Multicomponent reactions: development, scope, and applications

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Chapter 7

Highly Diastereoselective One Pot Five-Component Reaction toward 4-(Tetrazole)-1,3-Oxazinane

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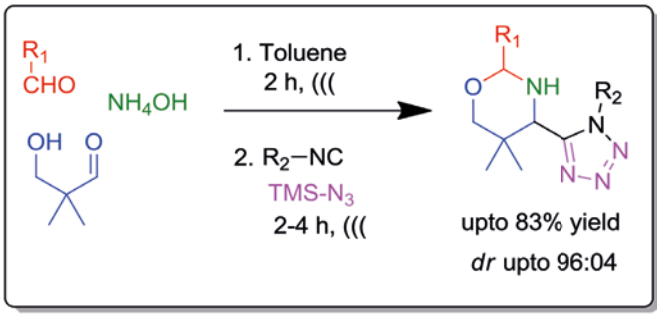


Abstract

A highly diastereoselective one pot five-component reaction toward the synthesis of 4-(tetrazole)-1,3-oxazinane has been reported. The sonication-accelerated, catalyst-free, simple, general and highly time efficient, Asinger-Ugi-tetrazole reaction was used for the synthesis of diverse 4-(tetrazole)-1,3-oxazinanes. The reaction exhibit excellent diastereoselectivity and broad substrate scope.

Introduction

Oxazines motif attained significant attention due to their widespread availability in natural products, such as aragupetrosine, bujeine, pagicerine, quimbeline, and upenamide. The oxazines scaffold is present in many pharmacologically active agents[1] and drugs, such as pranlukast, dirithromycin, and dolutegravir. It is also used as intermediate for the synthesis drugs like oxacephem antibiotics.[2]

The tetrazole is a highly important synthetic scaffold for a wide range of areas and applications. It is extensively used in the medicinal and organic chemistry, also in industries such as explosives, agrochemicals, materials, and polymers.[3] Their use as a carboxylic acid isostere and cis-amide bond isostere in peptides have many advantages, such as extra lipophilicity, metabolic stability, and hydrogen bonding to increase potency.[4] On the other hand, heterocycles are important in drug design and present in half of the top 200 drugs.[5] Thus, recently the use of heterocycle linked tetrazole scaffolds getting major consideration as a privileged core structure for the development of a drug candidate. This combination is an effective strategy to balance drug-like properties. Owning the importance of heterocycles linked tetrazoles resulted into reports of many examples of bioactive agents, such as pyridine-tetrazole, Akt1 and Akt2 dual inhibitors;[6] pyrazole-tetrazole, antileishmanials[7] or as cardiotonic agents;[8] pyridine-tetrazole, antibacterial;[9] piperazines-tetrazole, type 2 diabetes;[10] isoxazole-tetrazole, for AMPA receptors;[11] and also for ionotropic glutamate receptors.[12] Moreover, in non-medical applications, use of cyclic ketimines-tetrazoles as organocatalysts,[13] and pyridine-tetrazoles in lanthanide-based applications[14] are also well known.
Strategies for the synthesis of heterocycle-tetrazole can be categorized into three types. First, the coupling of heterocycle with tetrazole (Figure 1, **A**).[15] Second, synthesis of cyano-heterocycle followed by the tetrazole formation (Figure 1 **B**).[7] Third, tetrazole synthesis followed by post-condensation reaction toward heterocycle formation (Figure 1 **C**).[16] These methods mainly involve more than two steps, harsh coupling conditions, and also the synthesis of starting material for the coupling is tedious.

Here we are reporting the first example of oxazine-tetrazole motif synthesis by using one-pot five-component reaction. The oxazine-tetrazole scaffold is accessible in one pot, time efficiently with high diastereoselectivity and diversity.

