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ZINC IODIDE AS AN EFFICIENT CATALYST IN THE TMS-AZIDE MODIFIED PASSERINI REACTION

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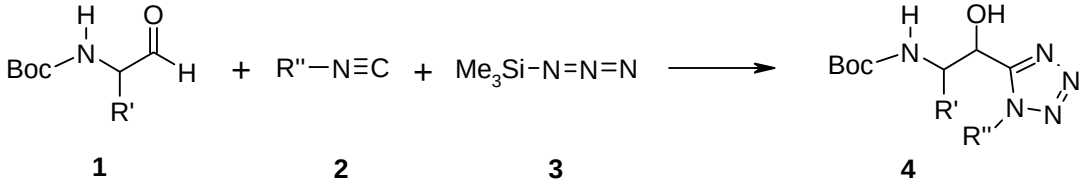
Abstract – Employing ZnI_2 as catalyst significantly improves the yields of the TMS-azide modified Passerini reaction as a short and simple method for the synthesis of 1,5-disubstituted tetrazoles.

The tetrazole moiety is commonly used as a bioisosteric replacement of the carboxyl group in medicinal chemistry. While 1,5-disubstituted tetrazoles have been tested as surrogates for cis-amide bonds,[1] tetrazoles with a free N-H bond can serve as an isoster of the carboxylic acid. Though both have a very similar acidity (pKa ~ 4.5 – 4.9) and a planar structure, the tetrazole group is larger and shows a greater delocalisation of the negative charge than a corresponding carboxylate.[2] When designing new bioactive compounds the greater lipophilicity and enhanced metabolic stability of 1*H*-tetrazoles could give it an advantage over comparable carboxylic acids.[2] Therefore, substitution of a carboxyl moiety by a tetrazole group is a promising measure when developing new drugs.

In the course of a study aimed at the development of new CNS active compounds we were especially interested in 1,5-disubstituted tetrazoles. The TMS-azide modified Passerini-reaction, a very convenient synthesis of 1,5-disubstituted tetrazoles, has been described by Nixey et al. only recently.[3] By combining a Boc-protected amino aldehyde **1**, an isocyanide **2**, and TMS-azide (**3**) in one pot, this multicomponent reaction[4] offers a short and simple method to yield a wide range of 1,5-disubstituted tetrazoles (see Scheme 1) and, at the same time, avoids the disadvantages of a lengthy linear synthesis and the use of toxic or explosive azide sources.



1 **2** **3** **4**

Scheme 1

*Dedicated to Prof. Dr. Ekkehard Winterfeldt with best wishes on the occasion of his 75th birthday

However, when we tried to synthesize a variety of 1,5-disubstituted tetrazoles according to this method, i.e. by stirring a Boc-protected α-amino aldehyde, an isocyanide and TMS-azide at a 0.033 M concentration for 18 h at room temperature as described by Nixey et al., [3] the results were often far from satisfying. For example, when the sterically demanding 2,6-dimethylphenylisocyanide (**8**) was employed in a reaction with the glycinal derivative **5** and TMS-azide (**3**), according to the ^{1}H NMR spectrum the crude reaction product consisted almost exclusively of the starting compounds (after 18 h at room temperature). At best, trace amounts of the desired Passerini product **12** or the silyl ether **23**, the silyl ethers **11** are thought to be the primary product of these reactions, could be detected (~ 1%) (see table 1 entry 1). To improve the yield, the reaction was repeated with a higher concentration (0.17 M instead of 0.033 M) as Passerini reactions are known to be best carried out in concentrated solutions.[5] As a result a perceptible amount, around 10 %, of tetrazole **12** together with the corresponding silyl ether derivative **23** was formed (according to the ^{1}H NMR spectrum of the crude product).

In literature a variety of examples can be found describing Lewis acids as catalysts in the formation of Passerini products.[6] An early report mentioned $Al(N_3)_3$ acting as both a source for hydrazoic acid and a Lewis acid.[7] Later also more common Lewis acids were employed with success.[6] Accordingly, a series of Lewis acids was tested, of which $ZnCl_2$, $ZnBr_2$, ZnI_2, $Zn(OTf)_2$ and $Mg(OTf)_2$ were found to catalyze the desired reaction. Of these ZnI_2 proved to be best suited for this purpose. By adding 10 mol % ZnI_2 as a catalyst and keeping the other reaction conditions unchanged (0.17 M solution, CH_2Cl_2, 18 h) the combined amount of the tetrazole derivatives **12** and **23** reached 90 % (according to ^{1}H NMR, see table 1, entry 2). The improved outcome of the reaction is probably the result of a complexation of the carbonyl function of the aldehyde by the zinc salt. This would facilitate the addition of the isocyanide to the carbonyl moiety. Considering the known high electrophilicity of zinc salts this explanation seems to be the most likely, and is also supported by literature data.[8] However, an alternative mechanism in which TMS-azide is activated by reaction with the zinc salt cannot be ruled out either.

