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A NOVEL ONE STEP SYNTHESIS OF PYRANO(2,3-d) PYRIMIDINES

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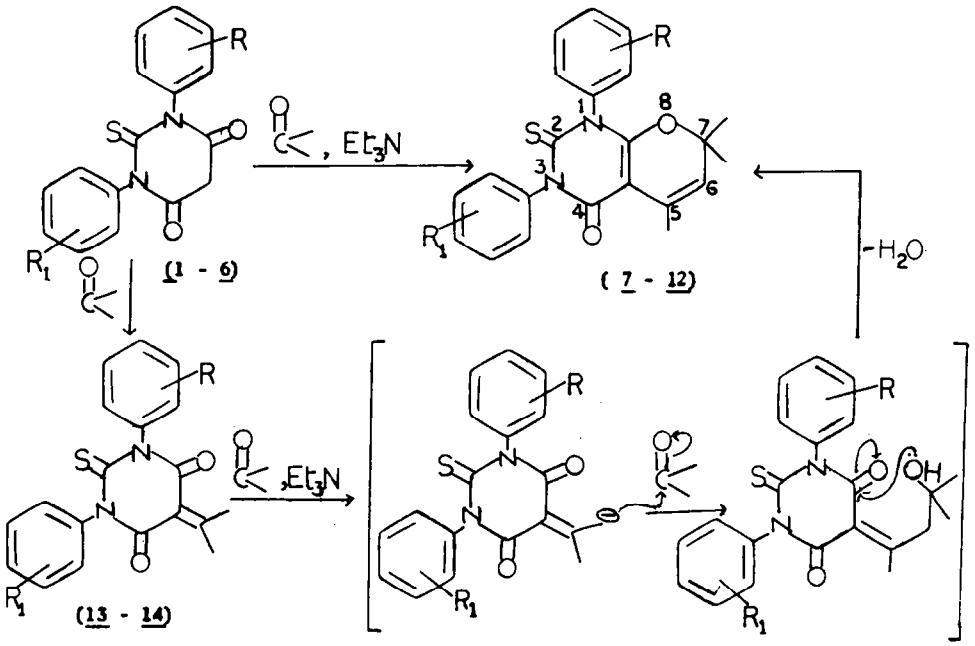
Abstract A novel and one step synthesis of pyrano(2,3-d) pyrimidines is described. It utilises the reaction of different thiobarbituric acid with ketones.

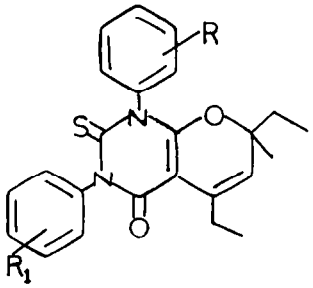
There is a continuous widespread interest in the synthesis of pyranopyrimidines because of the biological activity associated with this system. Although a variety of routes for the synthesis of these compounds have been described[1-7], the majority of them involve a number of steps and the yields are poor. In search of an efficient method for the synthesis of these compounds, we report here a novel and one step synthesis of pyrano(2,3-d)pyrimidines, which gave very good yields(80-90%). Thus, the reaction of 1,3-(diaryl)thiobarbituric acids[8] (1-6) with excess of acetone at reflux temperature in presence of triethylamine results in the cyclocondensation to yield 1,3-diaryl-1,2,3,4,7-pentahydro-5,7,7-trimethyl-4-oxo-2-thioxopyrano(2,3-d) pyrimidines (7-12).



(1 - 6)

(7 - 12)

(13 - 14)



(15 - 20)

1,7,13,15,	$R = R_1 = H$
2,8,14,16,	$R = R_1 = o\text{-}CH_3$
3,9,17,	$R = R_1 = p\text{-}CH_3$
4,10,18,	$R = R_1 = m\text{-}Cl$
5,11,19,	$R = R_1 = p\text{-}Cl$
6,12,20,	$R = R_1 = p\text{-}OCH_3$

Similar condensation was carried out using ethyl methyl ketone to give 1,3-diaryl-5,7-diethyl-1,2,3,4,7-pentahydro-7-methyl-4-oxo-2-thioxopyrano(2,3-d)pyrimidines (15-20). Structures of all these compounds have been assigned on the basis of ^{1}H-NMR spectral data and elemental analysis.

In an attempt to study the mechanism of the above reaction, the reaction of 1 was carried out with calculated amount (see experimental) of acetone without using base, this resulted in the formation of a compound different from 7. On the basis of ^{1}H NMR-spectral data it was assigned the structure 1,3-dihydro-5-(1-methyl ethylidene)-1,3-diphenyl-2-thioxo-2H,5H pyrimidine-4,6-dione (13) which on further treatment with excess of acetone in presence of triethylamine at reflux temperature gave the final product 7. Similar results were obtained in case of 2 and the intermediate 14 was isolated. However the intermediate in other cases could not be isolated under the reaction conditions used. It is thus believed that the final product pyrano(2,3-d)pyrimidines are obtained via the formation of the intermediate 13,14.

