Pergamon

Tetrahedron Letters 41 (2000) 5363–5366

TETRAHEDRON LETTERS

Easy and efficient synthesis of enantiomerically enriched 2*H*-azirines derived from phosphonates†

Francisco Palacios,* Ana M. Ochoa de Retana and José I. Gil

Departamento de Química Orgánica, Facultad de Farmacia, Universidad del País Vasco, Apartado 450, 01080 Vitoria, Spain

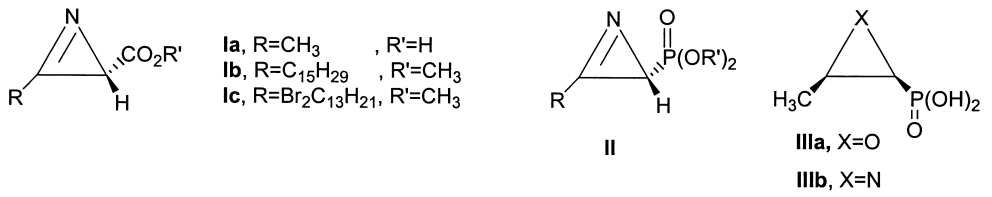
Received 13 April 2000; accepted 23 May 2000

Abstract

An efficient synthesis of 2*H*-azirines substituted with a phosphonate group is described. The key step is an alkaloid-mediated Neber reaction of β-ketoxime tosylates. Reduction of 2*H*-azirines with sodium borohydride in ethanol gives 2-phosphorylated *cis*-aziridines. © 2000 Published by Elsevier Science Ltd.

Keywords: azirines; aziridines; asymmetric synthesis; oximes; phosphonates; aminophosphonates.

The highly strained 2*H*-azirine ring system, the smallest of the nitrogen-unsaturated heterocycles, represents a very important class of compounds, not only for their theoretical interest but also because of their high reactivity towards nucleophilic and electrophilic reagents,[1,2] as well as in cycloaddition reactions.[2b] Optically active 2*H*-azirines, namely azirinomycin,[3a] (**Ia**, Scheme 1), and both (*R*)-(–)-,[3b] (*S*)-(+)-disydazirine,[3c] (**Ib**, Scheme 1) and (*S*)-(+)-antazirine,[3c] (**Ic**, Scheme 1), are naturally occurring antibiotics. Furthermore, it is known that phosphor substituents regulate important biological functions.[4] In particular, fosfomycin (**IIIa**, X=O, Scheme 1) is a broad spectrum antibiotic[5a] and is used in vitro[5b] and clinically.[5c] For these reasons, functionalized azirines (**II**, Scheme 1) and aziridines (**IIIb**, X=N, Scheme 1) containing a phosphonate group at the 2-position are expected to play a similar role to that observed in their isosteric analogues **I**,



Scheme 1. Biologically active three-membered heterocycles

* Corresponding author. E-mail: qoppagaf@vf.ehu.es

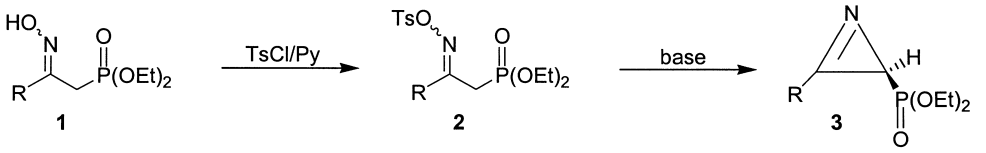
† Dedicated to Professor Dr. Rolf Huisgen on the occasion of his 80th birthday.

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)00843-1

and may even be used as key intermediates in the enantioselective synthesis of α- and β-amino-phosphorus derivatives. Aminophosphonates can be considered as surrogates for amino acids[6a] and have been used as haptens for catalytic antibodies,[6b] as enzyme inhibitors,[6c] and as pharmaceuticals.[6d]

Many procedures for the synthesis of 2*H*-azirines have been reported,[1] and enantiomerically enriched 2*H*-azirines, containing a carboxylic ester on the ring system, have been previously prepared either from chiral *N*-substituted aziridine 2-carboxylic esters,[7a–c] or by using the Neber reaction.[7d,e] However, 2*H*-azirines directly substituted with a phosphorus containing functional group have received scarce attention. To the best of our knowledge, only the 2-phosphino-, 2-phosphonio, and the thioxo-phosphoranyl-2-silyl-2*H*-azirines obtained by reaction of carbenes and aromatic nitriles,[8a,b] and regioisomeric mixtures of 2*H*- and 3*H*-azirinyl-phosphonates with a phenyl group at the 2-position, obtained by Swern oxidation of enantiopure substituted aziridines, have been recently reported.[8c] Continuing with our interest in the synthesis of new phosphorus substituted heterocycles,[9] we are involved in the design of new 2*H*-azirines bearing a phosphonate moiety. Here we report a simple asymmetric synthesis of 2*H*-azirinyl phosphonates from easily available tosyloximes, given that the modified Neber reaction[10] using tosylketoximes derived from phosphonates **2** seems to be an interesting method for the preparation of azirines.

