Pergamon

Tetrahedron Letters 41 (2000) 3161–3163

TETRAHEDRON LETTERS

Solid phase synthesis of sulfahydantoins

Fernando Albericio,[a,*] Javier Garcia,[a,b] Enrique L. Michelotti,[b,*] Ernesto Nicolás [a] and Colin M. Tice [b,*]

[a] *Department of Organic Chemistry, University of Barcelona, 08028- Barcelona, Spain*
[b] *Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477-0904, USA*

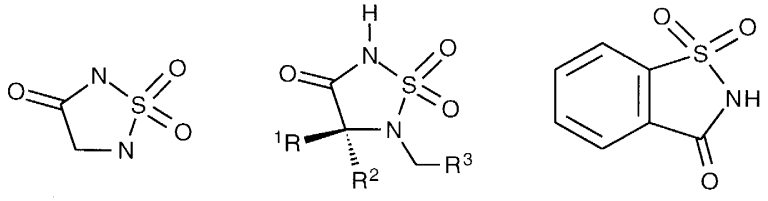
Received 17 December 1999; accepted 21 February 2000

Abstract

A five step solid phase synthesis of 2-unsubstituted 1,2,5-thiadiazolidin-3-one 1,1-dioxides (sulfahydantoins) from N^{α}-FMOC-amino acids and aromatic aldehydes is described. The key step is the base mediated cyclitive cleavage of a resin bound N^{α}-(aminosulfonyl)-N^{α}-benzyl-amino acid to afford the desired product. This synthesis allows the preparation of a diverse library of compounds based on this heterocycle.

Keywords: amino acids; combinatorial chemistry; cyclitive cleavage; libraries; thiadiazoles.

The first example of the 1,2,5-thiadiazolidin-3-one 1,1-dioxide ('sulfahydantoin', **1**) ring system was reported in the literature by Vorreither and Ziegler in 1965.[1] Subsequently several groups have reported syntheses of compounds containing this heterocycle.[2] In recent years sulfahydantoins have been extensively investigated as inhibitors of serine proteases with potential therapeutic application against diseases such as emphysema and rheumatoid arthritis mediated by these enzymes.[3] In addition sulfahydantoins have been investigated as antihypertensives,[4] artificial sweeteners,[2f] and histamine H_2-receptor antagonists.[5]



1 **1 a** **2**

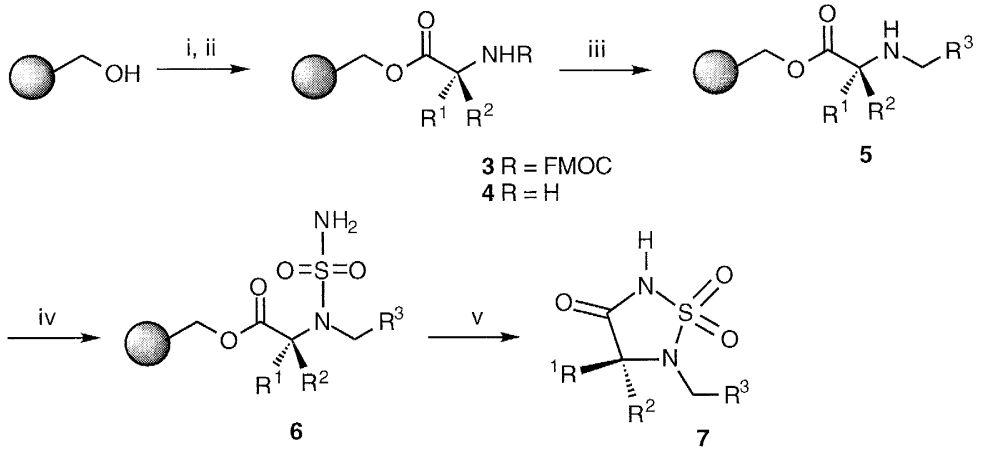
In the course of our efforts to apply solid phase methods to the production of libraries of compounds for the discovery of novel crop protection agents, we became interested in the sulfahydantoins. By analogy with the artificial sweetener saccharin (**2**), we anticipated that *N*-2-unsubstituted sulfahydantoins (**1a**) would be weakly acidic with pK_as in the same range as carboxylic acids.[6] Weakly acidic compounds

* Corresponding authors.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00321-X

are often phloem-mobile in plants and crop protection agents with this property ('systemicity') are particularly desirable.[7]

