ChemComm

Solid-phase synthesis of novel achiral hydantoin- and isoxazoline-substituted dispirocyclobutanoids†

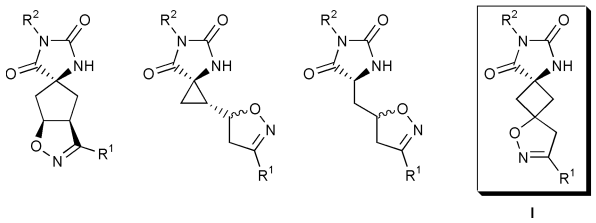
Kyung-Ho Park and Mark J. Kurth*

Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616 USA

Received (in Corvallis, OR, USA) 18th May 2000, Accepted 31st July 2000
First published as an Advance Article on the web 11th September 2000

A synthesis of novel achiral hydantoin- and isoxazoline-substituted dispirocyclobutanoids from solid-phase synthesis has been achieved. The facial and selective Boc-NH-mediated hydrogen-bond delivery of the nitrile oxide afforded 6 as the major compound.

In the field of drug discovery, considerable effort has been applied to the synthesis of hydantoin derivatives[1] using both solution- and solid-phase organic synthesis techniques. Many of the hydantoins reported to date are either racemic or diastereomeric mixtures. For example, we have synthesized a number of hydantoins.[1i–l]



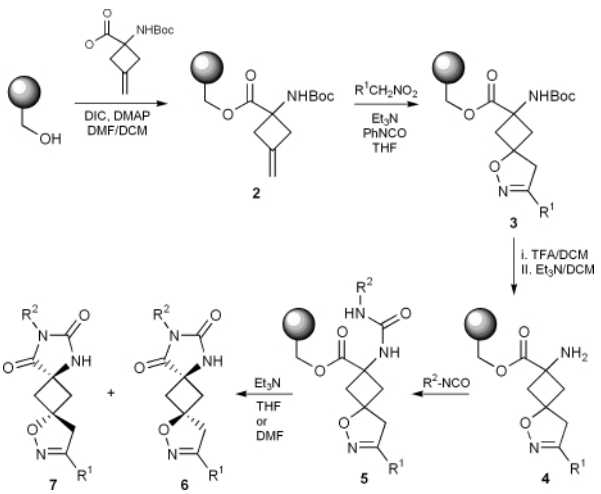
I

The need to further diversify these compounds, together with recent reports regarding the biological activities of spirohydantoins[2] and spiroisoxazolines,[3] led us to explore development of a solid-phase synthetic strategy for the construction of hydantoin- and isoxazoline-containing heterocycle **I** with its central cyclobutane core. In this dispiro [4.1.4.1] system, the target molecule itself is achiral and thus avoids the formation of racemic mixtures—an important synthetic consideration when designing a potential drug scaffold.

Our solid-phase approach to **I** began with the coupling of Boc-protected amino acid **1**[4] with hydroxymethyl substituted polystyrene (1.1 mmol OH gram^{-1}) in the presence of 1,3-diisopropylcarbodiimide (DIC). A solid-phase 1,3-dipolar cycloaddition reaction[5] of the alkene moiety in **2** with a Mukaiyama-generated nitrile oxide[6] delivered resin **3**. Deprotection of the Boc moiety (TFA–CH_2Cl_2) and neutralization (Et_3N) of the resin delivered amino ester **4**. Treatment of this intermediate with isocyanates gave the urea ester intermediate **5** which released the achiral dispirohydantoins **6** and **7** by treatment with Et_3N (Scheme 1, Table 1). In previous studies,[1i–j] we discovered that urea-NH in cyclopentenyl amino acids can be a very effective stereocontrol element in solid-phase intermolecular nitrile oxide 1,3-dipolar cycloaddition reactions. With **2** now in hand, we were positioned to probe whether the Boc-NH moiety here would mediate similar stereoselectivity.

