Tetrahedron Letters 53 (2012) 876–878

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Total synthesis of (−)-indolizidine 167B via an unusual Wolff rearrangement from an α,β-unsaturated diazoketone

Vagner D. Pinho, Antonio C. B. Burtoloso *

Instituto de Química de São Carlos, Universidade de São Paulo, CEP 13560-970, São Carlos, SP, Brazil

ARTICLE INFO

Article history:
Received 19 November 2011
Revised 6 December 2011
Accepted 8 December 2011
Available online 14 December 2011

Keywords:
Indolizidine alkaloids
Unsaturated diazoketones
Wolff rearrangement
Arndt–Eistert homologation
Photochemical

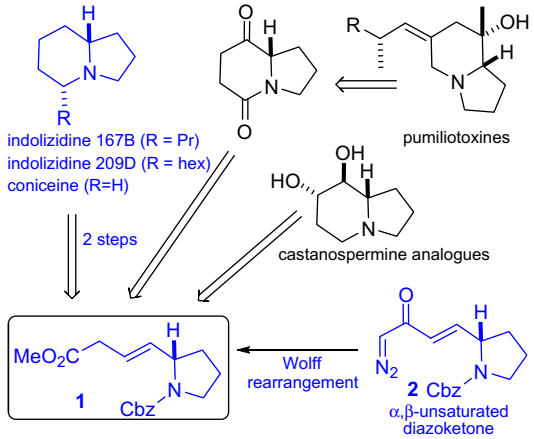
ABSTRACT

A concise synthesis of the (−)-indolizidine alkaloid 167B and two formal syntheses of (−)-indolizidine 209D and (−)-coniceine are described in just three steps from an α,β-unsaturated diazoketone, via an unusual photochemical Wolff rearrangement. Preparation of the unsaturated diazoketone is straightforward from *N*-Cbz-prolinal and a 3-diazo-2-oxopropylphosphonate, employing a Horner–Wadsworth–Emmons reaction. The strategy should be feasible and easily adaptable to the synthesis of other indolizidine alkaloids and analogues.

Indolizidine alkaloids are among the most important classes of nitrogen heterocycles. Possessing an azabicyclic unit, these compounds have become common targets in synthesis due to their unique structure and interesting pharmacological activities.[1] For example, non-natural[2] indolizidines 167B and 209D and the natural pumiliotoxins (Scheme 1), isolated from the skin secretions of certain neotropical amphibians, are noncompetitive blockers of neuromuscular transmission[3] and promising cardiotonics,[4] respectively. Despite many interesting total syntheses of these compounds, more general, short and diversity-oriented approaches are still desirable.

Recently, we described a new method[5] to prepare α,β-unsaturated diazoketones from aldehydes, employing a new Horner–Wadsworth–Emmons (HWE) reagent, and its application in a short synthesis of pyrrolidines. Herein, in continuation with this chemistry, we would like to describe an expedient synthesis of (−)-indolizidine 167B in four steps from commercially available and easily prepared (*S*)-*N*-Cbz-prolinal.[6] It is worth of mentioning that the majority of examples in the literature[1,7,8] describes the asymmetric total synthesis of these indolizidines in lengthy paths (8–14 steps) from commercially available reagents, only a few being shorter than that. Shibasaki[9] and Rovis[10] reported the shortest syntheses known to date of (−)-indolizidine 209D (five steps from glutarimide and 5-hexenoic acid, respectively), whereas O'Brien[11] and Settambolo[12] reported the syntheses of (−)-indolizidine 167B in six steps from *N*-Boc-Pyrrolidine and D-norvaline, respective.

As depicted in Scheme 1, we envisaged that the synthesis of indolizidines 167B and 209D, as well as other indolizidine alkaloids such as pumiliotoxins, coniceine, and castanospermine analogues, could be easily and concisely reached from β,γ-unsaturated ester **1**. In turn, key intermediate **1** could be prepared in a single step by an unusual Wolff rearrangement from an α,β-unsaturated diazoketone such as **2**. In contrast to the enormous number of applications from common saturated diazoketones, few reports of applications of the rarer α,β-unsaturated diazoketones are found in the literature. Despite that, we believe that α,β-unsaturated



Scheme 1. Indolizidines alkaloids from α,β-unsaturated diazoketones.