The solid phase synthesis of sulfahydantoins is shown in Scheme 1. The chemistry was developed on a Wang-resin (Polymer Labs, 1.7 mmol/g) and on an MBHA-resin (Novabiochem, 1.2 mmol/g) to which the *p*-alkoxybenzyl alcohol (AB) linker was anchored. FMOC protected phenylalanine was coupled to the resin under standard conditions using DIC and DMAP in a mixture of CH_2Cl_2 and DMF (2 cycles) to give **3a** (R^1=$PhCH_2$, R^2=H). The FMOC group was removed using 20% piperidine in DMF to afford **4a**. Reductive alkylation of the resin bound phenylalanine with 4-methoxybenzaldehyde was accomplished following the procedure of Szardenings et al. to give **5a**.[8] Sulfamoyl chloride was prepared from formic acid and chlorosulfonyl isocyanate[2a,2c,9] and immediately reacted with **5a** in the presence of 2,4,6-collidine to afford the resin bound sulfamide intermediate **6a**. An alternative procedure in which **5a** was reacted with sulfamide required temperatures >150°C and was not pursued.[10] Treatment of the substituted sulfamide **6a** with base was expected to afford the desired product **7a** by a cyclitive cleavage.[11] Initial attempts to effect this reaction using sodium methoxide in methanol and THF gave unsatisfactory results. Better results were obtained with DBU in CH_2Cl_2. Treatment of the crude product with Amberlyst A-15 served to remove DBU and **7a** was obtained in 76% purity and 23% yield.



Scheme 1. Solid phase synthesis of sulfahydantoins. (i) FMOC-$NHCR^1R^2CO_2H$ (3 equiv.), DIC (3 equiv.), DMAP (0.3 equiv.), CH_2Cl_2–DMF (5:1), 2 h, rt; (ii) piperidine–DMF (1:4), 20 min, rt; (iii) R^3CH_2CHO (11 equiv.), HOAc (2 equiv.), CH_2Cl_2–$(MeO)_3CH$ (1:1), 5 h, rt then $NaCNBH_3$ (11 equiv.), CH_2Cl_2–$(MeO)_3CH$ (1:1), 3×2 h, rt; (iv) H_2NSO_2Cl (6 equiv.), 2,4,6-collidine (10 equiv.), CH_2Cl_2, 4 h, rt; (v) DBU, CH_2Cl_2, 5 h, rt

This procedure was applied to several amino acids and aromatic aldehydes to give the products shown in Table 1. The use of Amberlyst A-15 to remove DBU precludes the use of amino acids with basic side chains and aldehydes with basic functionality. Furthermore when an aliphatic aldehyde was used no product was obtained. Despite these limitations, a diverse array of sulfahydantoins can be prepared using this methodology.

In conclusion, we have developed a workable solid phase synthesis of sulfahydantoins which has allowed the preparation of a library compounds for biological testing.

Acknowledgements

We wish to thank Mark Eisenschmied and Francis Acholla for analytical support.

Table 1
Sulfahydantoins synthesized

Entry	Resin	R^1	R^2	R^3	Product	Purity[a] (%)	Yield[b] (%)
1a	Wang	$PhCH_2$	H	4-MeO-C_6H_4	**7a**	76	23
1b	AB-MBHA				7a	75	26
2	AB-MBHA	$PhCH_2$	H	2,4-diCl-C_6H_3	**7b**	82	27
3	AB-MBHA	*i*-Pr	H	3-Me-C_6H_4	**7c**	86	20
4	AB-MBHA	*i*-Pr	H	3-thienyl	**7d**	100	11
5	AB-MBHA	*i*-Pr	H	4-CF_3-C_6H_4	**7e**	91	20
6	AB-MBHA	*i*-Pr	H	3,4-ethylenedioxy-C_6H_3	**7f**	95	31
7	Wang	*i*-Pr	H	2-Cl-C_6H_4	**7g**	96	20
8	AB-MBHA	Me	Me	4-MeO-C_6H_4	**7h**	100	16
9	AB-MBHA	$CH_2CO_2CH_2CH{=}CH_2$	H	3-thienyl	**7i**	60	7
10	Wang	$MeSCH_2CH_2$	H	2-Cl-C_6H_4	**7j**	87	18

