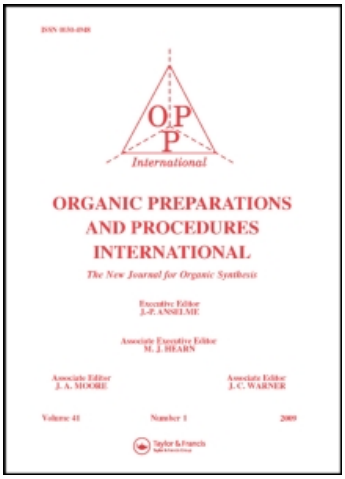

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A FACILE SYNTHESIS OF 5-BENZOYLCYTOSINE DERIVATIVES

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A FACILE SYNTHESIS OF 5-BENZOYLCYTOSINE DERIVATIVES

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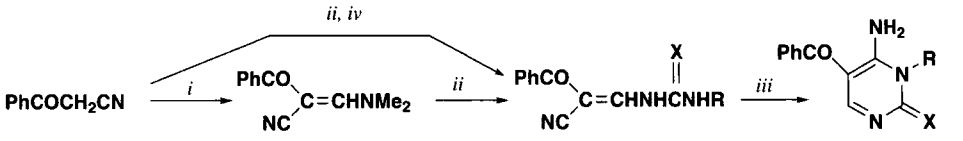
Fluorophoric heterocycles such as pyrimidine are exceedingly important in nucleic acid chemistry.[1] Pyrimidines in particular cytosine derivatives, are of special interest because of their potential use as therapeutic agents. Cytosines exhibit promising antiviral,[2] antitumour[3] and antiAIDS[4] activities. We recently reported the synthesis of novel heterocyclic compounds,[5-8] and also described new synthetic routes towards pyrimidines[9] and pyrazoles.[10] Previous papers have demonstrated the activity of fused pyrimidines as potential antineoplastic agents.[11,12] The results of these studies have encouraged us to develop new synthetic routes towards the pyrimidine nucleus. This communication reports a facile and novel synthesis of hitherto unknown 5-benzoylcytosine derivatives (**4**).

3-Dimethylamino-2-benzoylpropenenitrile (**2**), was obtained by condensation of benzoylacetonitrile (**1**) with dimethylformamide dimethyl acetal in 70% yield. Reactions of compound (**2**) with N-substituted ureas or thioureas in acidic medium yielded ureidopropenenitriles (**3a-l**). Cyclization of (**3a-l**) with sodium methoxide in methanol gave 3-substituted-5-benzoylcytosine derivatives (**4a-l**) in 50-65% yield. Compounds (**3a-l**) can also be synthesized in 85-87% yield by stirring benzoylacetonitrile (**1**), the N-substituted urea or thiourea and triethylorthoformate at 60-90°. The alternate procedure is better because it generated a higher product yield.



i) $Me_2NCH(OMe)_2$; ii) $RNHCONH_2$ or $RNHCSNH_2$; iii) NaOMe, ; iv) $CH(OEt)_3$

a) R = Me, X = O; b) R = Et, X = O; c) R = $CH_2CH{=}CH_2$, X = O; d) R = CH_2Ph, X = O
e) R = Ph, X = O; f) R = $_2$-F-C_6H_4, X = O; g) R = 2-Cl-C_6H_4, X = O; h) R = 3-Cl-C_6H_4, X = O
i) R = 4-Cl-C_6H_4, X = O; j) R = 3-CF_3-C_6H_4, X = O; k) R = Me, X = S; l) R = $CH_2CH{=}CH_2$, X = S

EXPERIMENTAL SECTION

Mps were determined on a Tottoli apparatus and are uncorrected. Elemental analysis were determined on a Carlo Erba Analyzer. ^{1}HNMR spectra were recorded on a Varian XL-300 MHz, Gemini 200 MHz spectrometer using TMS as an internal standard. IR spectra were obtained as KBr pellets on a Perkin-Elmer 421 spectrometer.