* Corresponding author. Tel.: +55 16 3373 8641; fax: +55 16 3373 9952.
E-mail address: antonio@iqsc.usp.br (Antonio C. B. Burtoloso).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.029

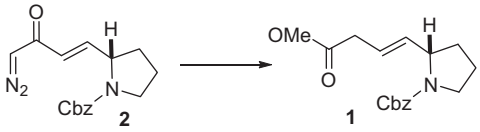
diazoketones are very promising multi-functional intermediates and can lead to short and diversity-oriented syntheses of many compounds, including alkaloids.

We started our work by preparing α,β-unsaturated diazoketone **2** in a 70% yield as a single *E* isomer, employing our recently described methodology[5] (Scheme 2). No epimerization occurred at this critical step according to careful HPLC analysis[13] (>99% ee). Conversion of diazoketone **2** into key intermediate **1** proved to be difficult, affording only low yields under usual thermal conditions for the Wolff rearrangement (30 mol % AgOBz, Et_3N, 25 °C). In view of that, a detailed study on the Wolff rearrangement was carried out, aiming the synthesis of the Arndt–Eistert homologated product **1** (Table 1).

Initially, silver benzoate was selected as the model catalyst to optimize the conditions. As described in entry 5, 50 mol % of the catalyst is necessary to obtain a moderate yield, together with its slow addition and a 50 °C reaction temperature. Sequential investigation employing different silver catalysts (entries 9–12) leads to practically similar results, CF_3SO_3Ag being the best catalyst. Although these conditions provided good yields for the Wollf rearrangement, high loadings of the expensive silver catalysts are needed, together with tedious experimental procedures such as the requirement of very slow addition of the catalyst for total substrate conversion. Fortunately, this problem was totally circumvented when photochemical conditions were applied, furnishing the desired ester **1** in almost quantitative yield with no need of purification.[14] Not withstanding the wide range of applications known of the Arndt–Eistert homologation from saturated diazoketones,[15] the use of α,β-unsaturated diazoketones as substrates for this transformation is scarcely described in the literature.[16] Moreover, unsaturated diazoketone **2** sets an even worse scenario due to the existence of an epimerizable stereocenter. Fortunately, comparison of the optical rotation value of the *N*-Boc derivative of compound **1** {[α]D −26.0 (*c* 1.0, MeOH)} with the one described in the literature[17] {[α]D −21.4 (*c* 1.0, MeOH)} demonstrated the integrity of the chiral center after the photochemical or thermal Wolff rearrangement.

After the synthesis of **1**, completion of the total synthesis of indolizidine 167B was straightforward. Removal of the Cbz protecting group in the presence of H_2/Pd and TEA as base (with concomitant reduction of the double bond and cyclization) afforded known lactam **3** in a 92% yield and in a single step. Synthesis of lactam **3** {>99% ee from chiral HPLC;[13] [α]D −6.7 (*c* 1.0, CH_2Cl_2); Lit[18] [α]D −6.6 (*c* 1.0, CH_2Cl_2)} also constitutes a very concise formal synthesis of the natural alkaloid coniceine[18] and of (−)-indolizidine 209D.[9] Addition of propylmagnesium bromide to lactam **3**, followed by AcOH/$NaBH_4$, concluded the total synthesis of indolizidine (−)-167B as a single diastereomer[19] in a 42% yield (Scheme 2), being its spectroscopic data and optical rotation value in accordance with the literature.[7,8]

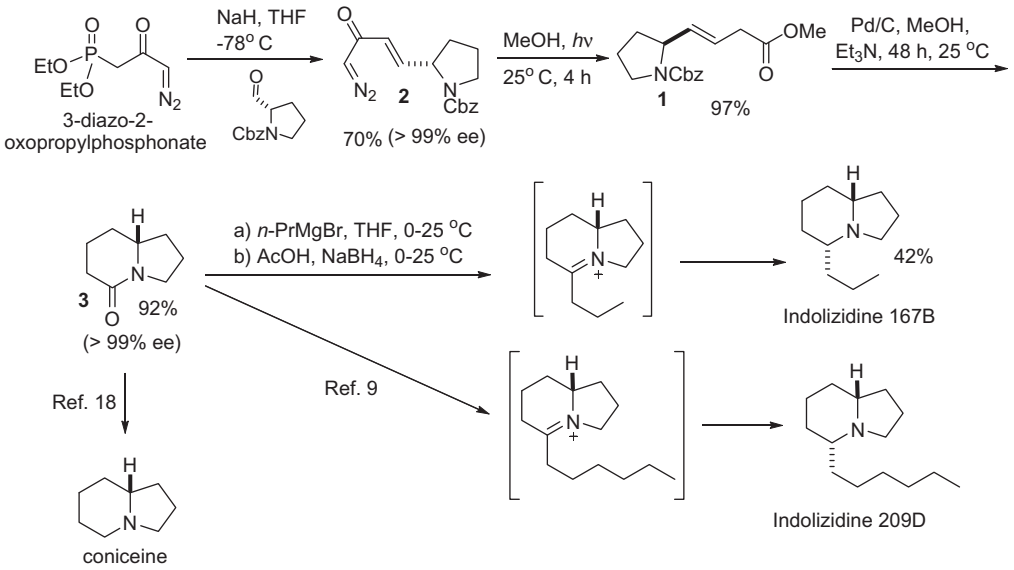
Table 1
Studies on the Arndt–Eistert homologation reaction