EXPERIMENTAL

M.ps are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) spectrometer using TMS as the internal standard.

1,2,3,4,7-pentahydro 5,7,7-trimethyl-4-oxo-1,3-diphenyl-2-thioxo pyrano(2,3,-d)pyrimidine (7)

1(1.48 g, 5 m.mol), dry triethylamine (0.2 ml) in dry acetone (65-70 ml) was refluxed for 10 h. Solvent was removed under reduced pressure and the residue treated with crushed ice. The separated solid was crystallised from benzene - petroleum ether to give 7 as light yellow needles (1.61 g) yield 91.5%; m.p. 206-207°C; ^{1}H NMR($CDCl_3$) δ 1.30[6H, s, $C(CH_3)_2$], 2.15(3H, s, CH_3-5), 4.96(1H, s, H-6), 7.10-7.51 (10H, m, H-Ar); Found : C, 70.0; H, 5.2; N, 7.4. Calcd. for $C_{22}H_{20}N_2O_2S$: C, 70.2; H, 5.3; N, 7.4%.

Compounds 8-12 (using acetone) and 15-20(using ethyl methyl ketone in place of acetone) were obtained in a similar way.

8: Yield 81.0%; m.p. 158-159°C; ^{1}H-NMR($CDCl_3$) δ 1.31[6H, s, $C(CH_3)_2$], 2.20 (3H, s, CH_3-5), 2.50 (6H, s, 2 x CH_3), 5.00 (1H, s, H-6), 7.10-7.40 (8H, m, H-Ar); Found: C, 71.1; H, 5.9; N, 6.8. Calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.2; H, 5.9; N, 6.9%.

9: Yield 82.8%; m.p. 190-191°C; ^{1}H NMR($CDCl_3$) δ 1.29[6H, s, $C(CH_3)_2$], 2.19 (3H, s, CH_3-5), 2.40(6H, s, 2 x CH_3), 4.90(1H, s, H-6), 7.25-7.35(4H, d, J=9 Hz, H-3',5',3" and 5"), 7.30-7.41(4H, d, J=9 Hz, H-2', 6', 2" and 6"); Found : C, 71.2; H, 5.8; N, 6.7. Calcd.for $C_{24}H_{24}N_2O_2S$: C, 71.2; H, 5.9; N, 6.9%.

10: Yield 90.2%; m.p. 200-201°C; ^{1}H NMR($CDCl_3$) δ 1.44[6H, s, $C(CH_3)_2$], 2.39(3H, s, CH_3-5), 5.10(1H, s, H-6), 7.25-7.65(8H, m, H-Ar); Found: C, 59.1; H, 4.0; N, 6.0. Calcd. for $C_{22}H_{18}N_2O_2SCl_2$: C, 59.3; H, 4.0; N, 6.2%.

11: Yield 79.2%; m.p. 214-215°C; ^{1}H NMR($CDCl_3$) δ 1.30[6H, s, $C(CH_3)_2$], 2.15(3H, s, CH_3-5), 5.00(1H, s, H-6), 7.10-7.21(4H, d, J=9 Hz, H-3', 5', 3" and 5"), 7.41-7.50(4H, d, J=9Hz, H=2', 6', 2" and 6"); Found C, 59.2; H, 4.1, N, 6.0. Calcd for $C_{22}H_{18}N_2O_2SCl_2$: C, 59.3; H, 4.0; N, 6.2%.

12: Yield 90.3%; m.p. 245-246°C; ^{1}H NMR ($CDCl_3$) δ 1.22[6H, s, $C(CH_3)_2$], 2.15(3H, S, CH_3-5), 3.75(6H, s, 2 x OCH_3), 4.90(1H, s, H-6), 6.89-7.00(4H, d, J=9 Hz, H-3', 5', 3" and 5"), 7.05-7.15(4H, d, J=9 Hz, H-2', 6", 2" and 6"). Found: C, 61.4; H, 5.0; N, 5.9. Calcd. for $C_{24}H_{24}N_2O_4S$: C, 61.5; H, 5.1; N, 5.9%.

15: Yield 92.7; m.p. 197-198°C; ^{1}H NMR($CDCl_3$) δ 0.60(3H, t, J=7 Hz, CH_2-$\underline{CH_3}$-7),0.95(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-5), 1.15(3H, s, CH_3-7), 1.42(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-7), 2.50(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-5), 4.80(1H, s, H-6), 7.01-7.41(10H, m, H-Ar): Found: C, 71.2; H, 5.8; N, 6.8. Calcd. for $C_{24}H_{24}N_2O_2S$: C, 71.2; H, 5.9; N, 6.9%.