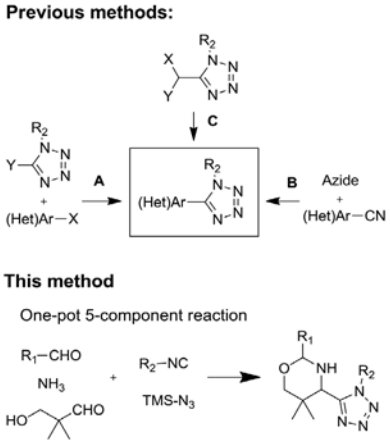


Figure 1. Heterocycle-tetrazole synthesis.

Results and Discussion

We envisioned the use of Asinger-Ugi-tetrazole union for the first time to synthesize an oxazines-tetrazole scaffold. We start our optimization by using isobutyraldehyde, ammonium hydroxide, 3-hydroxypivalaldehyde, benzyl isocyanide and $TMSN_3$. The reaction in methanol at room temperature resulted in only trace product formation (Table 1, Entry **1**). Union of Asinger reaction with other MCR is known to be low yielding.[17] Therefore we move our attention towards the use of sonication as a use of sonication in MCR is known to be effective.[18] Further optimization was carried out with sonication at room temperature.

First, we optimized the ammonia source. We screened different ammonia sources, like NH_4OH, NH_4Cl, and NH_4OAc. NH_4OH in 1.5 equivalent was found to be the best. When the reaction was performed in MeOH, a promising 51% yield was obtained (Table 1, Entry **2**). Next, we move our attention towards solvent screening. Use of MeOH:H_2O solvent systems, such as 3:1, 1:1 or 1:3 resulted in less product formation, like 21%, 17%, and 15% respectively (Table 1. Entries **3**–**5**). However, EtOH solvent gave desired product in trace amount. When water used as a solvent, the reaction did not proceed further which is due to water insolubility of reactants (Table 1, Entry **7**). Use of dioxane and THF provide the almost similar yield of 30% (Table 1, Entries **8**–**9**). TFE and DCM offered a lower yield. Toluene turned out to be the best solvent with 60% yield (Table 1, Entry **13**). However, an attempt to make the protocol greener by using toluene:water solvent system resulted in a lower than 25% yield (Table 1, Entries **14**–**16**). While xylene did not ameliorate the reaction yield.

Table 1. Optimization of reaction conditions.[a]

Entry	Solvent	Time (h)	Yield%[b]
1[c]	MeOH	12	trace
2	MeOH	2	51
3	MeOH : H_2O (3 : 1)	4	21
4	MeOH : H_2O (1 : 1)	4	17
5	MeOH : H_2O (1 : 3)	6	15
6	EtOH	2	nd
7	H_2O	7	nr
8	dioxane	2	32
9	THF	2	29
10	TFE	3	16
11	DCM	3	17
12	MeCN	3	33
13	toluene	2	60
14	toluene : H_2O (1 : 1)	4	11
15	toluene : H_2O (3 : 1)	3	19
16	toluene : H_2O (4 : 1)	2	25
17	p-xylene	4	15

[a]The reaction was carried out with isobutyraldehyde (1 mmol), ammonium hydroxide (1.5 mmol), 3-hydroxypivalaldehyde (1 mmol), benzyl isocyanide (1.2 mmol) and $TMSN_3$ (1.2 mmol) in 0.5 ml solvent. [b]Yield of isolated product. [c]Without sonication at room temperature. nd- not determined. nr- no reaction.

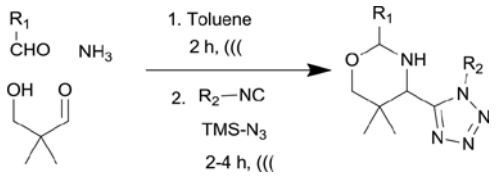
With optimized conditions in hand, next, we tested the scope and limitations of this reaction by reacting various aldehydes and isocyanides (Table 2). Different linear and branched aliphatic aldehydes such as isobutyraldehyde, propanal, butyraldehyde, and valeraldehyde provide moderate to good yields of 21% to 60% (Table 2, Entries **2**–**7**). Good to excellent yield were obtained with aliphatic-aromatic aldehydes like benzyl and phenylacetaldehyde. Benzaldehyde and 2-chloro benzaldehyde are valid substrates in this reaction with providing moderate yields of 35% and 45% respectively (Table 2, Entries **12** and **13**). However, the reaction with ketone resulted in only trace product formation. It is important to mention that, the preformation of imine from aldehyde and ammonium hydroxide is needed to get high yield which normally requires 30 minutes to 1 hour. The slow addition of 3-hydroxypivalaldehyde over 30 min also help to get a clean reaction. After the addition of isocyanide and $TMSN_3$, reaction completes within 2–4 hours.

