Scandium-Mediated Opening of Aziridine Carboxylates: A Facile Synthesis of Aryl Substituted Tryptophans

Youssef L. Bennani,* Gui-Dong Zhu and Jennifer C. Freeman

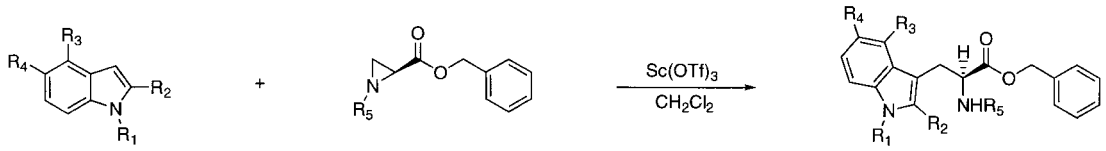
Abbott Laboratories, Metabolic Diseases Research, D4MG, AP10; 100 Abbott Park Rd, Abbott Park, IL 60064-3500, USA

Received 12 December 1997

Abstract: The treatment of enantiomerically pure L-serine-derived *N*-Cbz- or *N*-Fmoc-aziridine carboxylates with indole derivatives in the presence of a stoichiometric amount of $Sc(OTf)_3$ in dichloromethane at 0°C or RT gives the aryl-substituted and protected tryptophan derivatives in good yields. Attempts to catalyze the reaction are also reported.

The ubiquitous and important nature of amino acids in biology, biochemistry and chemistry, justifies the ever increasing research interest.[1] During the preparation of a series of short peptide and peptidomimetic sequences, we needed to synthesize a variety of indole-substituted tryptophans in order to alter tryptophan side-chain interactions and to further increase the diversity element in our intended chemical libraries.[2] A survey of the literature for the preparation of such systems revealed few methods,[3] with one seemingly suited for our needs. In 1989, Sato and Kozikowski reported on the treatment of protected aziridine carboxylates with indoles to give the corresponding tryptophans.[4] While this method is appealing, the reactions are sluggish, require the presence of typically 2-6 equivalents of zinc triflate, as well as heating in chloroform at 78°C under screw-cap sealed-tube conditions. Additionally, the reported yields vary between 3-46%,[5] with the majority in the low 30%, and in our hands, tended to be lower upon prolonged heating. We intended to find a mild and high yielding synthetic method which could eventually be used in solid phase synthesis.

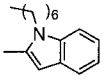
Interest in lanthanide-mediated organic transformations has recently gained momentum with applications ranging from aldol condensations,[6] to enantioselective Diels-Alder cycloadditions,[7] allylation of aldehydes,[8] Michael additions,[9] glycosylations,[10] and epoxide[11] and aziridine[12] opening. Recently, ytterbium triflate was successfully employed to catalyze the alkylation of indoles by electron-deficient olefins.[13] We sought to explore the possibility of other Lewis acid-mediated additions of substituted indoles to aziridinocarboxylates.[4] Thus, we prepared benzyl (*2S*)-*N*-benzyloxy carbonyl-2-aziridine carboxylate **2** from L-serine benzyl ester[14] and screened most commercially available lanthanide triflates, including both yttrium and scandium triflates as Lewis acids for this reaction. We wish to report



1 **2** **3**[a]

Scheme 1

Table 1

Entry	Indole Derivative				Aziridine	Reaction Time	Temperature	$Sc(OTf)_3$ (equivalent)	Yield [b]
	R_1	R_2	R_3	R_4	R_5				
1	H	H	H	H	Cbz	15 h	0°C	2	31%
2	Me	Me	H	H	Cbz	2.5 h	0°C	1	84%
3	Me	Me	H	H	Fmoc	12 h	RT	1	85%
4	H	Me	H	H	Cbz	15 h	0°C	1	66% (84%)
5	Me	H	H	H	Cbz	5.0 h	0°C	1	69%
6	H	Me	H	MeO	Cbz	20 h	0°C	1	72% (88%)
7	Bn	H	H	H	Cbz	5.0 h	0°C	1	42%
8		Me	H	H	Cbz	6.0 h	0°C	1	51% [c]
9	H	Me	H	NO_2	Cbz	30 h	RT	1	22%
10	H	Me	OH	H	Cbz	15 h	0°C	2	No Reaction
11	Ac	H	H	H	Cbz	15 h	RT	1	No Reaction

Notes : (**a**) Products for entries 1-9 are called **3.1 - 9**; (**b**) Isolated yields after silica gel chromatography; yields in parentheses are based on consumed aziridines; (**c**) Yield was based on the indole derivative. The only isolated product was from the opening of aziridine **2** by one of the two tethered 2-methylindoles

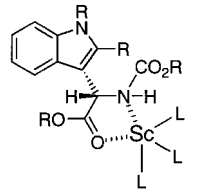
herein that a variety of substituted indoles of type **1** add to aziridine **2**, in the presence of $Sc(OTf)_3$ in dichloromethane at 0°C or RT, to give the corresponding substituted and protected tryptophans in good yields, Scheme 1; Table 1.