16: Yield 80.2%; m.p. 160-161°C; ^{1}H-NMR($CDCl_3$) δ 0.70(3H, t, J=7 Hz, CH_2-$\underline{CH_3}$-7),1.05(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-5), 1.22(3H, s, CH_3-7), 1.50(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-7), 2.17 (6H, s, 2 x CH_3), 2.55 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$-5), 4.90(1H, s, H-6), 7.10-7.30(8H, m, H-Ar): Found: C, 72.1; H, 6.2; N, 6.3. Calcd. for $C_{26}H_{28}N_2O_2S$: C, 72.2; H, 6.4; N, 6.4%.

17: Yield 87.1; m.p. 152-153°C; ^{1}H NMR($CDCl_3$) δ 0.72(3H, t, J=7 Hz, CH_2-$\underline{CH_3}$-7), 1.05(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-5), 1.23(3H, s, CH_3-7), 1.50(2H, q, J=7, $\underline{CH_2}CH_3$-7), 2.32(6H, s, 2 x CH_3) 2.60(2H, q, J=7 Hz, $\underline{CH_2}$-CH_3-5), 4.89(1H, s, H-6), 7.00-7.10(4H, d, J=9 Hz, H-3',5', 3" and 5"), 7.12-7.25(4H, d, J=9 Hz, H-2',6', 2" and 6"); Found: C, 72.0; H, 6.2; N, 6.3. Calcd. for $C_{26}H_{28}N_2O_2S$: C, 72.2; H, 6.4; N, 6.4%.

18: Yield 75.2%; m.p. 137-138°C; ^{1}H NMR($CDCl_3$) δ 0.72(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-7),1.04(3H, t, J=7 Hz, CH_2-$\underline{CH_3}$-5) 1,25(3H, s, CH_3-7), 1.52(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-7), 2.55(2H, q, $\underline{CH_2}CH_3$-5), 4.90(1H, s, H-6), 7.05-7.35(8H, m, Ar-H); Found: C, 60.8; H, 4.7; N, 6.0. Calcd. for $C_{24}H_{22}N_2O_2SCl_2$: C, 60.8;H,4.6; N, 5.9%.

19: Yield 81.7%; m.p. 182-183°C; ^{1}H NMR($CDCl_3$) δ 0.75(3H, t, J=7Hz, $CH_2\underline{CH_3}$-7), 1.07(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-5), 1.27(3H, s, CH_3-7), 1.59(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-7), 2.60(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-5), 4.91(1H, s, H-6), 7.09-7.20(4H, d, J=9 Hz, H-3', 5', 3" and 5"),7.33-7.45(4H, d, J=9 Hz, H-2', 6', 2" and 6"); Found: C, 60.8; H, 4.6; N, 5.8. Calcd for $C_{24}H_{22}N_2O_2SCl_2$: C, 60.8, H, 4.6; N, 5.9%.

20: Yield 80.1%; m.p. 155-156°C; ^{1}H NMR($CDCl_3$)δ 0.75(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-7), 1.06(3H, t, J=7 Hz, $CH_2\underline{CH_3}$-5), 1.26(3H, s, CH_3-7), 1.57(2H, q, J=7 Hz, $\underline{CH_2}CH_3$-7), 2.60(2H, q, J=7 Hz $\underline{CH_2}$-CH_3-5), 3.81(6H, s, 2 x OCH_3), 4.90(1H, s, H-6), 6.90-7.01(4H, d, J=9 Hz, H-3',5', 3" and 5") 7.08-7.18(4H, d, J=9Hz, H-2', 6', 2" and 6"); Found C, 67.3; H, 6.0 ; N, 6.0 . Calcd for $C_{26}H_{28}N_2O_4S$: C, 67.2; H, 6.0, N, 6.0%.

1,3-Dihydro-5-(1-methyl ethylidene)-1,3-diphenyl— 2-thioxo-2H,5H-pyrimidine-4,6-dione (13)

1 (1.48 g, 5 m.mol), dry acetone (20 ml, 240 m.mol) was refluxed for 20 min. A pale yellow solid separated out which was filtered and crystallised from chloroform - petroleum ether to give 13 as yellow crystals (1.60 g), m.p. 265-66°C, ^{1}H-NMR($CDCl_3$) δ 2.70 [6H, s, $C(CH_3)_2$] , 7.10-7.51(10H, m, H-Ar); Found: C, 67.8; N, 4.6; N, 8.2. Calcd for $C_{19}H_{16}N_2O_2$: C, 67.8; H, 4.7; N, 8.3%.

14 was also obtained in a similar way.

14 : Yield 90.1%; m.p. 212-213°C; ^{1}H NMR($CDCl_3$) δ 2.35(6H, s, 2 x CH_3), 2.80 [6H, s, $C(CH_3)_2$] , 7.20-7.55(8H, m, H-Ar); Found: C, 69.2; H, 5.5; N, 7.7. Calcd for $C_{21}H_{20}N_2O_2S$: C, 69.2; H, 5.4, N, 7.6%.

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