

**SYNTHESIS OF 6-PHENYLAMINOFURO[2,3-d]PYRIMIDINE-2,4(1H,3H)-DIONES  
FROM BARBITURYLBENZYLIDENES AND ISONITRILES †**

José Daniel Figueroa-Villar\*, Carisa Lopes Carneiro, and Elizabete Rangel Cruz

Seção de Química, Instituto Militar de Engenharia, Pç Gal. Tibúrcio 80

22290 Rio de Janeiro, RJ, Brasil. FAX: 5521-2759047.

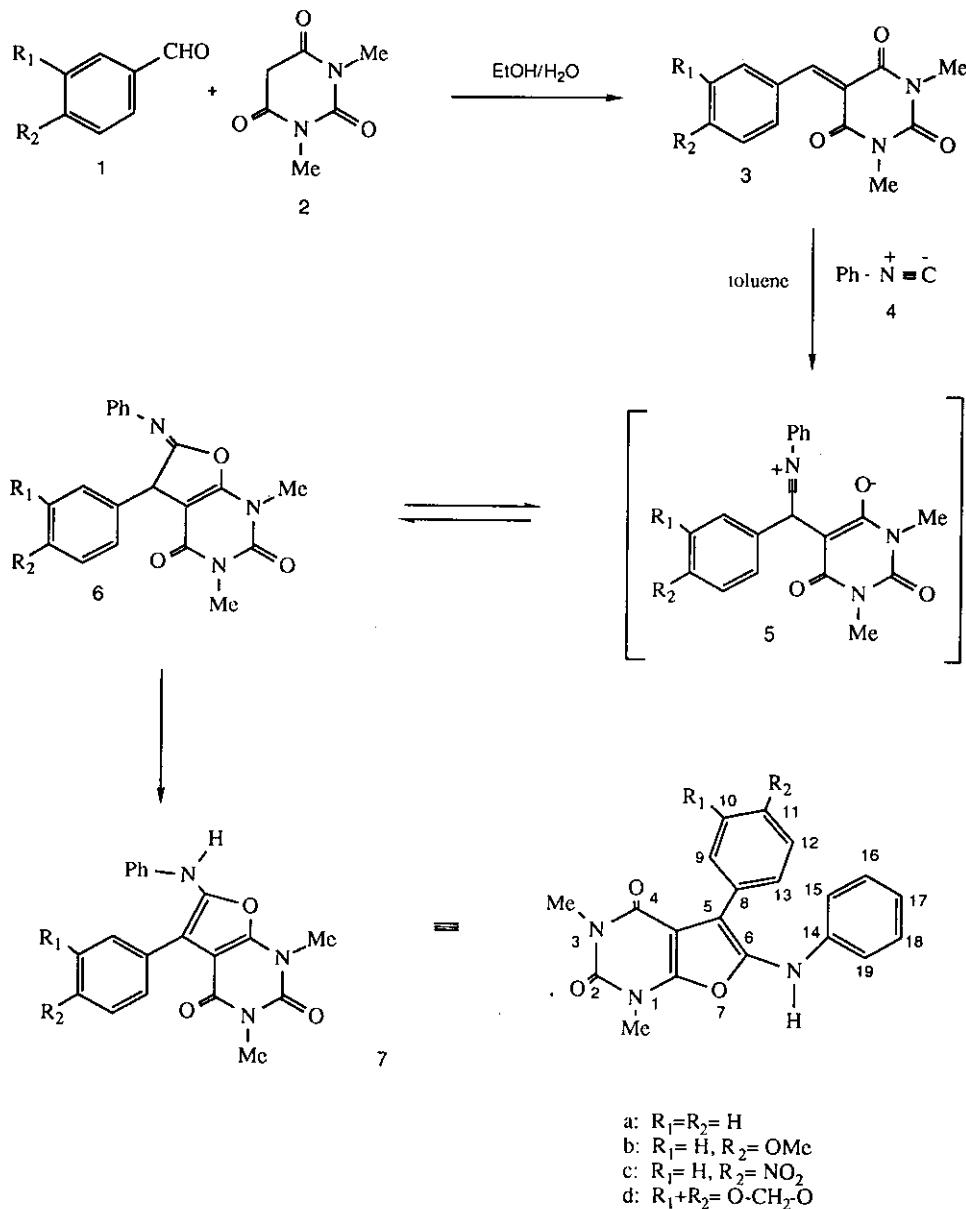
**Abstract** - Barbiturylbenzylidenes, prepared by Perkin condensation of aromatic aldehydes with 1,3-dimethylbarbituric acid, react with phenylisonitrile to yield four 5-aryl-6-phenylamino-1,3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H)-diones.