The preparation of the required functionalized β-tosyloximes **2**,‡ can be easily accomplished by simple reaction of β-oximes **1** derived from phosphonates[11] with tosyl chloride in pyridine (Scheme 2, Table 1, entries 1–3). Alkyl and phenyl substituted 2*H*-azirines **3**§ were prepared from β-ketoximes **2** by treatment with triethylamine at room temperature for 8 h in benzene (Table 1, entries 4–6). This process can also be extended to the asymmetric synthesis of 2*H*-azirine **3** when stoichiometric amounts of chiral bases are used. Alkaloids such as quinidine (QN), hydroquinidine (HQ), sparteine (SP) or quinine (Q) were used and the best results were obtained with quinidine in benzene (Scheme 3, Table 1, entries 7, 9 and 12). The enantiopurity of azirines derived from phosphonate **3**¶ (ee 2–52%) was determined by ^{31}P NMR measurements in $CDCl_3$ using a chiral shift reagent ($Yb(tfc)_3$).



Scheme 2. 2*H*-Azirines formation through modified Neber reaction of tosyl ketoximes **2**

‡ All new compounds reported here gave satisfactory elemental analysis. Spectral data for **2a**: δ_H (300 MHz, $CDCl_3$): 7.79 (d, $^3J_{HH}=7.5$ Hz, 4H), 7.27 (d, $^3J_{HH}=7.5$ Hz, 4H), 3.98 (m, 8H), 2.97 (d, $^2J_{PH}=23.7$ Hz, 2H), 2.73 (d, $^2J_{PH}=21.9$ Hz, 2H), 2.38 (s, 6H), 2.05 (s, 3H), 2.06 (s, 3H), 1.12 (t, $^3J_{HH}=7.2$ Hz, 6H), 1.22 (t, $^3J_{HH}=7.2$ Hz, 6H) ppm; δ_P (120 MHz, $CDCl_3$): 19.8 and 21.4 ppm; δ_C (75.4 MHz, $CDCl_3$): 160.9 (d, $^2J_{PC}=8.1$ Hz), 158.9 (d, $^2J_{PC}=8.1$ Hz), 144.9 (s), 132.4–129.0 (m), 62.5 (s), 62.4 (s), 33.4 (d, $^1J_{PC}=135.8$ Hz), 29.2 (d, $^1J_{PC}=133.9$ Hz), 21.5 (s), 21.4 (s), 20.9 (s), 16.3 (s), 16.1 (s) ppm; *m*/*z* 364 ($[M+1]^+$, 18).

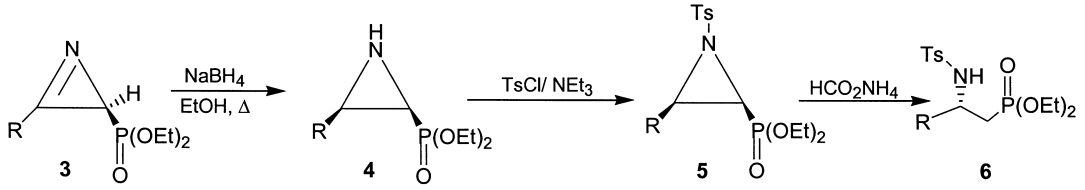
§ Spectral data for **3a** : δ_H (300 MHz, $CDCl_3$): 4.10 (m, 4H), 2.54 (s, 3H), 1.72 (d, $^2J_{PH}=39.3$ Hz, 1H), 1.32 (m, 6H) ppm; δ_P (120 MHz, $CDCl_3$): 23.1 ppm; δ_C (75.4 MHz, $CDCl_3$): 161.4 (d, $^3J_{PC}=3.5$ Hz), 62.1 (s), 22.5 (d, $^1J_{PC}=214.5$ Hz), 16.2 (s), 13.2 (d, $^3J_{PC}=2.0$ Hz) ppm; *m*/*z* 192 ($[M+1]^+$, 3).