Indeed, the *exo*-methylenecyclobutane system realized some diastereoselectivity such that the H-bond directed product (*i.e.* **6**) was obtained with ≈3:1 selectivity relative to the non-H-bond directed product (*i.e.* **7**). X-ray crystallographic analysis of **6c**‡ (Fig. 1) verified the relative stereochemistries of **6**/**7**. This solid-phase stereoselectivity is in accord with our preliminary solution-phase studies where the ethyl ester equivalent of **2** (R^1 = C_6H_5–) undergoes 1,3-dipolar cycloaddition giving the ethyl ester equivalent of **3** with ≈3:1 stereoselectivity. Moreover, the solution-phase parallels of **2** → **3** → **4** → **5** → **6** (R^1 = C_6H_5–; R^2 = $C_6H_5CH_2$–) proceed in 52% overall yield (64, 89, 96, and 95%, respectively), while the solid-phase overall yield of **6** + **7** from hydroxymethyl substituted polystyrene (*i.e.* one additional step; **1** → **2**) is 45–56%. Thus, while solution- and solid-phase yields are comparable, the solid-phase protocol reported here enjoys the typical advantages of bead-based chemistry[7] and it allows for the easy manipulation of diastereomer mixtures with only end-product (*i.e.* **6** and **7**) separation.

Typical procedure for solid-phase synthesis of dispirohydantoins. A solution of DMAP (20 mg, 0.16 mmol) in DMF–CH_2Cl_2 (1 mL–4 mL) was prepared. Boc-protected amino acid **1** (0.37 g, 1.65 mmol) and DIC (0.21 g, 1.65 mmol) were dissolved in DMF–CH_2Cl_2 (1–4 mL) and this solution was added to the flask which contained the hydroxymethyl substituted polystyrene (0.5 g, 0.55 mmol, 1.1 mmol OH gram^{-1}). Finally the DMAP solution was added and the reaction mixture was stirred overnight at ambient temperature. The resin was washed with DMF, CH_2Cl_2, and ether, and dried to give the resin **2**. Resin **2** was swollen in THF (15 mL) and nitropropane (0.15 g, 1.65 mmol), phenylisocyanate (0.39 g, 3.3 mmol), and Et_3N (15 mg) were added. The reaction mixture was stirred at 60 °C overnight, then washed with DMF, CH_2Cl_2, and ether. This 1,3-dipolar cycloaddition step was repeated a second time. Drying *in vacuo* gave the resin **3** (R^1 = Et) which was treated



Scheme 1

Table 1 Dispirocyclobutanoids (**6**/**7**) from solid-phase synthesis

Compound	R^1	R^2	% Yield[a]
6a	C_6H_5CO–	C_6H_5–	40
7a	C_6H_5CO–	C_6H_5–	16
6b	Et–	$C_6H_5CH_2$–[b]	36
7b	Et–	$C_6H_5CH_2$–[b]	11
6c	C_6H_5CO–	^{n}Bu–[b]	35
7c	C_6H_5CO–	^{n}Bu–[b]	10
6d	Et–	C_6H_5–	39
7d	Et–	C_6H_5–	15

[a] Overall yield from hydroxymethyl substituted polystyrene. [b] Cyclo-elimination was achieved using DMF.

