Tetrahedron Letters 54 (2013) 618–620

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of tryptophans by Lewis acid promoted ring-opening of aziridine-2-carboxylates: optimization of protecting group and Lewis acid

Ilaria Tirotta, Nathan L. Fifer, Julia Eakins, Craig A. Hutton *

School of Chemistry and Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, Victoria 3010, Australia

ARTICLE INFO

Article history:
Received 15 October 2012
Revised 20 November 2012
Accepted 28 November 2012
Available online 7 December 2012

Keywords:
Aziridines
Tryptophan
Lewis acids
Ring-expansion
Oxazolidinone

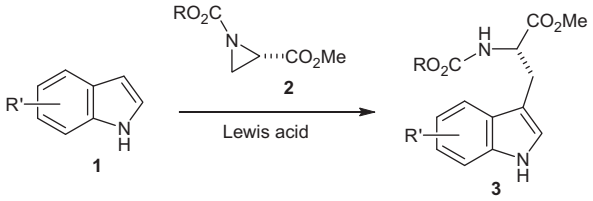
ABSTRACT

The preparation of tryptophan derivatives through the Lewis acid promoted substitution of aziridine carboxylates with indole was found to be accompanied by a ring-expansion reaction to generate an oxazolidinone byproduct. The ratio of tryptophan to oxazolidinone products can be optimized through a judicious choice of Lewis acid and N-protecting group.

The regioselective ring-opening of aziridine-2-carboxylates with a variety of nucleophiles has been employed as a synthetic route to a range of β-substituted amino acid derivatives.[1–6] The use of indole as the nucleophile allows for the generation of tryptophan derivatives (Scheme 1).[7–11] Sato and Kozikowski first reported this transformation using zinc triflate as a Lewis acid promoter,[7] though only low yields of the tryptophans were obtained. A variety of other Lewis acids were shown to be ineffective. Bennani et al. showed that scandium triflate gave improved yields, with fewer equivalents of the Lewis acid required.[8] Isobe and coworkers demonstrated that anhydrous scandium perchlorate results in further improvements;[9–11] however, this material is not commercially available and is potentially explosive.

Even under optimized conditions, the preparation of tryptophan derivatives by treatment of aziridine carboxylates with indoles can be limited by moderate yields due to the formation of byproducts. Surprisingly, little information has been reported regarding the byproducts formed during such reactions. Accordingly, we embarked upon a systematic investigation of the effect of the Lewis acid and of the N-protecting group to further understand the factors affecting the production of tryptophan derivatives via this route.

Herein we demonstrate that the yields of the tryptophan product are influenced by a competing reaction—the ring expansion of the aziridine to generate an oxazolidinone byproduct—the facility of which is determined by the nature of the carbamate protecting group and the Lewis acid employed.



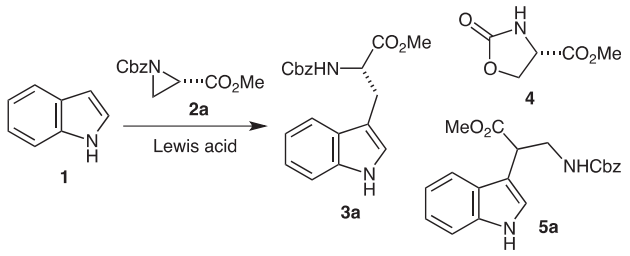
Scheme 1. Synthesis of tryptophan derivatives through ring-opening of aziridine carboxylates with indoles.

We initially performed a series of experiments in which indole (**1**) and Cbz-protected aziridine **2a** were treated with a range of Lewis acids, in order to investigate the nature of any byproducts produced. Use of zinc(II), ytterbium(III), and copper(II) triflate at 0 °C[10] gave no reaction, with aziridine **2a** recovered. Upon conducting the reactions at room temperature, Zn(II) and Yb(III) triflates still gave no reaction, but $Cu(OTf)_2$ gave a 1:2 mixture of tryptophan **3a** and a major byproduct, which was identified as the oxazolidinone **4**[13] (Table 1). There are numerous reports of the ring-expansion of acyl aziridines to give oxazolines or oxazolidinones,[14–19] though such byproducts have not been described during the preparation of tryptophan derivatives from aziridines. The degree of oxophilicity has been reported to be a determinant factor in the ratio of nucleophilic substitution to ring-expansion processes,[17] with oxophilic Lewis acids promoting substitution and azaphilic Lewis acids promoting ring-expansion. This effect is generally in line with $Sc(OTf)_3$ providing the best yields of the tryptophan product **3a** and the lowest amounts of oxazolidinone **4**, while the use of $Cu(OTf)_2$ and $Zn(OTf)_2$ results in greater amounts of the oxazolidinone **4**.

