HETEROCYCLES, Vol. 77, No. 2, 2009, pp. 865 - 872. © The Japan Institute of Heterocyclic Chemistry
Received, 15th October, 2008, Accepted, 17th November, 2008, Published online, 18th November, 2008
DOI: 10.3987/COM-08-S(F)121

SYNTHEIS OF NEW CHIRAL 5,6,7,8-TETRAHYDRO-TETRAZOLO[1,5-a]PYRAZINES FROM α-AMINO ACID DERIVATIVES FOLLOWING "CLICK" CHEMISTRY

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Abstract – An efficient and practical synthesis of new chiral fused tetrazoles have been synthesized following [3+2] cycloaddition reaction starting from α-amino acid derivatives.

Tetrazole ring system are important features in biological systems, natural products, and drugs.[1] These nitrogen rich systems are frequently used as a metabolically stable isosteric replacement for the carboxylic acid moiety and as a cis peptide bond mimetic.[2] Tetrazoles have also been used as precursors to other heterocycles.[3] For instance, Losartan (**1**) is a Angiotensin II antagonist and commonly used for treatment of hypertension.[4] Tetrazole **3** has also been found to possess binding affinity to benzodiazepine receptors.[5] Pentylentetrazole (PTZ**)** (**2**) has the opposite effect compared to **3** and is extensively used in models for anxiety, mediated by its unspecific interaction with a number of receptors in the CNS.[6] Mannose mimetics **4** and **5** have been reported to be inhibitors of α-mannosidase (Figure 1).[7]

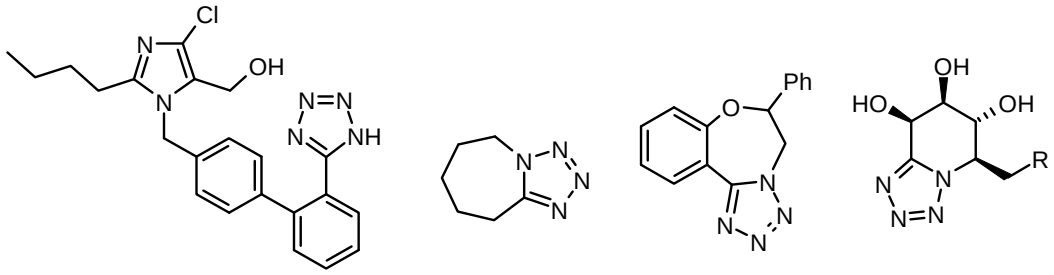


Figure 1. Some annulated benzodiazepines

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

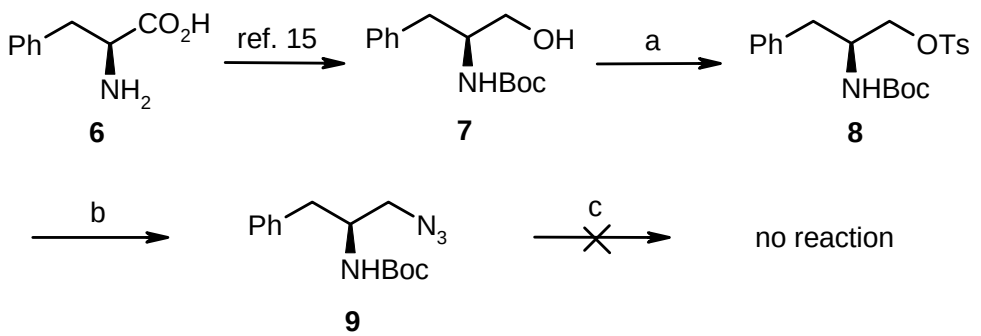
A variety of synthetic tetrazole containing biologically active substances are described in the current literature, such as glycin-tetrazole, modified S-alkyl-GSH analogues, α-methylene tetrazole based peptidomimetic HIV protease inhibitors, endothelin-converting enzyme (ECE-1), neutral endopeptidase 24.11 (NEP 24.11), non peptidic inhibitors and area-based inhibitors of glutamate carboxypeptidase II (GCP II). They have been investigated for medicinal applications in area as diverse as antibacterials,[8] cancer,[9] heart disease,[10] and neurodegenerative disease,[11] among others.[12]

When an organic azide is used as the dipole, only certain highly activated nitriles are competent dipolarophiles.[13] To-date only a few highly activated nitriles are known to undergo this cycloaddition in an intramolecular fashion with organic azides. When the azide and nitrile moieties are in the same molecule, rate of cycloaddition reaction can be greatly enhanced. Several groups have reported the efficient synthesis of polycyclic fused tetrazoles via intramolecular [3+2] cycloadditin reaction.[14]

To the best of our knowledge, this report describes the first synthesis of chiral fused tetrazole pyrazine derivatives via an intramolecular [3+2] cycloaddition reaction starting from amino acid derivatives.