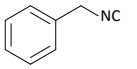
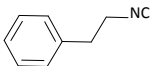
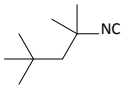
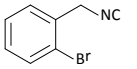
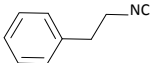
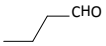
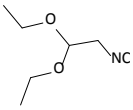
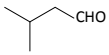
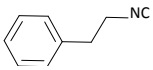
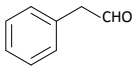
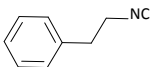
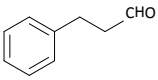
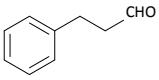
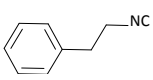
Further, we screened different isocyanides. Aliphatic isocyanides like *tert*-octyl isocyanide and cyclohexyl isocyanide worked well (Table 2, Entries **3** and **9**). Aromatic isocyanides like benzyl and

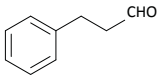
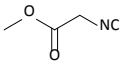
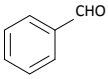
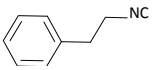
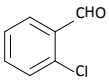
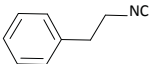
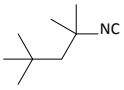
phenylethyl isocyanide with different aldehydes, product yields were good. The glycine isocyanide provides the excellent yield of 83% (Table 2, Entry **11**). While the functional group protected isocyanide, diethoxy-acetaldehyde also compatible in this reaction, which is interesting for further postmodification condensation or for the union with other MCR (Table 2, Entry **6**). Also, a tolerance of a 2-bromo benzyl isocyanide is interesting for the postmodification reaction (Table 2, Entry **4**).

In all examples a higher diastereoselectivity was observed. Aliphatic, aromatic aldehydes and also all isocyanides show more than 90:10 diastereoselectivity. However with benzyl isocyanide and 2-bromo benzylisocyanides low diastereoselectivity observed.

Table 2. Substrate scope.[a]



Entry	R_1-CHO	R_2-NC	Yield[b] (%)	*dr*
1			(**1a**) 60	78 : 22
2			(**1b**) 51	91 : 09
3			(**1c**) 56	90 : 10
4			(**1d**) 47	88 : 12
5			(**1e**) 38	90 : 10
6			(**1f**) 55	91 : 09
7			(**1g**) 25	90 : 10
8			(**1h**) 34	96 : 04
9			(**1i**) 48	94 : 06
10			(**1j**) 50	90 : 10

Entry	R_1-CHO	R_2-NC	Yield[b] (%)	*dr*
11			(**1k**) 83	91 : 09
12			(**1l**) 35	94 : 06
13			(**1m**)45	92 : 08
14			(**1n**) trace	—

[a]The reaction was carried out with isobutyraldehyde (1 mmol), ammonium hydroxide (1.5 mmol), 3-hydroxypivalaldehyde (1 mmol), benzyl isocyanide (1.2 mmol) and $TMSN_3$ (1.2 mmol) in 0.5 ml solvent. [b]Yield of isolated product.

The structures has been confirmed by NMR, MS (low and high resolution) and also by X-ray crystallography.

