Pergamon

Tetrahedron Letters 39 (1998) 3367–3370

TETRAHEDRON LETTERS

Synthesis of Tetrazole Analogs of α-Amino Acids by Alkylation of a Schiff Base of α-Aminomethyltetrazole

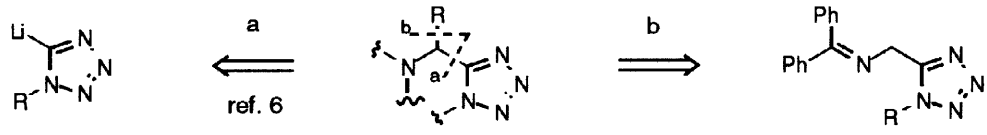
Yoshitaka Satoh,* Stéphane De Lombaert, Nicholas Marcopulos, John Moliterni, Michael Moskal, Jenny Tan, and Eli Wallace

Metabolic and Cardiovascular Diseases Research, Novartis Pharmaceuticals Corporation
556 Morris Avenue, Summit, NJ 07901, U.S.A.

Received 4 November 1997; revised 12 December 1997; accepted 25 February 1998

Abstract: A benzophenone imine of N-1 protected α-aminomethyltetrazoles was found to undergo alkylation with organic halides in good yields. Deprotection afforded tetrazole analogs of α-amino acids.

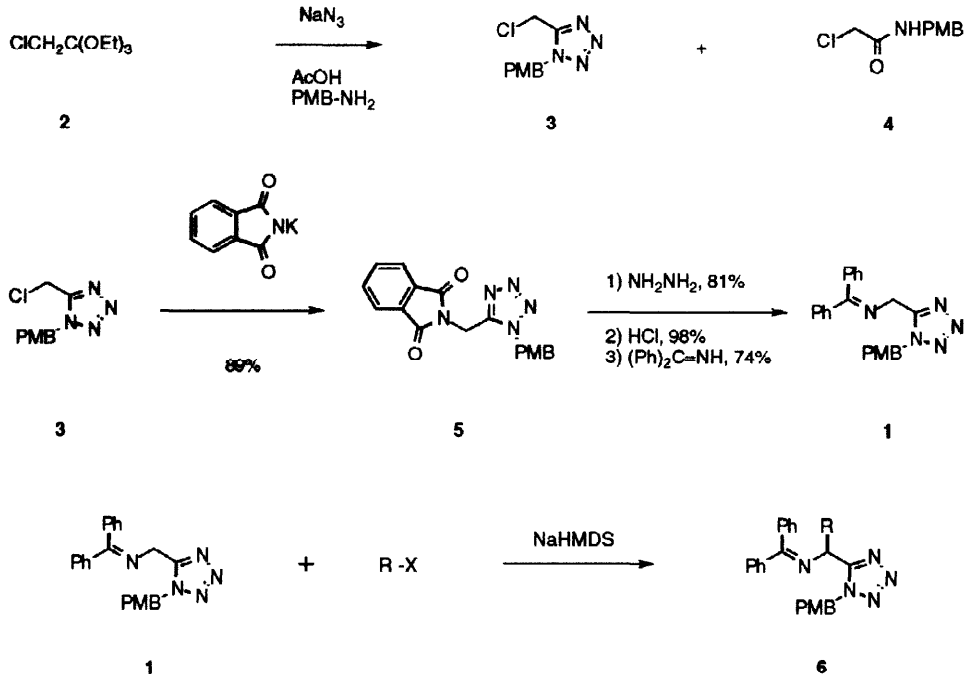
Synthesis of α-aminoalkyltetrazoles is becoming increasingly important in peptide and medicinal chemistry.[1] The cis-peptide bond can be successfully mimicked by replacing an amide group with the corresponding 1,5-disubstituted tetrazole.[2] Isosteric displacement of the C-terminus carboxylic acid with tetrazole often preserves or improves the biological activities of the parent peptides or their mimetic.[3] Since the majority of exiting methods[4,5] for the synthesis of 5–aminoalkyltetrazoles utilize α-amino acids or peptides as the starting materials, a more versatile method which allows preparation of a wide variety of such compounds from common intermediate(s) is highly desirable. We previously reported a facile reaction of suitably protected 5-lithiotetrazoles with aldehydes to give 5-(1-hydroxyalkyl)tetrazoles, which can be used as the precursors for α-aminotetrazoles (route a).[6] Herein, we wish to report an alternative approach to such compounds by alkylation of PMB (p-methoxybenzyl) protected tetrazole analogs of glycine (route b).[7]