DOI: 10.1039/b004033i

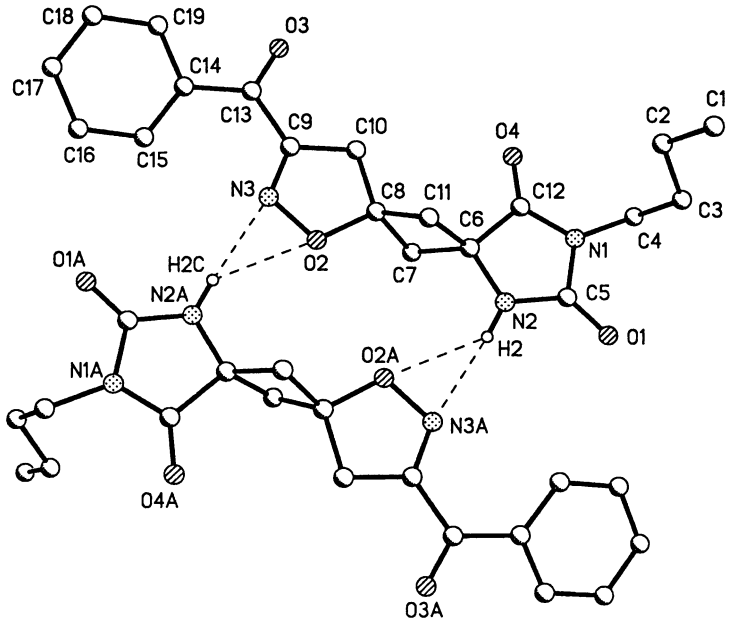


Fig. 1

with 50% TFA–CH_2Cl_2 (20 mL) at ambient temperature for 1 h. The resin was washed with DMF and CH_2Cl_2, followed by treatment with 10% Et_3N in CH_2Cl_2 (20 mL) for 1 h. The resulting resin was washed with DMF, CH_2Cl_2, and ether, and dried under vacuum to give resin-bound **4** with its free amine functional group. Resin **4** was treated with benzyl isocyanate (0.22 g, 1.65 mmol) in THF overnight at ambient temperature. The resin was washed with THF, DMF, and CH_2Cl_2 to afford the urea **5** (R^1 = Et–, R^2 = $C_6H_5CH_2$–). This resin was treated with Et_3N (0.33 g, 3.3 mmol) in DMF (20 mL) at 110 °C for 30 h to release the achiral dispirohydantoins as a mixture (**6b**:**7b** = 3:1), which was finally separated by column chromatography (ethyl acetate–hexane = 1:4) to give **6b** (62 mg, 0.2 mmol, 36% overall yield§) and **7b** (20 mg, 0.06 mmol, 11% overall yield§). **6b**: Mp 157 °C; FTIR (KBr) 3259, 2939, 1760, 1723, 1450 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37–7.23 (m, 5H), 7.11 (s, 1H), 4.62 (s, 2H), 3.32 (s, 2H), 2.95 (d, 2H, J = 13.8 Hz), 2.78 (d, 2H, J = 13.8 Hz), 2.34 (q, 2H, J = 7.4 Hz), 1.15 (t, 3H, J = 7.4 Hz); δ_C (75 MHz, $CDCl_3$) 176.8, 161.4, 155.7, 135.9, 128.6, 128.4, 127.8, 77.6, 53.4, 47.9, 46.6, 42.1, 21.3, 10.6; Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.11; H, 6.08; N, 13.27%. **7b**: Mp 194 °C; FTIR (KBr) 3196, 2934, 1778, 1714, 1431 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.21 (s, 1H), 7.32–7.25 (m, 5H), 4.63 (s, 2H), 3.26–3.23 (m, 4H), 2.42–2.34 (m, 4H), 1.16 (t, 3H, J = 7.5 Hz); δ_C (75 MHz, $CDCl_3$) 174.2, 160.4, 158.0, 135.8, 128.6, 128.3, 128.0, 79.0, 54.8, 48.1, 46.6, 42.4, 21.4, 10.8; Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.36; H, 6.17; N, 13.41%.

In summary, we have developed a synthetic strategy for the preparation of novel heterocycles of generalized structure **I** from solid-phase. The work reported here secures this stage in a program aimed at the structural diversification of hydantoin- and isoxazoline-based pharmacophores. Combinatorial library production employing this general and expedient synthetic solid-phase methodology and subsequent biological evaluation are underway.

Notes and references

† We thank the National Science Foundation for financial support of this research and the National Science Foundation CRIF program (CHE-9808183) for Varian Inova 400 MHz and Mercury 300 MHz NMR instrument purchases.

