Multicomponent reactions: development, scope, and applications

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Chapter 3

An Efficient Passerini Tetrazole Reaction (PT-3CR)

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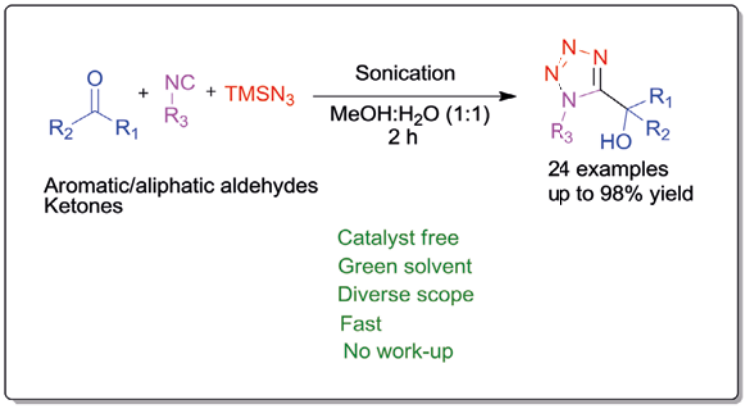


Abstract

A sonication accelerated, catalyst free, simple, high yielding and efficient method for the Passerini-type three component reaction (PT-3CR) has been developed. It comprises the reaction of an aldehyde/ketone, an isocyanide and a TMS-azide in methanol : water (1 : 1) as the solvent system. The use of sonication not only accelerated the rate of the reaction but also provided good to excellent quantitative yields. This reaction is applicable to a broad scope of aldehyde/ketone and isocyanides.

Introduction

Tetrazoles scaffolds are extensively used in medicinal chemistry and in industries like agriculture, explosives, and photography.[1] 1,5-Disubstituted tetrazoles are important ring systems, having applications as bio-active agents or in drugs like cilostazol, pentylenetetrazole, latamoxef, BMS-317180 and *cis*-amide bond isosteres in peptides (Figure 1). This propels the need for efficient synthetic methods for tetrazoles.[2] Different reactions have been developed for the direct access to diverse 1,5-disubstituted tetrazoles, but three- and four-component reactions (MCRs) are mostly preferred due to their convergent, atom-efficient and flexible nature.[3] Multicomponent reactions are considered ideal syntheses, and that's why their use in synthetic chemistry is increasing tremendously.[4]

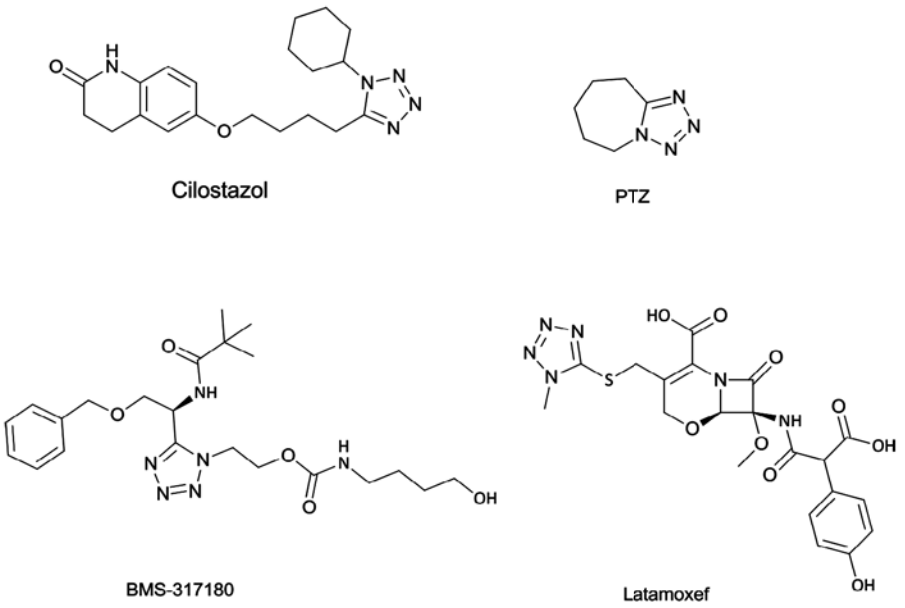


Figure 1. Some bio-active agents/drugs containing the tetrazole moiety.

In 1921, a three-component reaction between carboxylic acids, oxo components, and isocyanides for the synthesis of α-acyloxy amide was discovered by Passerini (P-3CR).[5,7c] In 1961, Ugi reported the synthesis of tetrazoles *via* a Passerini-type 3CR (PT-3CR) for the first time using HN_3 and $Al(N_3)_3$.[6] Even though the use of HN_3 or NaN_3 in Passerini reaction for the synthesis of tetrazoles was reported, the highly toxic and explosive nature of HN_3 and NaN_3 limit its application.[7] The use of $TMSN_3$ as a safe substitute for HN_3 was then introduced by Hulme.[8] However the use of $TMSN_3$ as an azide source in the PT-3CR resulted in a very low yield, and the TMS-ether was found as a major product. Similarly protected amino aldehydes in DCM also resulted in generally low yields[9] and the described reaction times were up to 96 hours.[9a] Reported PT-3CRs are not very suitable for aromatic aldehydes.[7] The

use of different Lewis acids as catalysts, like $AlCl_3$, to activate aldehydes forms an inseparable mixture of desired product with α-hydroxy-amide, with a maximum yield of 30%.[10] Zhu and co-workers used $TMSN_3$ as a test reaction component in the asymmetric PT-3CR; nevertheless, they could not avoid the formation of α-hydroxy-amide.[7b]

To the best of our knowledge, no efficient, diverse and high yielding PT-3CR reaction has yet been reported. We report herein a sonication-promoted catalyst free, $TMSN_3$-modified PT-3CR using methanol : water (1 : 1) as solvent with diverse scope and affording good to excellent yields.