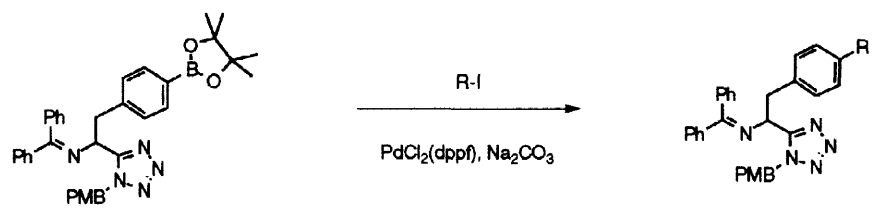
The requisite protected aminomethyltetrazole was prepared as follows. Condensation of p-methoxybenzylamine (PMB-NH_2) with 2-chloro-1,1,1-triethoxyethane (**2**) in the presence of sodium azide

0040-4039/98/$19.00
PII: S0040-4039(98)00492-4

[CAUTION][8] under the standard conditions (80 °C for 6 h in AcOH)[9] resulted in the formation of 1-*p*-methoxybenzyl-5-chloromethyltetrazole (**3**) in 50% yield. However, in contrast to the reaction with orthoformates, a substantial amount (~14%) of the corresponding amide (**4**)was also formed. This amide was extremely difficult to be separated from **3** by chromatographic means. Repeated crystallization from methanol gave pure **3** in 12% isolated yield. The amide **4** was likely to be produced by dealkylation of the imidate ester intermediate by a nucleophile in the reaction mixture. After considerable experimentation, it was found that the formation of **4** can be minimized by performing the reaction at lower temperature for longer period of time (40 °C for 16 h), thereby giving **3** in 68% yield.[10,11] This sample contained 4% of **4**, and used without further purification in the next step. Condensation of the chloride **3** with potassium phthalide (MeOH, reflux, 3 h) gave **5**[12] which, upon hydrazinolysis (EtOH, reflux, 16 h) and imine exchange (anhydrous HCl in MeOH, followed by $Ph_2C{=}NH$, CH_2Cl_2, 16 h) afforded **1** in 52% overall yield.[13]

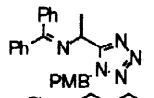
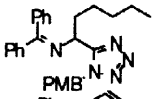
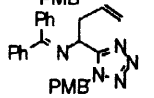
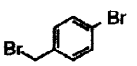
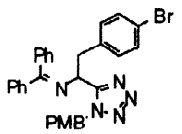
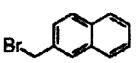
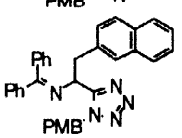
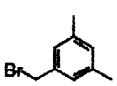
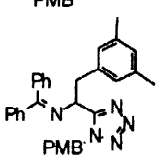
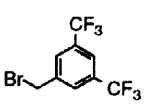
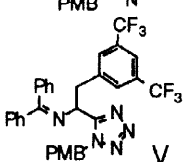
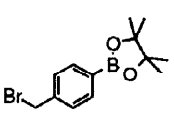
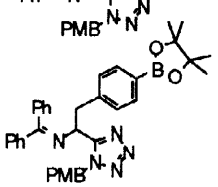


Alkylation of the Schiff base (**1**) was effected by treatment of an equimolar mixture of **1** and an alkyl halide in THF with one equivalent of NaHMDS (-78 °C to r.t.).[14,15] Table 1 shows a highly versatile nature of the current methodology which allows facile synthesis of monoalkylated product with alkyl, allyl and benzylic halides in good yields. The boron-containing alkylation product (**6h**) was found to be a good coupling partner in the Suzuki-Miyaura reaction.[16] For example, para-substituted phenylalanine tetrazole derivatives were obtained in good yields as shown below.



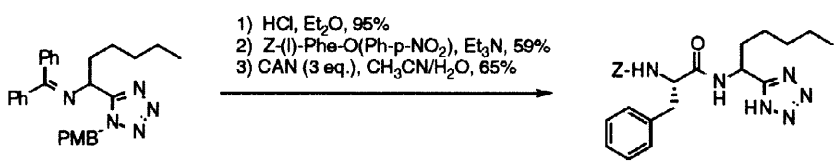
7a: R = p-F-Ph, 69%
7b: R = 2-thiophenyl, 91%
7c: R = 1-cyclohexenyl, 78%

Table 1. Alkylation of PMB Schiff Base (1)

Entry	R-X	Product, 6[a]	Yield, %[b]
a	CH_3-I		82
b			79
c			88
d			90
e			94
f			92
g			67
h			75

[a] The products reported here showed fully consistent spectral and analytical data. [b] Isolated yield.

