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

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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-dimethyl[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. Among them, the furo[2,3-d]pyrimidine system has received little attention, with only few synthetic procedures reported in the literature. Furo[2,3-d]pyrimidine derivatives act as sedatives, antihistaminics, diuretics, muscle relaxants, antiulcer agents, etc. Our interest in the unknown system 6-phenylamino[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. 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-dimethylbarbiturylbenzylidenes (3a-3d) in 90 to 98% yields. Phenylisonitrile (4) was prepared by dehydration of formanilide with Ph3P in ether. 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 pyrimidines (Scheme 1).

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

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REFERENCES AND NOTES
5. Compound 7a: yield 66%; mp 194-195°C (toluene); hreims (m/z) 347.1269 (C20H17N3O3); uv (MeOH) λmax (nm) 237 (log ε 4.3), 280 (sh); ir (KBr) νmax 3280, 1715, 1670 and 1655 cm⁻¹; ¹H nmr (360 MHz, DMSO-d6) 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); 13C nmr (DMSO-d6) 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 183-178°C (toluene); hreims (m/z) 377.3368 (C21H15N3O4); uv (MeOH) λmax (nm) 240 (log ε 4.3), 282 (sh); ir (KBr) νmax 3300, 1710, 1670 and 1655 cm⁻¹; ¹H nmr (360 MHz, DMSO-d6) 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); 13C nmr (DMSO-d6) 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); 127.1 (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_{4}O_{5}); uv (MeOH) \( \lambda_{\text{max}} \) (nm) 240 (sh), 265 (log \( e \) 4.2) and 345 (br); ir (KBr) \( \nu_{\text{max}} \) 3220, 1715, 1665 and 1660 cm\(^{-1}\); \(^1\)H nmr (360 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) 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-\( \text{d}_6 \)) \( \delta \) 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_{3}O_{5}); uv (MeOH) \( \lambda_{\text{max}} \) (nm) 242 (log \( e \) 4.2), 283 (sh); ir (KBr) \( \nu_{\text{max}} \) 3270, 1710, 1665 and 1660 cm\(^{-1}\); \(^1\)H nmr (360 MHz, DMSO-\( \text{d}_6 \)) \( \delta \) 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_{2}-O); 3.38 (3H, s, N-Me); 3.23 (3H, s, N-Me); \(^{13}\)C nmr (DMSO-\( \text{d}_6 \)) \( \delta \) 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_{2}O); 94.4 (C4a); 29.2 (N-Me) and 27.9 (N-Me).

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