Table 1. Yield, mps, Elemental Analysis and Spectral Data of Compounds **3**

Cmpd.	Yield (%)	mp. (°C)	Elemental Analysis (Found) C	H	N	IR (cm^{-1})	^{1}H NMR (δ)
3a	55	159	62.87 (62.59)	4.84 (4.70)		3400-3250, 2250, 1740, 1650, 1600, 1550	2.57 (d, *J* = 5Hz, 3H, CH_3), 7.47-7.61 (m, 5H, Ar-H), 7.84 (d, *J* = 12.5Hz, 1H, CH=), 8.47 (d, *J* = 5Hz, 1H, NH), 11.89 (d, *J* = 12.5Hz, 1H, NH)
3b	55	156	64.19 (63.91)	5.39 (5.15)		3350, 3250, 2250, 1745 1745, 1650 1600, 1560 1450	1.11 (t, *J* = 7.5Hz, 3H, CH_3), 3.22 (m, 2H, -NCH_2),7.27-7.71 (m, 5H, Ar-H), 7.87 (d, *J* = 12.5Hz, 1H CH=), 8.42 (d, *J* = 5.5Hz, 1H, NH) 11.89 (d, *J* = 12.5Hz, 1H, NH)
3c	65	147	65.87 (65.60)	5.13 (5.11)		3400-3100, 3400, 2250 1750, 1660, 1570	3.84 (dd, *J* = 4.8, 6.5Hz, 2H, CH_2) 5.15-5.23 (dd, *J* = 6.2, 10Hz 2H, CH_2), 5.85 (septate, *J* = 2, 4.95, 5.84Hz, 1H, CH=), 7.42-7.67 (m, 5H, Ar-H), 7.85 (d, *J* = 12.5Hz, 1H, CH=), 8.44 (d, *J* = 6.5Hz, 1H, NH), 11.78 (d, *J* = 12.5Hz, 1H, NH)
3d	78	198	70.81 (71.10)	4.95 (5.00)	13.76 (13.70)	3310, 3060, 2230, 1740 1655	4.21(d, *J* = 8Hz, 2H, CH_2), 7.11-7.89 (m, 10H, Ar-H), 8.35 (d, *J* = 12.5Hz, 1H,CH=), 8.47 (t, *J* = 8Hz 1H, NH), 11.75 (d, *J* = 12.5Hz, 1H, NH)

Table 1. *Continued...*

Cmpd.	Yield (%)	mp. (°C)	Elemental Analysis (Found) C	H	N	IR (cm^{-1})	^1H NMR (δ)
3e	80	212	70.09 (70.28)	4.50 (4.68)		3400-3100, 3400, 2230 1740, 1660, 1640, 1600 1530, 1510	7.06-7.79 (m, 10H, Ar-H), 7.88 (d, J = 12.5Hz, 1H, CH=), 9.61 (s, 1H, NH), 11.96 (d, J = 12.5Hz, 1H, NH)
3f	75	215	66.23 (66.21)	3.59 (3.89)		3310, 3060, 2230, 1760, 1740, 1610, 1510	7.09-7.31 (m, 4H, Ar-H), 7.50-7.71 (m, 5H, Ar-H), 7.81(d, J = 12.5 Hz, 1H, CH=), 8.11 (dd, *J* = 2, 8.1Hz, Ar-F), 9.7 (s, 1H, NH),11.78 (d, *J* = 12.5Hz, 1H, NH)
3g	75	222	62.88 (63.04)	3.41 (3.46)	12.94 (12.73)	3310, 3060, 2230, 1755 1740, 1610 1500	7.15-7.92 (m, 9H, Ar-H), 8.21 (d, *J* = 12.5Hz, 1H, CH=), 9.71 (s, 1H, NH), 11.90 (d, *J* = 12.5Hz, 1H, NH)
3h	75	205	62.88 (62.90)	3.41 (3.45)		3360, 3260, 2230, 1755, 1665, 1600	7.12-7.81 (m, 9H, Ar-H), 8.28 (d, *J* = 12.5Hz, 1H, CH=), 9.75 (s, 1H, NH), 11.88 (d, *J* = 12.5Hz, 1H, NH)
3i	70	205	62.88 (62.93)	3.41 (3.50)		3300-3100, 2225, 1750 1660, 1610 1560, 1500	7.32-7.81 (m, 9H, Ar-H), 8.31-8.34 (d, *J* = 12.5Hz, 1H, CH=), 10.71 (s, 1H, NH), 11.84-11.87 (d, *J* = 12.5Hz, 1H, NH)
3j	70	222	60.17 (59.98)	3.37 (3.24)	11.69 (11.72)	3282, 3216, 2226, 1739 1739, 1652 1610	7.41-8.05 (m, 9H, Ar-H), 8.35 (d, *J* = 12.5Hz, 1H, CH=), 9.95 (s, 1H, NH), 11.95 (d, *J* = 12.5Hz, 1H, NH)
3k	70	190	58.76 (58.87)	4.52 (4.55)		3320, 3250, 2280, 1655, 1625, 1590	3.04 (d, *J* = 5Hz, 3H, CH_3), 7.51-7.67 (m, 5H, Ar-H), 7.85 (d, *J* = 12.5Hz, 1H,CH=), 9.18 (d, *J* = 5Hz, 1H, NH), 11.22 (d, *J* = 12.5Hz, 1H, NH)
3l[a]	70	160	61.79 (61.59)	4.92 (4.82)	15.49 (15.59)	3280, 3240, 2270, 1660, 1620, 1585, 1490	3.84 (d, *J* = 4.8Hz, 2H, CH_2), 5.25 (dd, *J* = 2, 6.2Hz, 2H, CH_2=), 5.85 (septate, *J* = 2, 5, 5.84Hz, 1H, CH=), 7.46-7.78 (m, 5H, Ar-H), 8.15 (d, *J* = 12.5Hz,1H, CH=), 8.85 (t, *J* = 6.5Hz, 1H, NH), 11.81 (d, *J* = 12.5Hz, 1H, NH)