Further experiments with equimolar amounts of ZnI_2 did not achieve higher yields. With 10 mol % $ZnBr_2$ or 10 mol % $ZnCl_2$ the results were also very satisfying, similar to those with 10 mol % ZnI_2 as catalyst. But as ZnI_2 exhibits free solubility in organic solvents like Et_2O,[9] we decided to use ZnI_2 (10 mol %) for all further reactions.

The trimethylsilyl ether **23**, already reported by Nixey et al.[3] was also frequently found in the crude product of our Passerini reactions. It was obviously not entirely cleaved during the aqueous workup of the reaction mixture (1 M phosphate buffer pH 7). Therefore, an additional step was needed in order to obtain a more uniform product. This could be easily accomplished by adding two equivalents of K_2CO_3 to a solution of the crude product in methanol and stirring the mixture over night at room temperature. The

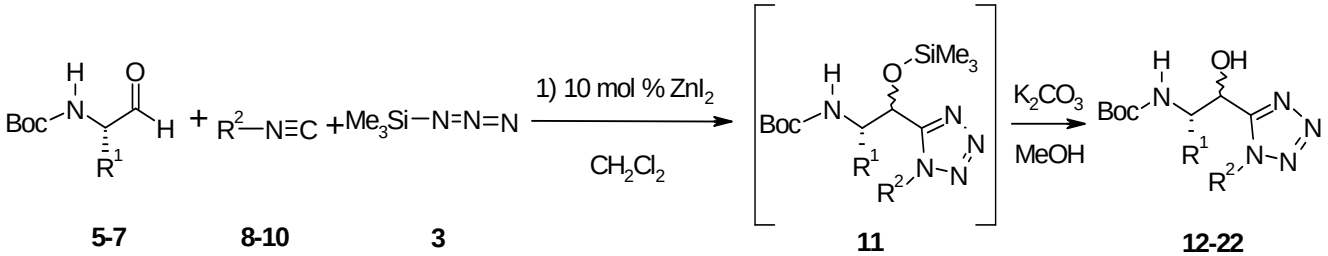
Passerini reaction between **8**, **5** and **3**, when repeated and supplemented by the aforementioned workup, then yielded a crude product that was free of the trimethylsilyl ether **23** but contained 92 % of the desired free tetrazole **12** (according to ^{1}H NMR, see table, 1 entry 2).

When in addition to these steps the reaction time was extended from 18 h to 48 h even the yield of isolated product, i.e the desired tetrazole derivative **12**, amounted to 80 % (see table 1, entry 3).

We subsequently applied our improved version of the TMS-azide modified Passerini reaction to the synthesis of various 1,5-disubstituted tetrazoles. All reactions performed under these conditions with 10 mol % ZnI_2 as catalyst proceeded smoothly and provided the aimed for tetrazoles in moderate to reasonable yields. The reaction of dimethylphenylisonitrile **8** with Boc protected (S)-alaninal **6** and (S)-phenylalaninal **7** gave the corresponding tetrazoles, which were formed and isolated as mixtures of diastereomeres in a ratio of approximately 1:1, in a reasonable yield of 50 % (**13**/**14**) and 44 % (**15**/**16**), respectively. These results demonstrate again the superiority of the ZnI_2 catalyzed over the uncatalyzed reactions. When performed under the published conditions[3] (concentration 0.033 M, 18 h) less than 5 % of the compounds **13**/**14** and **15**/**16** (see table 1, entries 4 and 5) are produced according to ^{1}H NMR.

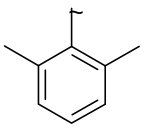
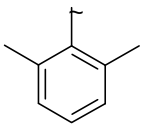
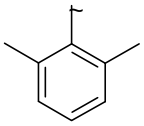
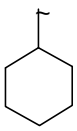
When employing *tert*-butylisocyanide (**9**) and cyclohexylisocyanide (**10**) the effect of the Lewis acid on the outcome of the TMS-azide modified Passerini reaction was less distinct but still significant (see table 1, entries 6 - 9). Here, the desired tetrazoles could be isolated in moderate yields even without ZnI_2 as catalyst probably indicating that the isocyanide function of **9** and **10** is sterically less shielded than it is in **8**. Nevertheless, on average a 10 % to over 20 % increase in yield could be gained by adding 10 mol % ZnI_2 to a 0.17 M solution of the reactants (see table 1 entries 6 - 9).

When starting from the chiral amino aldehydes **6** and **7**, in all cases, mixtures of diastereomers of the final compounds were formed. This raised the question whether in presence of the Lewis acid the reaction might proceed with a different stereoselectivity than those performed without the catalyst. While the catalyst could be expected to form a complex with the starting aldehyde no significant change in stereoselectivity was observed for the catalyzed versus the uncatalyzed reactions, which in all cases was roughly 1:1.