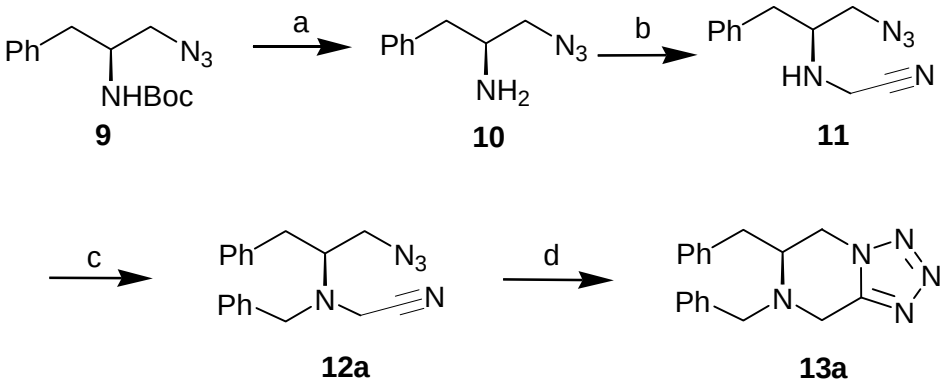
In this communication, we report an effective integration of Huisgen's 1,3 dipolar cycloaddition reaction (one of the prototype reaction in click chemistry) onto natural α-amino acid derivatives for the synthesis of tetrazole-fused pyrazines.

We first devoted our initial efforts toward the synthesis of the key intermediate **12a** from L-phenylalanine (**6**). Thus, Boc protected L-phenylalaninol (**7**) was prepared from L-phenylalanine (**6**) by reduction with I_2 and $NaBH_4$ in THF followed by Boc-protection with Boc_2O and TEA in CH_2Cl_2 according to the procedure reported in literature.[15] Tosyl protection of **7** was carried out by treatment with *p*-TsCl in pyridine at ambient temperature in good yield. Tosylate **8** was converted to azido derivative **9** by S_N2 displacement with NaN_3 in DMF at 70 °C in 94% yield. A characteristic peak at 2098 cm^{-1} in the IR spectrum indicated the presence of the azide functional group. However, the next step, which was to introduce nitrile functionality in azide **9** using bromoacetonitrile was unsuccessful under different reaction conditions (Scheme 1).



Scheme 1. *Reagents and conditions*: (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C-rt, 8 h, 88%; (b) NaN_3, DMF, 70 °C, 6 h, 94%; (c) (i) NaH, $BrCH_2CN$, DMF, 0 °C; (ii) K_2CO_3, $BrCH_2CN$, MeCN, rt; (iii) K_2CO_3, $BrCH_2CN$, DMF, 80 °C.

To overcome this failure, we at first deprotected Boc with 4N HCl-EtOAc at 0 °C and then nitrile functionality was introduced by treatment with K_2CO_3 and bromoacetonitrile in CH_3CN at room temperature to obtain **11**. The structure of **11** was established by NMR spectroscopy and mass spectrometry studies. The secondary amine group of compound **11** was protected with benzyl bromide and K_2CO_3 at 80 °C to afford **12a** in 94% yield. ^{1}H NMR, ^{13}C NMR, mass profile and elemental analysis confirmed the structure of **12a**. In the IR spectrum, a strong peak appearing at 2102 cm^{-1} indicated the presence of both azide and nitrile group. The structure was also confirmed by mass spectrum (ESI-MS), ion peak at *m/z* = 306 attributed to $[M+H]^+$. As per our previously reported conditions for 1,3-dipolar cycloaddition reaction,[16] heating the azido-nitrile derivative **12a** in $CHCl_3$ or CH_2Cl_2 resulted no formation of the cyclic product, the starting material remain unchanged. Then azido-nitrile **12a** was heated at 140 °C in DMF for 8 h under reagent free condition to convert tetrazole-fused pyrazine **13a**.



