NITRILES IN HETEROCYCLIC SYNTHESIS: NOVEL SYNTHESIS OF BENZO[c]-COUMARIN AND OF BENZO[c]PYRANO[3,2-c]QUINOLINE DERIVATIVES

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Abstract - Novel syntheses of benzo[c]coumarins and benzo[c]pyrano[3,2-c]-quinolines utilizing 3-cyano-4-methylcoumarin and pyrano[3,2-c]quinolin are reported.

In a recent paper we have shown that 1-phenylethylidenemalononitrile reacts with benzylidenemalononitrile to yield m-diarylaniline derivatives.[1] In continuation to our program directed for developing simple new and efficient procedures for synthesis of heterocycles from nitrile intermediates,[2] we became interested to see if reactions of this type can be adopted to enable synthesis of otherwise not readily accessible heterocycles. In the present paper we report two syntheses of benzo[c]coumarin and benzo[c]pyrano[3,2-c]quinoline derivatives utilising reaction sequence similar to that described above.

Thus, 3-cyano-4-methylcoumarin 2 was prepared by condensation of equimolecular amounts (0.1 mole) of o-hydroxyacetophenone (1) with malononitrile, ethyl cyanoacetate or cyanoacetamide in benzene (100 ml) containing ammonium acetate (2 g) and acetic acid (2 ml) using water separator, by refluxing for 6 h in 92, 85 and 95 % yields, respectively.[3] When 2 (0.01 mole) was heated for 0.5 h with arylidene malononitriles 3a-c (0.01 mole) in ethanol (30 ml) with few drops of piperidine, the benzo-[c]coumarins 4a-c were obtained. The formation of 4 from reaction of 2 and 3 is assumed to proceed via Michael type addition of the methyl function in 2 to the activated double bond to yield the acyclic Michael adduct 5a which then cyclizes into 6a. The latter readily loses HCN to yield the final isolable thermodynamically stable compound 4.

In contrast to anticipated formation of the esters 7, the reaction of 2 with ethyl arylidenecyanoacetate afforded 4a-c, and are assumed to proceed via elimination of ethyl formate from the intermediate 6b. Compounds 4a-c were also synthesized by refluxing of malononitrile or ethyl cyanoacetate with the styryl derivatives 8a-c in ethanol containing few drops of piperidine.

Reaction of 2 with 9 afforded only the condensation product 10, which was obtained by direct condensation of 2 and 4-formylantipyrine. Compound 10 is assumed to be formed via elimination of malononitrile or ethyl cyanoacetate from the acyclic Michael adduct. Similar elimination has been recently supposed to account for the formation of ylidenes on reacting cinnamonitriles with active methylene azoles.[4,5]

Pyrano[3,2-c]quinoline (12) was prepared by refluxing equimolecular amounts (0.1 mole) of 11[6] and malononitrile, ethyl cyanoacetate or cyanoacetamide in benzene (100 ml) containing ammonium acetate (2 g) and acetic acid (2 ml) in 88, 82, 92 % yields, respectively.

Table 1 : List of new compounds.

Compound* colour	Crystallization Solvent	Mp, (°C)	Yield (%)	Mol. Formula	Compound colour	Crystallization Solvent	Mp, (°C)	Yield (%)	Mol. Formula
4a yellow	DMF	>300	85[1]	$C_{20}H_{12}N_2O_2$	13b colourless	Dioxan	282-284	95[2]	$C_{24}H_{14}ClN_3O_3$
4b yellow	DMF/H_2O	261-263	92[1]	$C_{20}H_{11}ClN_2O_2$	13c colourless	Dioxan	251-253	92[3]	$C_{25}H_{17}N_3O_4$
4c yellow	DMF/H_2O	246-248	87[1]	$C_{21}H_{14}N_2O_3$	14a colourless	Dioxan	238-240	88	$C_{26}H_{20}N_2O_5$
8a colourless	DMF/H_2O	179-180	90	$C_{18}H_{11}NO_2$	14b colourless	Dioxan	245-247	98	$C_{26}H_{19}ClN_2O_5$
8b yellow	DMF	197-198	95	$C_{18}H_{10}ClNO_2$	14c colourless	DMF	241-243	95	$C_{27}H_{22}N_2O_6$
8c yellow	DMF	186-187	92	$C_{19}H_{13}NO_3$	15a colourless	Dioxan	230-232	90	$C_{22}H_{14}N_2O_3$
10 orange	DMF	260-262	98[2]	$C_{23}H_{17}N_3O_3$	15b colourless	Dioxan	232-234	92	$C_{22}H_{13}ClN_2O_3$
12 yellow	Dioxan	248-250		$C_{15}H_{10}N_2O_3$	15c colourless	Dioxan	208-210	88	$C_{23}H_{16}N_2O_4$
13a colourless	DMF	283-285	95[3]	$C_{24}H_{15}N_3O_3$					