a) Sulfur Analysis: Calcd: 11.81. Found: 11.72.

Table 2. Yield, mps, Elemental Analysis and Spectral Data of Compounds **4**

Cmpd.	Yield (%)	mp. (°C)	Elemental Analysis(Found) C	H	N	IR (cm^{-1})	^1H NMR (δ)
4a	55	265	62.88 (62.99)	4.80 (4.59)	18.34 (18.16)	3450, 3150, 1665, 1650, 1600	3.41 (s, 3H, CH_3), 7.52-7.54 (m, 5H, Ar-H), 8.24 (s, 1H, CH=), 8.72 (bs, 1H, NH), 9.98 (bs, 1H, NH)
4b	58	210	64.19 (64.30)	5.34 (5.39)	17.28 (17.38)	3250, 3000, 1690, 1625, 1600, 1500	1.69 (t, J = 6Hz, 3H, CH_3), 4.05 (q, J = 6Hz, 2H, CH_2), 7.05-7.13 (m, 5H, Ar-H), 7.64 (s, 1H, CH=), 8.13 (s,1H, NH), 9.17 (s, 1H, NH)
4c	60	235	65.88 (65.71)	5.09 (5.04)	16.47 (16.28)	3262, 3034, 1680, 1617 1575	4.61 (d, J = 6.5Hz, 2H, CH_2), 5.06-5.18 (dd, J = 6.8, 10.44Hz, 2H, CH_2), 5.81-5.90 (septate, J = 2, 4.89, 5.7Hz, 1H, CH=), 7.47-7.49 (m, 5H, Ar-H), 8.22 (s, 1H, CH=), 8.57 (s, 1H, NH), 9.96 (s, 1H, NH)
4d	65	213	70.81 (70.70)	4.91 (4.92)		3425, 3100, 1665, 1655 1615, 1500	5.29 (s, 2H, CH_2), 7.29-7.56 (m, 10H, Ar-H), 8.32 (s, 1H, CH=), 8.83 (s, 1H, NH), 10.01 (s, 1H, NH)
4e	50	241	70.10 (69.93)	4.46 (4.29)		3280, 3220, 3120, 1670, 1630, 1590, 1490	7.14-7.79 (m, 10H, Ar-H), 7.93 (s, 1H, CH=), 10.99 (s, 1H, NH), 11.65 (s, 1H, NH)
4f	53	290	66.01 (65.86)	3.88 (3.68)	13.59 (13.89)	3280, 2650, 1680, 1640, 1600, 1550	7.13-7.91 (m, 9H, Ar-H), 8.11 (s, 1H, CH=), 8.61 (dd, J = 2, 8Hz, 1F, Ar-F), 11.35 (s, 1H, NH), 11.85 (bs, 1H, NH)
4g	55	285	62.76 (63.04)	3.69 (3.46)	12.92 (12.73)	3400, 3250, 1680, 1640, 1600, 1545	7.15-7.91 (m, 8H, Ar-H), 8.11 (s, 1H, CH=), 8.75 (d, J = 8Hz, 1H, Ar-H), 11.40 (s, 1H, NH), 11.85 (s, 1H, NH)
4h	52	266	62.76 (62.90)	3.69 (3.45)		3400, 3250, 1670, 1645, 1600, 1530	6.91-7.96 (m, 9H, Ar-H), 8.17 (s, 1H, CH=), 11.45 (s, 1H, NH), 11.76 (s, 1H, NH)
4i	54	290	62.76 (62.96)	3.69 (3.54)		3400, 3250, 1670, 1640 1600, 1500	7.44-7.82 (m, 9H, Ar-H), 7.95 (s, 1H, CH=), 11.07 (s, 1H, NH), 11.69 (s, 1H, NH)
4j	51	241	60.16 (60.02)	3.34 (3.07)	11.69 (11.53)	3400, 3230, 1660, 1632 1600, 1528	7.42-7.81 (m, 9H, Ar-H), 7.95 (s, 1H, CH=), 11.15 (s, 1H, NH), 11.85 (s, 1H, NH)