A dipeptide C-terminal tetrazole (**8**) was prepared in order to demonstrate the usefulness of this methodology. Thus, hydrolysis of the benzophenone imine group of **6b** with hydrogen chloride in ether gave an aminoalkyltetrazole hydrochloride. Coupling with Z-(*l*)-phenylalanine and subsequent treatment with ceric ammonium nitrate afforded the corresponding free tetrazole (**8**).



6b **8**

Acknowledgment: We would like to thank Drs. J. L. Stanton and G. Ksander for helpful discussion and support.

References and Notes

(1) For recent review, see: Burger, A. *Prog. Drug Res.* **1991**, *37*, 287-371.

(2) (a) Beusen, D. D.; Zabrocki, J.; Slomczynska, U.; Head, R. D.; Kao, J. L. -F.; Marshall, G. R. *Biopolymers* **1995**, *36*, 181-200. (b) Boteju, L. W.; Zalewska, T.; Yamamura, H. I.; Hruby, V. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2011-6. (c) Boteju, L. W., Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 1757-60. (d) Zabrocki, J.; Dunbar, J. B., Jr.; Marshall, D. W.; Toth, M. V.; Marshall, G. R. *J. Org. Chem.* **1992**, *57*, 202-9. (e) Smith, G. D.; Zabrocki, J.; Flak, T. A.; Marshall, G. R. *Int. J. Peptide Protein Res.* **1991**, *37*, 191-7. (f) Lebl, M.; Slaninova, J.; Johnson, R. L. *Int. J. Peptide Protein Res.* **1989**, *33*, 16-21. (g) Valle, G.; Crisma, M.; Yu, K. -L.; Toniolo, C.; Mishra, R. K.; Johnson, R. L. *Coll. Czech. Chem. Commun.* **1988**, *53*, 2863-76. (h) Zabrocki, J.; Smith, G. D.; Dunbar, J. B., Jr.; Iijima, H.; Marshall, G. R. *J. Am. Chem. Soc.* **1988**, *110*, 5875-80. (i) Yu, K. -L.; Johnson, R. L. *J. Org. Chem.* **1987**, *52*, 1051-9.

(3) (a) Itoh, F.; Yukishige, K.; Wajima, M.; Ootsu, K.; Akimoto, H. *Chem. Pharm. Bull.* **1995**, *43*, 230-5. (b) Schoepp, D. D.; Lunn, W. H .W.; Salhoff, C. R.; McDonald, J. W. *Eur. J. Pharmacol.* **1994**, *270*, 67-72. (c) Lunn, W. H. W.; Schoepp, D. D.; Calligaro, D. O.; Vasileff, R. T.; Heinz, L. J.; Salhoff, C. R.; O'Malley, P. J. *J. Med. Chem.* **1992**, *35*, 4608-12. (d) Zabrocki, J. A.; Miyano, M.; Rao, S. N.; Panzer-Knodle, S.; Nicholson, N.; Feigen, L. *J. Med. Chem.* **1992**, *35*, 4914-7. (e) Schepp, D. D.; Smith, C. L.; Lodge, D.; Millar, J. D.; Leander, J. D.; Sacaan, A. I.; Lunn, W. H. W. *J. Pharmacol.* **1991**, *203*, 237-43. (f) Bartlett, P. A.; Acher, F. *Bull. Soc. Chim. Fr.* **1986**, 771-5. (g) Smissman, E. E.; Terada, A.; El-Antably, S. *J. Med. Chem.* **1976**, *19*, 165-7.

(4) For review, see: Butler, R. N. Comprehensive Heterocyclic Chemistry II; Storr, R. C. Ed.; Elsevier: Oxford, 1996, Vol. 4, pp 905-1006.

(5) (a) Darling, C. M. *J. Pharm. Sci.* **1982**, *71*, 356-8. (b) Grzonka, Z.; Gwizdala, E.; Kofluk, T. *Pol J. Chem.* **1978**, *52*, 1411-7. (c) McNeil, H. R.; Williams, B. B.; Darling, C. M. *J. Pharm. Sci.* **1977**, *66*, 1642-4. (d) Grzonka, Z. *Rocz. Chem.* **1973**, *47*, 1401-6.

(6) Satoh, Y.; Marcopulos, N. *Tetrahedron Lett.* **1995**, *36*, 1759-62.

(7) For similar alkylation reactions of stabilized Schiff bases, see: O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507-18, and references cited therein.

(8) All operations involving sodium azide should be performed in a well-ventilated hood behind a blast shield.

(9) The original literature procedure called for much more drastic conditions, i.e., reaction in refluxing acetic acid for several hours. See: (a) Kamiya, T., Saito, Y. *US Patent 3,767,667*, **1973**. (b) Litkei, G.; Patonay, T.; Patonay-Peli, E.; Khilya, V. P. *Pharmazie* **1989**, *44*, 791-2.

