Behaviour of 3(N-p-tolylcarbamido)-6-bromocoumarins towards Grignard reagents and Michael Reaction

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Summary: 4-Alkyl(aryl)-3-(N-p-tolylcarbamido)-6-bromo-3,4-dihydrocoumarins (2) have been prepared by action of Grignard reagents on 3 (N-p-tolyl-carbamido)-6-bromocoumarin (1). 4, α-substituted acetic acid derivatives (3, 4 and 5) have been prepared by Michael condensation of (1) with diethyl malonate and ketones in presence of sodium ethoxide. But Michael condensation of (1) with diethyl malonate, ethylacetoacetate or with ketones in presence of amines at 170-180° gave benzopyrano (3,4-c)-pyridine tri(or di) -ones (7,8,9,10 and 11). (1) reacted with acetylacetone in presence of amines at the boiling point of the mixture or at room temperature to give 3,4,5,6-tetrahydro-1,3-benzoxazocines (12). The structures assigned are supported by elemental analysis and spectral data.

In continuation of our studies on coumarins [1-9], we report in this paper the reactions of 3(N-p-tolylcarbamido)-6-bromocoumarin (1) with Grignard reagents and active methylene compounds.

3(N-p-tolycarbamido)-6-bromocoumarin (1)reacted with Grignard reagents namely methylmagnesium iodide, ethylmagnesium iodide, p-anisyl magnesium bromide, o-anisylmagnesium bromide, phenylmagnesium bromide and/or cyclohexyl magnesium bromide to afford 4-alkyl (aryl)-3-(N-p-tolyl-carbamido)-6-bromo-3,4-dihydrocoumarins (2a-f). The IR spectra of (2) showed bands attributable to ν CO of saturated δ-lactone (1740-1790), ν CO of amide (1650-1670) and ν NH (3275). The PMR spectrum of (2 e) showed signals at 2.3 (3H, s, $ArCH_3$), 4.0 (1H, d, H-4), 4.5 (1H, d, H-3), 6.7 - 7.35 (12H, m, Ar-H) and 7.5 (1H, broad, NH).

The Michael condensation of 1 with diethylmalonate in the presence of sodium ethoxide at 170-180° yielded 4 α -(6-bromo-3,4-dihydrocoumarin) acetic acid (3) while with ketones namely acetone, ethylmethyl ketone, diethyl ketone and/or cyclohexanone in the presence of sodium ethoxide at 170-180° gave the corresponding 4 α-(6-bromo-2,3-substituted)chrom -2'-ene acetic acid derivatives (4 a-c) and (5). The IR spectrum of (3) exhibited bands at 1670 (broad νCO of COOH group), 1740 (ν CO of δ -lactone and broad band centered at 3200 (ν OH). The PMR spectrum of (3) showed signals at 3.1 (2H, m, $-CH_2COOH$), 3.7 (1H, m, H-4), 4.2 (2H, d, H-3), 6.8 - 7.2 (3H, m, Ar-H and 11 (1H, broad, COOH). The IR spectra of (4) and (5) showed well defined absorption bands at 1660-1680 (ν CO of acid) and broad band centred at 3100-3220 (bonded OH). The PMR spectrum of (4b) showed signals at 1.9 and 2.2 (6H, s, CH_3), 2.8 (2H, d, CH_2COOH),3.6 (1H, t, H-4) and 6.9 - 7.3 (3H, m, Ar-H).

On the other hand (1) reacted with diethylketone in the presence

of sodium ethoxide at room temperature to give 2-ethyl-3-methyl-6-bromo-4- α -(N-p-tolylcarbamido) acetic acid lactone (6). The reaction involves a Michael type addition with subsequent fission of the heterocyclic ring followed by ring closure [10,11]. The PMR spectrum of (6) showed signals at 1.0 (3H, d, CH_3); 1.3 (3H, t, CH_3 of ethyl), 1.9 (2H, q, CH_2 of ethyl); 2.2 (1H, m, H-b); 2.7 (3H, s, Ar-CH_3); 3(1H,d, H-C); 4(1H, m, H-a), 6.9 - 7.5 (7H, m, Ar-H) and 7.9 (1H, broad, NH).

Interestingly, the reaction of (1) with diethylmalonate in the presence of amines namely aniline, p-toluidine and/or benzylamine at 170-180° gave 9-bromo-1-(substituted) carbamido-4a, 10b-dihydro 3H, 2H (1)-benzopyrano(3,4-c)-N(substituted)-2,4,5 (1H, 3H)-trione (7a-c). The structural assignments of (7) were based on their infrared spectra showing well defined absorption bands attributable to νCO of lactone (1710-1725), CO of amide (1650-1670) and νNH (3320-3380) and PMR spectrum of (7a) showed signals at 3.2 (1H, m, H-a); 3.6 and 3.9 (2H, d, H-b, and H-c); 6.9 - 7.5 (13H, m, Ar-H and 8.1 (1H, broad, NH).