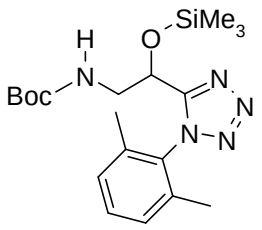


Scheme 2

Table 1. Results of TMS-azide modified Passerini reactions

Entry	Aldehyde	R^1	Isocyanide	R^2	Product No #	10 mol % ZnI_2 [a] Reaction time	10 mol % ZnI_2 [a] Yield	without ZnI_2 [b] Reaction time	without ZnI_2 [b] Yield
1	**5**	-H	**8**		**12**	18 h	73 %[c,d,f]	18 h	~1 %[c,f]
2						18 h	90 %[c,f] (92 %)[f]	18 h	10 %[c,e,f]
3						49 h	80 %		
4	**6**	-Me	**8**		**13**, **14**	48 h	50 %[g]	45 h	< 5% [f,g]
5	**7**	-CH_2Ph	**8**		**15**, **16**	53 h	44 %[g]	78 h	< 5% [f,g]
6	**5**	-H	**9**		**17**	63 h	58 %	63 h	42 %
7	**6**	-Me	**9**		**18**, **19**	63 h	61 %[g]	63 h	39 %[g]
8	**7**	-CH_2Ph	**9**		**20**, **21**	69 h	44 %[g]	-	-
9	**5**	-H	**10**		**22**	65 h	35 %	62 h	25 %

a: c = 0.17 M; addition of 10 mol % ZnI_2; aqueous workup; isolated yields after cleavage of the TMS ether (except where otherwise stated); b:c = 0.033 M, isolated yields after cleavage of the TMS ether (except where otherwise stated); c: before cleavage of the TMS ether; d: c = 0.033 M; e: c = 0.17 M; f: determined from ^{1}H NMR of the crude product; includes free and O-silylated tetrazole; g: both diastereomers



23

Scheme 3

In summary, we have discovered that the outcome of the TMS-azide modified Passerini reaction for the preparation of 1,5-disubstituted tetrazole derivatives can be significantly improved by employing catalytic amounts of a Lewis acid. The best results were found for ZnI_2 of which 10 mol % appeared to be sufficient for an efficient catalysis. This catalytic effect becomes especially apparent when sterically hindered isonitriles are employed. This is best demonstrated by the reaction with 2,6-dimethylphenylisocyanide (**8**), which, in the absence of the catalyst, in some cases even fails to undergo the desired reaction.

EXPERIMENTAL

General Experimental:

All reactions were performed using flame-dried glassware under Ar atmosphere. CH_2Cl_2 was freshly distilled from CaH and MeOH was freshly distilled from Mg prior to use. Solvents for extraction and column chromatography were distilled prior to use. Melting points were determined on a Büchi Melting Point apparatus and are uncorrected. IR spectra were recorded as a KBr disk on a Perkin-Elmer Model 1600 FTIR spectrometer. ^1H and ^{13}C were recorded on a JEOL JNMR-GX 400 and a JEOL JNMR-GX 500 and integrated with the NMR software Nuts (2D Professional Version). MS spectra were measured on a Mass Spectrometer 5989 A with 59980 B particle beam LC/MS interface and microanalytical data for carbon, hydrogen and nitrogen were determined on a Heraeus Rapid Analyser and on an Elementar Vario EL Analyser. Column chromatography (CC) was performed as flash-column chromatography according to W. C. Still[10] on silica gel 60 (0.035 – 0.070 mm, Acros). HPLC purification was performed by means of a Hibar® 250-25 LiChrospher® 100 RP-18 (5 μm) column, a VWR LaPrep pump (flow: 40 mL/min), a Merck Hitachi L-4000 UV-detector and a Merck Hitachi D-2000 Chromato-Integrator. Solvents for HPLC were degassed prior to use. All starting materials were commercially available and used without further purification.

General procedure for the formation of α-hydroxytetrazoles:

To a solution of ZnI_2 (0.34 mmol, 10 mol %) in CH_2Cl_2 (6.0 mL) the corresponding aldehyde (1.0 mmol)

and subsequently the relevant isocyanide (1.0 mmol) and $TMSN_3$ (1.0 mmol) were added. The resulting mixture was stirred at rt. After the time given the reaction was quenched by addition of 1 M phosphate buffer pH 7 (~ 6 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 6 mL) The combined organic layers were dried (Na_2SO_4) and the solvent was removed. For the hydrolysis of the TMS-ether intermediate the crude product was dissolved in MeOH (10.0 mL) and K_2CO_3 (2 equiv) was added. The resulting suspension was stirred at rt over night. The reaction was quenched with 1 M phosphate buffer pH 7 (~ 10 mL). After extraction with CH_2Cl_2 (4 x 10 mL) the combined organic layers were dried (Na_2SO_4), the solvent was removed and the resulting oil was purified by CC and HPLC, respectively.