(10) **3**: mp 62-63 °C. ^{1}H NMR (300 MHz, δ, $CDCl_3$) 3.82 (s, 3 H), 4.61 (s, 2 H), 5.62 (s, 2 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 7.27 (d, *J* = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75.47 MHz, δ, $CDCl_3$) 160.32, 150.86, 129.50, 124.23, 114.74, 55.39, 51.40, 31.47 ppm. IR (KBr) 1614, 1583, 1514, 1258, 1032, 781 cm^{-1}. MS (DCI/CH_4) 239 (M+1). Anal. Calcd for $C_{10}H_{11}ClN_4O$: C, 50.32; H, 4.64; N, 23.47. Found: C, 50.64; H, 4.61; N, 23.53.

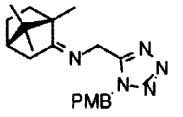
(11) This seems to be a general phenomenon for the reaction with ortho esters other than orthoformates. Details will be reported elsewhere.

(12) **5**: mp 88-89 °C. ^{1}H NMR (300 MHz, δ, $CDCl_3$) 3.74 (s, 3 H), 4.98 (s, 2 H), 5.69 (s, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.74 (m, 2 H), 7.83 (m, 2 H) ppm. IR (KBr) 1775, 1721, 1609, 1249, 1024, 1586, 1518, 788, 718 cm^{-1}. MS (DCI/CH_4) 350 (M+1). Anal. Calcd for $C_{18}H_{15}N_5O_3$: C, 61.88; H, 4.32; N, 20.04. Found: C, 61.73; H, 4.20; N, 19.72.

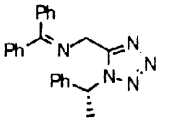
(13) **1**: mp 86-87 °C. ^{1}H NMR (300 MHz, δ, $CDCl_3$) 3.79 (s, 3 H), 4.62 (s, 2 H), 5.81 (s, 2 H), 6.84 (d, d, *J* = 8.7 Hz, 2 H), 7.14 (m, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.4-7.55 (m, 4 H), 7.60 (d, *J* = 7.2 Hz, 2 H) ppm. IR (KBr) 1620, 1514, 1253, 1027, 775, 698 cm^{-1}. MS (DCI/CH_4) 384 (M+1). Anal. Calcd for $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.27. Found: C, 71.97; H, 5.49; N, 18.15.

(14) **Typical Procedure for Alkylation of 1:** To a stirred solution of **1** (238 mg, 0.74 mmol) and methyl iodide (105 mg, 0.74 mmol) in 3 mL of THF was added NaHMDS (0.74 mL, 1.0M in THF, 0.74 mmol) dropwise at -78 °C. After stirring for 15 min at -78°C, the mixture was allowed to reach room temperature over 1 h. Water was added and the mixture was extracted with ethyl acetate (x3). The organic layer was dried and evaporated and the residue was chromatographed on silica gel (40% EtOAc/hexane) to give 244 mg of **6a** as colorless solids: mp 114-115 °C. ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.42 (d, *J* = 6.8 Hz, 3 H), 3.77 (s, 3 H), 5.14 (q, *J* = 6.8 Hz, 1 H), 5.71 (d, *J* = 15.0 Hz, 1 H), 5.90 (d, *J* = 15.0 Hz, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 6.99 (m, 2 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 7.34 (t, *J* = 7.9 Hz, 2 H), 7.4 - 7.5 (m, 4 H), 7.58 (d, *J* = 7.1 Hz, 2 H) ppm. IR (KBr) 1612, 1514, 1255, 1028, 785, 698 cm^{-1}. MS (ES+) 398 (M+1). Anal. Calcd for $C_{24}H_{23}N_5O$: C, 72.52; H, 5.83; N, 17.62. Found: C, 72.46; H, 6.04; N, 17.51.

(15) In an attempt towards asymmetric synthesis of aminoalkyltetrazoles, the following chiral Schiff bases (**9**, **10**) were prepared and subjected to alkylation with benzyl bromide. Under a variety of conditions, however, the disatereoselectivity failed to exceed ~ 60%. Compound **9** was prepared in a similar manner reported for the carboxylate esters (McIntosh, J. M.; Mishra, P. *Can. J. Chem.* **1985**, *64*, 726-31). Further efforts in this area will be reported in due course.



9



10

(16) For a similar reaction of *p*-boronophenylalanine derivatives, see: Satoh, Y.; Gude, C.; Chan, K.; Firooznia, F. *Tetrahedron Lett.* in press.