A representative procedure for the aziridine opening by 1,2-dimethylindole (Entry 2) is as follows: To a solution of 1,2-dimethyl indole (18.6 mg, 0.128 mmol) and benzyl *N*-CBz-2-aziridinecarboxylate (20 mg, 0.064 mmol) in dichloromethane (1 mL), at 0°C was added $Sc(OTf)_3$ (32 mg, 0.064 mmol) under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 3 hours. Water was added, and the mixture was extracted with dichloromethane (3x10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual oil was separated by flash chromatography (1:5 EtOAc/hexane) to afford dimethyl *N*-CBz-L-Trp-OBn **3.2** (24.7 mg, 84%).

Using indole as a nucleophile, reactions with most other lanthanide triflates were messy or led to no product, with the exception of $Yb(OTf)_3$, which induced a ~20% conversion of aziridine **2** to tryptophan **3**, along with other side products. The results depicted in the Table[15] clearly indicate that higher yields than previously reported by other methods could be obtained in this reaction by using $Sc(OTf)_3$ as a Lewis acid at 0°C or RT. The enantiomeric purity of the reaction product was examined by comparing the optical rotation of **3.1** ($[\alpha]^{23}$ –8.7°, c=1.7 in CH_3OH); with an authentic purchased sample of *N*-CBz-L-Trp-OBn (Senn Chemicals AG; $[\alpha]^{23}$ –8.5°, (c=0.655 in CH_3OH).[4] To further determine its optical purity, **3.1** was hydrogenated to tryptophan using 10% Pd/C in ethanol. HPLC analysis of this amino acid using a chiral column (Chiral Technologies Crownpak CR 4.6x150 mm, 10 mM aq $HClO_4$) revealed a 96% e.e. This minimal erosion of the enantiomeric purity could also be associated with the starting aziridine.

Lower yields were obtained for those indoles with electron withdrawing substituents. The reaction of aziridine carboxylate **2** with 5-nitro-2-methylindole (entry 9) afforded only 22% of product after 30 hours at 25°C, while *N*-acetyl indole (entry 11) failed to give any product. Indole (entry 1) and *N*-benzylindole (entry 7) gave lower yields as compared to other substituted counterparts, presumably due to self condensation of indole. Electron donating groups on indoles accelerated the reaction (entries 2, 4, 5, 6 *vs* entry 1) while the presence of a hydroxy group completely suppressed the $Sc(OTf)_3$ mediated opening of the aziridine. Interestingly, *bis*-*N*,*N*'-dialkyl 2,2'-dimethylindole (entry 8) gave the product resulting from addition of only one indole ring to the aziridine in an isolated 51% yield, thus opening the possibility of differentiating the two indole moieties.

Elemental scandium, with a smaller radius than any other rare earth element, has a chemical behavior known to be intermediate between that of aluminum and other lanthanides.[16] It is also known that various metal triflates have been efficiently used to catalyze C-C bond forming reactions such as Diels-Alder cycloadditions, and allylation of aldehydes and imines.[17] $Yb(OTf)_3$ catalyzed aminolysis of aziridines has also been reported.[12] Attempts to catalyze the indole opening of aziridine carboxylate **2** with up to 20% $Sc(OTf)_3$ in the presence of a variety of co-solvents and additives such as acids, tertiary amines, salts, and other metals have not been fruitful yet.[18] The possibility that the produced amino acid ester is chelated to scandium, Figure 1, and thus precluding a catalytic cycle, was investigated by the following experiment: N_a-benzyloxycarbonyl tryptophan benzyl ester (product from entry 1) (2.0 equiv.), the starting aziridine carboxylate **2** (R_5=Cbz, 1.0 equiv.) and 1,2-dimethylindole (1.0 equiv.) were mixed in dichloromethane at 0°C, followed by the addition of $Sc(OTf)_3$ (1.0 equiv.) The mixture was stirred at 0°C under nitrogen for 3 h and worked up as usual to give only 5% of 1,2-dimethylindole-derived product as compared to 84% yield in entry 2, Table 1. This result is indicative of a possible chelation of the amino acid ester to scandium.