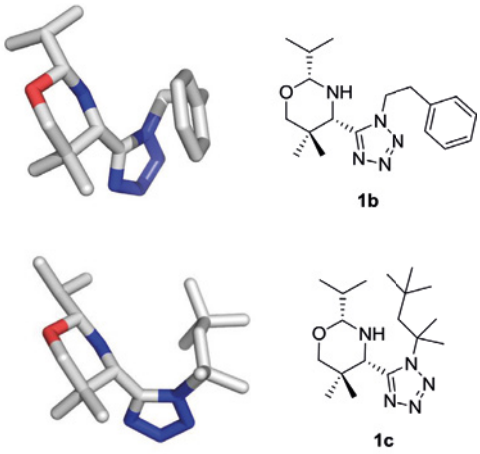


Figure 2. X-ray structures of **1b** and **1c**.

Conclusion

In conclusion, we have developed a highly diastereoselective one-pot five component reaction toward oxazinane-tetrazoles synthesis. This sonication-assisted, novel, and general reaction have many advances, such as high time efficiency, catalyst-free, diverse scope, and excellent diastereoselectivity. Moreover, due to diverse substrate compatibility, this reaction has become

significant potential for postcondensation to get more complex and diverse oxazine-tetrazole structures. Studies towards this area are now in progress.

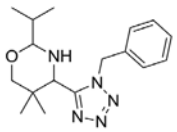
Experimental Procedures and Spectral Data

General procedure for the synthesis of 4-(tetrazole)-1,3-oxazinane:

A 10 mL tube was loaded with an aldehyde (1 mmol) and amonium hydroxyde 30% (1.5 mmol) in toluene (0.5 ml) and the mixture was sonicated for one hour in the water bath of an ultrasonic cleaner (220/240V, 25 Amps and frequency of 50/60 Hz). 3-hydroxy-2,2-dimethylpropanal (1 mmol) was added dropwise over 15 minutes and sonicated for 30 minutes. Isocyanide (1.2 mmol) and TMS-N_3 (1.2 mmol) was added to the reaction. The resulting reaction mixture was sonicated till the 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.

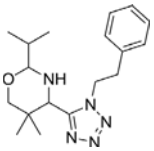
Spectral Data

5,5-dimethyl-2-phenethyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-1,3-oxazinane (1a)



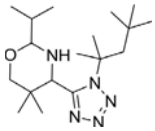
Obtained from 0.5 mmol reaction as a white crystal, yield: 190 mg (60%); as 78:22 diastereomeric mixture: ^{1}H NMR (major+minor diastereomer, 500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 7.22 – 7.15 (m, 3H), 5.82 (d, *J* = 15.4, 1H), 5.70 (d, *J* = 3.6, 2H), 5.52 (d, *J* = 15.4, 1H), 3.80 (d, J = 14.2, 2H), 3.62 (d, *J* = 11.3, 1H), 3.34 (d, *J* = 11.3, 1H), 3.23 (d, *J* = 8.5, 1H), 1.98 – 1.77 (m, 2H), 1.77 – 1.68 (m, 1H), 1.35 (s, 3H), 0.98 (dd, *J* = 6.8, 4.1, 6H), 0.85 (d, *J* = 6.6, 2H), 0.70 (s, 3H), 0.34 (d, *J* = 6.7, 2H). ^{13}C NMR (major+minor diastereomer, 126 MHz, $CDCl_3$) δ 153.2, 133.7, 129.1, 129.1, 128.9, 128.8, 127.7, 127.5, 92.9, 79.2, 58.5, 57.8, 51.4, 51.3, 32.7, 32.0, 22.5, 19.3, 19.0, 18.3, 17.8, 17.6. MS (ESI) m/z calculated $[M+H]^+$: 316.42; found $[M+H]^+$: 316.32. HRMS (ESI) m/z calculated $[M+H]^+$: 316.21319; found $[M+H]^+$: 316.21384.