{2-[1-(2,6-Dimethylphenyl)-1*H*-tetrazole-5-yl]-2-hydroxyethyl}carbamic acid *tert*-butyl ester (12)

According from GP from aldehyde **5** (79.8 mg, 0.501 mmol), isocyanide **8** (66.1 mg, 0.504 mmol), azide **3** (57.8 mg, 0.502 mmol, 66 µL) and ZnI_2 (55.0 mg, 0.172 mmol, 10.2 mol %) in CH_2Cl_2 (3.0 mL); reaction time 49 h. Purification by CC (*n*-pentane/EtOAc = 1:1) afforded **12** (133.1 mg, 0.399 mmol, 80 %) as a white solid; mp 142 °C. IR (KBr): $\tilde{\nu}$ = 3358, 3269, 2982, 1681, 1548, 1289, 1170, 1157, 1058, 946, 784 cm^{-1}. ^1H NMR (500 MHz, CD_3OD, 24 °C): δ = 1.41 [s, 9 H, $C(CH_3)_3$], 1.96 (s, 3 H, CH_3)[a], 2.02 (s, 3 H, CH_3)[a], 3.49 – 3.63 (m, 2 H, CH_2), 4.66 (t, J = 6.7 Hz, 1 H, C*H*OH), 7.33 (d, J = 7.7 Hz, 1 H, $H_{arom., meta}$)[a], 7.33 (d, J = 7.7 Hz, 1 H, $H_{arom., meta}$)[a], 7.47 (t, J = 7.7 Hz, 1 H, $H_{arom., para}$) ppm. ^{13}C NMR (125 MHz, CD_3OD, 25 °C): δ = 17.7 (q, Ar-CH_3),[a] 17.8 (q, Ar-CH_3)[a], 29.0 [q, $C(CH_3)_3$], 46.0 (t, CH_2), 63.6 (d, CHOH), 80.8 [s, $C(CH_3)_3$], 130.2 (d, $C_{arom., meta}$)[a], 130.3 (d, $C_{arom., meta}$)[a], 132.6 (d, $C_{arom., para}$), 133.5 (s, *Ar*-tetrazole), 137.2 (s, *Ar*CH_3)[a], 137.9 (s, *Ar*CH_3), 158.1 (s, $C_{tetrazole}$), 158.6 (s, C=O) ppm. MS (CI, CH_5^+): *m/z* (%) = 334 (43) $[M+1]^+$, 278 (100), 260 (68), 234 (9), 204 (14), 146 (10), 104 (18). HRMS (EI^+, 70 eV): calcd for $C_{16}H_{23}N_5O_3$, 333.1801; found 333.1819. Anal. Calcd for $C_{16}H_{23}N_5O_3$ (333.39): C 57.64, H 6.95, N 21.01. Found: C 57.41, H 6.95, N 20.84.

[a] two signals due to hindered rotation

^1H and ^{13}C data are in accord with those in literature.[3]

{(*1S,2R*)-2-[1-(2,6-Dimethylphenyl)-1*H*-tetrazole-5-yl]-2-hydroxy-1-methylethyl}carbamic acid *tert*-butyl ester (13) and {(*1S,2S*)-2-[1-(2,6-Dimethylphenyl)-1*H*-tetrazole-5-yl]-2-hydroxy-1-methylethyl}carbamic acid *tert*-butyl ester (14)

According to GP from alaninal **6** (34.5 mg, 0.199 mmol), isocyanide **8** (26.8 mg, 0.204 mmol), azide **3** (23.7 mg, 0.205 mmol, 27 µL) and ZnI_2 (24.0 mg, 0.075 mmol, 11.0 mol %) in CH_2Cl_2 (1.2 mL); reaction time 48 h. Purification by CC (n-pentane/ EtOAc = 1:1) and prep. HPLC (H_2O/MeCN = 65:35, UV 200 nm) afforded a mixture of **13** and **14** (34.5 mg, 0.099 mmol, 50 %, dr = 53/47) as a white solid; IR (KBr):