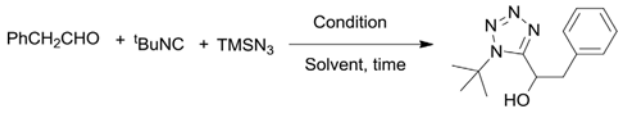
Results and Discussion

We started our investigation by using *tert*-butyl isocyanide, phenylacetaldehyde and $TMSN_3$ as starting materials (Table 1). We hypothesized that the use of fluoride ion sources like TBAF, CsF and KF could trigger $TMSN_3$ activation.[11] However, when the reaction was carried out with TBAF with different solvents like DCM water, or neat, the product was formed only in trace amounts (Table 1, entries **1**–**3**). Surprisingly, using methanol as a solvent increased the isolated yield to 25%. Carrying out the reaction with alternative F-sources, such as KF in DCM or CsF in DCM, methanol and water, resulted only in small amounts of product formation.

The use of Iodine, to trap TMS as TMSI, also failed to improve the reaction yield. 17% product formed when the reaction was carried out in water without any additive. TBAF in methanol : water (1 : 1) enhanced the yield up to 63%; however comparable yields were obtained when the reaction was carried out without TBAF in the same solvent system. Thus we concluded that the use of TBAF is not fruitful, whereas the solvent system has a major impact.

We foresaw that the accelerating effect of sonication could potentially speed up the reaction and increases yields. Ultrasound in general[1,2] and also in the context of MCR[12d] is often used in organic synthesis due to its advantages such as increasing the reaction efficacy while decreasing waste byproducts, short reaction times, cleaner reactions, easier experimental procedure and having low energy requirements. Recently, the popularity of sonication-assisted synthesis as a green synthetic approach has significantly increased and has resulted in a plethora of 'better' reactions.[13] Ultrasound in chemical reactions works via a physical phenomenon called acoustic cavitation, which forms, expands and collapses gaseous and vaporous cavities in an ultrasound irradiated liquid. The mechanical effect of cavitation destroys the attractive forces of molecules in the liquid phase and so accelerates reaction rates by facilitating mass transfer in the microenvironment.[13]

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Time (h)	Product Yield[b] (%)
1	TBAF[c]	—	12	trace
2	TBAF[d]	DCM	12	trace
3	TBAF[c]	H_2O	12	trace
4	TBAF[c]	MeOH	12	25
5	KF[e]	DCM	12	nd
6	CsF[f]	DCM	12	nd
7	CsF[f]	MeOH	12	nd
8	CsF[f]	H_2O	12	nd
9	I_2[f]	DCM	12	nd
10	I_2[f]	H_2O	12	nd
11		H_2O	12	17
12	TBAF[c]	MeOH : H_2O (1 :)	12	63
13		MeOH : H_2O (1 : 1)	12	64
14	**Sonication**	**MeOH : H_2O (1 : 1)**	2	97
15	Sonication[g]	—	3	31
16	Sonication	DCM	2	34
17	Sonication	H_2O	2	71

[a]The reaction was carried out with phenylacetaldehyde (1 mmol), tert-butyl isocyanide (1 mmol), and $TMSN_3$ (1 mmol) at room temperature. [b]Yield of isolated product. [c]1 equivalent TBAF. $3H_2O$. [d]1 equivalent TBAF in 1M THF. [e]1 equivalent KF. [f]1 equivalent CsF. [g]Reaction carried out at 70°C. nd = not determined

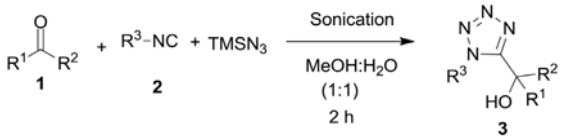
To our delight, the use of sonication not only accelerated the reaction time from 12 to two hours but provided quantitative yield in methanol : water (1 : 1) as the solvent system, noteworthily without the necessity of any previously used additive (Table 1, entry 14). We used a simple ultrasonic cleaning bath which is the most widely available and cheapest source of ultrasonic irradiation. A recent study has shown that both ultrasonic cleaning bath and ultrasonic probe systems are efficient in Passerini reaction.[14] The ultrasonic cleaning bath offers further advantages; for example, the reaction vessel can be put directly into the ultrasonic bath without any adaptation. This is in contrast to the ultrasonic probe system, which is more expensive and also requires special vessels, making it inconvenient to use.