‡ *Crystal data*: for **6c** $C_{19}H_{21}N_3O_4$, colorless plate, M = 355.39, triclinic, space group $P1$, a = 6.1496(7) Å, α = 93.194(2)°, b = 96315(11) Å, β = 92.728(2)°, c = 15.2827(10) Å, γ = 106.031(2)°, U = 866.77(15) $Å^3$, Z = 2, D_c = 1.362 Mg m^{-3}, μ = 0.097 mm^{-1}, R = 0.0515, wR = 0.1206, GOF = 1.008, T = 89(2) K, $F(000)$ = 376, 4328 independent reflections were collected on a Bruker SMART 1000 (λ = 0.71073 Å).

§ The optimized solid-phase overall yield of **6b** + **7b** is 47% which translates to ≈86% yield per step from **1**.

1 (*a*) B. A. Dressman, L. A. Spangle and S. W. Kaldor, *Tetrahedron Lett.*, 1996, **37**, 937; (*b*) S. Hanessian and R. Y. Yang, *Tetrahedron Lett.*, 1996, **37**, 5835; (*c*) J. Matthews and R. A. Rivero, *J. Org. Chem.*, 1997, **62**, 6090; (*d*) X. Xiao, K. Ngu, C. Chao and D. V. Patel, *J. Org. Chem.*, 1997, **62**, 6968; (*e*) J. Stadlweiser, E. P. Ellmerer-Muller, A. Taco, N. Maslouh and W. Bannwarth, *Angew. Chem. Int. Ed.*, 1998, **37**, 1402; (*f*) L. J. Wilson, M. Li and D. E. Portlock, *Tetrahedron Lett.*, 1998, **39**, 5135; (*g*) A. Nefzi, C. Dooley, J. M. Ostresh and R. A. Houghten, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2273; (*h*) A. Boeijen, J. A. W. Kruijtzer and R. M. J. Liskamp, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2375; (*i*) K.-H. Park, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 1998, **63**, 113; (*j*) K.-H. Park, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 1998, **63**, 6579; (*k*) K.-H. Park, E. Abbate, S. Najdi, M. M. Olmstead and M. J. Kurth, *Chem. Commun.*, 1998, 1679; (*l*) K.-H. Park and M. J. Kurth, *Tetrahedron Lett.*, 1999, **40**, 5841.

2 (*a*) T. W. Brandstetter, Y. Kim, J. C. Son, H. M. Taylor, P. M. de Q. Lilley, D. J. Watkin, L. N. Johnson, N. G. Oikonomakos and G. W. J. Fleet, *Tetrahedron Lett.*, 1995, **36**, 2149; (*b*) H. Haruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima and T. Haneishi, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1637; (*c*) S. Mio, H. Sano, M. Shindou, T. Honma and S. Sugai, *Agric. Biol. Chem.*, 1991, **43**, 133.

3 (*a*) J. Wityak, T. M. Sielecki, D. J. Pinto, G. Emmett, J. Y. Sze, J. Liu, A. E. Tobin, S. Wang, B. Jiang, P. Ma, S. A. Mousa, R. R. Welxler and R. E. Olson, *J. Med. Chem.*, 1997, **40**, 50; (*b*) P. Ciminiello, C. Dell'Aversano, E. Fattorusso, S. Magno and M. Pansini, *J. Nat. Prod.*, 1999, **62**, 590.

4 K.-H. Park and M. J. Kurth, *J. Org. Chem.*, 2000, **65**, in the press.

5 *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley; New York, 1984, Vol. 1 and 2.

6 For reviews of nitrile oxide–isoxazoline methodology, see (*a*) D. P. Curran, *Advances in Cycladdition*, 1988, **1**, 129; (*b*) K. B. G. Torssel, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH Publishers, Weinheim, 1988.

7 M. J. Kurth, *Chimia*, 1996, **50**, 261.