The synthesis of fused pyrimidine systems is of importance as a source of new purine analogues of potential biological interest.<sup>1</sup> Among them, the furo[2,3-d]pyrimidine system has received little attention, with only few synthetic procedures reported in the literature.<sup>1</sup> Furo[2,3-d]pyrimidine derivatives act as sedatives, antihistaminics, diuretics, muscle relaxants, antiulcer agents, etc.<sup>1</sup> Our interest in the unknown system 6-phenylaminofuro[2,3-d]pyrimidine led us to develop an efficient two step procedure for the synthesis of the novel 5-aryl-6-phenylamino-1,3-dimethylfuro[2,3-d]pyrimidine-2,4(1H,3H)-diones (**7a-7d**) from 1,3-dimethylbarbituric acid (**2**). The strategy used took advantage of the known ability of benzylidene barbituric acids to undergo nucleophilic attack in a Michael fashion.<sup>2,3</sup> Thus, one equivalent of **2** reacts with another equivalent of benzaldehyde (**1a**), anisaldehyde (**1b**), p-nitrobenzaldehyde (**1c**), and piperonal (**1d**) in 1:1 ethanol-water solution under reflux for 5 minutes to give the corresponding 1,3-dimethyl-barbiturylbenzylidenes (**3a-3d**) in 90 to 98% yields.<sup>2</sup> Phenylisonitrile (**4**) was prepared by dehydration of formanilide with Ph<sub>3</sub>P in ether.<sup>4</sup> The reaction of the benzylidenes (**3a-3d**) with an excess of the ethereal solution of **4** in refluxing toluene for 3 hours gave the expected fused pyridimines (Scheme 1).<sup>5-8</sup>

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† This paper is dedicated to Professor William A. Ayer on the occasion of his 60th birthday.

Scheme 1:



The zwitterionic nature of the isonitrile (4) favors a Michael-type addition reaction to the benzylidenes (3a-3d) to give the intermediate (5). Cyclization of 5 affords the imine (6), which after tautomerization would yield the furo[2,3-d]pyrimidines (7a-7d). However, the possibility of having a concerted [4+2] cheletropic

cycloaddition to explain the formation of **6** is not ruled out. The reversibility of the reaction is supported by the observation that compounds (**7a-7d**) give off an isonitrile odor when heated above their melting points. This simple reaction sequence provides a facile route to the synthesis of fused furopyrimidines.

#### ACKNOWLEDGEMENTS

This work was accomplished with financial aid from CNPq and FINEP. We thank Professor W. A. Ayer, Chemistry Department of the University of Alberta, for allowing us to record the nmr spectra.

#### REFERENCES AND NOTES

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5. Compound **7a**: yield 66%; mp 194-195°C (toluene); hreims (m/z) 347.1269 ( $C_{20}H_{17}N_3O_3$ ); uv (MeOH)  $\lambda_{max}$  (nm) 237 (log ε 4.3), 280 (sh); ir (KBr)  $\nu_{max}$  3280, 1715, 1670 and 1655  $cm^{-1}$ ;  $^1H$  nmr (360 MHz, DMSO- $d_6$ ) δ 7.61 (2H, d, J=7 Hz, H9, H13); 7.33 (2H, t, J=7 Hz, H10, H12); 7.30 (1H, t, J=7 Hz, H11); 7.24 (2H, t, J=7 Hz, H16, H18); 6.93 (1H, t, J=7 Hz, H17); 6.75 (2H, d, J=7 Hz, H15, H19); 5.71 (1H, s, N-H); 3.53 (3H, s, N-Me); 3.40 (3H, s, N-Me);  $^{13}C$  nmr (DMSO- $d_6$ ) δ 158.1 (C4); 152.8 (C7a); 150.5 (C2); 144.4 (C14); 141.4 (C6); 129.6 (C16, C18); 129.3 (C9, C13); 129.2 (C11); 129.1 (C8); 128.1 (C10, C12); 120.9 (C17); 117.2 (C5); 114.3 (C15, C19); 95.6 (C4a); 29.5 (N-Me) and 28.4 (N-Me).
6. Compound **7b**: yield 43%; mp 183-184°C (toluene); hreims (m/z) 377.1368 ( $C_{21}H_{19}N_3O_4$ ); uv (MeOH)  $\lambda_{max}$  (nm) 240 (log ε 4.3), 282 (sh); ir (KBr)  $\nu_{max}$  3300, 1710, 1670 and 1655  $cm^{-1}$ ;  $^1H$  nmr (360 MHz, DMSO- $d_6$ ) δ 7.55 (2H, d, J=9 Hz, H9, H13); 7.25 (2H, dd, J=8, 9 Hz, H16, H18); 6.92 (1H, t, J=7 Hz, H17); 6.85 (2H, d, J=9 Hz, H10, H12); 6.74 (2H, d, J=7 Hz, H15, H19); 5.74 (1H, s, N-H); 3.77 (3H, s, O-Me); 3.51 (3H, s, N-Me); 3.39 (3H, s, N-Me);  $^{13}C$  nmr (DMSO- $d_6$ ) δ 159.4 (C11); 158.2 (C4); 152.7 (C7a); 150.5 (C2); 144.6 (C14); 141.0 (C6); 130.6 (C9, C13); 129.6 (C16, C18); 121.4 (C8); 120.7 (C17); 117.0 (C5); 114.2 (C10, C12); 113.6 (C15, C19); 95.7 (C4a); 55.2 (O-Me); 29.5 (N-Me) and 28.3 (N-Me).