Lastly, reactions under sonication in DCM or in neat conditions provided smaller yields, 34% and 31% respectively, and the formation of TMS-ether as a side product was observed. The use of pure water as the solvent under sonication conditions provided the product in 71% yield. The use of 1

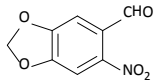
equivalent of $TMSN_3$ avoids the danger of forming hydrazide from excess azide. This catalyst free reaction does not require any work-up.

With these optimized conditions in hand, we next examined the generality of this PT-3CR by reacting different aldehydes with different isocyanides (Table 2). Good to excellent yields were obtained with linear and branched aliphatic aldehydes. Aromatic aldehydes are also compatible substrates for this process (Table 2, entries **15**–**22**). Electron donating (methoxy) and withdrawing groups (Cl, Br, NO_2) at different positions like *ortho*, *meta* and *para* are valid, providing moderate to good yields. Paraformaldehyde also reacts when pure water was used as the solvent. Reaction with one or six equivalent paraformaldehyde in methanol : water system only forms mono-substituted tetrazole. The reaction of benzyl isocyanide with aliphatic aldehydes gave excellent yields.

Table 2. Substrate scope for the PT-3CR.[a]



Entry	1	R^3	Yield[c] (%)
	Aldehydes		
1	C_6H_5-CH_2-CHO	C_6H_5-CH_2	96 (**3a**)
2	*i*Pr-CHO	$(CH_3)_3$-C	98 (**3b**)
3	CH_3-$(CH_2)_2$-CHO	C_6H_5-CH_2	80 (**3c**)
4	C_6H_5-CH_2-CHO	[t]Octyl	77 (**3d**)
5	*i*Pr-CHO	CN-CH_2-CH_2	72 (**3e**)
6	C_6H_5-$(CH_2)_2$-CHO		53 (**3f**)
7	C_6H_5-$(CH_2)_2$-CHO	Cy	76 (**3g**)
8	C_6H_5-CH_2-CHO	2-BrC_6H_4-CH_2	77 (**3h**)
9	H-CHO[d]	2-BrC_6H_4-CH_2	42 (**3i**)
10	*i*Pr-CHO	2-BrC_6H_4-CH_2	80 (**3j**)
11	C_6H_5-$(CH_2)_2$-CHO	$(CH_3)_3$-C	88 (**3k**)
12	CH_3-CH_2-CHO	C_6H_5-CH_2	91 (**3l**)
13	$(CH_3)_2$-CH-CH_2-CHO	C_6H_5-CH_2	92 (**3m**)
14	C_6H_5-CH_2-CHO	$(CH_3)_3$-C	97 (**3n**)
15	C_6H_5-CHO	$(CH_3)_3$-C	41 (**3o**)
16	2,6-$(Cl)_2C_6H_3$-CHO	C_6H_5-CH_2	71 (**3p**)
20[b]	2,3-$(Cl)_2C_6H_3$-CHO	Cy	73 (**3q**)
17	2-MeO-5-BrC_6H_3-CHO	C_6H_5-CH_2-CH_2	46 (**3r**)
18	2-BrC_6H_4-CHO	Cy	60 (**3s**)
19	2-Cl-3,4-$(OCH_3)_2C_6H_2$-CHO	Cy	42 (**3t**)

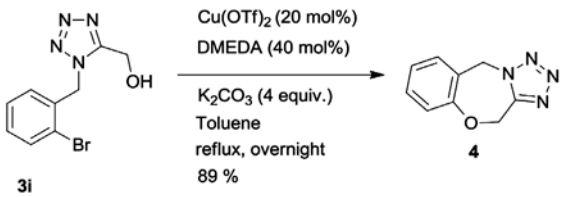
Entry	1	R^3	Yield[c] (%)
21		Cy	39 (**3u**)
22	2,5-$(OCH_3)_2C_6H_3$-CHO	Cy	48 (**3v**)
	Ketones		
23	cyclohexanone	C_6H_5-CH_2	84 (**3w**)
24	1-benzylpiperidin-4-one	C_6H_5-CH_2	46 (**3x**)

[a]The reaction was carried out with 1 mmol **1**, 1 mmol **2**, 1 mmol $TMSN_3$. [b]cy = cyclohexyl, octyl = 2-isocyano-2,4,4-trimethylpentane. [c]Yield of isolated product. [d]6 equivalent of paraformaldehyde in water as solvent and at 60°C. *i*Pr = isopropyl

Isocyanides, easy to deprotect in acidic and basic conditions, are compatible with the developed methodology (Table 2, entries **2**, **4** and **5**). The functional group tolerance of the isocyanide (Table 2, entries **5**–**6** and **8**–**10**), in this protocol provides multiple opportunities for various further chemical manipulations. For example, the compatibility of 1,1-diethoxy-2-isocyanoethane as the isocyanide component could be used in further reactions as aldehyde or halogens functional groups for coupling reactions.

We also explore the scope of ketones in the developed method (Table 2, entries **23** and **24**). Cyclohexanone gives a good yield of 84%. The important building block piperidone is also compatible with the reaction.

