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SYNTHEIS OF UNUSUAL TRICYCLIC RING SYSTEMS OF BIOLOGICAL INTEREST

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Abstract – We describe a new synthesis of tricyclic scaffolds that incorporate a fusion of triazole with 1,4-benzodiazepine utilizing intramolecular "click" chemistry.

Heterocyclic chemistry has always been one of the most invaluable sources of novel compounds with diverse biological activity,: many heterocycles exhibit unique ability in a wide array of functions such as mimicking the structure of peptides and binding reversibly to proteins.[1] Among the drugs used during the last 40 years, for treatment of central nervous system (CNS) disorders, 1,4-benzodiazepines have occupied a prominent place.[2] Consequently, elegant and practical syntheses of these heterocyclic systems have been developed.[3] Benzodiazepines have been the first class of molecules recognized as privileged structures introduced by Evans *et al.*,[4] as a descriptor that mirrors the recognition that minor changes in the structures of benzodiazepine scaffold can produce a host of different biological activities and responses, which bind G-protein-coupled receptors[5] and in several drugs used for central nervous system diseases.[6] It has found applications for the synthesis of peptidomimetics,[7] peptide antagonists,[8] inhibitors of DNA interactions,[9] anti-viral or anti-malarial compounds[10] and many other potentially active molecules[11] are vivid examples of this phenomenon. Alprazolam (**1**) and Estazolam (**2**) are common anxiolytic agents and with demonstrated clinical and commercial success[12]; they belong to this family that possesses a 1,2,4-triazole ring fused to benzodiazepine (Figure 1).

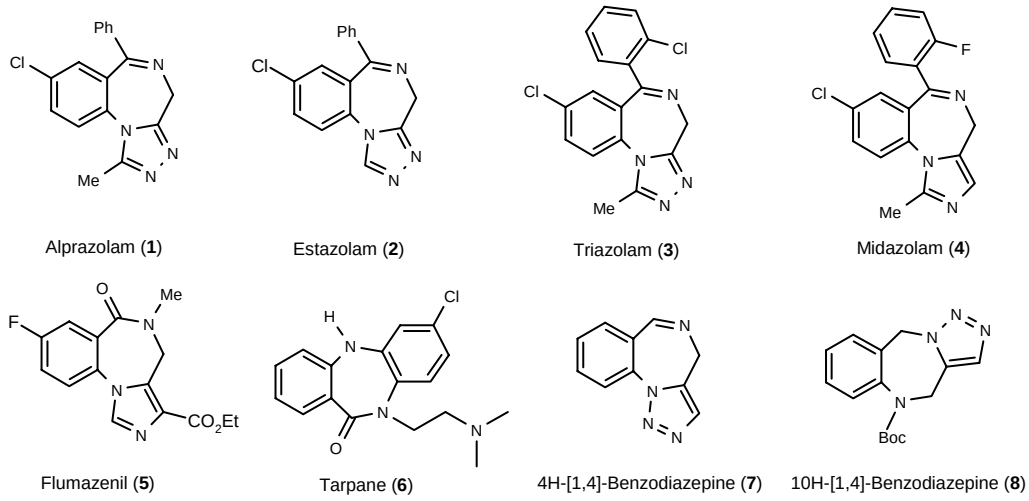
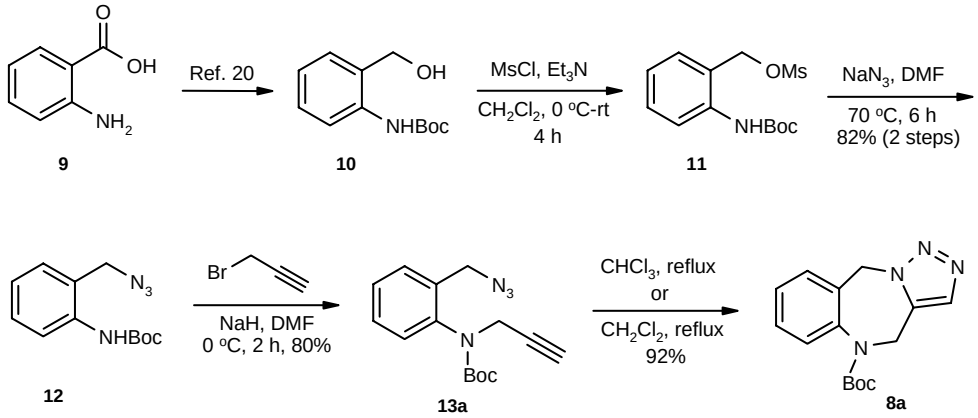


Figure 1. Some annulated benzodiazepine

Triazolam (**3**) and Midazolam (**4**), respectively, are more efficacious as anti-anxiety drugs,[13]; Flumazenil (**5**) belongs better to the class of anti-depressants and cognition enhancers.[14] Dibenzoannulated 1,4-benzodiazepines such as Tarpane (**6**) exhibit antihistaminic properties.[15] Recently, compound (**7**) was reported by Alajarín *et al.*,[16] utilizing a modular and flexible approach. We wished to explore of the effect of varying the position of the triazole ring to modulate the biological activities of the expected new compounds.