$\tilde{\nu}$ = 3369, 3225, 2975, 2932, 1687, 1515, 1240, 1167, 1054, 778 cm^{-1}. ^1H NMR (400 MHz, tetrachloroethane, 100 °C): δ = 1.23 (d, J = 7.0 Hz, 3 H, CH_3, **13** or **14**), 1.28 (d, J = 7.0 Hz, 3 H, CH_3, **13** or **14**), 1.42 [s, 9 H, $C(CH_3)_3$, **13** or **14**], 1.45 [s, 9 H, $C(CH_3)_3$, **13** or **14**], 1.94 (s, 3 H, $ArCH_3$, **13** or **14**) [a], 1.96 (s, 3 H, $ArCH_3$, **13** or **14**) [a], 2.00 (s, 3 H, $ArCH_3$, **13** or **14**) [a], 2.01 (s, 3 H, $ArCH_3$, **13** or **14**) [a], 3.50 (s_{br}, 1 H, OH, **13** or **14**), 3.67 (s_{br}, 1 H, OH, **13** or **14**), 4.12 – 4.30 (m, 1 H, C*H*CH_3, **13** and **14**), 4.56 (s_{br}, 1 H, C*H*OH, **13** or **14**), 4.63 ($s_{br,}$ 1 H, C*H*OH, **13** or **14**), 4.84 (d, J = 7.9 Hz, 1 H, NH, **13** or **14**), 5.41 (d, J = 7.9 Hz, 1 H, NH, **13** or **14**), 7.21 – 7.29 (m, 2 H, $H_{arom., meta}$, **13** and **14**), 7.40 (t, J = 7.6 Hz, 1 H, $H_{arom., para}$, **13** or **14**), 7.41 (t, J = 7.6 Hz, 1 H, $H_{arom., para}$, **13** or **14**) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 26 °C): 17.3 (q, CH_3, **13** or **14**), 17.3 (q, CH_3, **13** or **14**), 17.4 (q, *C*H_3Ar, **13** or **14**), 17.4 (q, *C*H_3Ar, **13** or **14**), 28.2 [q, $C(CH_3)_3$, **13** or **14**], 28.3 [q, *C*$(CH_3)_3$, **13** or **14**], 49.8 (d, *C*HCH_3, **13** or **14**) 50.2 (d, *C*HCH_3, **13** or **14**), 66.8 (d, CHOH, **13** or **14**), 68.2 (d, CHOH, **13** or **14**), 80.3 [s, *C*$(CH_3)_3$, **13** and **14**], 128.6 (d, $C_{arom., meta}$, **13** or **14**)[a], 128.7 (d, $C_{arom., meta}$, **13** or **14**)[a], 128.8 (d, $C_{arom., meta}$, **13** or **14**)[a], 129.0 (d, $C_{arom., meta}$, **13** or **14**)[a], 130.8 (d, $C_{arom., para}$, **13** or **14**), 130.9 (d, $C_{arom., para}$, **13** or **14**), 131.8 (s, *Ar*-tetrazole, **13** or **14**), 132.0 (*Ar*-tetrazole, **13** or **14**), 135.1 (s, *Ar*CH_3, **13** or **14**)[a], 135.5 (s, *Ar*-CH_3, **13** or **14**)[a], 136.0 (s, *Ar*CH_3, **13** or **14**)[a], 136.7 (s, *Ar*CH_3, **13** or **14**)[a], 155.0 (s, $C_{tetrazole}$, **13** or **14**), 155.7 (s, $C_{tetrazole}$, **13** or **14**), 156.4 (s, C=O, **13** or **14**), 156.9 (s, C=O, **13** or **14**) ppm. MS (CI, CH_5^+): *m/z* (%) = 348 [M+1] (46), 292 (100), 274 (55), 248 (15), 204 (17), 175 (10), 147 (18), 146 (13), 118 (19). HRMS (EI^+, 70 eV): calcd for $C_{17}H_{25}N_5O_3$, 347.1979; found 347.1957.

[a] two signals due to hindered rotation

{(*1S,2R*)-1-Benzyl-2-[1-(2,6-dimethylphenyl)-1*H*-tetrazole-5-yl]-2-hydroxyethyl}carbamic acid *tert*-butyl ester (15)[a] and {(*1S,2S*)-1-Benzyl-2-[1-(2,6-dimethyl-phenyl)-1H-tetrazole-5-yl]-2-hydroxyethyl}carbamic acid *tert*-butyl ester (16)[a]

According to GP from aldehyde **7** (491.3 mg, 1.971 mmol), isocyanide **8** (262.9 mg, 2.004 mmol), azide **3** (231.3 mg, 2.007 mmol, 264 µL) and ZnI_2 (222.3 mg, 0.696 mmol, 10.4 mol %) in CH_2Cl_2 (12.0 mL); reaction time 53 h. Purification by CC ($CHCl_3$/MeOH = 99:1) and prep. HPLC (H_2O/MeCN = 4:6, UV 254 nm) afforded a mixture of **15** and **16** (367 mg, 0.867 mmol, 44 %; dr = 45/55) as a white solid; IR (KBr): $\tilde{\nu}$ = 3392, 2978, 2931, 2527, 1698, 1407, 1366, 1162, 1030, 777, 700 cm^{-1}. ^1H NMR (400 MHz, tetrachloroethane, 100 °C): δ = 1.40 [s, 9 H, $C(CH_3)_3$, **15** or **16**], 1.42 [s, 9 H $C(CH_3)_3$, **15** or **16**], 1.84 (s, 3 H, CH_3, **15** or **16**)[a], 1.90 (s, 3 H, CH_3, **15** or **16**)[a], 2.00 (s, 3 H, CH_3, **15** or **16**)[a], 2.05 (s, 3 H, CH_3, **15** or **16**)[a], 2.92 – 3.09 (m, 2 H, CH_2, **15** and **16**), 3.57 (s_{br}, 1 H, OH, **15** or **16**), 3.64 (s_{br}, 1 H, OH, **15** or **16**), 3.95 – 4.06 (m, 1 H, C*H*Bn, **15** or **16**), 4.39 - 4.50 (m, 1 H, C*H*Bn, **15** or **16**), 4.72 (s_{br}, 1 H, C*H*OH, **15** or **16**), 4.76 (s_{br}, 1 H, C*H*OH, **15** or **16**), 4.99 (d, J = 8.7 Hz, 1 H, NH, **15** or **16**), 5.41 (d, J = 8.7 Hz, 1 H, NH, **15** or **16**), 7.06 – 7.45 (m, 8 H, $H_{arom.}$, **15** and **16**) ppm. ^{13}C NMR (125 MHz, tetrachloroethane,