Fused tetrazoles are important scaffolds as it possess a wide spectrum of activity and vast industrial applications. As functional group bearing isocyanides are compatible in our developed method, we foresaw a quick and easy access to fused tetrazole. According to our synthetic plan, the use of functionalized PT-3CR product for post modification would allow an anticipated cyclization process. (1-(2-Bromobenzyl)-1*H*-tetrazol-5-yl)methanol (**3i**), when refluxed with Copper(II) triflate in the presence of a base, formed 5,11-dihydrobenzo[*f*]tetrazolo[5,1-*c*][1,4]oxazepine in 89% yield (Scheme 1).



DMEDA = N,N'-Dimethylethylenediamine

Scheme 1. Synthesis of fused tetrazole.

Conclusions

In conclusion, we have developed a novel, efficient, safe and general sonication assisted Passerini tetrazole reaction (PT-3CR) to access 5-(1-hydroxyalkyl)tetrazoles in good to excellent yield. The herein described Passerini tetrazole procedure provides multiple advantages over previously described procedures. The reaction does not use highly toxic and explosive staring materials like HN_3, $Al(N_3)_3$ or NaN_3. This catalyst-free reaction avoids the use of any dangerous or adverse catalysts such as Al-salen chiral complex, $AlCl_3$. Sonifications was found to provide superior reaction conditions, resulting in high conversion and giving high yields of Passerini products and no TMS-ether side product, as often observed previously. Sonification is also well known to be compatible with upscaling procedures. The scope of the reaction could be dramatically extended, including aliphatic, aromatic aldehydes and also ketones. Due to the extended functional group compatibility of the reaction, many new scaffolds amenable by post-condensation reactions can be foreseen as we have illustrated by the synthesis of a Cu-mediated fused tetrazole. Altogether, we believe that our procedure is superior to all previously reported Passerini tetrazole reactions and will be the method of choice for the future.

General Information

Reagents were available from commercial suppliers (Sigma Aldrich, ABCR, Acros and AK Scientific) and used without any purification unless otherwise noted. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230–400 mesh) and on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). All ultrasonic irradiation reactions were carried out in a Sonicor "SC" Ultrasonic Table Top Cleaner with 220/240V, frequency of 50/60 Hz and 25 Amps. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shifts for ^1H NMR were reported relative to TMS (δ 0 ppm) and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dt = double triplet, ddd = doublet of double doublet, and m = multiplet. Chemical shifts for ^{13}C NMR reported in ppm relative to the solvent peak ($CDCl_3$ δ 77.23 ppm). Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 × 250 mm, 5 µm particle size) and reported as (m/z).

Experimental Procedures and Spectral Data

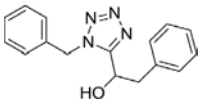
General procedure for the synthesis of tetrazole

A 10 ml tube was charged with aldehyde/ketone (1.0 mmol) and isocyanide (1.0 mmol) and trimethylsilyl azide (1 mmol) in methanol : water (1 : 1) (1 ml). The mixture was sonicated in the water

bath of an ultrasonic cleaner (220/240V, 25 Amps and frequency of 50/60 Hz) at room temperature till completion of the reaction (monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using EtOAc–hexane as eluent.

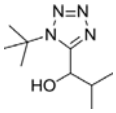
Spectral Data

1-(1-benzyl-1*H*-tetrazol-5-yl)-2-phenylethanol (3a)



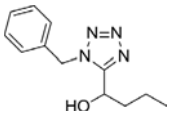
Colourless liquid, mp 79-80°C, yield: 268 mg (96%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 3H), 7.29 – 7.23 (m, 3H), 7.18 (dd, *J* = 6.6, 2.9, 2H), 7.11 – 7.04 (m, 2H), 5.49 (d, *J* = 15.1, 1H), 5.37 (d, *J* = 15.1, 1H), 5.25 – 5.09 (m, 1H), 3.39 (s, 1H), 3.19 (dd, *J* = 13.8, 5.4, 1H), 3.07 (dd, *J* = 13.8, 8.3, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 135.8, 133.8, 129.6, 129.0, 128.8, 128.7, 128.0, 127.2, 66.2, 51.3, 42.3. MS (ESI) m/z calculated $[M+H]^+$: 281.13; found $[M+H]^+$: 281.16.

1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-2-methylpropan-1-ol (3b)



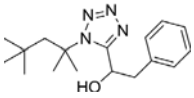
White solid, mp 126-127°C, yield: 195 mg (98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (dd, *J* = 10.2, 8.5, 1H), 3.23 (d, *J* = 10.1, 1H), 2.53 – 2.39 (m, 1H), 1.78 (s, 9H), 1.18 (d, *J* = 6.6, 3H), 0.85 (d, *J* = 6.7, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 70.8, 61.6, 34.1, 30.3, 19.5, 18.2. MS (ESI) m/z calculated $[M+Na]^+$: 221.14; found $[M+Na]^+$: 221.18.

1-(1-benzyl-1*H*-tetrazol-5-yl)butan-1-ol (3c)



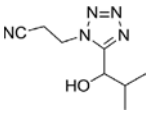
Colourless liquid, yield: 186 mg (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 3H), 7.31 – 7.24 (m, 2H), 5.72 (q, *J* = 15.1, 2H), 4.99 (t, *J* = 6.4, 1H), 3.98 (s, 1H), 1.92 – 1.78 (m, 1H), 1.77 – 1.67 (m, 1H), 1.49 – 1.36 (m, 1H), 1.30 – 1.24 (m, 1H), 0.84 (t, *J* = 7.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 133.9, 129.0, 128.7, 127.9, 64.7, 51.5, 37.6, 18.4, 13.5. MS (ESI) m/z calculated $[M+Na]^+$: 255.12; found $[M+Na]^+$: 255.08.