7. Compound 7c: yield 67%; mp 197-198°C (toluene); hreims (m/z) 392.1120 ( $C_{20}H_{16}N_4O_5$ ); uv (MeOH)  $\lambda_{max}$  (nm) 240 (sh), 265 (log  $\epsilon$  4.2) and 345 (br); ir (KBr)  $\nu_{max}$  3220, 1715, 1665 and 1660  $cm^{-1}$ ;  $^1H$  nmr (360 MHz, DMSO- $d_6$ )  $\delta$  8.13 (2H, d,  $J=9$  Hz, H10, H12); 7.82 (2H, d,  $J=9$  Hz, H9, H13); 7.26 (2H, t,  $J=8$  Hz, H16, H18); 6.96 (1H, t,  $J=7.5$  Hz, H17); 6.75 (2H, d,  $J=8$  Hz, H15, H19); 5.86 (1H, s, N-H); 3.55 (3H, s, N-Me); 3.41 (3H, s, N-Me);  $^{13}C$  nmr (DMSO- $d_6$ )  $\delta$  158.0 (C4); 153.0 (C7a); 150.2 (C2); 146.9 (C14); 143.3 (C6); 142.7 (C11); 136.1 (C8); 130.1 (C9, C13); 129.7 (C16, C18); 123.3 (C10, C12); 121.5 (C17); 114.6 (C5); 114.5 (C15, C19); 95.1 (C4a); 29.6 (N-Me) and 28.4 (N-Me).
8. Compound 7d: yield 59%; mp 216-217°C (95% ethanol); hreims (m/z) 391.1168 ( $C_{21}H_{17}N_3O_5$ ); uv (MeOH)  $\lambda_{max}$  (nm) 242 (log  $\epsilon$  4.2), 283 (sh); ir (KBr)  $\nu_{max}$  3270, 1710, 1665 and 1660  $cm^{-1}$ ;  $^1H$  nmr (360 MHz, DMSO- $d_6$ )  $\delta$  8.40 (1H, s, NH); 7.15 (3H, br s, H9, H16, H18); 7.14 (1H, d,  $J=8$  Hz, H13); 6.89 (1H, d,  $J=8$  Hz, H12); 6.68 (2H, d,  $J=8$  Hz, H15, H19); 6.75 (1H, t,  $J=7$  Hz, H17); 5.99 (2H, s, O-CH<sub>2</sub>-O); 3.38 (3H, s, N-Me); 3.23 (3H, s, N-Me);  $^{13}C$  nmr (DMSO- $d_6$ )  $\delta$  157.6 (C4); 152.8 (C7a); 149.9 (C2); 146.7 (C10); 146.6 (C11); 145.3 (C14); 141.5 (C6); 129.2 (C16, C18); 123.1 (C8); 123.0 (C13); 119.2 (C17); 115.2 (C5); 113.6 (C15, C19); 109.5 (C9); 107.8 (C12); 100.9 (OCH<sub>2</sub>O); 94.4 (C4a); 29.2 (N-Me) and 27.9 (N-Me).

Received, 22nd January, 1992