Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 9039–9042
Tetrahedron Letters

Synthesis of arylglycines via the Dötz benzannulation reaction

Shon R. Pulley,[†] Barbara Czakó* and Gregory D. Brown

Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA

Received 27 August 2005; revised 20 October 2005; accepted 20 October 2005
Available online 8 November 2005

Abstract—Arylglycines are biologically active α-amino acids. Our approach toward the synthesis of arylglycines features the Dötz benzannulation reaction between a variety of Fischer chromium carbene complexes **3** and alkyne **4**. This leads to the formation of protected arylglycinols **5**, which can be transformed to the corresponding N-protected arylglycines.

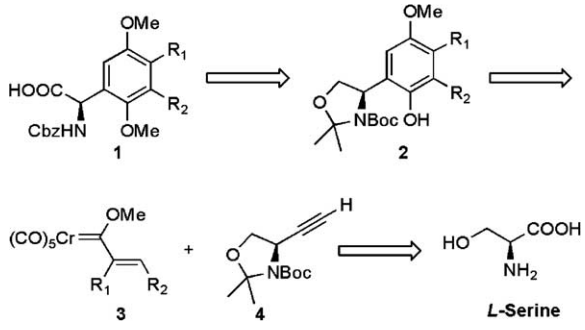
Arylglycines are an important class of nonproteinogenic amino acids.[1] They have been found to be potential agonists and antagonists at the glutamate receptor of the central nervous system.[2,3] The arylglycine moiety also occurs in several biologically active natural products. Representative examples are the glycopeptide antibiotics, such as vancomycin,[4] ristocetin,[5] and teicoplanin.[6] Several members of the monocyclic β-lactam antibiotics, known as nocardicins, also have the arylglycine moiety.[7,8] In addition to the naturally occurring arylglycines, there are synthetic arylglycine containing compounds; for example, synthetic D-arylglycines can be found in the side chain of penicillins and cephalosporins.[9]

Due to the importance of the arylglycine structural feature, several approaches were developed for their synthesis.[10] The most important methods include the asymmetric Strecker synthesis,[11] asymmetric alkylation of electrophilic glycinates,[12] asymmetric alkylation of nucleophilic glycinates,[13] asymmetric electrophilic amination of enolates,[14] asymmetric nucleophilic amination of α-substituted acids,[15] and asymmetric aminohydroxylation.[16]

All the known approaches for the synthesis of arylglycines start out from an aromatic compound, which is modified in the desired way to form the amino acid sidechain. We have developed a novel strategy, where we construct the aromatic portion of the molecules utilizing the Dötz benzannulation reaction[17] between a variety Fischer chromium carbene complexes **3a–e** and alkyne **4**, which provides mild reaction conditions (Scheme 1). The resulting protected arylglycinols **2a–e** can be converted to arylglycines by protecting group manipulation followed by oxidation.

The α,β-unsaturated Fischer chromium carbene complexes **3a–e** used in the benzannulation were prepared by modified literature procedures.[18] Alkyne **4** was synthesized from L-serine via *Garner's* aldehyde.[19]

The key Dötz benzannulation reaction between Fischer chromium carbenes **3a–e** and alkyne **4** was carried out under both thermal and ultrasonic conditions (Table 1).[20] While the thermal reaction gave moderate yields,

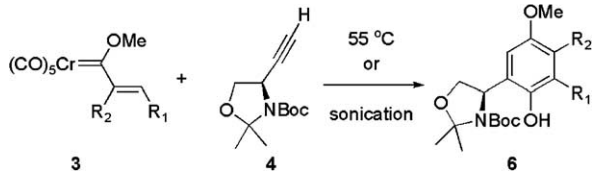


Scheme 1. Synthetic strategy.

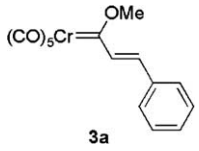
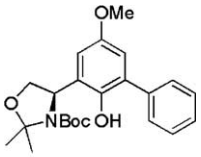
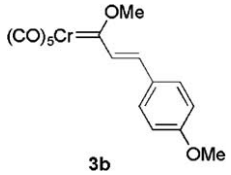
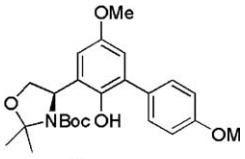
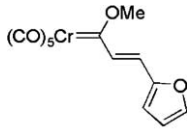
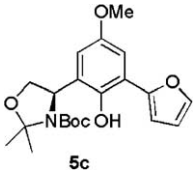
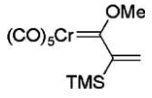
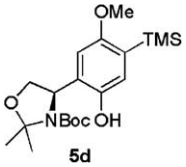
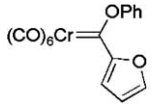
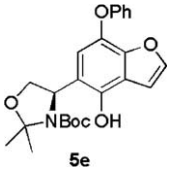
Keywords: Dotz benzannulation; Arylglycine.
* Corresponding author at present address: Roy and Diana Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA. Tel.: +1 2155 734919; fax: +1 2155 737165; e-mail: barbarac@sas.upenn.edu
† Eli Lilly and Company, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, USA. Tel.: +1 317 433 6079.