2-phenyl-1-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)ethanol (3d)



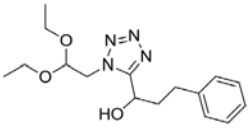
White solid, mp 135-136°C, yield: 232 mg (77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H), 7.21 – 7.16 (m, 3H), 5.38 – 5.20 (m, 1H), 4.09 (d, *J* = 9.6, 1H), 3.48 (qd, *J* = 13.4, 7.2, 2H), 1.96 (d, *J* = 15.2, 1H), 1.81 (d, *J* = 17.6, 4H), 1.57 (s, 3H), 0.68 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 136.2, 129.7, 128.7, 127.1, 67.1, 65.3, 53.8, 43.2, 31.6, 30.5, 30.3, 30.2. MS (ESI) m/z calculated $[M+Na]^+$: 325.20; found $[M+Na]^+$: 325.20.

3-(5-(1-hydroxy-2-methylpropyl)-1*H*-tetrazol-1-yl)propanenitrile (3e)



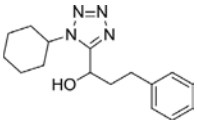
Colorless liquid, yield: 140 mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (dt, *J* = 13.9, 6.9, 2H), 4.77 (dt, *J* = 13.7, 6.8, 1H), 4.30 (s, 1H), 3.12 (t, *J* = 6.9, 2H), 2.29 – 2.16 (m, 1H), 1.08 (d, *J* = 6.7, 3H), 0.91 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 116.3, 70.9, 43.7, 33.8, 18.7, 18.6, 17.8. MS (ESI) m/z calculated $[M+Na]^+$: 218.10; found $[M+Na]^+$: 218.09.

1-(1-(2,2-diethoxyethyl)-1*H*-tetrazol-5-yl)-3-phenylpropan-1-ol (**3f**)



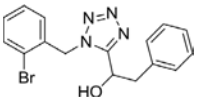
Colorless liquid, yield: 170 mg (53%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 2H), 7.23 – 7.12 (m, 3H), 5.04 (dd, *J* = 12.8, 6.4, 1H), 4.82 (t, *J* = 5.5, 1H), 4.63 (dd, *J* = 14.2, 5.6, 1H), 4.52 (dd, *J* = 14.2, 5.4, 1H), 4.08 (d, *J* = 5.8, 1H), 3.85 – 3.66 (m, 2H), 3.59 – 3.38 (m, 2H), 2.93–2.72 (m, 2H), 2.44 – 2.24 (m, 2H), 1.12 (dt, *J* = 14.3, 7.0, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 140.7, 128.5, 128.5, 126.1, 100.5, 64.3, 64.2, 64.0, 50.0, 36.9, 31.2, 15.0, 15.0. MS (ESI) m/z calculated $[M+H]^+$: 321.18; found $[M+H]^+$: 321.05.

1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-3-phenylpropan-1-ol (**3g**)



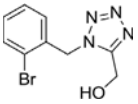
White solid, mp 104-105°C, yield: 217 mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 5.08–4.93 (m, 2H), 4.57 – 4.39 (m, 1H), 2.92–2.80 (m, 1H), 2.79 – 2.68 (m, 1H), 2.41 – 2.26 (m, 1H), 2.26 – 2.10 (m, 1H), 2.05 – 1.82 (m, 6H), 1.71 (d, *J* = 12.4, 1H), 1.48 – 1.17 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 140.7, 128.6, 128.5, 126.2, 63.7, 58.4, 37.4, 33.0, 31.5, 25.3, 25.2, 24.9. MS (ESI) m/z calculated $[M+H]^+$: 287.18; found $[M+H]^+$: 287.21.

1-(1-(2-bromobenzyl)-1*H*-tetrazol-5-yl)-2-phenylethanol (**3h**)



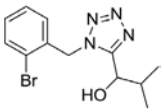
White solid, mp 94-95°C, yield: 275 mg (77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.5, 1.6, 1H), 7.29 – 7.21 (m, 3H), 7.17 (td, *J* = 7.1, 1.8, 2H), 7.09 (dd, *J* = 7.5, 1.6, 2H), 6.72 (dd, *J* = 7.3, 1.9, 1H), 5.49 (d, *J* = 16.0, 1H), 5.41 (d, *J* = 16.0, 1H), 5.26 (t, *J* = 6.7, 1H), 4.05 (s, 1H), 3.26 (dd, *J* = 13.7, 5.9, 1H), 3.19 (dd, *J* = 13.7, 7.7, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 135.6, 133.3, 133.1, 130.1, 129.6, 129.1, 128.8, 128.1, 127.3, 122.7, 66.2, 51.1, 42.5. MS (ESI) m/z calculated $[M+H]^+$: 359.04; found $[M+H]^+$: 359.04.

