce the requisite amount of HCl in the reaction to increase the yield did not have any effect on the reaction.

The synthesis of tetrazoles by using nitriles and NaN_3 at 220 °C under microwave conditions is known,[14] and this encouraged us to try microwave conditions at a higher temperature. A reaction at 150 °C gave the product but required 25 min to obtain complete conversion. Increasing the temperature to 180 °C accelerated the reaction to 3 min with 100 % conversion. We used 1.5 equiv. of $TMSN_3$, which avoided the danger of forming hydrazide from an excess amount of azide. With these optimized conditions in hand, we next examined the generality of this novel 3CR by treating different carbonyl compounds such as acid chlorides, carboxylic acids, and esters with different amines (Table 1). The majority of the acid chlorides gave complete conversion into the corresponding tetrazoles under these optimized conditions in good to high yields (Table 1, entries 1–17). Aromatic and aliphatic acid chlorides proved to be equally effective in this reaction. The functional group tolerance of the acid chloride (e.g., methoxy, nitro, and chloro; Table 1, entries 4–7 and 12–14) in this protocol provides multiple opportunities for various further chemical manipulations. The conversions of aromatic and aliphatic carboxylic acids were as effective as those of the acid chlorides, but these substrates delivered the products in slightly lower yields. The bicyclic compound naphthylcarboxylic acid gave a good yield of the corresponding product (Table 1, entry 22). Application of this method to esters was also successful; however, a longer reaction time was required (25–30 min) for total conversion, and moderate to good yields were provided with aliphatic and aryl esters. Esters with nitrile and chloro substituents also displayed decent reactivity in this reaction (Table 1, entries 29–31). Aliphatic and aromatic amine compounds were compatible substrates for this process. Good conversions were also observed in the case of sterically hindered groups, including 2-chloroaniline, 2-benzylaniline, and 2-methylaniline, which provided the products in good to excellent yields of 91, 80, and 72 %, respectively (Table 1, entries 6, 15 and 17). Amine derivatives containing both electron-withdrawing and electron-donating functionalities such as methoxy, chloro, and nitrile were equally compatible and afforded the expected adducts. Easily cleavable groups such as cyanoethyl and benzyl were also compatible with this method, and they readily give access to 1*H*-5-tetrazoles (Table 1, entries 2, 11, and 26). Bistetrazoles are also accessible by our method (Table 1, entries 37–40), and these compounds are highly important in high-energy nitrogen-rich compounds and in polymerization.[15]

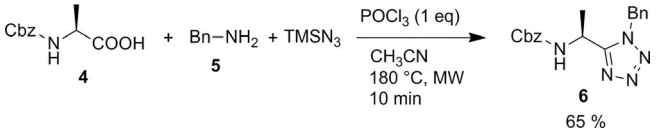
Table 1. Synthesis of tetrazoles from carbonyl compounds, amines, and $TMSN_3$.[a]