Possible Chelation Mode

Figure 1

In summary, the above described method is simple, does not require heating and allows for simple purification of the end products. We are presently extending this method to other aziridines and to various carbon and heteroatom[3] nucleophilic systems both in solution and on solid support.

Acknowledgment The authors are grateful to Mr. Michael Fitzgerald for optical purity analysis of the synthetic tryptophan by HPLC.

References

1. **a**. Schultz, G. E.; Shriner, R. H. "Principles of Protein Structure" Springer-Verlag, N.Y.; **1985**;**b**. Williams, R. M.; "Synthesis of Optically Active α-Amino Acids", Pergamon Press, **1989**.
2. For Combinatorial Chemical Library review articles see: **a**. DeWitt, S.H.; Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 114; **b**. Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132; **c**. Gordon, E.M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144; **d**. Rinnova, M.; Lebl, M. *Collect. Czech. Chem. Comm.* **1996**, 171; **e**. *Chem. Rev. 97*, **1997**, March-April entire issue.
3. **a**. Pfeil, E.; Harder, V. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 178; **b**. Styngach, E. P.; Kuchkova, K. I.; Efremova, T. M.; Semenov, A. A. *J. Heterocycl. Chem.* **1973**, 1378; **c**. Nakajima, K.; Okawa, K. *Bull. Chem. Soc. Jpn* **1983**, *56*, 1565; **d**. Kogami, Y.; Okawa, K. *Bull. Chem. Soc. Jpn* **1987**, *60*, 2963; **e**. Larsson, U.; Carlson, R. *Acta Chemica Scandinavica* **1994**, *48*, 511; For the preparation of β-amino ketones and esters by SmI_2-mediated opening of aziridines, see: Molander, G. A.; Stengel, P. J. *J. Org. Chem.* **1995**, *60*, 6660.
4. Sato, K. Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073
5. Under similar conditions, a 68% yield was obtained for the reaction with 2-methylindole: Fukami, T., Yamakawa, T.; Niiyama, K.; Kojima, H.; Amano, Y.; Kanda, F.; Osaki, S.; Fukoroda, T.; Ihara, M.; Yano, M.; Ishikawa, K. *J. Med. Chem.* **1996**, *39*, 2313.
6. Kobayashi, S.; Hachiya, I.; *J. Org. Chem.* **1994**, *59*, 3590 and references cited therein.
7. **a**. Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623; **b**. Markó, I. E.; Evans, G. R. *Tetrahedron Lett.* **1994**, *35*, 2771.
8. Aspinall, H. C.; Browning, A. F.; Greeves, N.; Ravenscroft, P. *Tetrahedron Lett.* **1994**, *35*, 4639.
9. Kobayashi, S. *Synlett* **1994**, 689 and references cited therein.
10. Kiessling, L. L.; Sanders, W. J. *Tetrahedron Lett.* **1994**, *35*, 7335.

11. **a**. Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineshi, *Tetrahedron Lett.* **1994**, *35*, 433; **b**. Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc. Perkin Trans. 1* **1994**, 2597.

12. Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395.