(1-(2-bromobenzyl)-1*H*-tetrazol-5-yl)methanol (**3i**)



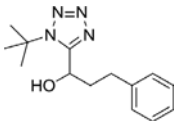
White solid, mp 64-65 °C, yield: 112 mg (42%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.9, 1.1, 1H), 7.28 (td, *J* = 7.3, 1.1, 1H), 7.21 (td, *J* = 7.7, 1.6, 1H), 7.04 (dd, *J* = 7.7, 1.5, 1H), 5.73 (s, 2H), 5.13 (s, 1H), 4.94 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 133.3, 132.7, 130.5, 129.9, 128.2, 123.2, 53.6, 51.4. MS (ESI) m/z calculated $[M+H]^+$: 269.00; found $[M+H]^+$: 269.00.

1-(1-(2-bromobenzyl)-1*H*-tetrazol-5-yl)-2-methylpropan-1-ol (**3j**)



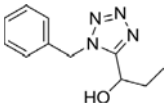
White solid, mp 86-87°C, yield: 249 mg (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 0.9, 1H), 7.24 (dt, *J* = 7.6, 3.8, 1H), 7.19 (td, *J* = 7.7, 1.5, 1H), 6.88 (dd, *J* = 7.6, 1.1, 1H), 5.79 (s, 2H), 4.89 – 4.73 (m, 1H), 4.67 (d, *J* = 6.2, 1H), 2.11 (dq, *J* = 13.6, 6.8, 1H), 1.03 (d, *J* = 6.7, 3H), 0.77 (d, *J* = 6.8, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 133.5, 133.1, 130.1, 129.2, 128.0, 122.8, 70.3, 51.4, 33.4, 18.7, 18.0. MS (ESI) m/z calculated $[M+H]^+$: 311.04; found $[M+H]^+$: 311.09.

1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-3-phenylpropan-1-ol (**3k**)



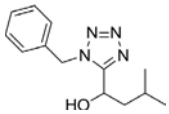
White solid, mp 102-103 °C, yield: 228 mg (88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.20 (d, *J* = 7.3, 3H), 5.00 (td, *J* = 9.3, 4.8, 1H), 3.96 (d, *J* = 9.9, 1H), 3.01 – 2.78 (m, 2H), 2.55 – 2.40 (m, 1H), 2.34 – 2.19 (m, 1H), 1.63 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 140.6, 128.6, 128.5, 126.2, 63.9, 61.7, 38.2, 31.6, 29.9. MS (ESI) m/z calculated $[M+H]^+$: 283.15; found $[M+H]^+$: 283.06.

1-(1-benzyl-1*H*-tetrazol-5-yl)propan-1-ol (**3l**)



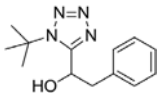
White solid, mp 77-78 °C, yield: 198 mg (91%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 5H), 5.73 (d, *J* = 15.1, 1H), 5.68 (d, *J* = 15.1, 1H), 4.94 (dd, *J* = 13.3, 6.3, 1H), 4.84 (d, *J* = 6.2, 1H), 1.94 – 1.73 (m, 2H), 0.87 (t, *J* = 7.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 134.0, 129.0, 128.7, 127.9, 66.3, 51.5, 28.9, 9.6. MS (ESI) m/z calculated $[M+H]^+$: 219.12; found $[M+H]^+$: 219.10.

1-(1-benzyl-1*H*-tetrazol-5-yl)-3-methylbutan-1-ol (**3m**)



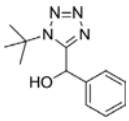
White solid, mp 85-86 °C, yield: 226 mg (92%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 3H), 7.28 – 7.23 (m, 2H), 5.74 (d, *J* = 15.2, 1H), 5.67 (d, *J* = 15.1, 1H), 5.15 – 4.95 (m, 1H), 4.55 (d, *J* = 6.4, 1H), 1.81 – 1.60 (m, 2H), 1.54 – 1.42 (m, 1H), 0.82 (d, *J* = 6.6, 3H), 0.77 (d, *J* = 6.5, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 133.9, 129.0, 128.7, 127.9, 63.2, 51.5, 44.3, 24.2, 22.8, 21.6. MS (ESI) m/z calculated $[M+Na]^+$: 269.14; found $[M+Na]^+$: 269.13.

1-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-2-phenylethanol (**3n**)



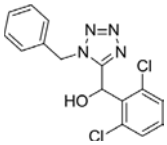
White solid, mp 160-161 °C, yield: 239 mg (97%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 3H), 7.28 – 7.23 (m, 2H), 5.74 (d, *J* = 15.2, 1H), 5.67 (d, *J* = 15.1, 1H), 5.15 – 4.95 (m, 1H), 4.55 (d, *J* = 6.4, 1H), 1.81 – 1.60 (m, 2H), 1.54 – 1.42 (m, 1H), 0.82 (d, *J* = 6.6, 3H), 0.77 (d, *J* = 6.5, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 133.9, 129.0, 128.7, 127.9, 63.2, 51.5, 44.3, 24.2, 22.8, 21.6. MS (ESI) m/z calculated $[M+Na]^+$: 269.14; found $[M+Na]^+$: 269.19.