a. Purity was determined by HPLC with UV detection at 220 nm. All products were identified by negative ion electrospray mass spectroscopy and by ^{1}H-NMR (200 MHz, $CDCl_3$). For instance, for **1a**: 7.2-7.3 (3 H, m, Ar); 7.0-7.1 (2 H, m, Ar); 7.02 (2 H, d, J = 8.7 Hz, Ar); 6.78 (2 H, d, J = 8.7 Hz, Ar); 4.33 (1 H, d, J = 15.0 Hz, CH benc.); 4.08 (1 H, m, $C^{\alpha}H$); 3.92 (1 H, d, J = 15.0 Hz, CH benc.); 3.78 (3 H, s, OCH_3); 3.10 (2 H, m, $C^{\beta}H_2$).

b. Yield was calculated based on the initial functionalisation of the polymeric support.

References

1. Vorreither, H. K.; Ziegler, E. *Monatsh. Chem*. **1965**, *96*, 216–219.
2. (a) Timberlake, J. W.; Ray, W. J.; Stevens, E. D.; Klein, C. L. *J. Org. Chem*. **1989**, *54*, 5824–5826. (b) Lee, C.-H.; Korp, J. D.; Kohn, H. *J. Org. Chem*. **1989**, *54*, 3077–3083. (c) Lee, C.-H.; Kohn, H. *J. Org. Chem.* **1990**, *55*, 6098–6104. (d) Aouf, N.; Dewynter, G.; Montero, J. L. *Tetrahedron Lett*. **1991**, *32*, 6545–6546. (e) Dewynter, G.; Aouf, N.; Regainia, Z.; Montero, J. L. *Tetrahedron* **1996**, *52*, 993–1004. (f) Muller, G. W.; DuBois, G. E. *J. Org. Chem*. **1989**, *54*, 4471–4473. (g) Hanewacker, G. A.; Mester, Z.; Unterhalt, B. *Arch. Pharm.* **1993**, *326*, 497–505.
3. (a) Kuang, R.; Epp, J. B.; Ruan, S.; Yu, H.; Huang, P.; He, S.; Tu, J.; Schechter, N. M.; Turbov, J.; Froelich, C. J.; Groutas, W. C. *J. Am. Chem. Soc.* **1999**, *121*, 8128–8129. (b) Groutas, W. C.; Schechter, N. M.; He, S.; Yu, H.; Huang, P.; Tu, J. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2199–2204. (c) Groutas, W. C.; Kuang, R.; Ruan, S.; Epp, J. B.; Venkataraman, R.; Truong, T. M. *Bioorg. Med. Chem.* **1998**, *6*, 661–671. (d) Groutas, W. C.; Kuang, R.; Venkataraman, R.; Epp, J. B.; Ruan, S.; Prakash, O. *Biochemistry* **1997**, *36*, 4739–4750 (e) Groutas, W. C.; Kuang, R. WO 9909977 (f) Court, J. J.; Desai, R. C. WO 9616970. (g) Desai, R. C. WO 9616951. (h) Desai, R. C. WO 9616654. (i) Desai, R. C.; Hlasta, D. J. US 5512576. (j) Court, J. J.; Desai, R. C.; Hlasta, D. J. US 5494925.
4. Mantegani, S.; Brambilla, E.; Caccia, C.; Chiodini, L.; Ruggieri, D.; Lamberti, E.; Di Salle, E.; Salvati, P. *Farmaco* **1998**, *53*, 293–304.
5. Crenshaw, R. R.; Algieri, A. A. US 4394508.
6. (a) Lipinski, C. A.; Fiese, E. F.; Korst, R. J. *Quant. Struct.-Act. Relat*. **1991**, *10*, 109–117. (b) Lipinski, C. A. *Annu. Rep. Med. Chem*. **1986**, *21*, 283–291. (c) Lipinski, C. A.; Chenard, B. L. *Pestic. Sci.* **1990**, *29*, 227–240.
7. (a) Kleier, D. A. *Pestic. Sci*. **1994**, *42*, 1–11. (b) Brudenell, A. J.P.; Baker, D. A.; Grayson, B. T. *Plant Growth Regulation* **1995**, *16*, 215–231.
8. Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem*. **1996**, *61*, 6720–6722
9. Graf, R. *Chem. Ber*. **1959**, *92*, 509–513.
10. Paquin, A. M. *Angew. Chem*. **1948**, *60*, 316–320.
11. DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M.R.; Pavia, M. R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909–6913.