2-isopropyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-1,3-oxazinane (1b)



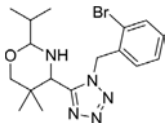
Obtained from 1 mmol reaction as a yellow liquid, yield: 168 mg (51%); as 91:09 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 3H), 7.04 (d, *J* = 6.7, 2H), 4.89 – 4.75 (m, 1H), 4.68 – 4.55 (m, 1H), 3.71 (dd, *J* = 12.0, 5.1, 1H), 3.57 (d, *J* = 11.3, 1H), 3.28 – 3.19 (m, 4H), 1.85 – 1.71 (m, 2H), 1.24 (s, 3H), 0.97 (dd, *J* = 6.8, 4.6, 6H), 0.67 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.3, 137.0, 129.1, 128.8, 127.3, 92.8, 79.0, 58.0, 49.4, 36.3, 32.7, 22.4, 18.1, 17.9, 17.6. MS (ESI) m/z calculated $[M+H]^+$: 330.45; found $[M+H]^+$: 330.18. HRMS (ESI) m/z calculated $[M+H]^+$: 330.22884; found $[M+H]^+$: 330.22867.

2-isopropyl-5,5-dimethyl-4-(1-(2,4,4-trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)-1,3-oxazinane (**1c**)



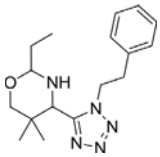
Obtained from 0.5 mmol reaction as a colorless crystal, yield: 95 mg (56%); as 90:10 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 4.30 (d, *J* = 12.8, 1H), 3.88 (dd, *J* = 12.8, 5.4, 1H), 3.72 (d, *J* = 11.2, 1H), 3.48 (d, *J* = 11.2, 1H), 1.95 – 1.80 (m, 9H), 1.53 (s, 3H), 0.96 (dd, *J* = 8.2, 6.9, 6H), 0.80 (s, 9H), 0.73 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.4, 93.2, 80.3, 65.5, 59.1, 53.7, 33.9, 32.8, 31.7, 31.5, 30.5, 29.9, 23.0, 19.7, 18.1, 17.7. MS (ESI) m/z calculated $[M+H]^+$: 338.51; found $[M+H]^+$: 338.37. HRMS (ESI) m/z calculated $[M+H]^+$: 338.29144; found $[M+H]^+$: 338.29129.

4-(1-(2-bromobenzyl)-1*H*-tetrazol-5-yl)-2-isopropyl-5,5-dimethyl-1,3-oxazinane (**1d**)



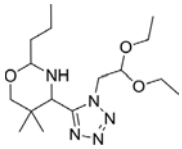
Obtained from 1 mmol reaction as a colorless liquid, yield: 185 mg (47%); as 88:12 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9, 1H), 7.32 – 7.26 (m, 1H), 7.25 – 7.18 (m, 1H), 6.84 (d, *J* = 7.6, 1H), 5.89 (d, *J* = 16.1, 1H), 5.67 (d, *J* = 16.1, 1H), 3.94 (d, *J* = 12.2, 1H), 3.84 (dd, *J* = 12.0, 5.1, 1H), 3.64 (d, *J* = 11.3, 1H), 3.41 (d, *J* = 11.3, 1H), 1.87 (t, *J* = 12.3, 1H), 1.81 – 1.73 (m, 1H), 1.36 (s, 3H), 0.94 – 0.88 (m, 6H), 0.74 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.7, 133.5, 133.1, 130.2, 128.7, 128.2, 122.5, 92.9, 79.0, 58.4, 50.9, 32.8, 32.6, 22.5, 18.4, 17.7, 17.5. MS (ESI) m/z calculated $[M+H]^+$: 394.12; found $[M+H]^+$: 394.25. HRMS (ESI) m/z calculated $[M+H]^+$: 394.1237; found $[M+H]^+$: 394.12332.