* Corresponding author. Tel.: +61 3 8344 2393; fax: +61 3 9347 8124.
E-mail address: chutton@unimelb.edu.au (C.A. Hutton).

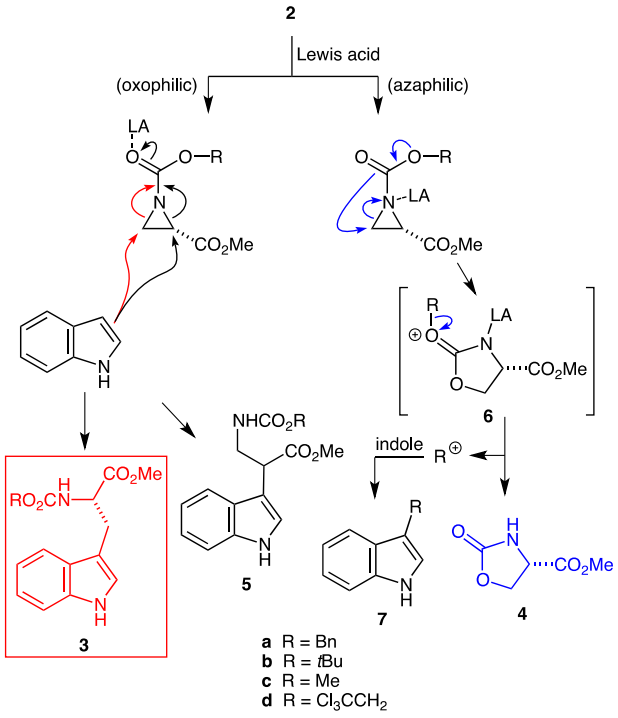
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.11.139

Table 1[a]



Entry	Lewis acid	% Conversion			
		2a	**3a**	**4**	**5a**
1	$Zn(OTf)_2$	100	—	—	—
2	$Yb(OTf)_3$	100	—	—	—
3	$Hf(OTf)_4$	—	—	100	—
4	$Bi(OTf)_3$	—	22	78	—
5	$Cu(OTf)_2$	—	32	68	—
6	$Sc(OTf)_3$	—	57	19	24

[a] 1 equiv Lewis acid, 2 equiv **1**, room temperature, 24 h.[12]



Scheme 2. Potential reaction pathways of carbamate-protected aziridine carboxylate **2**.

However, $Sc(OTf)_3$ did result in the formation of large amounts of regioisomer **5a** (24%), which was not observed in significant amounts with other Lewis acids. Surprisingly, the use of $Hf(OTf)_4$ gave only the oxazolidinone **4**, with no substitution product formed.

Minimizing the proportion of ring expansion yielding the oxazolidinone **4** appears a key to improve the yield of the tryptophan derivative **3**. Other than the effect of the Lewis acid, we considered that the aziridinyl carbamate protecting/activating group should influence the proportion of ring expansion versus substitution products. Ring expansion of aziridine **2** to give the oxazolidinone **4** requires loss of the carbamate alkyl group, presumably as a benzyl carbocation in the case of the *N*-Cbz aziridine **2a**. Indeed, we isolated 3-benzylindole (**7a**) as a minor byproduct from the reaction of Cbz-aziridine **2a** with indole **1** and $Cu(OTf)_2$, in accordance with the mechanism postulated in Scheme 2. Consequently, the stability of the carbocation generated from cleavage of the carbamate group should influence the relative rate of ring expansion vs. substitution. Reactions of aziridines with various carbamate groups were therefore investigated.

Treatment of the Boc-protected aziridine **2b** with $Cu(OTf)_2$ yielded a greater amount of the oxazolidinone **4** (**3b**:**4**, 14:86, Table 2, entry 2) than in the corresponding reaction of Cbz-aziridine **2a** (**3a**:**4**, 32:68, Table 1, entry 5), consistent with more facile generation of the stable *t*-butyl carbocation. Treatment of the Boc-protected aziridine **2b** with $Sc(OTf)_3$ gave qualitatively similar results to the Cbz-version **2a** (Table 2, entry 3 cf. Table 1, entry 6).

We envisaged that a methyl carbamate group (Moc) would not undergo ring expansion via the mechanism shown in Scheme 2, due to the instability of the methyl cation. Indeed, no oxazolidinone **4** was formed in the crude reaction mixture from treatment of Moc-aziridine **2c** with any Lewis acid (Table 2, entries 4–6). However, the yields of tryptophan **3c** remained moderate, and ^1H NMR analysis of the reaction mixture showed evidence of a byproduct characterized by an ABX system of resonances (three dd peaks at δ 4.69, 4.63, 4.56), consistent with a substituted serine-type derivative. Attempted isolation of the byproduct by chromatography on silica yielded only the oxazolidinone **4**. We speculate that the compound observed in the reaction mixture is the oxazoline intermediate **6c** (R = Me), which decomposes to oxazolidinone **4** on silica.