(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)(phenyl)methanol (**3o**)



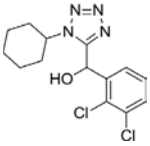
White solid, mp 122-123 °C, yield: 95 mg (41%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, *J* = 5.8, 3H), 7.33 – 7.25 (m, 2H), 6.30 (d, *J* = 7.3, 1H), 4.29 (s, 1H), 1.63 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 139.2, 129.0, 128.9, 127.2, 68.5, 62.1, 29.9. MS (ESI) m/z calculated $[M+Na]^+$: 255.12; found $[M+Na]^+$: 255.08.

(1-benzyl-1*H*-tetrazol-5-yl)(2,6-dichlorophenyl)methanol (**3p**)



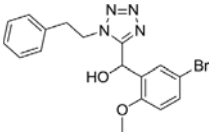
White solid, mp 144-145 °C, yield: 237 mg (71%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 4H), 7.29 (s, 1H), 7.24 (dd, *J* = 13.1, 6.0, 1H), 7.18 (dd, *J* = 6.5, 2.8, 2H), 6.63 (d, *J* = 9.3, 1H), 5.70 (d, *J* = 4.5, 2H), 3.94 (d, *J* = 9.4, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 135.2, 133.4, 132.9, 130.9, 129.4, 129.0, 128.7, 127.5, 65.2, 51.8. MS (ESI) m/z calculated $[M+H]^+$: 335.04; found $[M+H]^+$: 335.10.

(1-cyclohexyl-1*H*-tetrazol-5-yl)(2,3-dichlorophenyl)methanol (3q)



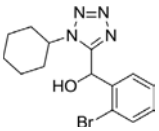
White soild, mp 156-157 °C, yield: 238 mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 1.3, 1H), 7.50 (dd, *J* = 8.0, 1.5, 1H), 7.33 (t, *J* = 7.9, 1H), 6.49 (d, *J* = 6.2, 1H), 4.72 (d, *J* = 6.3, 1H), 4.29 (tt, *J* = 11.4, 3.8, 1H), 1.99 – 1.77 (m, 6H), 1.75 – 1.70 (m, 1H), 1.41 – 1.20 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.9, 138.3, 133.6, 130.9, 130.6, 127.9, 126.4, 64.2, 58.6, 32.8, 32.7, 25.3, 25.3, 24.8. MS (ESI) m/z calculated $[M+H]^+$: 327.07; found $[M+H]^+$: 327.03.

(5-bromo-2-methoxyphenyl)(1-phenethyl-1*H*-tetrazol-5-yl)methanol (3r)



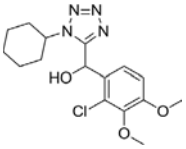
White soild, mp 133-134 °C, yield: 178 mg (46%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.35 – 7.27 (m, 3H), 7.04 (dd, *J* = 7.6, 1.4, 2H), 6.76 (d, *J* = 9.4, 1H), 5.85 (d, *J* = 7.0, 1H), 4.56 (t, *J* = 7.5, 2H), 3.86 (d, *J* = 7.0, 1H), 3.70 (s, 3H), 3.18 – 3.01 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 155.3, 136.5, 132.9, 130.5, 129.0, 128.8, 128.1, 127.3, 113.5, 112.8, 63.1, 55.9, 49.2, 36.2. MS (ESI) m/z calculated $[M+H]^+$: 389.03; found $[M+H]^+$: 389.03.

(2-bromophenyl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methanol (3s)



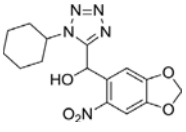
White soild, mp 141-142 °C, yield: 201 mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.4, 1H), 7.57 (dd, *J* = 8.0, 0.8, 1H), 7.40 (t, *J* = 7.6, 1H), 7.24 (td, *J* = 7.8, 1.6, 1H), 6.48 (d, *J* = 6.0, 1H), 4.90 (d, *J* = 6.0, 1H), 4.25 (tt, *J* = 11.3, 3.8, 1H), 1.92 – 1.79 (m, 5H), 1.78 – 1.63 (m, 2H), 1.35 – 1.18 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 137.5, 133.1, 130.5, 128.8, 128.2, 122.3, 66.0, 58.5, 32.7, 32.7, 25.3, 24.8. MS (ESI) m/z calculated $[M+H]^+$: 337.06; found $[M+H]^+$: 337.05.

(2-chloro-3,4-dimethoxyphenyl)(1-cyclohexyl-1*H*-tetrazol-5-yl)methanol (3t)



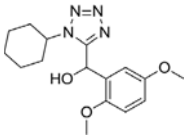
White soild, mp 167-168 °C, yield: 147 mg (42%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7, 1H), 6.89 (d, *J* = 8.8, 1H), 6.46 (d, *J* = 6.0, 1H), 4.62 (d, *J* = 6.1, 1H), 4.25 (tt, *J* = 11.5, 3.8, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 1.91 – 1.81 (m, 4H), 1.76 – 1.64 (m, 2H), 1.38 – 1.15 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 154.01, 145.5, 128.8, 127.1, 123.5, 110.9, 63.8, 60.7, 58.4, 56.1, 32.7, 32.7, 25.3, 24.8. MS (ESI) m/z calculated $[M+H]^+$: 353.13; found $[M+H]^+$: 353.05.

