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1-Isocyanomethylbenzotriazole and 2,2,4,4-tetramethylbutylisocyanide—cleavable isocyanides useful for the preparation of α-aminomethyl tetrazoles

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Dedicated to Professor Georg Olah on his 78th birthday

Abstract—1-Isocyanomethylbenzotriazole and 2,2,4,4-tetramethylbutylisocyanide smoothly undergo Ugi type reaction toward 1,5-disubstituted aminomethyl tetrazoles and can be subsequently cleaved under acidic conditions yielding substituted α-aminomethyl tetrazoles.

α-Aminomethyl tetrazoles are of general interest because they are isosteric to α-amino acids. Isosteric replacement of a functional group is of major interest in medicinal chemistry to alter unfavorable ADME properties and/or to access free patent space,[1,2] for example, carboxylic acid functional group replacement against five-substituted tetrazole in angiotensin-II receptor antagonists,[1] VLA-4 antagonists,[3] in hepatitis C NS3 protease inhibitors,[4] histone deacylase inhibitors,[5] negamycin derivatives,[6] AMPA antagonists,[7] 5-HT_3 receptor antagonists,[8] CRH antagonists,[9] or NK_1 receptor antagonists.[10] Moreover, α-aminomethyl tetrazoles have also been described as potent inhibitors of *Escherichia coli* isoleucine biosynthesis.[11] Tetrazole anions are considered to be 10 times more lipophilic as compared to the carboxylate while exhibiting similar acidity and planarity, thus potentially facilitating crossing of the blood–brain-barrier. At the same time, the tetrazolate is larger and its charge is more delocalized as compared to the carboxylate group. Moreover chiral α-aminomethyl tetrazoles are useful as catalysts for enantioselective aldol-type condensations.[12] A recent publication on a cleavable isocyanide useful to synthesize α-aminomethyl tetrazoles prompted us to report our preliminary results in this area.[13]

1-Isocyanomethylbenzotriazoles (BetMIC) are versatile and commercially available synthons for the synthesis of α-hydroxy aldehydes, 4-ethoxy-2-oxazolines, oxazoles,[14] formamidines,[15] imidazoles, pyrroles[16] and useful in isocyanide-based multi component reactions (IMCR).[17,18] During the search for novel cleavable isocyanides, we investigated BetMIC in the tetrazole variation of the U-4CR. In initial experiments we found that the reaction of BetMIC with an enamine and TMS-N_3 in methanol forming the expected tetrazole in good yields (Scheme 1). We hypothesized that the resulting diheterocyclic *N*,*N*-aminal should be a good candidate for acidic cleavage. Gratifyingly, we observed the almost quantitative and mild cleavage of the Ugi product to give the expected α-aminomethyl tetrazole (Scheme 1). The sequence can be performed under isolation of the intermediate Ugi tetrazole and subsequent acidic hydrolysis or in one-pot.[20] Although the yields are superior in the two stage process, we felt the one-pot process to be less labor intensive since it involves only one purification. In order to find out the scope and limitations we synthesized a small array of α-aminomethyl tetrazoles (Table 1). From the results it can be concluded that the combination of an Ugi tetrazole reaction employing BetMIC and a subsequent acidic hydrolysis is useful for the preparation of diverse α-aminomethyl tetrazoles.