13. Harrington, Paul E.; Kerr, Michael A. *Synlett* **1996**, 1047.

14. Nakajima, K.; Takai, F.; Tanaka, T.; Okawa, K. *Bull. Chem. Soc. Jpn* **1978**, *51*, 1978.

15. Representative spectrometric data for the products of entries 2, 4, 6, and 8 of Table 1.
3.2: IR(KBr) 3400(m), 1705(s) cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 2.21(s, 3H); 3.24(dd, J=6.3, 14.4Hz, 1H); 3.32(dd, J=4.8, 14.7Hz, 1H); 3.58(s, 3H); 4.71 (ddd, J=8.0, 6.0, 5.5Hz, 1H); 4.95(d, J=12.1Hz, 1H); 5.06-5.14(m, 3H); 5.30(d, J=8.9Hz, 1H); 7.03(t, J=8.0Hz, 1H); 7.10-7.37(m, 12H); 7.43(d, J=7.7Hz, 1H)ppm. MS(DCI/NH_3) m/z:457(100%, M+1). Anal. calcd for $C_{28}H_{28}N_2O_4$: C, 73.66; H, 6.18; N, 6.14. Found: C, 73.85; H, 6.26; N, 6.22.
3.4: IR(KBr) 3398,3350 (m), 1707 (s) cm^{-1}. ^1H NMR(300MHz, $CDCl_3$) δ 2.24(s, 3H); 3.22(dd, J=6.3, 14.5Hz, 1H); 3.28(dd, J=4.8, 14.5Hz, 1H); 4.72(ddd, J=8.1, 6.0, 5.0Hz, 1H); 4.97(d, J=12.1Hz, 1H); 5.08(d, J=12.0Hz, 1H); 5.06(d, J=12.0Hz, 1H); 5.10(d, J=12.0Hz, 1H); 5.31(d, J=8.5Hz, 1H); 7.00-7.14(m, 4H); 7.23-7.33(m, 9H); 7.42(d, J=7.7Hz,1H); 7.76(brs, 1H) ppm. ^{13}C NMR(75MHz, $CDCl_3$) δ 188.9, 171.9, 135.3, 135.1, 132.8, 128.5, 128.3, 128.2, 128.1, 125.0, 121.3, 119.6, 117.9, 110.3, 105.8, 67.3, 66.9, 54.8, 27.5, 11.6ppm. MS(DCI/NH_3) m/z: 443(100%, M+1), 460 (80%, M+NH_4^+). Anal. calcd for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 73.08; H,6.08; N, 6.17.
3.6: IR(KBr) 3354 (m), 1713(s)cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 2.21(s, 3H); 3.19(dd, J=6.3, 13.8Hz, 1H); 3.25(dd, J=6.0, 14.0Hz, 1H); 3.76(s, 3H); 4.72(ddd, J=8.0, 6.0, 5.0Hz, 1H); 4.98(d, J=12.2Hz, 1H); 5.06-5.12(m, 3H); 5.33(d, J=8.1Hz, 1H); 6.76(dd, J=8.8, 2.5Hz, 1H); 6.94(d, J=2.2Hz, 1H); 7.10-7.13(m, 3H); 7.26-7.34(m, 8H); 7.64 (brs,1H)ppm. ^{13}C NMR(75MHz, $CDCl_3$) δ 172.0, 155.8, 154.2, 136.2, 135.1, 133.8, 130.4, 128.5, 128.3, 128.1, 128.0, 111.0, 110.9, 105.4, 100.4, 67.2, 66.9, 55.9, 54.8, 27.6, 27.5, 11.6 ppm. MS(DCI/NH_3) m/z: 473(20%, M+1). Anal. calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.97; N, 5.93. Found: C, 71.18; H, 6.01; N, 5.88.
3.8: IR(KBr) 3397(s), 1743(s), 1686(s) cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 1.22-1.38(m, 4H); 1.54-1.76(m, 4H); 2.19(s, 3H); 2.37(s, 3H); 3.23(dd, J=6.0, 14.1Hz, 1H); 3.30(dd, J=4.2, 15.0Hz, 1H); 3.94(t, J=7.7Hz, 2H); 4.00(t, J=7.4Hz, 2H); 4.69(ddd, J=8.2, 6.5, 5.0Hz, 1H); 4.92(d, J=12.1Hz, 1H); 5.05(d, J=12.1Hz, 1H); 5.07(d, J=12.2Hz, 1H); 5.10(d, J=12.2, 1H); 5.28(d, J=9.0Hz, 1H); 6.22(t, J=0.7Hz, 1H); 7.00-7.40(m, 16H); 7.42(d, J=7.7Hz, 1H); 7.51(d, J=7.3Hz,1H)ppm. ^{13}C NMR(75MHz, $CDCl_3$) δ 172.0, 136.2, 135.9, 134.8, 134.0, 130.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.3, 120.8, 120.4, 120.0, 119.3, 119.2, 117.9, 108.9, 108.8, 105.4, 99.9, 67.2, 66.8, 54.9, 43.2, 43.0, 30.1, 30.0, 26.8, 12.8, 10.3 ppm. MS(DCI/NH_3) m/z: 656(100%, M+1). Anal. calcd for $C_{42}H_{45}N_3O_4$: C, 76.92; H, 6.92; N, 6.41. Found: C, 77.08; H, 7.06; N, 6.28.

16. Cotton, F. A.; Wilkinson, G. “Advanced Inorganic Chemistry” 5th Ed., John Wiley & Sons: N.Y., **1988**.

17. Bellucci, C.; Cozzi, G. P.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7289.

18. Among the additives we tried: HMPA; triflic acid; triflic anhydride; acetic acid, Et_3N, Pyridine, LiBr, $CeCl_3$-$(H_2O)_7$, molecular sieves, Zn dust, $ZnCl_2$, $Zn(OTf)_2$, $Ti(iPrO)_4$ and various others.