(1-cyclohexyl-1*H*-tetrazol-5-yl)(6-nitrobenzo[*d*][1,3]dioxol-5-yl)methanol (3u)



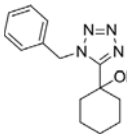
Yellow soild, mp 198-199 °C, yield: 135 mg (39%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.45 (s, 1H), 6.67 (d, *J* = 5.9, 1H), 6.19 (d, *J* = 11.5, 2H), 4.60 (t, *J* = 11.6, 1H), 4.06 (d, *J* = 5.7, 1H), 2.22 (d, *J* = 12.3, 1H), 2.15 – 1.94 (m, 5H), 1.78 (d, *J* = 12.1, 1H), 1.49 – 1.32 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.2, 132.7, 129.8, 108.0, 106.6, 105.9, 105.9, 103.5, 58.5, 33.1, 32.7, 25.3, 24.9. MS (ESI) m/z calculated $[M+H]^+$: 348.12; found $[M+H]^+$: 348.27.

(1-cyclohexyl-1*H*-tetrazol-5-yl)(2,5-dimethoxyphenyl)methanol (**3v**)



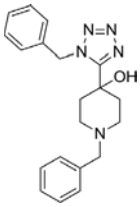
White soild, mp 189-190 °C, yield: 152 mg (48%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 2.2, 1H), 6.86 (d, *J* = 3.1, 2H), 6.34 (d, *J* = 6.5, 1H), 4.35 (tt, *J* = 11.3, 3.7, 1H), 3.98 (d, *J* = 6.7, 1H), 3.75 (s, 6H), 1.94 – 1.83 (m, 4H), 1.80 – 1.67 (m, 2H), 1.40 – 1.19 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 154.0, 150.5, 127.4, 114.89, 113.4, 112.15, 63.4, 58.23, 56.1, 55.8, 32.8, 32.7, 25.4, 24.9. MS (ESI) m/z calculated $[M+H]^+$: 319.17; found $[M+H]^+$: 319.22.

1-(1-benzyl-1*H*-tetrazol-5-yl)cyclohexanol (**3w**)



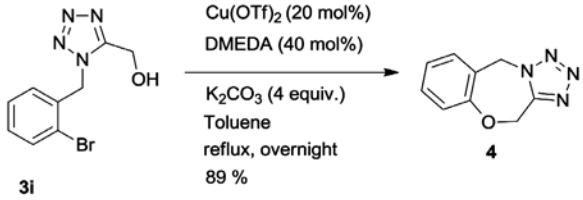
Colorless liquid, yield: 216 mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 3H), 7.25 – 7.21 (m, 2H), 5.83 (s, 2H), 3.84 (s, 1H), 1.98 – 1.87 (m, 2H), 1.85 – 1.76 (m, 2H), 1.76 – 1.53 (m, 5H), 1.36 – 1.21 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 134.9, 128.8, 128.3, 127.8, 70.45, 52.2, 37.0, 24.9, 21.1. MS (ESI) m/z calculated $[M+H]^+$: 259.15; found $[M+NH]^+$: 259.17.

1-benzyl-4-(1-benzyl-1*H*-tetrazol-5-yl)piperidin-4-ol (**3x**)



Colourless liquid, yield: 160 mg (46%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.26 (m, 7H), 7.25 – 7.18 (m, 3H), 5.82 (s, 2H), 3.52 (s, 2H), 3.40 (s, 1H), 2.79 – 2.59 (m, 2H), 2.43 (td, *J* = 11.6, 2.1, 2H), 2.31 – 2.11 (m, 2H), 1.77 (d, *J* = 12.8, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 138.3, 134.8, 129.0, 128.9, 128.5, 128., 127.6, 127., 68.70, 62., 52., 48., 36.6. MS (ESI) m/z calculated $[M+H]^+$: 350.19; found $[M+H]^+$: 350.22.

Procedure for the synthesis of 5,11-dihydrobenzo[*f*]tetrazolo[5,1-*c*][1,4]oxazepine



DMEDA = N,N'-Dimethylethylenediamine

A 10 ml RBF equipped with a magnetic stirring bar was charged with (1-(2-bromobenzyl)-1*H*-tetrazol-5-yl)methanol (0.5 mmol, 134 mg), Copper triflate (20 mol%, 36 mg), N,N'Dimethylethylenediamine (40 mol%, 21ml), K_2CO_3 (4 equivalent, 276 mg) in toluene (2ml) and refluxed overnight. Then the reaction mixture was added to a 25 ml saturated $NaHCO_3$ solution and extracted in ethyl acetate. The solvent was removed under reduced pressure and the mixture was purified by flash chromatography on silica gel (eluent: hexane/EtOAc) to afford the titled compound as a white solid.

5,11-dihydrobenzo[*f*]tetrazolo[5,1-*c*][1,4]oxazepine (4)

White solid, yield: 83 mg (89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (td, *J* = 7.9, 1.4, 1H), 7.43 – 7.38 (m, 1H), 7.30 (d, ***J*** = 8.0, 1H), 7.25 (t, *J* = 7.5, 1H), 5.65 (s, 2H), 5.48 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 152.1, 131.7, 129.3, 127.8, 126.1, 122.2, 67.6, 49.5. MS (ESI) m/z calculated $[M+H]^+$: 189.07; found $[M+Na]^+$: 189.10.

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