Scheme 2. *Reagents and conditions*: (a) 4N HCl-EtOAc, 0 °C-rt, 3 h, 88%; (b) K_2CO_3, $BrCH_2CN$, MeCN, rt, 6 h, 88%; (c) K_2CO_3, BnBr, DMF, 80 °C, 6 h, 94%; (d) DMF, 140 °C, 8 h, 90%.

Simple purification by silica gel column chromatography afforded the product **13a** with excellent yield (90%). The structure of bicyclic tetrazole **13a** was established by NMR spectroscopy, mass spectroscopy and elemental analysis. The characteristic resonances observed at δ 149.7 and 56.9 ppm, respectively, were attributed to quarternary and methylene carbon adjacent to double bond. Resonances due to the rest of the carbons were appeared at their expected region. The product was also confirmed by the presence of peaks at *m/z* = 306 and 328 attributed to $[M+H]^+$ and $[M+Na]^+$ in its ESI-MS spectra.[17] Finally, single crystal X-ray crystallography analysis unambiguously confirmed the assigned structure (Figure 2).[18-20] It is noteworthy to mention here that **13a** was also obtained with almost similar yield when compound **11** was treated with K_2CO_3, benzyl bromide in DMF at 140 °C.

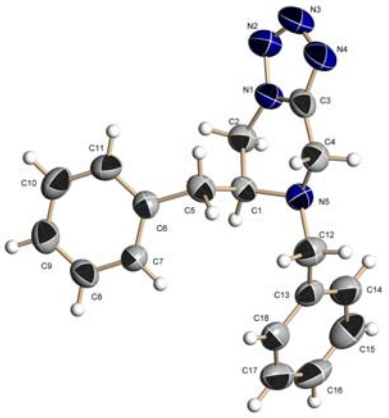
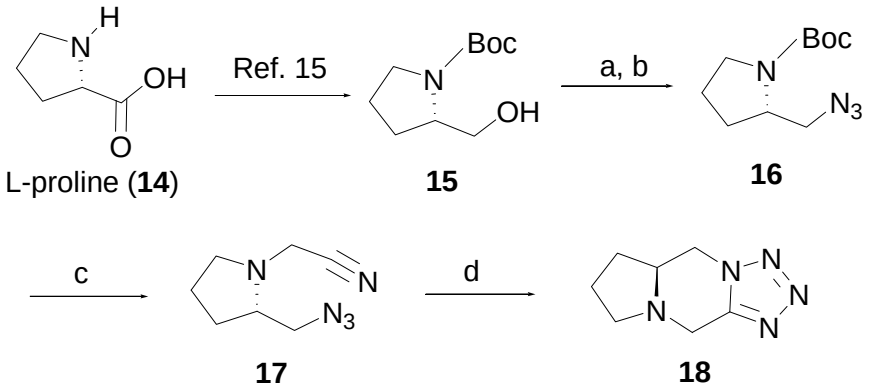


Figure 2. ORTEP diagram of compound **13a**

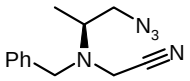
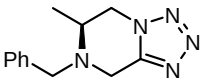
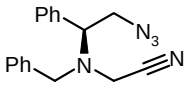
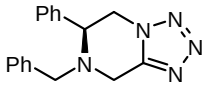
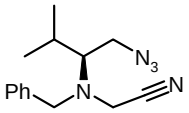
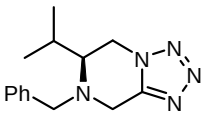
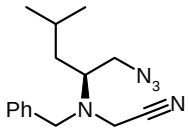
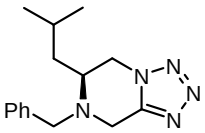
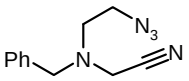
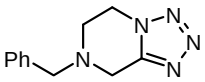
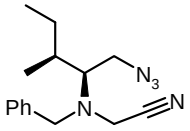
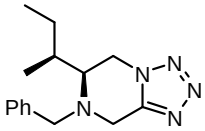
These results encouraged us to verify the feasibility of this cycloaddition reaction using the other benzyl protected azido-nitriles obtained from different natural amino acids under identical reaction conditions. As examplified in Table 1, the reaction proceeded smoothly to completion, and the corresponding tetrazole-fused 4,5,6,7-tetrahydropyrazine products were obtained in 8 to 12 h with excellent yield and high purity. All bicyclic tetrazole-fused products were fully characterized by NMR spectroscopy, mass spectra and elemental analysis.[21]