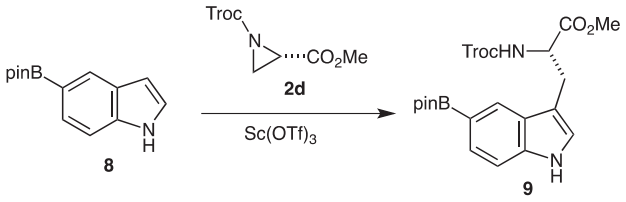
Table 2

Entry	Aziridine	Lewis acid	**3**	**4**	**5**
1	**2b**	$Hf(OTf)_4$	—	100	—
2	**2b**	$Cu(OTf)_2$	14	86	—
3	**2b**	$Sc(OTf)_3$	55	11	34
4	**2c**	$Hf(OTf)_4$	—	(100)[a]	—
5	**2c**	$Cu(OTf)_2$	27	(73)[a]	—
6	**2c**	$Sc(OTf)_3$	58	(13)[a]	29
7	**2d**	$Hf(OTf)_4$	—	—	—
8	**2d**	$Cu(OTf)_2$	50	—	—
9	**2d**	$Sc(OTf)_3$	67	—	33

[a] No oxazolidinone **4** was detected in the crude product mixture; only **3** (and **5**) and an unidentified compound, which converted into oxazolidinone **4** on silica.

It is apparent, therefore, that ring expansion cannot be suppressed solely through manipulation of the carbamate alkyl group to disfavor loss of the alkyl carbocation. Hence, we attempted to minimize the proportion of ring expansion through an electronic effect. We anticipated that the electron-withdrawing *N*-trichloroethoxycarbonyl (*N*-Troc) group would suppress ring expansion through both a reduction in the nucleophilicity of the carbamate oxygen and a reduced propensity to lose the alkyl group as a carbocation.

Indeed, use of the Troc-protected aziridine **2d** in Lewis acid catalysed reactions with indole (**1**) resulted in no formation of the oxazolidinone byproduct **4** (Table 2, entries 7–9). The use of $Hf(OTf)_4$ resulted in mainly recovered starting material—highlighting the effect of the Troc-group to suppress oxazolidinone formation. Use of $Cu(OTf)_2$ or $Sc(OTf)_3$ similarly gave none of the oxazolidinone **4**: $Cu(OTf)_2$ resulted in formation of the tryptophan **3d**[20] as the major product, but with several unidentifiable byproducts, while the use of $Sc(OTf)_3$ gave the best yield of the tryptophan **3d** (though again with a significant amount of the regioisomer, **5d**).



Scheme 3.

It is apparent that the Troc protecting/activating group suppresses the ring expansion pathway, thereby allowing for the greatest yields of tryptophan product through the substitution pathway.

Substituted tryptophan derivatives have been used in the synthesis of peptide natural products.[21–27] For example, boronate-substituted tryptophan derivatives[28,29] have been employed in conjugate additions and Suzuki–Miyaura couplings in the preparation of the biaryl-linked peptides, celogentin,[30] and complestatin.[31–34] Accordingly, we sought to demonstrate the utility of Troc-aziridine **2d** through the preparation of enantiopure tryptophan boronate derivative **9**. Treatment of indole-5-boronate **8** with aziridine **2d** in the presence of $Sc(OTf)_3$ gave the tryptophan boronate **9**[35] in 45% isolated yield, with no oxazolidinone **4** or other byproducts detected (Scheme 3).

In conclusion, we have demonstrated that ring-opening of aziridine-2-carboxylates with indoles to generate tryptophan derivatives is optimized through the use of an *N*-Troc protecting group on the aziridinyl nitrogen in combination with an oxophilic Lewis acid, in order to disfavor the competing ring expansion reaction that generates an oxazolidinone byproduct.

Acknowledgment

Financial support from the Australian Research Council (DP110100112) is acknowledged.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.139.