Recently, we exemplified an application of "click" chemistry to different azido-alkynes derived from α-amino acids, resulting in the synthesis of new chiral 4,5,6,7-tetrahydro[1,2,3]-triazolo[1,5-*a*]pyrazines.[17] Though, the first synthesis of this type of ring system was reported utilizing intermolecular 1,3-dipolar cycloaddition reaction leading to two isomeric triazoles which on separation by silica gel column chromatography and subsequent cyclization afforded the required triazole fused

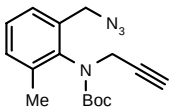
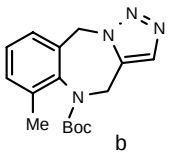
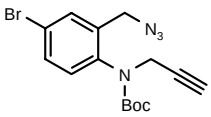
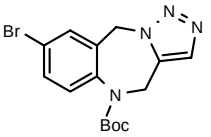
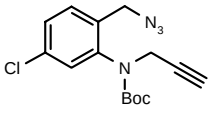
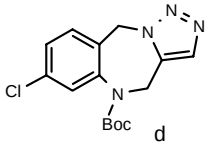
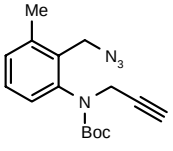
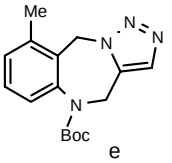
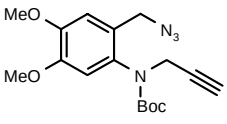
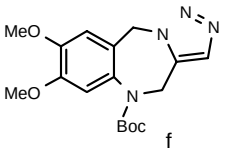
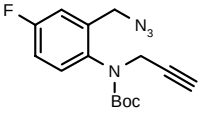
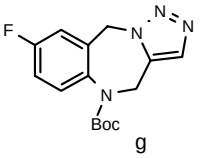


Scheme 1. Synthesis of triazole fused benzodiazepine

benzodiazepine analogue.[18] We report herein a synthesis of nitrogen-rich polycyclic hetero-systems starting from 2-aminobenzoic acid(s) and its derivatives utilizing intramolecular 1,3-dipolar cycloaddition as a pivotal reaction to obtain the single isomer.[19]

Initially, we directed our efforts to the synthesis of compound (**10**) from 2-aminobenzoic acid following standard literature procedure.[20] Activation of the benzylic hydroxyl group was achieved in good yield, by treatment of (**10**) with methanesulfonyl chloride in triethyl amine at ambient temperature. Subsequent introduction of azide group was achieved, in 82% yield over two steps, by S_N2 displacement of the corresponding mesylate with sodium azide in DMF at 70 ^oC (Scheme 1). The alkyne functionality was then introduced by treatment of **12** with NaH and propargyl bromide in DMF. The structure of **13a** was confirmed by ^1H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis. As per our previously reported optimized conditions for 1,3-dipolar cycloaddition reaction, heating the azido-alkyne derivative

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

Entry	Azido-alkynes (**13**)	Product (**8**)	Time (h)	Yield (%)
2	 b	 b	15	90
3	 c	 c	13	94
4	 d	 d	16	92
5	 e	 e	14	96
6	 f	 f	12	94
7	 g	 g	15	91

13a in $CHCl_3$ or CH_2Cl_2 resulted in complete consumption of starting material in 12 h. As expected, the pure cycloaddition product **8a** was obtained in 92% yield by simple evaporation of the solvent. At room temperature, the reaction took 5 days for complete conversion and proceeded with identical yield. The structure of tricyclic benzodiazepine was established by ^{1}H NMR, ^{13}C NMR, mass spectroscopy and elemental analysis.[21]

Encouraged by our result with compound **8a**, we extended our studies to other azido-alkynes obtained from the corresponding 2-aminobenzoic acid derivatives. As exemplified in Table 1, the reaction proceeded smoothly to completion, and the corresponding 1,2,3-triazole fused benzodiazepines were obtained in 12-16 h with excellent yields and high purity. Compound **8c** furnished a crystalline solid and its single crystal X-ray crystallography studies unambiguously confirmed the assigned structure.[22-24]