Entry	Catalyst (mol %)	Temp (°C)	Time (h)	Yield (%)
1[16,a,c]	$C_6H_5CO_2Ag$ (30)	25	1	30
2[a,b]	$C_6H_5CO_2Ag$ (50)	25	1	37
3[a,b]	$C_6H_5CO_2Ag$ (40)	25–50	1	50
4[a,c]	$C_6H_5CO_2Ag$ (50)	50	1	50
5[a,b]	$C_6H_5CO_2Ag$ (50)	50	1	66
6[c]	Ag_2O (15)	25	1	16
7[a,b]	CF_3CO_2Ag (30)	50	1	26
8[a,b]	CF_3SO_3Ag (30)	50	1	28
9[a,b]	$AgNO_3$ (50)	50	1	51
10[a,b]	CF_3CO_2Ag (50)	50	1	71
11[a,b]	CF_3SO_3Ag (50)	50	1	76
12[a,b]	CH_3CO_2Ag (50)	50	1	66
13[d]	None	25	4	97

[a] 5 equiv of Et_3N and a 0.1 M solution of **2** in dry MeOH was used, except in entry 6 where no base was used.
[b] Very slow addition of the catalyst as a solution in Et_3N.
[c] Fast and direct addition of the catalyst as a solution in Et_3N.
[d] The photochemical reactions (0.3 M solution of **2** in dry MeOH) were carried out using UV light generated by an Osram 150 Xenon lamp accommodated in an Oriel Model 8500 Universal arc lamp source with focusing quartz lens, a water-filled infrared filter, and a thermostated cell holder.

In conclusion, we have shown that α,β-unsaturated diazoketones can be powerful substrates for the short and diversity-oriented synthesis of indolizidine alkaloids. This was demonstrated by preparing indolizidine 167B in four steps from L-Cbz-prolinal and with an overall yield of 26%. Success in this endeavor was possible after a



Scheme 2. Synthesis of (−)-indolizidine alkaloids 167B, 209D and coniceine.

high yielding unusual photochemical Arndt–Eistert homologation from an unsaturated diazoketone. This strategy should be feasible and can be easily adaptable to the concise synthesis of other indolizidine alkaloids. The total syntheses of some pumiliotoxins and castanospermine analogues using the present strategy will be reported in due course.

Acknowledgments

We thank FAPESP (Research Supporting Foundation of the State of Sao Paulo) for financial support and a fellowship to V.D.P. We also thank CNPq for research fellowship to A.C.B.B. and IQSC-USP for facilities. We also would like to thank Professor Marcio Paixão (UFSCar), Ana M. Deobald (UFSCar), Professor André Porto (IQSC-USP) and Lenilson Coutinho (IQSC-USP) for help with the HPLC instrument, Professor Daniel Cardoso for help with the photochemical system and DQO-UFSCar for some NMR analyses.

Supplementary data

Supplementary data (experimental procedures and copies of the NMR spectra of all compounds and chiral HPLC chromatograms of diazoketone **2** and lactam **3**.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.029.