Entry	R^1	R^2[b]	Time [min]	Yield[c] (product) [%]
	R^1-COCl			
1	Bn	$C_6H_5(CH_2)_2$	4	68 (**3a**)
2	$C_6H_5(CH_2)_2$	Bn	3	72 (**3b**)
3	$CH_3(CH_2)_2$	$CH_3(CH_2)_2$	4	78 (**3c**)
4	*p*-$ClC_6H_4CH_2$	*p*-$CH_3OC_6H_4(CH_2)_2$	5	76 (**3d**)
5	*p*-$ClC_6H_4CH_2$	$C_6H_5(CH_2)_2$	5	73 (**3e**)
6	*p*-$ClC_6H_4CH_2$	*o*-ClC_6H_4	5	91 (**3f**)
7	*p*-$ClC_6H_4CH_2$	Cy	5	48 (**3g**)
8	CH_3CH_2	CH_2=$CHCH_2$	7	70 (**3h**)
9	CH_3CH_2	$C_6H_5(CH_2)_2$	5	73 (**3i**)
10	CH_3CH_2	Ph	5	86 (**3j**)
11	$CH_3(CH_2)_2$	$NC(CH_2)_2$	10	60 (**3k**)
12	$Cl(CH_2)_2$	$C_6H_5(CH_2)_2$	5	71 (**3l**)
13	*m*-$CH_3OC_6H_4$	Ph	4	72 (**3m**)
14	*p*-$O_2NC_6H_4$	*m*,*p*-$(CH_3O)_2C_6H_3$	7	87 (**3n**)
15	*p*-$ClC_6H_4CH_2$	*o*-BnC_6H_4	7	88 (**3o**)
16	$ClCH_2$	Ph	5	73 (**3p**)
17	$ClCH_2$	*o*-$CH_3C_6H_4$	5	72 (**3q**)
	R^1-COOH			
18	$C_6H_5(CH_2)_2$	$CH_3(CH_2)_2$	4	92 (**3r**)
19	$C_6H_5(CH_2)_2$	Bn	4	72 (**3s**)
20	*m*,*p*-$(CH_3O)_2C_6H_3CH_2$	*i*Pr	4	56 (**3t**)
21	*p*-$ClC_6H_4CH_2$	$C_6H_5(CH_2)_2$	5	63 (**3u**)
22	2-naphthylCH_2	$CH_3(CH_2)_2$	5	73 (**3v**)
23	Ph	Ph	5	56 (**3w**)
24	Ph	$C_6H_5(CH_2)_2$	5	48 (**3x**)
25	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	4	63 (**3y**)
26	$CH_3(CH_2)_2$	$NC(CH_2)_2$	7	62 (**3z**)
27	$CH_3(CH_2)_2$	$C_6H_5(CH_2)_2$	5	71 (**3aa**)
28	$CH_3(CH_2)_2$	CH_2=$CHCH_2$	3	52 (**3ab**)
	R^1-$COOCH_3$			
29	$NCCH_2$	$C_6H_5(CH_2)_2$	30	67 (**3ac**)
30	$ClCH_2$	*o*-ClC_6H_4	30	57 (**3ad**)
31	$ClCH_2$	Bn	25	63 (**3e**)
32	CH_3CH_2	*o*-ClC_6H_4	25	60 (**3af**)
33	$C_6H_5(CH_2)_2$	Bn	25	69 (**3ag**)
34	$C_6H_5(CH_2)_2$	$CH_3(CH_2)_2$	25	60 (**3ah**)
35	*p*-$ClC_6H_4CH_2$	*p*-$ClC_6H_4CH_2$	25	70 (**3ai**)
36	Ph	Bn	30	63 (**3aj**)
	R^1-COCl[d]	(Bistetrazoles)		
37	Bn	o,*p*-$(NH_2)_2C_6H_4$	8	60 (**3ak**)
38	$C_6H_5(CH_2)_2$	$NH_2(CH_2)_3NH_2$	8	57 (**3al**)
39	CH_3CH_2	$NH_2(CH_2)_3NH_2$	8	61 (**3am**)
40	*p*-$ClC_6H_4CH_2$	$NH_2(CH_2)_3NH_2$	8	66 (**3an**)

[a] The reaction was performed with **1** (1 mmol), **2** (1 mmol), $TMSN_3$ (1.5 mmol), and $POCl_3$ (1 mmol). [b] Cy = cyclohexyl, *i*Pr = isopropyl, Bn = benzyl. [c] Yield of isolated product. [d] Acid chloride (2 equiv.), $POCl_3$, and $TMSN_3$ (3 equiv.) were used.

The use of PCl_5 in the synthesis of amino acid tetrazoles often results in racemization of the products, as ketamine formation leads to racemization, and careful control over the amount of base is required.[16] To check the stereochemical retention of our method, we used *N*-benzyloxycarbonyl (Cbz)-L-alanine (**4**) and benzylamine (**5**) for the synthesis of amino acid tetrazole **6** (Scheme 1). To our delight, the reaction proceeded with full stereoretention, as shown by HPLC on a chiral stationary phase (see the Supporting Information). Our method, therefore, provides enantiopure products likely by avoiding the use of a base. This opens the opportunity to introduce chiral tetrazoloamino acids into peptides.