2-ethyl-5,5-dimethyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-1,3-oxazinane (**1e**)



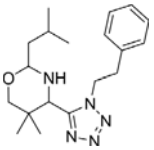
Obtained from 1 mmol reaction as a pale yellow solid, yield: 120 mg 38%); as 90:10 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 3H), 7.10 – 7.02 (m, 2H), 4.83 – 4.71 (m, 1H), 4.65 – 4.56 (m, 1H), 3.94 – 3.86 (m, 1H), 3.57 (d, *J* = 11.3, 1H), 3.34 (d, *J* = 12.5, 1H), 3.30 – 3.21 (m, 3H), 1.77 (t, *J* = 12.4, 1H), 1.69 – 1.57 (m, 2H), 1.24 (s, 3H), 0.98 (t, *J* = 7.5, 3H), 0.67 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 154.4, 129.1, 129.0, 128.8, 127.4, 89.7, 78.9, 58.0, 49.4, 36.4, 28.4, 22.5, 18.2, 9.3. MS (ESI) m/z calculated $[M+H]^+$: 316.42; found $[M+H]^+$: 316.07. HRMS (ESI) m/z calculated $[M+H]^+$: 316.21319; found $[M+H]^+$: 316.21283.

4-(1-(2,2-diethoxyethyl)-1*H*-tetrazol-5-yl)-5,5-dimethyl-2-propyl-1,3-oxazinane (**1f**)



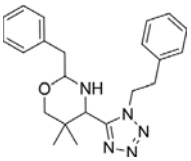
Obtained from 1 mmol reaction as a colorless solid, yield: 187 mg (55%); as 91:09 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 4.83 (t, *J* = 5.6, 1H), 4.70 (dd, *J* = 14.1, 5.7, 1H), 4.41 (dd, *J* = 14.1, 5.5, 1H), 4.27 (s, 1H), 4.21 – 4.11 (m, 1H), 3.82 – 3.70 (m, 2H), 3.66 (d, *J* = 11.3, 1H), 3.53 – 3.41 (m, 3H), 2.06 (s, 1H), 1.70 – 1.51 (m, 2H), 1.49 – 1.40 (m, 2H), 1.27 (s, 3H), 1.19 – 1.12 (m, 6H), 0.92 (t, *J* = 7.4, 3H), 0.84 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 154.3, 101.3, 88.4, 78.9, 64.7, 64.6, 57.7, 50.3, 37.5, 33.0, 22.7, 18.5, 18.1, 15.2, 15.1, 13.9. MS (ESI) m/z calculated $[M+H]^+$: 342.46; found $[M+H]^+$: 342.22. HRMS (ESI) m/z calculated $[M+H]^+$: 342.24997; found $[M+H]^+$: 342.24976.

2-isobutyl-5,5-dimethyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-1,3-oxazinane (1g)



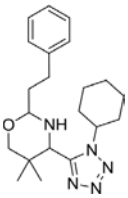
Obtained from 0.5 mmol reaction as a white solid, yield: 43 mg (25%); as 90:10 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 3H), 7.10 – 6.99 (m, 2H), 4.76 (dt, *J* = 13.8, 7.7, 1H), 4.66 – 4.56 (m, 1H), 4.01 (brs, 1H), 3.56 (d, *J* = 11.3, 1H), 3.33 (d, *J* = 8.6, 1H), 3.30 – 3.18 (m, 3H), 1.85 – 1.73 (m, 2H), 1.70 – 1.59 (m, 1H), 1.56 – 1.47 (m, 1H), 1.44 – 1.34 (m, 1H), 1.24 (s, 3H), 0.93 (dd, *J* = 6.6, 4.2, 6H), 0.67 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.2, 136.9, 129.1, 128.8, 127.4, 87.3, 78.9, 58.0, 49.4, 44.4, 36.3, 32.7, 24.3, 22.8, 22.6, 22.6, 18.3. MS (ESI) m/z calculated $[M+H]^+$: 344.48; found $[M+H]^+$: 344.30. HRMS (ESI) m/z calculated $[M+H]^+$: 344.24449; found $[M+H]^+$: 344.24417.