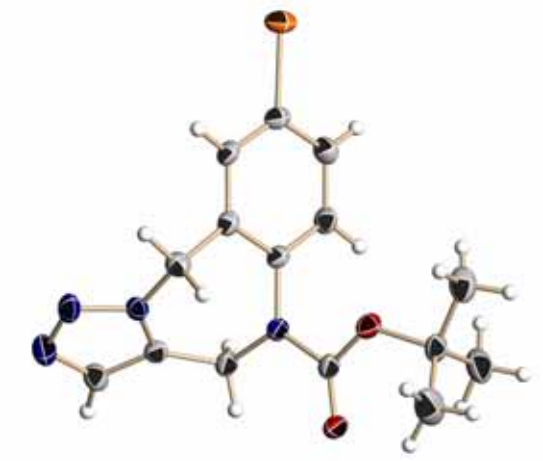


Figure 2. ORTEP diagram of **8c**

In conclusion, our present protocol allows the efficient synthesis of novel polycyclic hetero-systems, from commercially available 2-aminobenzoic acid derivatives, with excellent yield and high purity under mild reaction conditions. The method obviates product purification; evaporation of solvent is enough to provide the pure benzodiazepine products thereby rendering the process an ideal intramolecular "click" reaction. This, in turn, has set a stage for wider application of this powerful reaction for the synthesis of structurally diverse and novel poly-heterocyclic skeletons.

ACKNOWLEDGEMENT

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21. Analytical and Spectral Data
Compound **8a:** IR ($CHCl_3$): 3019, 1701, 1383, 1215 cm^{-1} ; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.41 (s, 9H), 5.02 (s, 2H), 5.54 (s, 2H), 7.29-7.48 (m, 5H) ; ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.1, 42.8, 51.5, 81.5, 128.2, 128.4, 129.2, 130.2, 131.3, 132.1, 132.7, 141.6, 153.7. Anal. Calcd (%) for $C_{15}H_{18}N_4O_2$: C 62.92; H 6.34; N 19.57. Found C 62.20; H 6.23; N 19.43.
Compound **8b:** IR ($CHCl_3$): 3386, 2980, 1703, 1383 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (s, 6.8H), 1.53 (s, 2.2H), 2.33 (s, 3H), 4.18 (d, .75H, *J* = 17.2 Hz), 4.28 (d, .25H, *J* = 17.2 Hz), 5.41 (d, .75H, *J* = 14.3 Hz), 5.46 (d, .25H, *J* = 14.3 Hz), 5.60-5.64 (m, 1.25H), 5.86 (d, .75H, *J* = 17.2 Hz), 7.23-7.35 (m, 3H), 7.48 (s, 1H). (Rotamers); ^{13}C NMR ($CDCl_3$,100 MHz): δ 17.3, 28.1, 41.8, 51.6, 81.2, 126.9, 128.3, 131.3, 131.7, 132.6, 132.7, 136.3, 139.8, 153.4. Anal. Calcd (%) for $C_{16}H_{20}N_4O_2$: C 63.98; H 6.71; N 18.65. Found C 63.74; H 6.98; N 18.32.
Compound **8c:** IR($CHCl_3$): 3017, 1704, 1488, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.41 (s, 9H), 5.00 (br s, 2H), 5.49 (s, 2H), 7.20 (d, 1H, *J* = 8.3 Hz), 7.55-7.57 (dd, 1H, *J* = 8.3, 2.2 Hz), 7.47(s, 1H), 7.62(d, 1H, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.2, 42.7, 50.9, 82.1, 121.8, 130.2, 131.4, 132.4, 132.5, 133.3, 134.1, 140.8, 153.4; Anal. Calcd (%) for $C_{15}H_{17}BrN_4O_2$: C 49.33; H 4.69; N 15.34. Found C 49.56; H 4.36; N 15.69.
Compound **8d:** IR ($CHCl_3$): 3361, 3019, 1704, 1215 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.41 (s, 9H), 5.00 (s, 2H), 5.49 (s, 2H), 7.29-7.42 (m, 3H), 7.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.0, 42.8, 50.8, 82.1, 128.4, 128.9, 130.2, 130.6, 131.3, 132.3, 135.3, 142.6, 153.2; Anal. Calcd (%) for $C_{15}H_{17}ClN_4O_2$: C 56.17; H 5.34; N 17.47. Found C 56.39; H 5.16; N 17.29.
22. 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)[23] 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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24. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 658332 for **8c**. 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].