¶ Optical rotation of compounds **3a** $[\alpha]_D^{20}=-19$ from quinidine, $[\alpha]_D^{20}=-2$ from (–)-sparteine, **3b** $[\alpha]_D^{20}=-27$ from quinidine, $[\alpha]_D^{20}=-24$ from hydroquinidine, $[\alpha]_D^{20}=+8$ from quinine, **3c** $[\alpha]_D^{20}=-104$ from quinidine, determined using a concentration c = 0.75 in CH_2Cl_2.

Table 1
Tosyloximes **2**, 2*H*-azirines **3**, aziridines **4**, **5** and β-aminophosphonates **6** obtained

Entry	Comp.	R	Base[a]	Yield (%)[b]	ee (%)	Entry	Comp.	R	Base[a]	Yield (%)[b]	ee (%)
1	**2a**	Me	-	73	-	10	**3b**	Et	HQ	92	22 (*S*)[c]
2	**2b**	Et	-	70	-	11	**3b**	Et	Q	94	8 (*R*)[c]
3	**2c**	Ph	-	35	-	12	**3c**	Ph	QN	85	52 (*S*)[c]
4	**3a**	Me	NEt_3	70	-	13	**4a**	Me	-	81	20 (2*S*, 3*R*)
5	**3b**	Et	NEt_3	79	-	14	**4b**	Et	-	82	24 (2*S*, 3*R*)
6	**3c**	Ph	NEt_3	69	-	15	**5a**	Me	-	60	20 (2*S*, 3*R*)
7	**3a**	Me	QN	90	20 (*S*)[c]	16	**5b**	Et	-	85	24 (2*S*, 3*R*)
8	**3a**	Me	SP	87	2 (*S*)[c]	17	**6a**	Me	-	74	20 (*R*)
9	**3b**	Et	QN	95	24 (*S*)[c]	18	**6b**	Et	-	76	24 (*R*)

[a] QN= Quinidine; SP= (-)- Sparteine; HQ= Hydroquinidine; Q= Quinine. [b] All compounds were isolated as oils. [c] Determined by ^{31}P-NMR using $Yb(tfc)_3$ as chiral shift reagent.



Scheme 3. Formation of aziridines **4**, **5** and β-aminophosphonates **6**

The absolute configuration of alkyl substituted azirines **3a**,**b** (R = Me, Et) was established by correlation with optically active β-aminophosphonates **6**,[12‖] and in the case of azirine **3c** the absolute configuration was established by correlation with the optical rotation of optically active 3-phenyl-2*H*-azirine,[8c] ($[\alpha]_D^{20} = -202$, $c = 0.32$, $CHCl_3$). Reduction of azirines derived from phosphonates **3** with sodium borohydride in ethanol gave exclusively *cis*-aziridines **4** (Table 1, entries 13 and 14). The stereochemical assignment was based on the large ring proton coupling constant observed for **4a** ($^3J_{HH} = 6.8$ Hz).[8c,13] Furthermore, no loss of chirality was observed. Enantiomerically enriched *N*-*p*-toluenesulfonyl-*cis*-aziridines **5** were prepared by treatment of aziridines **4** with *p*-toluenesulfonyl chloride in dichloromethane at room temperature in the presence of triethylamine (Scheme 3). The products were isolated by flash chromatography and the new aziridines **5** were obtained in excellent yields (Table 1, entries 15 and 16). Hydrogenolysis of *N*-substituted aziridines **5** was accomplished with HCO_2NH_4 and palladium on carbon in refluxing ethanol for 2 h (Table 1, entries 17 and 18), to give β-aminophosphonates **6** in good yields and retention of the configuration, in a similar way to that previously reported for aziridines derived from carboxylates.[2a,14]

In conclusion, we have devised a simple, mild, and convenient strategy for the synthesis, from readily available starting materials, of enantiomerically enriched 2*H*-azirines **3**, as well as *cis*-aziridines **4** and **5** substituted with a phosphonate group. These heterocycles may be very useful intermediates in organic synthesis[1,2] and for the preparation of a large variety of molecules that

‖ Optical rotation of compounds **4a** $[\alpha]_D^{20} = +1$, $c = 0.30$ in CH_2Cl_2, **4b** $[\alpha]_D^{20} = +1$, c = 0.75 in CH_2Cl_2, **5a** $[\alpha]_D^{20} = +2$, c = 0.45 in CH_2Cl_2, **5b** $[\alpha]_D^{20} = +2$, $c = 1.00$ in CH_2Cl_2, **6a** $[\alpha]_D^{20} = +6$, $c = 0.24$ in MeOH, **6b** $[\alpha]_D^{20} = +4$, $c = 0.38$ in MeOH.

could be useful in the synthesis of biologically active compounds of interest to medicinal chemistry.[3–6] Further studies on phosphonyl-2*H*-azirines **3** and -aziridines **4**, **5** are now in progress in our laboratory.