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.10.105

Table 1. Key step: The Dötz benzannulation reaction



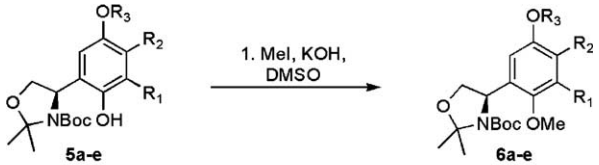
3 4 6

α,β-Unsaturated chromium carbene complexes	Product	Thermal/ultrasonic %	
 3a	 5a	65	87
 3b	 5b	51	66
 3c	 5c	69	85
 3d	 5d	67	83
 3e	 5e	53	59

the ultrasonic conditions afforded the formation of the protected arylglycinols in good to excellent yields.

Subsequent protection of the hydroxyl group with MeI/KOH in DMSO led to compounds **6a**–**e** (Scheme 2).

Selective deprotection of the aminohydroxyl moiety leading to the Boc-protected arylglycinols could not be achieved. Under standard conditions, we obtained a mixture of the partially and fully deprotected arylglycinols. To avoid this problem, we decided to fully deprotect the arylglycinol derivatives using *p*-toluenesulfonic acid or trifluoroacetic acid.

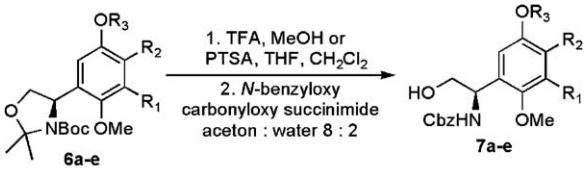


5a-e 6a-e

6a R_1 = Ph	R_2 = H	R_3 = Me	85%
6b R_1 = pOMePh	R_2 = H	R_3 = Me	76%
6c R_1 = 2-furyl	R_2 = H	R_3 = Me	73%
6d R_1 = H	R_2 = TMS	R_3 = Me	74%
6e R_1 = R_2 =		R_3 = Ph	73%

Scheme 2. Protection of the benzannulation product.

It is known in the literature that the benzyloxycarbonyl (Cbz) group is often more favorable for the protection of amines than the Boc group under oxidation conditions due to its higher stability.[21]



7a R_1 = Ph	R_2 = H	R_3 = Me	75%
7b R_1 = pOMePh	R_2 = H	R_3 = Me	72%
7c R_1 = 2-furyl	R_2 = H	R_3 = Me	72%
7d R_1 = H	R_2 = TMS	R_3 = Me	72%
7e R_1 = R_2 =		R_3 = Ph	75%

Scheme 3. Formation of N-protected arylglycinols.

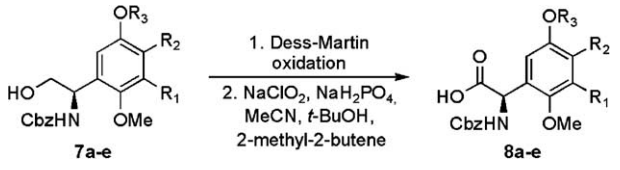
For this reason, we decided to form the Cbz-protected arylglycinols. This was accomplished by reacting the free amines with benzyloxycarbonyloxy succinimide to form compounds **7a**–**e** (Scheme 3).

Oxidation of arylglycinols to the corresponding arylglycines is known to be problematic due to the sensitivity of the structure. Indeed, we found this transformation very challenging.

During the course of our studies, we have surveyed a wide array of oxidation methods. Metal mediated oxidations such as CrO_3/H_5IO_6,[22] $RuCl_3$, H_2O/HIO_4,[23] and TPAP, NMO[24] led to complete decomposition of the starting arylglycinols, most probably due to the oxidation of the electron rich aromatic ring. We have tried several variants of the TEMPO oxidation,[25] but TEMPO proved to be a capricious oxidant, which was not reliable and the results were not reproducible. Swern oxidation also led to the decomposition of the starting material.[26]

For solving the oxidation problem, eventually we decided to test a two-step sequence, applying Dess–Martin oxidation[27] for the formation of aldehyde followed by sodium chlorite oxidation.[28] This method proved to be viable and provided the desired *N*-Cbz-protected arylglycines **8a**–**e** with good yields (Scheme 4).[29]

In summary, we have developed a novel strategy for the synthesis of arylglycines, where we constructed the aromatic skeleton via the Dötz benzannulation reaction. Oxidation of the arylglycinol moiety was problematic, but it could be achieved by Dess Martin oxidation followed by sodium chlorite oxidation. The above method



8a R_1 = Ph	R_2 = H	R_3 = Me	66%
8b R_1 = pOMePh	R_2 = H	R_3 = Me	70%
8c R_1 = 2-furyl	R_2 = H	R_3 = Me	66%
8d R_1 = H	R_2 = TMS	R_3 = Me	59%
8e R_1 = R_2 =		R_3 = Ph	67%

Scheme 4. Synthesis of N-protected arylglycines.

provides a convenient and mild approach for the synthesis of electron rich arylglycine derivatives.