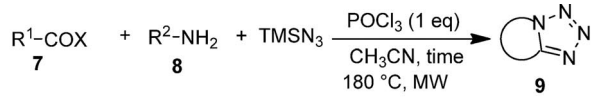


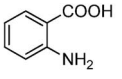
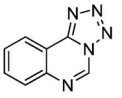
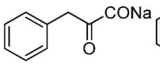
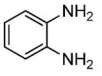
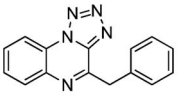
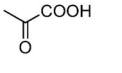
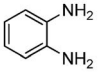
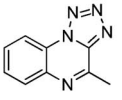
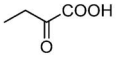
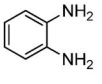
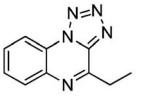
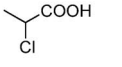
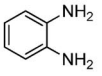
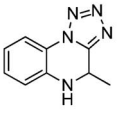
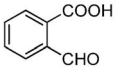
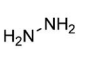
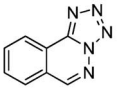
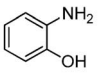
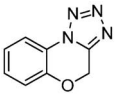
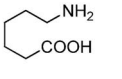
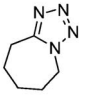
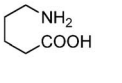
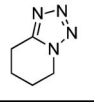
Scheme 1. Synthesis of amino acid tetrazoles.

Next, we tried to access more elaborate fused tetrazole scaffolds. We envisaged a second strategy by exploiting a MCR for the synthesis of fused tetrazoles. Although multicomponent reactions have lately emerged as a powerful tool in the synthesis of biologically important diverse scaffolds and even though fused tetrazoles possess a wide spectrum of biological activities, only very limited access to these fused tetrazoles is currently possible by a simple one-pot MCR.[1,17] For example, fused tetrazoles are accessible through the isocyanide-based synthesis of tetrazoles followed by cyclization.[18] Using our highly flexible and robust methodology, we foresaw a quick and easy way to access therapeutically interesting complex molecular structures.

According to our synthetic plan, the use of functionalized carboxylic acids with amines bearing an additional functional group would allow an anticipated domino cyclization process in one step. The reaction of formamide, which works as an ammonia and formaldehyde surrogate, and 2-aminobenzoic acid under the optimized conditions led to the formation of the tetrazolo[1,5-*c*]quinazoline scaffold in moderate yield (Table 2, entry 1). Biologically important tetrazolo[1,5-*a*]quinoxaline derivatives[19] were synthesized by using 2-oxoacids or their sodium salts with *o*-phenylenediamine, and they generally worked well with complete reaction conversion; furthermore, the products were delivered in good yields (Table 2, entries 2–4). 4-Methyl-4,5-dihydrotetrazolo[1,5-*a*]quinoxaline was formed by the reaction of 2-chloropropanoyl chloride and *o*-phenylenediamine (Table 2, entry 5). Tetrazolo[5,1-*a*]phthalazine (Table 2, entry 6), for example, was reported as an anticonvulsant.[20] Using our method, the reaction between hydrazine, 2-formylbenzoic acid, and $TMSN_3$ permitted the construction of tetrazolo[5,1-*a*]phthalazine in one step in 48 % yield. Next, we attempted the synthesis of 4*H*-benzo[*b*]tetrazolo[1,5-*d*][1,4]oxazine, which is an antidepressant/anxiolytic agent.[21] Treating 2-aminophenol with 2-chloroacetyl chloride in the presence of $TMSN_3$ allowed the preparation of a tetrazole ring fused to a benzooxazine (Table 2, entry 7). Pentylenetetrazole (PTZ) is a $GABA_A$ receptor antagonist and prototypical anxiogenic drug that is used experimentally as a probe to study seizure phenomena.[22] It is typically synthesized by a multistep method starting with caprolactam to form the imino ether followed by addition of hydrazine to form hydrazine derivatives, which are further treated with nitrous acid finally to afford the targets.[23] We hypothesized that PTZ could rapidly be accessed through a three-center, two-component reaction between commercially available and cheap 6-aminohexanoic acid and $TMSN_3$. We isolated this compound in a good 76 % yield by using our one-pot method after a reaction time of 8 min (Table 2, entry 10).