We then decided to extend this reaction condition to L-proline (**14**) in order to obtain tetrazole-fused tricyclic compound **18**. The azido-nitrile **17** obtained from L-proline (**14**) was heated in DMF at 140 °C to afford the corresponding tetrazole-fused 4,5,6,7-tetrahydropyrazine (**18**) in 88% yield (Scheme 3). The spectroscopic and analytical data established the structure.[21]



Scheme 3. *Reagents and conditions*: (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C-rt, 8 h, 88%; (b) NaN_3, DMF, 70 °C, 6 h, 94%; (c) (i) TFA, CH_2Cl_2, 0 °C-rt, 3 h; (ii) K_2CO_3, $BrCH_2CN$, MeCN, rt, 8 h, 85% (over two steps); (d) DMF, 140 °C, 8 h, 88%.

Table 1. Intramolecular 1,3-Dipolar cycloaddition reaction under catalyst free condition in DMF

S. No	Azido-nitriles (**12**)	Product (**13**)	Time (h)	Yield (%)
b			10	92
c			08	88
d			12	86
e			09	89
f			12	90
g			12	88

In conclusion, we have designed and synthesized a series of new chiral fused bicyclic and tricyclic tetrazole derivatives of biologically important starting from easily available α-amino acids and its derivatives. Structural resemblance of these new compounds with substances possessing important pharmacological properties suggests interesting bioactivity. This study is currently being performed on our synthesized compounds and the results will be presented in due course.

ACKNOWLEDGEMENT

PKM and RVG thank CSIR, New Delhi and NCL, Pune, for the financial assistance in the form of research fellowship. We are thankful to Dr. Ganesh Pandey, HOD, Organic Chemistry Division, for his constant support and encouragement. We thank also Dr. Mohan M. Bhadbhade, Dr. Rajesh G. Gonnade and Dr. P. R. Rajmohanan for the X-ray crystallographic assistance and NMR data, respectively.

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17. Compound **12a**: mp 102 ^{o}C; $[\alpha]^{25}_{D}$ –16.4 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 3369, 3027, 2928, 2102, 1601, 1454, 1273, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.80 (dd, 1H, *J* = 9.3, 13.1 Hz), 3.19 (dd, 1H, *J* = 5.3, 13.1 Hz), 3.25 (m, 1H), 3.46 (s, 2H), 3.60 (s, 2H), 3.99 (s, 2H), 7.20 (d, 2H, *J* = 7.3 Hz), 7.34 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 35.0, 38.3, 51.0, 54.6, 63.8, 116.7, 126.7, 127.9, 128.8, 129.1, 136.8, 138.1; ESI-MS: *m/z* = 306 $[M+H]^+$. Anal. Calcd (%) for $C_{18}H_{19}N_5$: C, 70.80; H, 6.27; N, 22.93. Found: C, 70.95; H, 6.12; N, 23.18. Compound **13a**: mp = 106-108 ^{o}C; $[\alpha]^{25}_{D}$ -6.3 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$): 3401, 2924, 1601, 1454, 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.52 (dd, 1H, *J* = 10.5, 13.4 Hz), 3.16 (dd, 1H, *J* = 4.6, 13.4 Hz), 3.55 (m, 1H), 3.87 (d, 1H, *J* = 13.0 Hz), 3.98 (d, 1H, *J* = 13.0 Hz), 4.10 (d, 1H, *J* = 16.0 Hz), 4.18-4.23 (m, 2H), 4.34 (dd, 1H, *J* = 3.3, 13.0 Hz), 7.09 (d, 2H, *J* = 7.3 Hz), 7.29-7.40 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.7, 43.6, 46.5, 56.7, 56.9, 126.9, 127.8, 128.5, 128.6, 128.8, 128.9, 136.7, 136.9, 149.7; ESI-MS *m/z* = 306 $[M+H]^+$, 328 $[M+Na]^+$. Anal. Calcd (%) for $C_{18}H_{19}N_5$: C, 70.80; H, 6.27; N, 22.93. Found: C, 71.03; H, 6.40; N, 22.67.
18. X-Ray intensity data was collected on Bruker SMART APEX CCD diffractometer with graphite-monochromatized (MoKα = 0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (ShelxTL)[22] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.
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20. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 705302 for **13a**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (1223) 336033; or e-mail: deposit@ccdc.cam.ac.uk].
21. Compound **13b**: $[\alpha]^{25}_{D}$ +4.6 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 3369, 2972, 1600, 1448, 1219 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.24 (d, 3H, *J* = 6.7 Hz), 3.37-3.45 (m, 1H), 3.69 (d, 1H, *J* = 13.0 Hz), 3.86 (d, 1H, *J* = 13.0 Hz), 3.95 (ABq, 2H, *J* = 16.7 Hz), 4.19 (dd, 1H, *J* = 5.0, 12.6 Hz), 4.44 (dd, 1H, *J* = 4.6, 12.6 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.4, 43.9, 50.3, 51.0, 56.8, 127.8,