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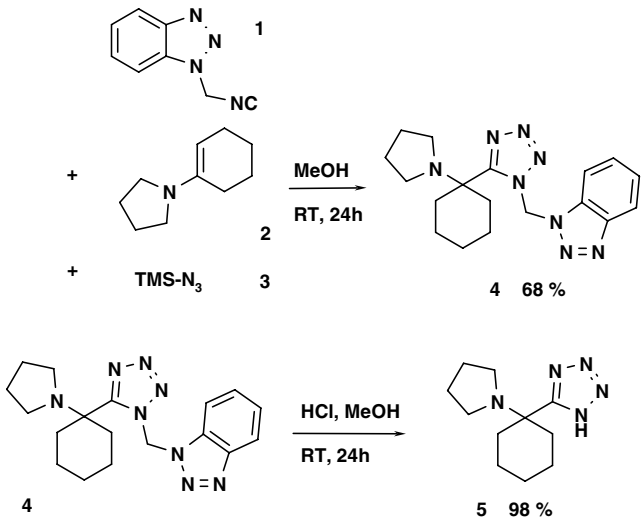
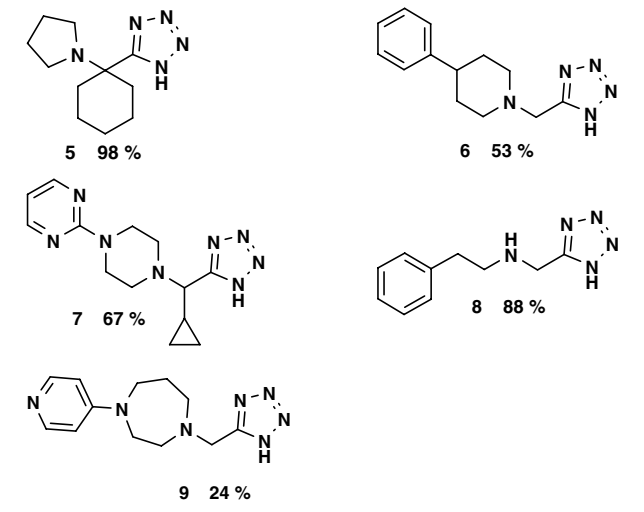
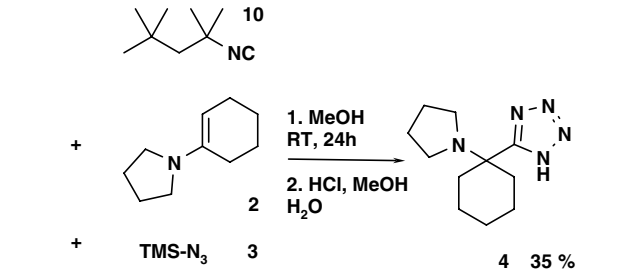


Scheme 1. U-4CR of BetMIC **1** and subsequent acid hydrolysis yielding α-aminomethyl tetrazole **5**.

Table 1. Different α-aminomethyl tetrazoles synthesized according to Scheme 1



Similarly we found that 2,2,4,4-tetramethylbutylisocyanide smoothly undergoes tetrazole formation according to Ugi and can be subsequently cleaved under acidic conditions yielding α-aminomethyl tetrazole, albeit in overall less yield (Scheme 2).



Scheme 2. U-4CR of 2,2,4,4-tertramethylbutylisocyanide **10** and subsequent acid hydrolysis yielding α-aminomethyl tetrazole **5**.

Whereas α-aminomethyl tetrazoles have been synthesized in the past mainly by a multistep sequence involving synthesis of a nitrile and its reaction with azide, the herein reported synthesis comprise a versatile alternative to diverse arrays of this important class of compounds.[19] The described isocyanides are useful and complementary alternatives (cleavable under acidic conditions) to the recently reported use of β-aminoacid derived isocyanides (cleavable under basic conditions) for the one-pot assembly of α-amino tetrazoles.[13] Advantageously the herein used isocyanides are commercially available. Moreover BetMIC comprise an odorless, easy to handle solid.

