Pergamon

Tetrahedron Letters 40 (1999) 2907–2908

TETRAHEDRON LETTERS

Application of the Intramolecular Azomethine Imine Cycloaddition to the Construction of a Novel, Orthogonally Protected Spirodiamino Acid Scaffold

Roland E. Dolle,*,† Michael C. Barden,†,[1a] Paul E. Brennan,†,[1b] Gulzar Ahmed,† Vinh Tran,† and Douglas M. Ho‡

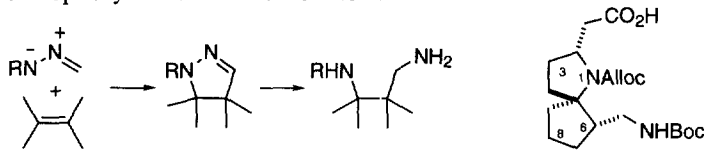
†Pharmacopeia Inc., CN 5350, Princeton, NJ 08543-5350 and the ‡Department of Chemistry, Princeton University, Princeton, NJ 08544

Received 18 January 1999; accepted 8 February 1999

Abstract: Hydrazone **4** undergoes tandem intramolecular Michael addition - intramolecular azomethine imine cycloaddition in ethanol at reflux to furnish the tricyclic pyrazoline methyl ester **3** in 75% yield. A five-step conversion of **3** to N[1]-Alloc-6-(N-Boc-aminomethyl)-1-azaspiro[4.4]nonane-2-acetic acid **1** provides access to a unique tri-functionalized scaffold for combinatorial chemistry.

Key words: Azomethine imine, intramolecular dipolar cycloaddition, combinatorial chemistry

The design and synthesis of novel scaffolds for combinatorial chemical applications is paramount to the identification of new biologically active agents.[2] One successful approach relies on the pre-construction of orthogonally protected multi-functionalized scaffolds in solution followed by their immobilization and dervatization on solid support.[2] The azomethine imine 1,3-dipolar cycloaddition reaction[3] and subsequent N-N bond cleavage (**i** → **iii**) was thought to represent a potential route to the preparation of low molecular weight scaffolds containing 1,3-diamines. Although first described in 1960 by Huisgen[3b] and later by Oppolzer,[3c] the use of azomethine imines in synthesis is quite limited, in contrast to the extensively used nitrone, nitrile oxide, and azomethine dipoles.[4] Azomethine imines have been employed in the total synthesis of saxitoxin,[3d] the asymmetric synthesis of *C*-nucleoside analogs,[3e] and most recently, in the preparation of functionalized cyclopentanoids.[3f] To date, this dipole has not been investigated in scaffold design. Because of our interest in creating libraries possessing conformationally defined structural motifs, the intramolecular azomethine imine cycloaddition was utilized to prepare N[1]-Alloc-6-(N-Boc-aminomethyl)-1-azaspiro[4.4]nonane-2-acetic acid **1**, a differentially protected spirocyclic diamino acid scaffold.



i **ii** **iii** **1**

A solution of keto-ester **2**[5] and *t*-butylcarbazate ($BocNHNH_2$) in xylene was heated at reflux (140 °C) for 8 h to provide the unique tricyclic pyrazoline **3** (oil; R_f = 0.25, 4:1 hexane-ethyl acetate) in 25% yield as a single diastereomer (Scheme).[6] The reaction presumably proceeds via the initial formation of hydrazone **4** which undergoes tandem intramolecular Michael addition, generating azomethine imine **5**, and intramolecular cycloaddition to yield **3**.[5] A three-fold increase in the reaction yield was achieved by refluxing a solution of purified **4** (prepared by the reaction of 1.05 equiv $BocNHNH_2$ and **2** in diethyl ether, 1 h, 25 °C; mp 103-105 °C) in absolute ethanol for 72 h (**4** → **3**; 75% yield). Saponification of **3** provided the crystalline acid **6** (mp 111-112 °C, acetone) from which an X-ray crystallographic analysis was obtained, securing the relative stereochemical assignment as indicated (ORTEP drawing, Scheme).

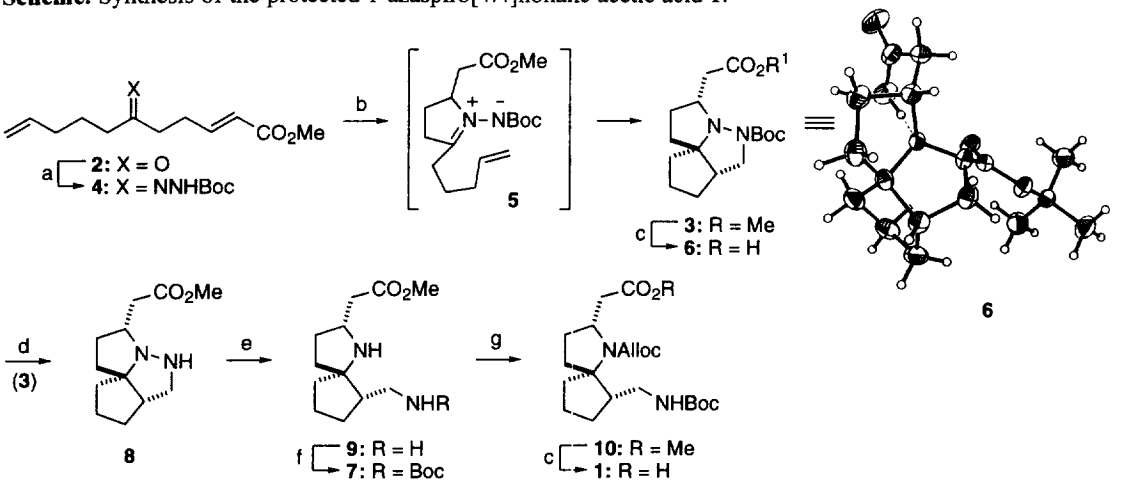
Numerous methods are available for the reductive cleavage of the N-N bond and these methods have been reviewed by Mellor.[7] All attempts to effect the direct reduction of **3** to provide the corresponding mono-Boc protected diamine **7** failed. It was found necessary to first remove the Boc protecting group in **3** to permit N-N

