Reverse Regioselection in the Synthesis of Spiropyrazolobarbiturates Using C-Br and C-H Nitrilimines

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Received 30 September 2004

Abstract: The 1,3-dipolar cycloaddition of arylmethylenebarbiturates **4** with C-Br **2** and C-H **3** nitrilimines gives spiropyrazolobarbiturates **5** and **6** with reverse regioselectivities.

Key words: dipolar cycloaddition, nitrile imines, spirans, bromoderivatives

Barbituric acid derivatives are a class of compounds whose potential biopharmacological activity is strictly dependent on the side groups attached to the ring. Thus, many efforts have been made to synthesize new barbiturates, often with contradictory results. Indeed, while these derivatives have historically been employed as sedative-hypnotic drugs,[1] they have more recently found promising applications in fields such as cancer and AIDS therapy and as protease inhibitors.[2]

In this direction and on the basis of our experience, we studied the possibility of generating spiropyrazolobarbiturates of interest by means of cycloaddition reactions between arylidenebarbiturates and the C-Br[3] and C-H nitrilimine dipoles, which we were the first to synthesize. Using this synthetic approach and encouraged by the promising results obtained in a preliminary study,[4] we developed a strategy that allows complete control of the regioselectivity of cycloaddition.

By making suitable variations in the experimental conditions already described for the preparation of C-Br nitrilimines **2**,[3a] we were also able to obtain the new C-H nitrilimine **3**.[5] This is generated in situ at –60 °C by treatment of **1** with *N*-bromosuccinimide (NBS) in dimethylformamide (DMF) followed by dehydrohalogenation with TEA at room temperature.

Having thus established the conditions necessary for the preparation of the two dipoles, we performed the reaction with arylidenebarbiturates **4**, which led to the formation of spirans **5**[6] and **6**[7] (Scheme 1).

In all cases studied (Table 1) a single regioisomer was always isolated in moderate yields (21–55%).

The results clearly indicate the influence of reaction conditions on the regiochemical behavior of the two dipoles. The useful and complete inversion of regioselectivity can only be obtained under the stringent experimental conditions described.[8]

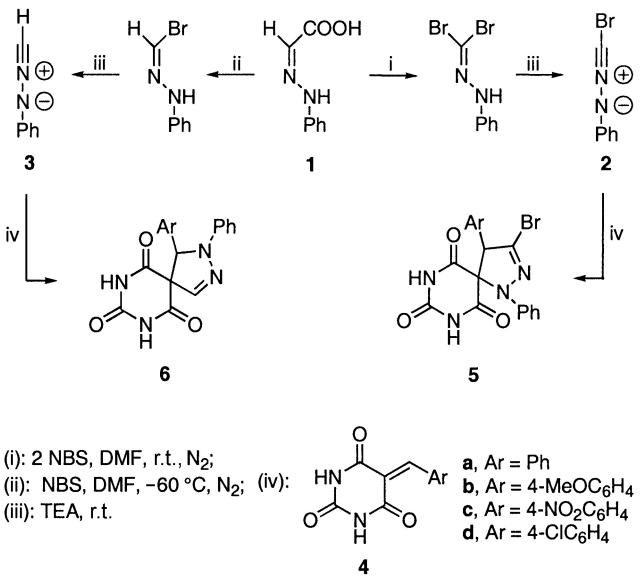
Table 1 Synthesis of Spiroderivatives **5** and **6**

Entry	Substrate **4**	Dipole	Spiran	Yield (%)[a]
1	**a**	**2**	**5a**	55
2	**a**	**3**	**6a**	25
3	**b**	**2**	**5b**	26
4	**b**	**3**	**6b**	46
5	**c**	**2**	**5c**	42
6	**c**	**3**	**6c**	21
7	**d**	**2**	**5d**	31
8	**d**	**3**	**6d**	39

[a] Yields are of isolated pure products.

All new compounds were fully consistent with the spectral data.[9,10]

The structure of spirans **5** and **6** was confirmed by X-ray crystallographic analysis carried out on **5a** and **6b**.[11]



Scheme 1

SYNLETT 2005, No. 1, pp 0125–0126
Advanced online publication: 29.11.2004
DOI: 10.1055/s-2004-836046; Art ID: G34304ST

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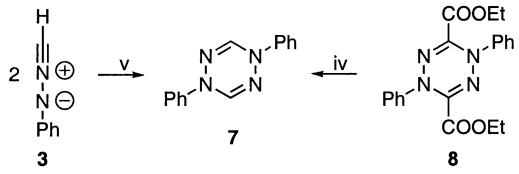
(4) This initial biological screening was carried out exclusively on the mixtures of bromospiranic derivatives obtained in the initial experiments, see: Galati, E. M.; Monforte, M. T.; Miceli, N.; Ranieri, E. *Il Farmaco* **2001**, *56*, 459.