25 °C): δ = 17.2 (q, CH_3, **15** or **16**)[a)], 17.4 (q, CH_3, **15** or **16**)[a)], 17.4 (q, CH_3, **15** or **16**)[a)], 17.6 (q, CH_3, **15** or **16**)[a)], 28.3 [q, $C(CH_3)_3$, **15** and **16**], 36.9 (t, CH_2, **15** or **16**), 37.2 (t, CH_2, **15** or **16**), 55.3 (d, *C*HBn , **15** or **16**, 56.7 (d, *C*HBn, **15** or **16**), 65.3 (d, CHOH, **15** or **16**), 65.8 (d, CHOH, **15** or **16**), 80.2 (s, $C(CH_3)_3$, **15** or **16**), 80.6 (s, $C(CH_3)_3$, **15** or **16**), 126.7 (d, $CH_{arom.}$, **15** or **16**), 126.9 (d, $CH_{arom.}$, **15** or **16**), 128.7 (d, $CH_{arom.}$, **15** or **16**), 128.8 (d, $CH_{arom.}$, **15** or **16**), 128.9 (d, $CH_{arom.}$, **15** or **16**), 129.1 (d, $CH_{arom.}$, **15** or **16**) 129.2 (d, $CH_{arom.}$, **15** or **16**), 131.0 (d, $CH_{arom.}$, **15** or **16**), 131.1 (d, $CH_{arom.}$, **15** or **16**), 131.6 (s, $C_{arom.}$, **15** or **16**), 131.9 (s, $C_{arom.}$, **15** or **16**), 135.0 (s, $C_{arom.}$, **15** or **16**), 135.1 (s, $C_{arom.}$, **15** or **16**), 135.8 (s, $C_{arom.}$, **15** or **16**), 136.7 (s, $C_{arom.}$, **15** or **16**), 137.1 (s, $C_{arom.}$, **15** or **16**), 137.3 (s, $C_{arom.}$, **15** or **16**), 155.3 (s, Cq **15** or 1**6**), 156.0 (s, Cq, **15** or **16**), 156.4 (s, Cq, **15** or **16**), 156.9 (s, Cq, **15** or **16**) ppm. MS (CI, CH_5^+): *m/*z (%) = 424 (45) $[M+H]^+$, 368 (100), 350 (36), 324 (23), 232 (16), 204 (29), 194 (46), 175 (41), 164 (23), 147 (54), 120 (25). HRMS (EI^+, 70 eV): calcd for $C_{23}H_{29}N_5O_3$, 423.2270; found 423.2290.

a) compound described but not characterized by Nixey et al.[3]

[2-(1-*tert*-Butyl-1*H*-tetrazole-5-yl)-2-hydroxyethyl]carbamic acid *tert*-butyl ester (17)

According to GP from aldehyde **5** (32.0 mg, 0.201 mmol), isocyanide **9** (15.4 mg, 0.208 mmol, 21 µL) azide **3** (23.7 mg, 0.208 mmol, 27 µL) and ZnI_2 (23.2 mg, 0.073 mmol, 10.6 mol %) in CH_2Cl_2 (1.2 mL); reaction time 63 h. Purification by CC (*n*-pentane/EtOAc = 1:1) and prep. HPLC (H_2O/MeCN = 35:65, UV 200 nm) afforded **17** (33.0 mg, 0.117 mmol, 58 %) as a white solid; mp 111 °C. IR (KBr): $\tilde{\nu}$ = 3352, 2981, 2938, 1700, 1692, 1681, 1519, 1368, 1172 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2, 19 °C): δ = 1.38 (s, 9 H, $OC(CH_3)_3$), 1.76 (s, 9 H, $C(CH_3)_3$), 3.68 – 3.83 (m, 2 H, CH_2), 4.28 (d, *J* = 6.1 Hz, OH), 5.17 (dt, *J* = 6.1/0.6 Hz, CHOH), 5.50 (t, 1 H, *J* = 5.9 Hz, NH) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 20 °C): δ = 28.0 [q, $OC(CH_3)_3$], 29.6 [q, $C(CH_3)_3$], 45.1 (t, CH_2), 62.2 [s, $C(CH_3)_3$], 64.5 (d, CHOH), 80.1 [s, $OC(CH_3)_3$], 154.3 (s, $C_{tetrazole}$), 157.3 (s, C=O) ppm. MS (CI, CH_5^+); *m/z* (%) = 286 (73) [M+1], 230 (66), 174 (100), 156 (33), 127 (14), 104 (16). HRMS (EI^+, 70 eV): calcd for $C_{12}H_{23}N_5O_3$, 285.1801; found 285.1797.