Compound (1) was condensed with ethyl acetoacetate in the presence of amines namely aniline, p-toluidine or benzylamine at 170°-180° to afford 9-bromo-1 (N-substituted) carbamido-2-methyl-4a, 10b-dihydro-3H, 2H [1] benzopyrano (3,4-c)-N-(substituted) pyridine-4,5-(3H)-diones (8a-c) and 9-bromo-1(N-substituted)acetamidoyl-4a,10b-dihydro-3H,2H [1] -benzopyrano (3,4-c) N-(substituted)pyridine 2,4,5 (1H,3H) -trione (9). The infrared spectra of (8) exhibited bands at 1700-1680 CO of δ-lactone), 1660-1630 (ν CO of amide) and 3290-3300 (ν NH). The PMR spectrum of (8a) showed signals at 2.3 (3H, s, CH_3); 3.5 (1H, d, H-a); 4.1 (1H, d, H-b); 7.0 - 7.4 (13H, m, Ar-H) and 8.2 (1H, broad, NH). But the infrared spectrum of (9) showed broad band centred at 1700 (ν CO) and absence of any band at attributable to NH.

Similarly (1) reacted with ketones namely diethylketone, ethylmethyl ketone, cyclopentanone or cyclohexanone in the presence of aniline or benzylamine at 170-180° to give 9-bromo-1,2-dialkyl (cycloalkyl)-4a, 10b-dihydro-4H [1] benzopyrano (3,4-c) N-arylpyridine-4,5-diones (10a,b) and (11a-c), respectively. The infrared spectra of (10) and (11) showed bands at 1710-1720 (νCO of δ-lactone),1650-1680 (ν CO of pyridone) and the PMR spectrum of (11b) showed signals at 1.2- 2.3 (8H, m, of cyclohexyl); 3 (1H, d, H-a); 3.8 (1H, d, H-b), 6.7 - 7.7 (8H, m, Ar-H).

Compound (1) also reacted with acetylacetone in the presence of amines namely aniline or p-toluidine at the boiling point of the reaction mixture or at the room temperature to give 3,4,5,6-tetrahydro-2-methyl -11-acetyl (iminoaryl)-2, 6-methano-2H, 1,3-benzoxazocine-5N-(p-tolyl) -carbamides (12a,b). The IR spectra of (12) showed bands at 1670-1680(ν CO of amide and δ-lactone) and 3300 (ν NH).

Experimental

Melting points reported are uncorrected, IR spectra in KBr wafer technique were taken on a Pye Unicam (641749) spectrophotometer. PMR spectra were recorded on a Jeol LTD FX-2 instrument in $CDCl_3$ using TMS as internal standard.