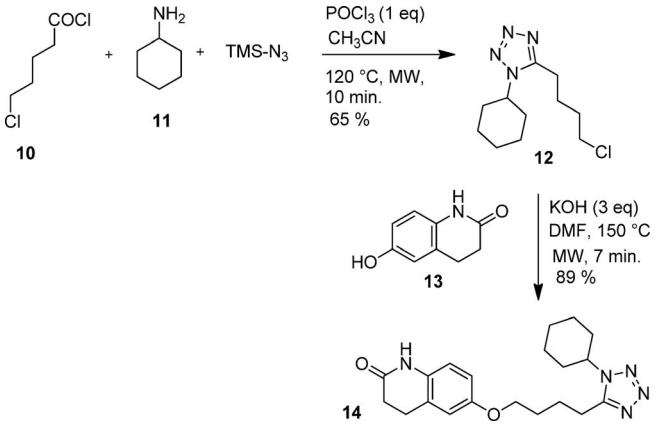
Table 2. Synthesis of 1,5-fused tetrazoles from carboxylic acid derivatives, amines, and $TMSN_3$.[a]



Entry	7	8	Time [min]	Yield (%)[b]	9
1[c]			10	50 (**9a**)	
2			25	61 (**9b**)	
3			15	59 (**9c**)	
4			15	61 (**9d**)	
5			15	63 (**9e**)	
6[d]			10	48 (**9f**)	
7			7	56 (**9g**)	
8			8	76 (**9h**)	
9			5	67 (**9i**)	

[a] The reaction was performed with **7** (1 mmol), **8** (1 mmol), and $TMSN_3$ (1.5 mmol). [b] Yield of isolated product. [c] Formamide was used as the solvent. [d] Excess amount of hydrazine hydrate was used.

Finally, we validated our novel one-pot synthetic pathway towards the preparation of the marketed drug cilostazol, which targets phosphodiesterase and inhibits platelet aggregation; it is employed as a direct arterial vasodilator. Notably, this drug is usually synthesized by multistep procedures, also with the use of toxic and explosive HN_3 and PCl_5.[24] Our rapid two-step cilostazol synthesis involved the 3CR of 5-chloropentanoic acid chloride (**10**), cyclohexylamine (**11**), and $TMSN_3$ to form tetrazole intermediate **12**, which was followed by coupling with commercially available 6-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**13**, Scheme 2).



Scheme 2. Two-step synthesis of cilostazol by our MCR methodology.

First, we performed the reaction of 5-chloropentanoic acid chloride (**10**), cyclohexylamine (**11**), and $TMSN_3$ with $POCl_3$ at 180 °C in a microwave to form tetrazole **12**, but we observed the formation of several side products, likely involving nucleophilic substitution reactions. Then, we sequentially performed amide formation between **10** and **11** in one pot at room temperature followed by the addition of $POCl_3$ and $TMSN_3$ and heated the reaction mixture at 120 °C for 10 min. Tetrazole **12** was isolated in good yield. Coupling of **12** with **13** under microwave heating at 150 °C for 7 min afforded cilostazol (**14**) in 89 % yield (Scheme 2).

Conclusion

In conclusion, we developed a novel, efficient, safe, and general microwave-assisted first-in-class MCR-based method to gain access to diverse and fused tetrazoles in a single step. Multiple inter- and intramolecular examples pinpoint the versatility of the reaction. The use of $TMSN_3$ in an almost equimolar ratio makes the process safer than reported protocols. Moreover, the synthetic utility of this developed methodology was illustrated in the synthesis of biologically active 1,5-fused tetrazoles, an amino acid tetrazole, and the marketed drug cilostazol.

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Keywords: Multicomponent reactions · Microwave chemistry · Azides · Fused-ring systems · Nitrogen heterocycles

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