* 1. Yields based on reaction of 2 with 3a-c. 2. Yield based on reaction of 2 with 4-formylantipyrine. 3. Yields based on reaction of 12 with 3a-c.

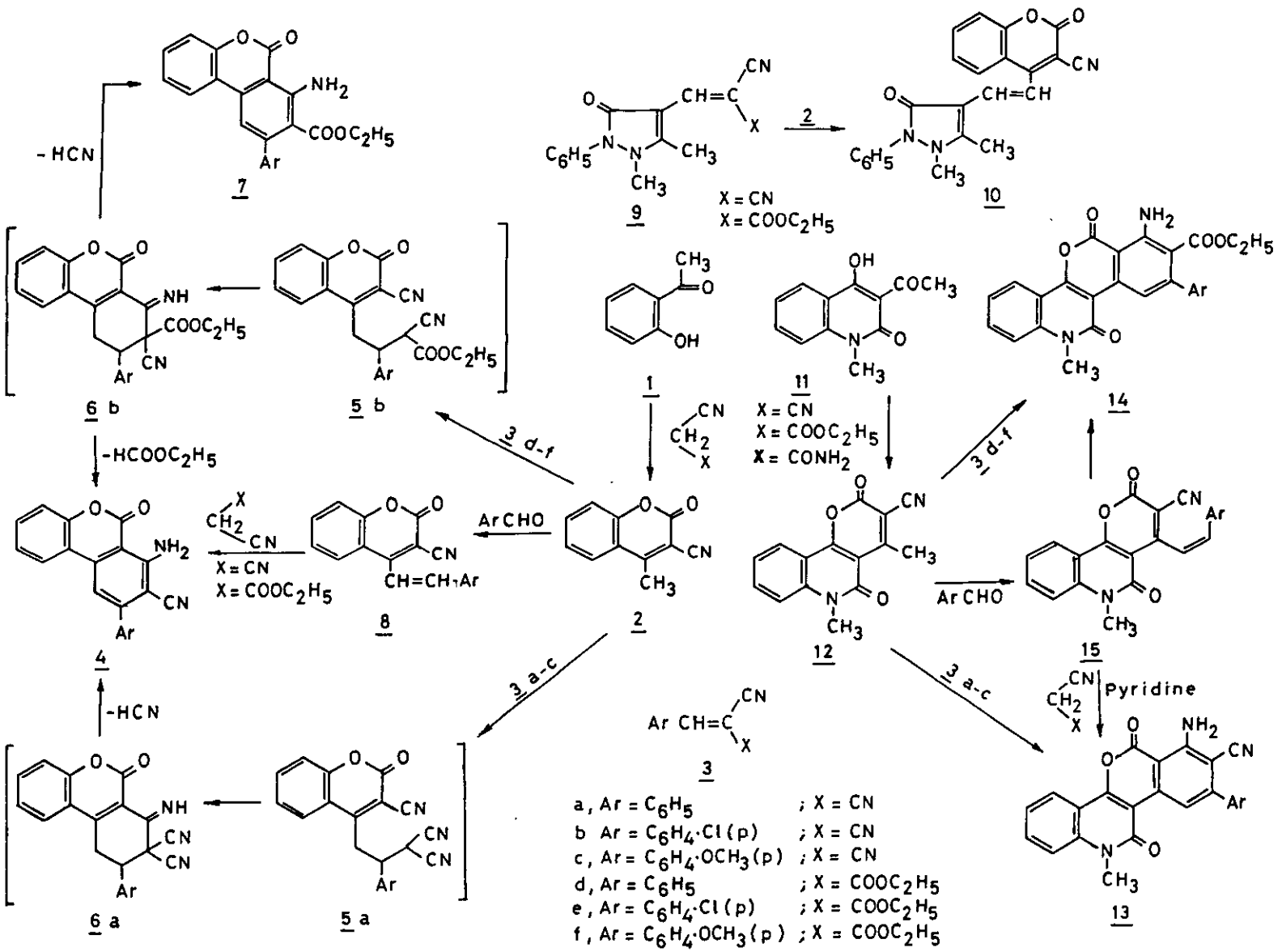
- HCN
7
9
X = CN
X = COOC2H5
2
10
1
11
X = CN
X = COOC2H5
X = CONH2
14
6 b
5 b
3 d-f
-HCOOC2H5
ArCHO
X = CN
X = COOC2H5
8
4
2
12
3 d-f
ArCHO
15
-HCN
3 a-c
3 a-c
Pyridine
3
a, Ar = C6H5 ; X = CN
b Ar = C6H4·Cl(p) ; X = CN
c, Ar = C6H4·OCH3(p) ; X = CN
d, Ar = C6H5 ; X = COOC2H5
e, Ar = C6H4·Cl(p) ; X = COOC2H5
f, Ar = C6H4·OCH3(p) ; X = COOC2H5
6 a
5 a
13