Acknowledgement

Financial support from the National Institutes of Health and the University of Missouri-Columbia is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.105.

References and notes

1. Williams, R. W.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
2. Watkins, J.; Collingridge, G. *Trends Pharm. Sci.* **1994**, *15*, 333.
3. Bedingfield, J. S.; Kemp, M. C.; Jane, D. E.; Tse, H. W.; Roberts, P. J.; Watkins, J. *Br. J. Pharmacol.* **1995**, *116*, 3323.
4. McCormic, M. H.; Stark, W. M.; Pittenger, G. F.; Pittenger, R. C.; McGuire, G. M. *Antibiot. Annu.* **1955–1956**, *9*, 606.
5. Harris, C. M.; Kibby, J. J.; Fehlner, J. R.; Raabe, H. B.; Barber, T. A.; Harrus, T. M. *J. Am. Chem Soc.* **1979**, *101*, 437.
6. Coronelly, C.; Bardone, M. R.; DePaoli, A.; Ferrari, P.; Tuan, G.; Gallo, G. G. *J. Antibiot.* **1984**, *37*, 621.
7. Townsand, C. A.; Brown, A. M. *J. Am. Chem. Soc.* **1983**, *105*, 913.
8. Kamiya, T.; Hashimoto, M.; Nakaguchi, O.; Oku, T. *Tetrahedron* **1979**, *35*, 323.
9. Meijer, E. M.; Boesten, W. H. J.; Shoemaker, H. E.; Balken, J. A. M. *Studies in Organic Chemistry*; Elsevier: Amsterdam, 1985.
10. Williams, R. W.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.
11. (a) Weinges, K.; Brune, G.; Droste, H. *Liebigs Ann. Chem.* **1980**, *2*, 212; (b) Weinges, K.; Koltz, K. P.; Droste, H. *Chem. Ber.* **1980**, *113*, 722; (c) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H.; Nixdorf, M.; Irngartinger, H. *Liebigs Ann. Chem.* **1985**, *3*, 566.
12. Schollkopf, U.; Guttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem., Int. Ed.* **1987**, *26*, 683.
13. Harwig, W.; Schollkopf, U. *Liebigs Ann. Chem.* **1982**, *11*, 1952.
14. (a) Oppoltzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991; (b) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452.
15. (a) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123; (b) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.
16. Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.
17. Dötz, K. H. *Angew. Chem., Int. Ed.* **1975**, *14*, 644.
18. (a) Wulff, W. D.; Gilbertson, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 503; (b) Aumann, R.; Fischer, E. O. *Chem. Ber.* **1968**, *101*, 945; (c) Aumann, R.; Heinen, H. *Chem. Ber.* **1987**, *120*, 5379; (d) Chan, T. H.; Mychajlowski, W.; Ong, B. S.; Harpp, D. N. *J. Org. Chem.* **1978**, *43*, 1526; (e) Wulff, W. D.; Bax, B. *Tetrahedron* **1993**, *49*, 5331; (f) Connor, J. A.; Jones, E. M. *J. Chem. Soc. A* **1971**, *21*, 3368.

19. (a) Garner, P.; Park, J. M. *Synthesis* **1991**, *70*, 18; (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
20. Harrity, J. P. A.; Kerr, J. W.; Middlemiss, D. *Tetrahedron* **1993**, *49*, 5565.
21. Later in the synthesis the two-step oxidation involving a Dess–Martin oxidation and $NaClO_2$ oxidation of **7b**, and the *N*-Boc-protected derivative of the same compound was compared. Indeed, the oxidation of the *N*-Cbz-protected arylglycinol proceeded with higher yield (70% vs 43%).
22. Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowsky, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323.
23. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S. *J. Org. Chem.* **1981**, *46*, 3936.
24. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.
25. (a) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207; (b) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, 5029.
26. (a) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480; (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
27. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
28. Bal, B. S.; Childers, W. E.; Pinnic, H. W. *Tetrahedron* **1981**, *37*, 2091.
29. For full characterization, the resulting acids were converted to the corresponding methyl esters by diazomethane.