PII: S0040-4039(99)00391-3

bond cleavage. Thus, treatment of **3** with trifluoroacetic acid (25% TFA in CH_2Cl_2 (v/v) 1 h, 25 °C) followed by hydrogenation using platinum oxide in 1.0 M HCl in methanol under 80 psi H_2 for 12 h (**3** → **8** → **9**) furnished diamine **9**. Without purification, selective protection of the primary amino group in **9** with Boc anhydride was readily performed, providing 6-(N-Boc-aminomethyl)-1-azaspiro[4.4]nonane acetic acid methyl ester **7** in 87% overall yield for the three steps. Introduction of the Alloc protecting group onto the secondary amine N(1) (**7**→ **10**; 77% yield) and ester hydrolysis (**10** → **1**; 85% yield) using standard reaction conditions, furnished the orthogonally protected spirodiamino acid **1**[6] in *ca.* 30% overall yield from **3**.

The suitability of **1** as a scaffold for combinatorial synthesis has been established, and the preparation of an encoded library[8] exploiting its unique molecular architecture will be reported elsewhere. Further application of azomethine imine dipoles in novel scaffold design are envisaged.

Scheme. Synthesis of the protected 1-azaspiro[4.4]nonane acetic acid **1**.[a]



[a]Reagents and conditions: (a) 1.05 equiv $BocNHNH_2$, 12 h, 25 °C (100%); (b) absolute EtOH, reflux, 72 h (75%); (c) 1 M aq NaOH in MeOH, 12 h, 25 °C (80%); (d) 25% trifluoroacetic acid in CH_2Cl_2 (v/v), 1 h, 25 °C; (e) PtO_2, 1 M HCl in MeOH, 80 psi H_2, 12 h, 25 °C; (f) 1.2 equiv Boc anhydride, CH_2Cl_2, 12 h, 25 °C (**3** → **7**; 87% overall); (g) 2 equiv allyl chloroformate, 4 equiv *i*-Pr_2EtN, CH_2Cl_2, 12 h, 25 °C (77%).

REFERENCES AND NOTES

[1.] (a) Current address: SIDDCO, Tucson, AZ 85747 (b) Pharmacopeia summer intern, 1998. Current address: Department of Chemistry, University of California, Berkeley, CA 94720-1460.

[2.] (a) Dolle, R. E. *Mol. Diversity* **1998**, *3*, 199. (b) Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

[3.] (a) Grashey, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984; Vol. 1, p 733. (b) Huisgen, R.; Fleischmann, R.; Eckell, A. *Tetrahedron Lett.* **1960**, 1. (c) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10. (d) Jacobi, P. A.; Martinelli, M. J.; Polanc, S. *J. Org. Chem.* **1984**, *106*, 5594. (e) Zlicar, M.; Stanovnik, B.; Tisler, M. *J. Heterocycl. Chem.* **1993**, *30*, 1209. (f) Gallos, J. K.; Koumbis, A. E.; Apostolakis, N. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2457.

[4.] (a) Little, R. D. In *Comprehensive Organic Synthesis*; Troast, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 239. (c) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

[5.] Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399.

[6.] All new compounds gave satisfactory physical and spectrometric properties consistent with their structure. For **1**: ^1H NMR ($CDCl_3$) δ 5.93 (m, 1H), 5.26 (m, 2H), 4.76 (broad s, 1H), 4.55 (m, 2H), 4.33 (broad s, 1H), 3.33 (broad s, 1H), 3.08 (m, 1H), 2.92 (m, 2H), 2.33 (m, 1H), 2.13 (m, 1H), 1.89 (m, 6H), 1.70 (m, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 176.06, 154.37, 132.83, 117.35, 79.13, 72.27, 65.39, 56.01, 50.79, 42.55, 42.08, 38.74, 37.65, 31.27, 28.24, 27.53, 24.08; MS (ES+) *m/z*: 397 $(M+H)^+$.

[7.] Mellor, J. M.; Smith, N. M. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2927.

[8.] (a) Carroll, C. D.; Patel, H.; Johnson, T. O.; Guo, T.; Orlowski, M.; He, Z.-M.; Cavallaro, C. L.; Guo, J.; Oksman, A.; Gluzman, I. Y.; Connelly, J.; Chelsky, D.; Goldberg, D. E.; Dolle, R. E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2315. (b) Carroll, C. D.; Johnson, T. O.; Tao, S.; Lauri, G.; Orlowski, M.; Gluzman, I. Y.; Goldberg, D. E.; Dolle, R. E. *ibid.*, 3203. (c) Baldwin, J. J.; Burbaum, J. J.; Henderson, I.; Ohlmeyer, M. H. *J. Am. Chem. Soc.* **1995**, *117*, 5588.