Table 2. *Continued...*

Cmpd.	Yield (%)	mp. (°C)	Elemental Analysis(Found) C	H	N	IR (cm^{-1})	^1H NMR (δ)
4k[a]	65	273	58.77 (58.82)	4.48 (4.44)	17.14 (17.13)	3300, 3130, 1665, 1625 1600, 1500	3.93 (s, 3H, CH_3), 7.42-7.82 (m, 5H, Ar-H), 8.15 (s, 1H, CH=), 8.95 (s, 1H, NH), 9.95 (s, 1H, NH)
4l	63	242	61.99 (62.03)	4.79 (4.77)	15.49 (15.51	)1650, 1620 1570, 1500	5.25 (d, J = 6.5Hz, 2H, CH_2), 5.35 (dd, J = 6.5, 10.40Hz, 2H, CH_2=), 5.81-5.95 (septate, J = 5.7, 6.5, 10.4Hz, 1H, CH=), 7.45-7.75 (m, 5H, Ar-H), 8.15 (s, 1H, CH=), 8.75 (s, 1H, NH), 9.97 (s, 1H, NH)

a) Sulfur Analysis: Calcd: 13.06. Found: 12.98.

3-Dimethylamino-2-benzoylpropenenitrile (2).- To benzoylacetonitrile (1.45g, 0.01mole) was added dimethylformamide dimethyl acetal (2.39g, 0.02mole) and the clear solution obtained was stirred at room temperature for 1 hr. The precipitated product was collected, washed with petroleum ether and recrystallized from ethanol to give 2.56g (70%) of colorless crystals, mp. 107-108°. IR (KBr): 2200, 1645 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.73-7.85 (m, 2H, Ar-H), 7.35-7.59 (m, 3H, Ar-H), 3.30 (s, 3H, CH_3), 3.50 (s, 3H, CH_3), 7.97 (s, 1H, CH=) ppm.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.00; N, 14.00. Found: C, 71.84; H, 5.98; N, 14.00

2-Benzoyl-3-ureido or thioureidopropenenitrile (3a-l).- To a solution of 3-dimethylamino-2-benzoylpropenenitrile (2.0g, 0.01mole) in ethanol (20mL), and conc. hydrochloric acid (1.2mL) was added the N-substituted urea or thiourea (0.01mole). The mixture was stirred at 80° for 2 hrs. The solvent was removed on the rotary evaporator and the crude product was recrystallized from ethanol:DMF (2:8) (70-80% yield).

Alternate Procedure.- To benzoylacetonitrile (1.45g, 0.01mole) was added N-substituted urea or thiourea (0.012mole) and triethyl orthoformate (2.22g, 0.015mole); the mixture was stirred at 90° which produced clear solution that immediately solidified. The precipitated product was stirred with ether (10mL), collected, washed with ether and recrystallized from ethanol:DMF (2:8) (85-87% yield). The alternate procedure gave a higher product yield. The yields, mps, elemental analyses and spectral data of compounds **(3a-3l)** are given in Table 1.

5-Benzoylcytosine Derivatives (4a-l).- To a solution of **3** (0.01mole) in dry methanol (40mL) was added solution of sodium methoxide (0.23g sodium metal in 10 mL methanol). The reaction mixture was then refluxed for 1 hr. The solvent was removed under reduced pressure and the solid residue was dissolved in cold water and acidified with 2N hydrochloric acid. The separated product was recrystallized from ethanol. The yields, mps, elemental analyses and spectral data of compounds **(4a-4l)** are given in Table 2.

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