(5) The formation of the new dipole **3** is further confirmed by the formation of tetrazine **7**. Indeed, after being prepared and left for one hour under stirring in the same reaction conditions, compound **3** is transformed into the known self-condensation derivative **7** (obtained by the alkaline hydrolysis of ester derivative **8**, Scheme 2).[12]



(v): 1h, DMF, –60 °C, N_2
(iv): H^+ or OH^-, $-CO_2$

Scheme 2

(6) **Typical Procedure for C-Br Nitrilimine Cycloaddition.** To a stirred solution of phenylhydrazone **1** (10 mmol) in DMF (20 mL) at r.t. was added dropwise a solution of NBS (20 mmol) in DMF (20 mL) under nitrogen. After additional stirring (15 min), dipolarophile **4** (50 mmol) was added at r.t. and then dropwise TEA (10 mmol). The reaction mixture was left to stand for 2 h, poured into cold H_2O (100 mL) and extracted three times with Et_2O; the organic layer was washed with H_2O and brine, dried over anhyd Na_2SO_4 and concentrated. The cycloadducts **5** were isolated by flash chromatography on silica gel (eluent: Et_2O).

(7) **Typical Procedure for C-H Nitrilimine Cycloaddition.** This procedure is similar to the above but with an operating temperature in the first phase of –60 °C and the addition of 10 mmol of NBS in DMF (10 mL). Cycloadducts **6** were isolated by flash chromatography on silica gel (eluent: Et_2O).

(8) By varying the above conditions, traces of the other regioisomers can be detected.

(9) Selected data. Compound **5a**: mp 254–255 °C. IR (nujol): 1714 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.53 (s, 1 H), 6.75–7.41 (m, 10 H). ^{13}C NMR (DMSO-d_6): δ = 68.6, 76.7, 112.8, 120.3, 128.6, 129.3, 130.1, 130.8, 142.1, 148.7, 164.3, 167.2. MS (EI): *m/z* = 412/414 [M^+]. Compound **5b**: mp 236–237 °C. IR (nujol): 1724 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.74 (s, 3 H), 5.45 (s, 1 H), 6.71–7.33 (m, 9 H). ^{13}C NMR (DMSO-d_6): δ = 55.2, 68.3, 76.7, 112.8, 114.1, 120.3, 129.2, 129.3, 131.5, 142.2, 146.0, 148.9, 159.9, 164.5, 167.4. MS (EI): *m/z* = 442/444 (M^+). Compound **5c**: mp 251–252 °C. IR (nujol): 1718 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.84 (s, 1 H), 6.71–8.42 (m, 9 H). ^{13}C NMR (DMSO-d_6): δ = 67.0, 76.4, 113.0, 120.6, 123.7, 127.3, 129.3, 131.7, 138.4, 141.8, 148.0, 148.6, 164.1, 166.5. MS (EI): *m/z* = 457/459 (M^+). Compound **5d**: mp 250–251 °C. IR (nujol): 1720 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.61 (s, 1 H), 6.68–7.88 (m, 9 H). ^{13}C NMR (DMSO-d_6): δ = 67.6, 76.5, 112.9, 120.5, 128.2, 128.8, 129.4, 130.0, 132.0, 142.0, 148.8, 162.4, 164.3, 167.0. MS (EI): *m/z* = 446/448/450 (M^+).

(10) Selected data. Compound **6a**: mp 138–139 °C. IR (nujol): 1713 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.39 (s, 1 H), 6.86 (s, 1 H), 6.70–7.40 (m, 10 H). ^{13}C NMR (DMSO-d_6): δ = 70.3, 73.8, 114.6, 120.3, 128.6, 128.8, 134.3, 137.4, 144.3, 146.0, 150.1, 166.4, 169.7. MS (EI): *m/z* = 334 (M^+). Compound **6b**: mp 130–131 °C. IR (nujol): 1713 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 3.71 (s, 3 H), 5.31 (s, 1 H), 6.87 (s, 1 H), 6.78–7.20 (m, 9 H). ^{13}C NMR (DMSO-d_6): δ = 55.0, 70.3, 73.5, 112.8, 113.9, 114.6, 125.9, 128.7, 144.3, 145.9, 150.1, 159.4, 167.1, 169.7. MS (EI): *m/z* = 364 (M^+). Compound **6c**: mp 135–136 °C. IR (nujol): 1713 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.75 (s, 1 H), 6.90 (s, 1 H), 6.75–8.32 (m, 9 H). ^{13}C NMR (DMSO-d_6): δ = 70.1, 71.5, 114.3, 120.4, 123.5, 129.0, 129.1, 137.2, 142.2, 143.6, 147.6, 149.9, 166.1, 168.8. MS (EI): *m/z* = 379 (M^+). Compound **6d**: mp 155–156 °C. IR (nujol): 1718 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 5.48 (s, 1 H), 6.84 (s, 1 H), 6.72–7.42 (m, 9 H). ^{13}C NMR (DMSO-d_6): δ = 70.1, 72.3, 112.8, 114.4, 120.2, 128.5, 128.8, 129.3, 133.3, 137.2, 143.9, 145.9, 150.0, 166.3, 169.3. MS (EI): *m/z* = 368/370 (M^+).

(11) X-ray data to be submitted to *Acta Crystallogr.*

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