(*1S,2R*)-[2-(1-*tert*-Butyl-1*H*-tetrazole-5-yl)-2-hydroxy-1-methylethyl]carbamic acid *tert*-butyl ester (18) and (*1S,2R*)-[2-(1-*tert*-Butyl-1H-tetrazole-5-yl)-2-hydroxy-1-methylethyl]carbamic acid *tert*-butyl ester (19)

According to GP from aldehyde **6** (35.1 mg, 0.203 mmol), isocyanide **9** (15.4 mg, 0.208 mmol, 21 µL), azide **3** (23.7 mg, 0.205 mmol, 27 µL) and ZnI_2 (21.9 mg, 0.069 mmol, 10.1 mol %) in CH_2Cl_2 (1.2 mL); reaction time 63 h. Purification by CC (*n*-pentane/EtOAc = 1:1) and prep. HPLC (H_2O/MeCN = 1:1, UV 200 nm) afforded a mixture of **18** and **19** (36.8 mg, 0.123 mmol, 61 %; dr = 43/57) as a white solid. IR (KBr): $\tilde{\nu}$ = 3406, 3356, 2987, 2940, 1687, 1520, 1171 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, 20 °C): δ =

1.22 (d, J = 6.9 Hz, 0.43 x 3 H, CHCH_3), 1.33 (d, J = 6.9 Hz, 0.57 x 3 H, CHCH_3), 1.37 [s, 0.57 x 9 H, $(CH_3)_3CO$], 1.44 [s, 0.43 x 9 H, $(CH_3)_3CO$], 1.78 [s, 0.57 x 9 H, $(CH_3)_3C$], 1.81 [s, 0.43 x 9 H, $(CH_3)_3C$], 3.94 – 4.20 (s_{br}, 0.57 x 1 H, OH), 4.24 – 4.41 (m, 1 H, CHCH$_3$), 4.46 – 4.73 (s_{br}, 0.43 x 1 H, OH), 5.03 (d, J = 5.2 Hz, 0.57 x 1 H, CHOH), 5.10 (s_{br}, 0.57 x 1 H, NH), 5.14 (d, J = 3.6 Hz, 0.43 x 1 H, CHOH), 5.99 (d, J = 8.9 Hz, 0.43 x 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C): δ = 16.8 (q, CHCH$_3$, min), 17.2 (q, CHCH$_3$, maj), 28.2 [q, OC(CH$_3$)$_3$, min or maj], 28.3 [q, OC(CH$_3$)$_3$, min or maj], 29.9 [q, C(CH$_3$)$_3$, min or maj], 30.0 [q, C(CH$_3$)$_3$, min or maj], 50.5 (d, CHCH$_3$), 62.0 [s, C(CH$_3$)$_3$, maj], 62.3 [s, C(CH$_3$)$_3$, min], 67.4 (d, CHOH, min), 69.0 (d, CHOH, maj), 80.1 [s, OC(CH$_3$)$_3$, min], 80.2 [s, OC(CH$_3$)$_3$, maj], 153.5 (s, $C_{tetrazole}$, min), 154.1 (s, $C_{tetrazole}$, maj), 156.5 (s, C=O, maj), 157.3 (s, C=O, min) ppm.[a] MS (CI, CH_5^+); *m/z* (%) = 300 $[M+1]^+$ (17), 244 (56), 226 (12), 200 (13), 188 (100), 170 (66), 144 (24), 127 (12), 118 (20). HRMS (EI^+, 70 eV): calcd for $C_{13}H_{25}N_5O_3$ 299.1957; found 299.1991.

[a] maj: major diastereomer; min: minor diastereomer

(*1S,2R*)-[1-Benzyl-2-(1-*tert*-butyl-1*H*-tetrazole-5-yl)-2-hydroxyethyl]carbamic acid *tert*-butyl ester (20) and (*1S,2S*)-[1-Benzyl-2-(1-*tert*-butyl-1*H*-tetrazole-5-yl)-2-hydroxyethyl]carbamic acid *tert*-butyl ester (21)

According to GP aldehyde **7** (74.8 mg, 0.300 mmol), isocyanide **9** (22.8 mg, 0.308 mmol, 31 µL), azide **3** (35.0 mg, 0.304 mmol, 40 µL) and ZnI_2 (34.8 mg, 0.109 mmol, 10.7 mol %) in CH_2Cl_2 (1.8 mL) afforded **20** and **21** (49.7 mg, 0.132 mmol, 44 %) as white solids after purification by CC (*n*-pentane/EtOAc = 1:1) and prep. HPLC (H_2O/MeCN = 55:45 and 6:4 respectively, UV 200 nm).

Isomer 1 [t_r (H_2O/MeCN = 55:45) = 16 min; 27.1 mg, 0.072 mmol, 24 %]: mp 128.5 °C. IR (KBr): $\tilde{\nu}$ = 3369, 3248, 3066, 2981, 2931, 1690, 1556, 1171, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 21 °C): δ = 1.37 [s, 9 H, OC(CH$_3$)$_3$], 1.56 [s, 9 H, C(CH$_3$)$_3$], 3.00 – 3.18 (m, 2 H, CH$_2$), 4.21 (m, 1 H, CHBn), 4.50 (s_{br}, 1 H, OH), 5.08 (d, J = 3.2 Hz, 1 H, CHOH), 5.26 (s_{br}, 1 H, NH), 7.29–7.36 (m, 5 H, $H_{arom.}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C): δ = 28.2 [q, (H$_3C$)$_3$CO], 29.7 [q, (H$_3C$)$_3$C], 37.5 (t, CH$_2$), 55.8 (d, CHBn), 62.1 (s, (H$_3$C)$_3C$), 65.6 (d, CHOH), 80.2 (s, (H$_3$C)$_3C$O), 126.9 (d, $C_{arom.}$), 128.7 (d, $C_{arom.}$), 129.5 (d, $C_{arom.}$), 137.5 (s, $C_{arom.}$), 154.8 (s, $C_{tetrazole}$), 157.0 (s, C=O) ppm. MS (CI, CH_5^+); *m/z* (%) = 376 (3) $[M+1]^+$ 320 (28), 276 (18), 264 (48), 246 (100), 220 (36), 194 (35), 127 (22). HRMS (EI^+, 70 eV): calcd for $C_{19}H_{22}N_5O_3$, 375.2270; found 375.2277.