Acknowledgements

The present work has been supported by the Dirección General de Enseñanza Superior e Investigación Científica (Madrid. DGESIC, PB96-0252) and by the Departamento de Educación, Universidades e Investigación del Gobierno Vasco (Vitoria, PI 98-53). J. I. Gil thanks the Universidad del País Vasco for a predoctoral fellowship.

References

1. For reviews on azirines, see: (a) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 1, pp. 1–60. (b) Backes, J. In *Methoden der Organische Chemie (Houben-Weyl);* Thieme, G., Eds.; Stuttgart, 1992; Vol. E16c; pp. 317–369.
2. (a) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T. V.; Reddy, G. V.; Zhang, Y. L. *J. Org. Chem.* **1999**, *64*, 7559–7567. (b) Albrecht, E.; Mattay, J.; Steenken, S. *J. Am. Chem. Soc.* **1997**, *119*, 11605–11610.
3. (a) Miller, T. M.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48–50. (b) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103–2105. (c) Salomon, C. E.; William, D. H.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 1463–1466.
4. For reviews, see: (a) Engel, R. In *Handbook of Organophosphorus Chemistry*; Dekker, M. Inc.: New York, 1992. (b) Kafarski, P.; Lejezak, B. *Phosphorus & Sulfur* **1991**, *63*, 193–215.
5. (a) Allenberger, F.; Klare, Y. *J. Antimicrob. Chemother.* **1999**, *43*, 211–217. (b) Kawakami, Y.; Furuwatari, C.; Akahane, T.; Okimura, Y.; Fusihata, K.; Katsuyama, T.; Matsumoto, H. *J. Antibiot.* **1994**, *47*, 507–510. (c) Tsuboi, T.; Ida, H.; Yoshikawa, E.; Hiyoshi, S.; Yamagi, E.; Nakayama, Y.; O'Hara, K.; Nonomiya, T.; Shigenobu, F.; Toniguchi, K.; Shimizu, M.; Sawai, T.; Mizuokowa, K. *Clin. Chim. Acta* **1999**, *279*, 175–179.
6. (a) Smith, A. B.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879–10888. (b) Hirschmann, R.; Smith, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Spengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234–237. (c) Meyer, J. H.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4600–4609. (d) Smith, A. B.; Yager, K. M.; Taylor, C. M. PCT Int. Appl. WO 95 25,11, 1995; *Chem. Abstr.* **1996**, *124*, 87370.
7. (a) Davis, F. A.; Liu, H.; Liang, C.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 8929–8935. (b) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651–3652. (c) Gentillucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665–4668. (d) Verstappen, M. M. H.; Arians, G. J. A.; Zwanenburg, B. *J. Am. Chem. Soc.* **1996**, *118*, 8491–8492. (e) Piskunova, I. P.; Eremeev, A. V.; Mishnev, A. F.; Vosekalna, I. A. *Tetrahedron* **1993**, *49*, 4671–4676.
8. (a) Alcaraz, G.; Wecker, U.; Baceiredo, A.; Dahan, F.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1246–1248. (b) Piquet, V.; Baceiredo, A.; Gornitzka, H.; Dahan, F.; Bertrand, G. *Chem. Eur. J.* **1997**, *3*, 1757–1264. (c) Davis, F. A.; McCoull, W. *Tetrahedron Lett.* **1999**, *40*, 249–252.
9. (a) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron* **1999**, *55*, 13767–13778. (b) Palacios, F.; Ochoa de Retana, A.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 5947–5964. (c) Palacios, F.; Gil, M. J.; Martínez, E.; Rodríguez, M. *Tetrahedron Lett.* **1999**, *40*, 2411–2414.
10. (a) Neber, P. W.; Burghard, A. *Justus Liebigs Ann. Chem.* **1932**, *493*, 281–294. (b) McCarthy, C. G. In *The Chemistry of the Carbon–Nitrogen Bond*; Patai, S., Ed.; Interscience: New York, 1973; pp. 447–452.
11. Palacios, F.; Aparicio, D.; de los Santos, J. M.; Rodríguez, E. *Tetrahedron* **1998**, *54*, 599–614.
12. Duggan, M. E.; Karanewsky, D. S. *Tetrahedron. Lett.* **1983**, *24*, 2935–2938.
13. (a) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379–8385. (b) Hori, K.; Sugihara, H.; Ito, Y. N.; Katsubi, T. *Tetrahedron Lett.* **1999**, *40*, 5207–5210.
14. (a) Chandrasekhar, S.; Ahmed, M. *Tetrahedron Lett.* **1999**, *40*, 9325–9327. (c) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243–3245.