Table 2 : ^{1}H NMR and IR data of compounds 4b, 8b, 10, 12, 13b, 14a and 15a.

Compound	^{1}H NMR (DMSO-d_6) δ ppm	IR cm^{-1}
4b	3.7 (s, 3H, OCH_3); 6.7-7.8 (m, 9H, aromatic protons)	3435, 3340, 3250 (NH_2); 2980 (CH_3); 2220 (CN); 1670 (C=O).
8b	3.8 (s, 3H, OCH_3); 7.1 (d, J=9Hz,1 H); 7.4-8 (m, 8H, aromatic protons); 8.3 (d, J=9Hz, 1H, ylidene proton).	3010, 2995 (CH_3); 2220 (CN); 1695 (C=O); 1630 (C=C).
10	Insoluble in available NMR solvents	3080, 3010, 2990 (CH_3); 2210 (CN); 1700, 1660 (C=O).
12	2.4 (s, 3H, CH_3); 3.8 (s, 3H. N-CH_3); 7.2-8.4 (m, 4H, aromatic protons)	3050, 3010, 2995 (CH_3); 2220 (CN); 1700, 1660 (C=O).
13b	3.3 (s, 3H, N-CH_3); 3.8 (s, 3H, OCH_3); 4.5 (s, 2H, NH_2); 6.8-8.1 (m, 9H, aromatic protons).	3440, 3360, 3270 (NH_2); 3010, 2995, 2900 (CH_3); 2210 (CN); 1690, 1660 (C=O).
14a	0.7 (t, 3H, ester CH_3); 3.3 (s, 3H, N-CH_3); 3.8 (q, 2H, ester CH_2); 4.5 (s, 2H, NH); 6.8-7.6 (m, 10H, aromatic protons).	3400, 3300 (NH_2); 3000, 2940, 2800 (CH_3; and CH_2); 1710 (ester CO); 1680, 1660 (C=O).
15a	Insoluble in available NMR solvents	3000, 2980 (CH_3); 2210 (CN); 1700, 1690 (C=O); 1630 (C=C).

Similar to the formation of 4, compounds 13a-c were also obtained by refluxing of 12 with equivalent amounts of 3a-c in ethanol containing piperidine for few minutes. Compounds 13a-c were also prepared by refluxing of ethyl cyanoacetate or malononitrile with 15 in ethanol and pyridine for 6 h. Compound 12 reacted with 3d-f to yield the corresponding esters 14a-c. It is of value to report here that the signals for the ester group of compounds 14a-c appeared as triplet and quartet at δ 0.7 and δ3.8 respectively, higher by about δ 0.4 ppm than the usual ester group signals. This shielding effect of the ester protons is due to the benzene ring pi-electrons over which the OCH_2CH_3 moiety is located in the most stable conformation. Compounds 15a-c were obtained from the reaction of 12 with aromatic aldehydes in ethanol containing piperidine for few minutes. Although compounds 15a-c can also be written in the trans form the cis conformation was assigned based on the J value of the ylidenic vessinal protons. Trials to obtain 14 from 15 and ethyl cyanoacetate under several different conditions were unsuccessful.

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