2-benzyl-5,5-dimethyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-1,3-oxazinane (1h)



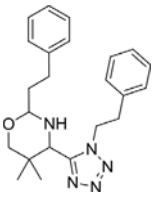
Obtained from 1 mmol reaction as a yellow liquid, yield: 128 mg (34%); as 96:04 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.26 – 7.19 (m, 6H), 6.89 (dd, J = 7.0, 2.3, 2H), 4.71 – 4.59 (m, 1H), 4.53 – 4.44 (m, 1H), 4.21 – 4.09 (m, 1H), 3.56 (d, *J* = 11.4, 1H), 3.22 (d, *J* = 11.4, 1H), 3.17 – 3.07 (m, 3H), 2.94 (dd, *J* = 13.9, 5.0, 1H), 2.84 (dd, *J* = 13.9, 5.8, 1H), 1.75 (t, *J* = 12.4, 1H), 1.19 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.1, 137.0, 136.6, 129.7, 129.0, 128.8, 128.4, 127.5, 126.8, 89.0, 79.0, 58.0, 49.4, 41.8, 36.3, 22.5, 18.1. MS (ESI) m/z calculated $[M+H]^+$: 378.49; found $[M+H]^+$: 378.32. HRMS (ESI) m/z calculated $[M+H]^+$: 378.22884; found $[M+H]^+$: 378.22894.

(E)-4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-5,5-dimethyl-2-styryl-1,3-oxazinane (1i)



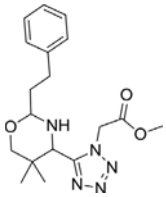
Obtained from 0.5 mmol reaction as a white solid, yield: 89 mg (48%); as 94:06 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.22 – 7.15 (m, 3H), 4.35 – 4.23 (m, 1H), 4.19 – 4.07 (m, 1H), 3.95 (d, *J* = 12.5, 1H), 3.73 (d, *J* = 11.4, 1H), 3.52 (d, *J* = 11.4, 1H), 2.76 (t, *J* = 7.8, 2H), 2.30 – 2.11 (m, 2H), 2.03 – 1.89 (m, 7H), 1.44 – 1.33 (m, 3H), 1.29 (s, 3H), 0.77 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 152.10, 141.37, 128.48, 128.42, 125.96, 87.79, 87.64, 78.75, 58.14, 36.72, 33.14, 30.99, 25.38, 24.85, 22.78, 18.77, 18.64. MS (ESI) m/z calculated $[M+H]^+$: 370.50; found $[M+H]^+$: 370.45. HRMS (ESI) m/z calculated $[M+H]^+$: 370.26014; found $[M+H]^+$: 370.26004.

5,5-dimethyl-2-phenethyl-4-(1-phenethyl-1H-tetrazol-5-yl)-1,3-oxazinane (1j)



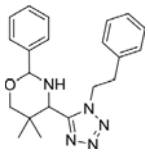
Obtained from 1 mmol reaction as a yellow solid, yield: 196 mg (50%); as 90:10 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4, 2H), 7.27 – 7.19 (m, 7H), 6.99 (dd, *J* = 7.3, 1.9, 2H), 4.75 (dt, *J* = 13.8, 7.6, 1H), 4.67 – 4.53 (m, 1H), 4.01 – 3.89 (m, 1H), 3.66 – 3.55 (m, 1H), 3.31 – 3.21 (m, 4H), 2.77 (t, *J* = 7.8, 2H), 2.07 – 1.93 (m, 1H), 1.93 – 1.79 (m, 2H), 1.27 (s, 3H), 0.66 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.2, 141.3, 136.9, 129.1, 128.8, 128.5, 128.5, 127.3, 126.1, 87.6, 78.9, 57.9, 49.4, 36.5, 36.3, 32.7, 31.0, 22.5, 18.3. MS (ESI) m/z calculated $[M+H]^+$: 392.52; found $[M+H]^+$: 392.24. HRMS (ESI) m/z calculated $[M+H]^+$: 392.24449; found $[M+H]^+$: 392.24426.

methyl 2-(5-(5,5-dimethyl-2-phenethyl-1,3-oxazinan-4-yl)-1*H*-tetrazol-1-yl)acetate (*1k*)