References and notes

1. Botuha, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH GmbH & Co. KGaA, 2011; pp 3–40.
2. Zhou, P.; Chen, B.-C.; Davis, F. A. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH GmbH & Co. KGaA: Weinheim, Germany, 2006; pp 73–115.
3. Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichim. Acta* **2003**, *36*, 39–50.
4. Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.
5. Wu, Y.-C.; Zhu, J. *Org. Lett.* **2009**, *11*, 5558–5561.
6. Li, P.; Evans, C. D.; Wu, Y.; Cao, B.; Hamel, E.; Joullie, M. M. *J. Am. Chem. Soc.* **2008**, *130*, 2351–2364.
7. Sato, K.; Kozikowski, A. P. *Tetrahedron Lett.* **1989**, *30*, 4073–4076.
8. Bennani, Y. L.; Zhu, G.-D.; Freeman, J. C. *Synlett* **1998**, 754–756.
9. Nishikawa, T.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Synthesis* **2002**, 1658–1662.
10. Nishikawa, T.; Koide, Y.; Kajii, S.; Wada, K.; Ishikawa, M.; Isobe, M. *Org. Biomol. Chem.* **2005**, *3*, 687.
11. Nishikawa, T.; Koide, Y.; Kanakubo, A.; Yoshimura, H.; Isobe, M. *Org. Biomol. Chem.* **2006**, *4*, 1268.
12. *Representative procedure:* Aziridine **2** (1.27 mmol), indole (**1**) (298 mg, 2.54 mmol), and the Lewis acid (1.27 mmol) were dissolved in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for 24 h. The reaction was concentrated under reduced pressure and analysed by ^1H NMR spectroscopy. The crude material was purified on silica to give tryptophan **3** and/or oxazolidinone **4** (see text).
13. Sibi, M. P.; Rutherford, D.; Sharma, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1675.
14. Armaroli, S.; Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Org. Lett.* **2000**, *2*, 1105–1107.
15. Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153–2156.
16. Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727–732.
17. Ferraris, D.; Drury, W. J., III; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568–4569.
18. Hori, K.; Nishiguchi, T.; Nabeya, A. *J. Org. Chem.* **1997**, *62*, 3081–3088.
19. Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2073–2080.
20. *Data for **3d**:* ^1H NMR (400 MHz, $CDCl_3$); δ 8.11 (br s, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.20 (m, 1H), 7.12 (m, 1H), 7.02 (d, J = 2.3 Hz, 1H), 5.57 (br d, J = 8.3 Hz, 1H), 4.80 (d, J = 12.0 Hz, 1H), 4.75 (dt, J = 8.4, 5.4 Hz, 1H), 4.66 (d, J = 12.0 Hz, 1H), 3.70 (s, 3H), 3.32–3.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$); δ 171.8, 153.9, 136.1, 127.5, 122.8, 122.3, 119.8, 118.6, 111.2, 109.7, 95.4, 74.6, 54.7, 52.5, 27.9. HRMS: m/z 393.0171, $[M+H]^+$; $C_{15}H_{16}Cl_3N_2O_4$ requires 393.0176. $[\alpha]_D^{22}$ − 44.44 (c 0.65, $CHCl_3$).
21. Yuen, A. K. L.; Hutton, C. A. *Nat. Prod. Commun.* **2006**, *1*, 907–913.
22. Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2009**, *49*, 958–961.
23. Ma, B.; Litvinov, D. N.; He, L.; Banerjee, B.; Castle, S. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 6104–6107.
24. Li, B. T. Y.; White, J. M.; Hutton, C. A. *Aust. J. Chem.* **2010**, *63*, 438.
25. Bentley, D. J.; Moody, C. J. *Org. Biomol. Chem.* **2004**, *2*, 3545.
26. Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032–9034.
27. Ma, C.; Liu, X.; Li, X.; Flippen-Anderson, J.; Yu, S.; Cook, J. M. *J. Org. Chem.* **2001**, *66*, 4525–4542.
28. Bartolucci, S.; Bartoccini, F.; Righi, M.; Piersanti, G. *Org. Lett.* **2012**, *14*, 600–603.
29. Prieto, M.; Mayor, S.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **2009**, *74*, 9202–9205.
30. Michaux, J.; Retailleau, P.; Campagne, J.-M. *Synlett* **2008**, 1532–1536.
31. Wang, Z.; Bois-Choussy, M.; Jia, Y.; Zhu, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2018–2022.
32. Jia, Y.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 4167–4172.
33. Yamada, Y.; Akiba, A.; Arima, S.; Okada, C.; Yoshida, K.; Itou, F.; Kai, T.; Satou, T.; Takeda, K.; Harigaya, Y. *Chem. Pharm. Bull.* **2005**, *53*, 1277–1290.
34. Shinohara, T.; Deng, H.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 7334–7336.
35. *Data for **9**:* ^1H NMR (500 MHz, $CDCl_3$); δ 8.18 (br s, 1H), 8.02 (s, 1H), 7.64 (dd, J = 8.2, 1.0 Hz, 1H), 7.34 (dd, J = 8.2, 0.8 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 5.56 (br d, J = 8.1 Hz, 1H), 4.76–4.71 (m, 3H), 3.75 (s, 3H), 3.37–3.41 (m, 2H), 1.37 (s, 6H), 1.35 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$); δ 171.8, 153.9, 138.1, 128.5, 127.2, 126.3, 122.9, 110.6, 110.2, 95.4, 83.5, 74.5, 54.5, 52.2, 27.5, 25.0, 24.8. MS(ESI) m/z 519.09, $[M+H]^+$. $[\alpha]_D^{22}$ +35.58 (c 0.90, $CHCl_3$).