128.7, 136.8, 149.8; ESI-MS *m/z* = 230 $[M+H]^+$, 252 $[M+Na]^+$. Anal. Calcd (%) for $C_{12}H_{15}N_5$: C, 62.86; H, 6.59; N, 30.54. Found: C, 62.91; H, 6.42; N, 30.78. Compound **13e**: $[\alpha]^{25}_D$ –6.0 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 3402, 2957, 1600, 1453, 1367, 1219, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, 6H, *J* = 7.0 Hz), 1.21-1.29 (m, 1H), 1.57-1.64 (m, 1H), 1.73-1.83 (m, 1H), 3.37 (m, 1H), 3.60 (d, 1H, *J* = 13.2 Hz), 3.82 (d, 1H, *J* = 13.2 Hz), 4.05 (ABq, 2H, *J* = 17.2 Hz), 4.26 (dd, 1H, *J* = 4.8, 12.9 Hz), 4.44 (dd, 1H, *J* = 4.8, 12.9 Hz), 7.28-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.5, 22.7, 24.9, 36.3, 43.5, 46.9, 53.4, 55.3, 127.9, 128.6, 128.7, 137.0, 149.6; ESI-MS *m/z* = 272 $[M+H]^+$, 294 $[M+Na]^+$. Anal. Calcd (%) for $C_{15}H_{21}N_5$: C, 66.39; H, 7.80; N, 25.81. Found: C, 66.18; H, 7.71; N, 25.96. Compound **17**: $[\alpha]^{25}_D$ -88.2 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): 3391, 2968, 2101, 1646, 1224, 1277, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.58-1.73 (m, 1H), 1.77-1.91 (m, 2H), 1.93-2.07 (m, 1H), 2.70 (ABq, 1H, *J* = 8.5 Hz), 2.84-2.96 (m, 1H), 3.01-3.11 (m, 1H), 3.22 (dd, 1H, *J* = 5.9, 12.5 Hz), 3.39 (dd, 1H, *J* = 4.6, 12.5 Hz), 3.76 (ABq, 2H, *J* = 17.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 22.8, 28.5, 40.8, 53.4, 54.0, 60.2, 115.1; ESI-MS *m/z* = 166 $[M+H]^+$, 188 $[M+Na]^+$. Anal. Calcd (%) for $C_7H_{11}N_5$: C, 50.89; H, 6.71; N, 42.39. Found: C, 51.15; H, 6.49; N, 42.50. Compound **18**: $[\alpha]^{25}_D$ +60.1 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): 2923, 1654, 1384, 1220, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.64-1.74 (m, 1H), 1.98-2.08 (m, 2H), 2.12-2.21 (m, 1H), 2.44 (q, 1H, *J* = 8.8 Hz), 2.73-2.81 (m, 1H), 3.29-3.34 (m, 1H), 3.56 (d, 1H, *J* = 15.7 Hz), 3.99 (t, 1H, *J* = 11.4 Hz), 4.52 (d, 1H, *J* = 15.5 Hz), 4.68 (dd, 1H, *J* = 3.9, 12.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8, 27.5, 47.3, 50.8, 53.5, 59.5, 151.2; ESI-MS *m/z* = 166 $[M+H]^+$, 188 $[M+Na]^+$. Anal. Calcd (%) for $C_7H_{11}N_5$: C, 50.89; H, 6.71; N, 42.39. Found: C, 50.74; H, 6.97; N, 42.42.