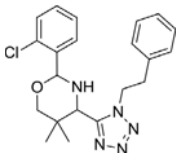
Obtained from 2 mmol reaction as a yellow liquid, yield: 598 mg (83%); as 91:09 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.23 – 7.17 (m, 3H), 5.37 (d, *J* = 17.3, 1H), 5.25 (d, *J* = 17.4, 1H), 4.09 (t, *J* = 5.6, 1H), 3.97 (s, 1H), 3.78 (s, 3H), 3.68 (d, *J* = 11.5, 1H), 3.46 (d, *J* = 11.5, 1H), 2.73 (t, *J* = 7.8, 2H), 2.17 (s, 1H), 2.02 – 1.91 (m, 1H), 1.90 – 1.79 (m, 2H), 1.38 (s, 3H), 1.03 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 166.4, 153.6, 141.2, 128.5, 128.4, 126.1, 87.7, 79.1, 58.9, 53.4, 53.2, 49.0, 36.7, 30.9, 22.6, 18.1. MS (ESI) m/z calculated $[M+H]^+$: 360.43; found $[M+H]^+$: 360.30. HRMS (ESI) m/z calculated $[M+H]^+$: 360.20302; found $[M+H]^+$: 360.20306.

5,5-dimethyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-2-phenyl-1,3-oxazinane (1l)



Obtained from 0.5 mmol reaction as a white solid, yield: 64 mg (35%); as 94:06 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.50 – 7.46 (m, 2H), 7.40 – 7.34 (m, 3H), 7.30 – 7.26 (m, 3H), 7.06 – 7.01 (m, 2H), 5.02 (d, *J* = 12.0, 1H), 4.93 – 4.80 (m, 1H), 4.72 – 4.63 (m, 1H), 4.61 – 4.58 (m, 0H), 3.75 (d, *J* = 11.4, 1H), 3.52 (d, *J* = 12.1, 1H), 3.46 (d, *J* = 11.4, 1H), 3.26 (t, *J* = 7.0, 2H), 2.11 – 1.95 (m, 1H), 1.33 (s, 3H), 0.74 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 153.1, 139.2, 136.9, 129.1, 128.9, 128.6, 128.4, 127.4, 125.8, 88.9, 79.2, 58.4, 49.5, 36.4, 32.7, 22.5, 18.3. MS (ESI) m/z calculated $[M+H]^+$: 364.47; found $[M+H]^+$: 364.33. HRMS (ESI) m/z calculated $[M+H]^+$: 364.21319; found $[M+H]^+$: 364.21304.

2-(2-chlorophenyl)-5,5-dimethyl-4-(1-phenethyl-1*H*-tetrazol-5-yl)-1,3-oxazinane (1m)



Obtained from 1 mmol reaction as a yellow liquid yield: 179 mg (45%); as 92:08 diastereomeric mixture: ^{1}H NMR (major diastereomer, 500 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 1H), 7.42 – 7.37 (m, 1H), 7.33 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 6.97 (dd, *J* = 7.2, 2.1, 2H), 5.33 (d, *J* = 12.0, 1H), 5.05 – 4.93 (m, 1H), 4.81 – 4.70 (m, 1H), 3.72 (d, *J* = 11.4, 1H), 3.39 (dd, *J* = 18.6, 11.9, 2H), 3.31 – 3.13 (m, 2H), 1.66 (t, *J* = 12.2, 1H), 1.41 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (major diastereomer, 126 MHz, $CDCl_3$) δ 152.9, 137.1, 136.7, 132.4, 129.8, 129.6, 129.0, 127.3, 127.3, 127.0, 86.3, 79.5, 58.3, 49.5, 36.5, 32.3, 22.3, 18.2. MS (ESI) m/z calculated $[M+H]^+$: 398.91; found $[M+H]^+$: 398.04. HRMS (ESI) m/z calculated $[M+H]^+$: 398.17421; found $[M+H]^+$: 398.1741.

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