Isomer 2 [t_r (H_2O/MeCN) = 55:45 = 21 min; 22.6 mg, 0.060 mmol, 20 %]: mp 113 °C. IR (KBr): $\tilde{\nu}$ = 3343, 3135, 3065, 2978, 2933, 1695, 1498, 1391, 1170, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 19 °C): δ = 1.41 [s, 9 H, OC(CH$_3$)$_3$], 1.65 [s, 9 H, C(CH$_3$)$_3$], 2.89 (dd, J = 13.7/8.3 Hz, 1 H, CH$_2$), 3.13 (dd, J = 13.8/8.0 Hz, 1 H, CH$_2$), 3.44 – 3.86 (s_{br}, 1 H, OH) 4.50 – 4.63 (m, 1 H, CHBn), 4.96 (d, J = 4.0 Hz, 1 H, CHOH), 6.14 (d, J = 9.5 Hz, 1 H, NH), 7.03 (d, J = 7.1 Hz, 2 H, $H_{arom.}$), 7.17 – 7.29 (m, 3 H, H_{arom}) ppm.

^{13}C NMR (100 MHz, $CDCl_3$, 13 °C): δ = 28.2 [q, OC(CH_3)$_3$], 29.8 [q, C(CH_3)$_3$], 37.9 (t, CH_2), 56.8 (d, *C*HBn), 62.6 [s, *C*(CH_3)$_3$], 64.9 (d, CHOH), 80.2 [s, O*C*(CH_3)$_3$], 126.8 (d, $C_{arom.}$), 128.7 (d, $C_{arom.}$), 128.9 (d, $C_{arom.}$), 137.2 (s, $C_{arom.}$), 153.0 (s, $C_{tetrazole}$), 157.0 (s, C=O) ppm. MS (EI^+, 70 eV): *m/*z (%) = 375 (8) [M^+], 350 (2), 302 (10), 284 (100). HRMS (EI^+, 70 eV): calcd for $C_{19}H_{29}N_5O_3$ 375.2270; found 375.2262.

[2-(1-Cyclohexyl-1*H*-tetrazole-5-yl)-2-hydroxyethyl]carbamic acid *tert*-butyl ester (22)

According to GP from aldehyde **5** (31.8 mg, 0.200 mmol), isocyanide **10** (22.0 mg, 0.201 mmol, 25 µL), azide **3** (23.7 mg, 0.205 mmol, 27 µL) and ZnI_2 (23.0 mg, 0.072 mmol, 10.6 mol %) in CH_2Cl_2 (1.2 mL); reaction time 65 h. Purification by prep. HPLC (H_2O/MeCN = 6:4, UV 200 nm) afforded **22** (22.0 mg, 0.071 mmol, 35 %) as a white solid; mp 126°C. IR (KBr): $\tilde{\nu}$ = 3321, 2976, 2937, 2862, 1684, 1440, 1148, 1104 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C): δ = 1.24 – 1.51 (m, 2 H, C_6H_{11}), 1.42 [s, 1 H, (CH_3)$_3$], 1.71 – 2.20 (m, 8 H, C_6H_{11}), 3.71 -3.91 (m, 2 H, CH_2), 4.60 – 4.71 (m, 1 H, C_6H_{11}), 4.88 (s_{br}, 1 H, OH), 5.10 (t, *J* = 4.8 Hz, 1 H, CH), 5.51 (t, *J* = 6.0 Hz, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 21 °C): δ = 24.9 (t, C_6H_{11}), 25.3 (t, C_6H_{11}), 25.3 (t, C_6H_{11}), 28.2 [q, (CH_3)$_3$], 44.9 (t, CH_2), 58.6 (d, C_6H_{11}), 65.3 (d, CHOH), 80.6 [s, *C*(CH_3)$_3$], 153.6 (s, $C_{tetrazole}$), 157.9 (s, C=O) ppm. MS (CI, CH_5^+): *m/z* (%) = 312 (47) [M+1]$^+$, 256 (73), 238 (77), 182 (17), 174 (19), 156 (100). HRMS (EI^+, 70 eV): calcd for $C_{14}H_{25}N_5O_3$, 311.1937; found 311.1957. Anal. Calcd for $C_{14}H_{25}N_5O_3$ (311.19): C 54.00, H 8.09, N 22.49. Found: C 53.80, H 8.16, N 22.30.

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