References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139; (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603; (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625; (d) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458; (e) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719; (f) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520; (g) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 579.
2. Most publications describe indolizidines 167B and 209D as natural. However, according to Daly's recent reviews, the two isolated natural alkaloids (proposed tentatively to be indolizidines 167B and 209D) were found to be 3,5-disubstituted pyrrolizidines and were, therefore, tabulated as indolizidines 167F and 209K in the appendix. The code names 167B and 209D are maintained for the synthetic indolizidines, although they have not yet been detected in nature. Please see: (a) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556; (b) Pelletier, S. W. *Alkaloids: Chemical and Biological Perspectives*; Elsevier Science Ltd: Oxford, 1999.
3. Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227.
4. Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, *28*, 482.
5. Pinho, V. D.; Burtoloso, A. C. B. *J. Org. Chem.* **2011**, *76*, 289.
6. (*S*)-*N*-Cbz-prolinal can also be prepared in multigram quantities and in two steps from the cheaper amino acid (*S*)-*N*-Cbz-proline. From (*S*)-*N*-Cbz-proline, the total synthesis of indolizidine 167B is accomplished in 6 steps.
7. For the first asymmetric total synthesis of indolizidine 167B and 209D see: Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688.
8. For recent examples of the asymmetric synthesis of indolizidine 167B and 209D see: (a) Lazzaroni, R.; Settambolo, R. *Chirality* **2011**, *23*, 730; (b) Chou, S.-S. P.; Chung, Y. C.; Chen, P.-A.; Chiang, S.-L.; Wu, C. J. *J. Org. Chem.* **2011**, *76*, 692; (c) Liu, H.; Su, D.; Cheng, G.; Xu, J.; Wang, X.; Hu, Y. *Org. Biomol. Chem.* **2010**, *8*, 1899; (d) Gracia, S.; Jerpan, R.; Pellet-Rostaing, S.; Popowycz, F.; Lemaire, M. *Tetrahedron Lett.* **2010**, *51*, 6290. and references cited therein.
9. Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.
10. Yu, R. T.; Lee, E. E.; Malik, G.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, 2379.
11. Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.
12. Settambolo, R.; Guazzelli, G.; Lazzaroni, R. *Beilstein J. Org. Chem.* **2005**, *2*, 176.
13. See Supplementary data for details.
14. *Experimental procedure for the photochemical Wolff rearrangement*: A solution of diazoketone **2** (269.0 mg, 0.9 mmol) in dry methanol (3.0 mL), in a 1 cm optical path quartz cell, was irradiated with a Osram 150 Xenon white lamp for 4 h under magnetic stirring (nitrogen gas evolution observed). Next, the solvent was evaporated off in a rotary evaporator to furnish 272.0 mg (97%) of ester **1** with no need of purification. ^{1}H NMR (200 MHz, $CDCl_3$, mixture of rotamers) δ 7.30 (br s, 5H), 5.79–5.44 (m, 1H,), 5.18 (d, 1H, J = 12.0 Hz), 5.08 (d, 1H, J = 12.0 Hz), 4.50–4.31 (m, 1H), 3.66 (s, 3H), 3.53–3.41 (m, 2H), 3.16–2.96 (m, 2H), 2.08–1.68 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$, mixture of rotamers) δ 172.0, 161.2, 136.9, 134.3, 133.9, 128.3, 127.7, 122.0, 66.6, 58.5, 58.2, 51.7, 46.6, 46.3, 37.31, 32.2, 31.3, 29.6, 23.5, 23.5, 22.7; FT-IR (neat, cm^{-1}): 2954, 2927, 1737, 1701, 1452, 1411, 1353, 1270, 1189, 1170; HRMS (ESI) calcd for $C_{17}H_{21}NNaO_4$ [M+Na]: 326.1368 found: 326.1360; $[\alpha]_D^{25}$ −30.0 (c 4.0 CH_2Cl_2); R_f: 0.4 (40% EtOAc/hexanes).
15. Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.
16. Although no example of the photochemical Wolff rearrangement applied to the Arndt–Eistert reaction is described in the literature for an α,β-unsaturated diazoketone, a single example is described for the thermal rearrangement by Brueckner. However, the 2 diazoketones employed in this example are simple ones, containing no epimerizable stereocenters or heteroatoms in the chain. For this single example, see: (a) Kapferer, T.; Brueckner, R.; Herzig, A.; Koenig, W. A. *Chem. Eur. J.* **2005**, *11*, 2154; (b) Kapferer, T.; Brueckner, R. *Eur. J. Org. Chem.* **2006**, *9*, 2119.
17. Miles, N. J.; Sammes, P. G.; Kennewell, P. D.; Westwood, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2299.
18. Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621.
19. The highly stereoselective reduction of the iminium ion in indolizidine skeleton is reported by several groups. For examples see Ref.[9] and references cited therein.