References and notes

1. Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379.
2. Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.
3. Venkatraman, S.; Lim, J.; Cramer, M.; Gardner, M. F.; James, J.; Alves, K.; Lingham, R. B.; Mumford, R. A.; Munoz, B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4053.
4. Johansson, A.; Poliakov, A.; Kerblom, A.; Wiklund, K.; Lindeberg, G.; Winiwarter, S.; Danielson, U. H.; Samuelsson, B.; Hallberg, A. *Bioorg. Med. Chem.* **2003**, *11*, 2551.
5. Suzuki, T.; Matsuura, A.; Kouketsu, A.; Hisakawa, S.; Nakagawa, H.; Miyata, N. *Bioorg. Med. Chem.* **2005**, *13*, 4332.
6. Raju, R. et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2413.
7. Jimonet, P. et al. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 127.
8. Campiani, G. et al. *J. Med. Chem.* **1999**, *42*, 4362.
9. Arvanitis, A. G. et al. *J. Med. Chem.* **1999**, *42*, 805.
10. Owens, A. P.; Harrison, T.; Moseley, J. D.; Swain, C. J.; Sadowski, S.; Cascieri, M. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 51; Ladduwahetty, T. et al. *J. Med. Chem.* **1996**, *39*, 2907.
11. Willshaw, G. A.; Tristam, H. *J. Bacteriol.* **1975**, *123*, 862.
12. Longbotton, A. J. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808; Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831.
13. Mayer, J.; Umkehrer, M.; Kalinski, C.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2005**, *46*, 7393.
14. Katritzky, A. R.; Chen, Y. X.; Yannakopoulou, K.; Lue, P. *Tetrahedron Lett.* **1989**, *30*, 6657.
15. Katritzky, A. R.; Sutharchanadevi, M.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1847.
16. Katritzky, A. R.; Alan, R.; Cheng, D.; Musgrave, R. P. *Heterocycles* **1997**, *44*, 67.
17. Sperka, T.; Pitlik, J.; Bagossi, P.; Toezser, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3086; Golebiowski, A.; Jozwik, J.; Klopfenstein, S. R.; Colson, A.-O.; Grieb, A. L.; Russell, A. F.; Rastogi, V. L.; Diven, C.; Portlock, D. E.; Chen, J. J. *J. Comb. Chem.* **2002**, *4*, 584; Saikachi, H.; Sasaki, H.; Kitagawa, T. *Chem. Pharm. Bull.* **1983**, *31*, 723.
18. Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
19. McManus, J. M.; Herbst, R. M. *J. Org. Chem.* **1959**, *24*, 1643.
20. Procedure for 1-[5-(1-pyrrolidin-1-yl-cyclohexyl)-tetrazole-1-ylmethyl]-1*H*-benzotriazole **4**: 5 M mol each of the three components 1-pyrrolidino-1-cyclohexene, BETMIC and TMS-N_3 are stirred in 5 ml dry methanol at 20 °C for 24 h. The solvent is evaporated and the residue is purified by silica gel chromatography (ethyl acetate, DCM) yielding 68% of the product **4**. ^{1}H NMR (400 MHz, $CDCl_3$): 1.07–1.22 (m, 1H), 1.23–1.40 (m, 2H), 1.51–1.61 (m, 3H), 1.61–1.82 (m, 4H), 2.41–2.5 (m, 2H), 2.60 (s, 4H), 7.41 (m, 1H), 7.50 (s, 2H, $-CH_2$), 7.61–7.70 (m, 1H), 8.03–8.07 (m,

2H). ^{13}C NMR (100 MHz, $CDCl_3$): 22.6 (CH_2), 23.7 (CH_2), 25.6 (CH_2), 30.7 (CH_2), 45.1 (CH_2), 57.6 (CH_2), 58.9 (C), 110.7 (CH_{ar}), 120.1 (CH_{ar}), 124.8 (CH_{ar}), 128.7 (CH_{ar}), 132.9 (C_{ar}), 146.1 (C_{ar}), 158.8 ($C_{tetrazole}$). MS: MH^+ ($C_{18}H_{24}N_8$): 353.3, MNa^+: 375.2. Procedure for 5-(1-pyrrolidin-1-yl-cyclohexyl)-1*H*-tetrazole **5**: 1 M mol of **4** are dissolved in 5 ml HCl in methanol and stirred at 40 °C for 4 h and 12 h at 20 °C. The solvent is evaporated and 5 ml of water is added. The aqueous phase is extracted several times with diethylether and the water is removed at the rotation evaporator under gentle heat, yielding the crude product **5**. The residue can be further purified on Sephadex. ^{1}H NMR (400 MHz, CD_3OD): 1.05–1.89 (m, 10H), 2.91–2.99 (m, 8H), 4.50 (br s, *NH*). ^{13}C NMR (100 MHz, CD_3OD): 23.8, 24.1, 25.6, 34.9, 65.8, 111.8. MS: MH^+ ($C_{11}H_{19}N_5$): 222.3.