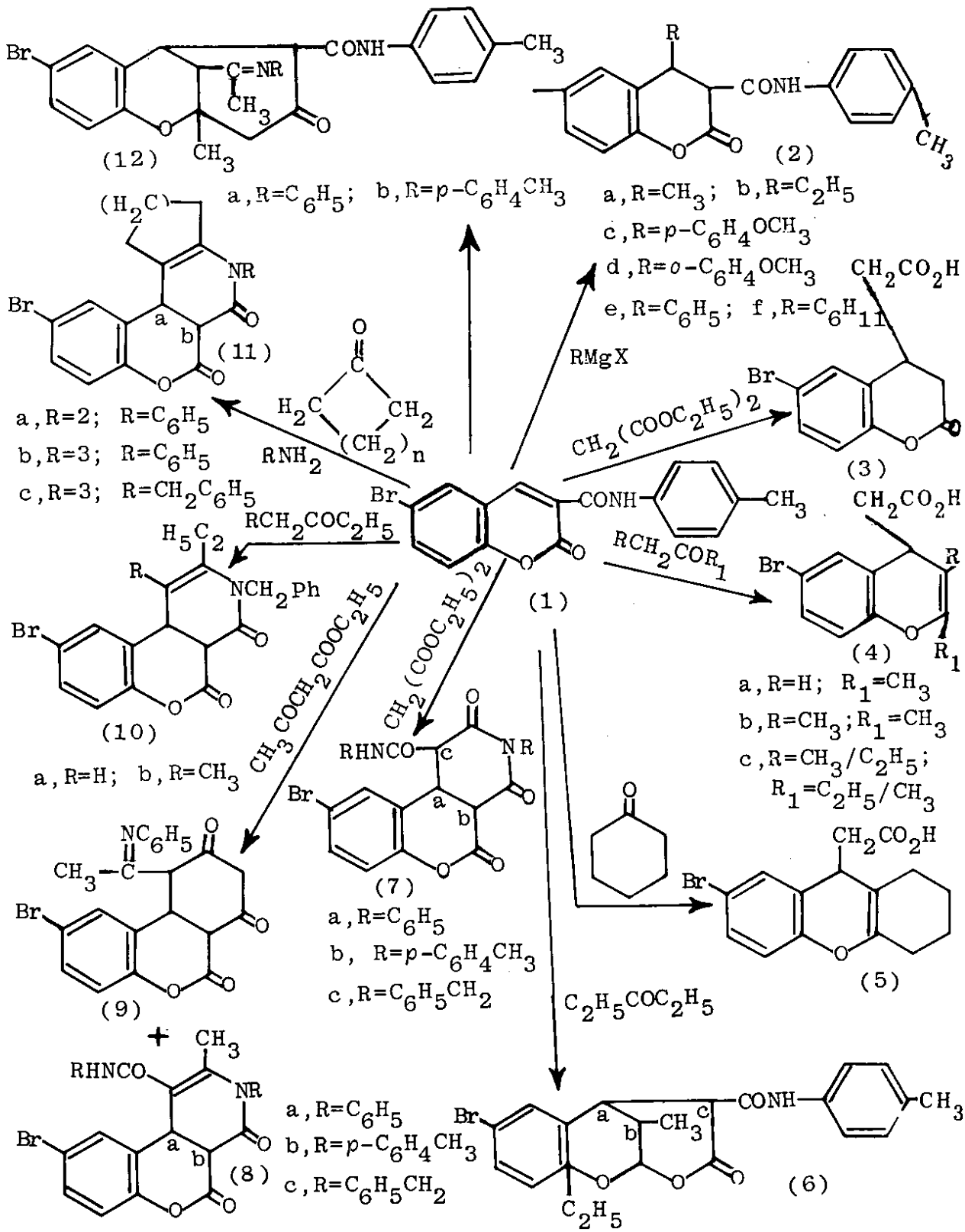
(12)
a, R=C6H5; b, R=p-C6H4CH3
(2)
a, R=CH3; b, R=C2H5
c, R=p-C6H4OCH3
d, R=o-C6H4OCH3
e, R=C6H5; f, R=C6H11
RMgX
(11)
a, R=2; R=C6H5
b, R=3; R=C6H5
c, R=3; R=CH2C6H5
RNH2
CH2(COOC2H5)2
(3)
(1)
RCH2COC2H5
RCH2COR1
(4)
a, R=H; R1=CH3
b, R=CH3; R1=CH3
c, R=CH3/C2H5; R1=C2H5/CH3
(10)
a, R=H; b, R=CH3
CH3COCH2COOC2H5
CH2(COOC2H5)2
(7)
a, R=C6H5
b, R=p-C6H4CH3
c, R=C6H5CH2
(5)
(9)
(8)
a, R=C6H5
b, R=p-C6H4CH3
c, R=C6H5CH2
C2H5COC2H5
(6)

Table-1: Physical data of Compounds Prepared

Compound	M.P.°C (Colour)	Formula (Solvent)	Analysis Found C	H	N	Calc. Br
2a	157 (pale yellow)	$C_{18}H_{16}NO_3Br$ (ethanol)	58.01 (57.75)	4.53 (4.27)	3.34 (3.74)	21.89 (21.39)
2b	202 (Pale yellow)	$C_{19}H_{18}NO_3Br$ (ethanol)	58.35 (58.76)	4.94 (4.63)	3.72 (3.60)	20.92 (20.61)
2c	164 (pale grey)	$C_{24}H_{20}NO_4Br$ (ethanol)	61.42 (61.80)	4.53 (4.29)	3.31 (3.00)	17.93 (17.16)
2d	150 (yellow)	$C_{24}H_{20}NO_4Br$ (ethanol)	62.13 (61.80)	4.21 (4.29)	3.15 (3.00)	17.72 (17.16)
2e	90 (pale yellow)	$C_{23}H_{18}NO_3Br$ (Benzene/ light pet. 60-80°)	63.64 (63.30)	4.52 (4.12)	3.14 (3.21)	18.56 (18.34)
2f	205 (pale grey)	$C_{23}H_{24}NO_3Br$ (ethanol)	62.13 (62.44)	5.72 (5.42)	3.36 (3.16)	18.62 (18.09)
3	128 (colourless)	$C_{11}H_{19}O_4Br$ (light pet. 60-80°)	46.23 (64.31)	3.34 (3.15)	- -	28.62 (28.07)
4a	134 (colourless	$C_{12}H_{11}O_3Br$ (light pet. 60-80°)	50.50 (50.88)	4.13 (3.88)	- -	28.56 (28.26)
4b	177 (colourless)	$C_{13}H_{13}O_3Br$ (benzene)	52.70 (52.52)	4.60 (4.37)	- -	27.32 (26.93)
4c	162 (colourless)	$C_{14}H_{15}O_3Br$ (light pet. 60-80°)	54.35 (54.01)	4.42 (4.82)	- -	26.31 (25.72)
5	165 (pale yellow)	$C_{15}H_{15}O_3Br$ (light pet. 60-80°)	55.53 (55.72)	4.33 (4.64)	- -	24.21 (24.76)

6	163	$C_{22}H_{22}NO_4Br$	59.67	5.03	3.62	17.75
	(pale yellow)	(light pet. 60-80°)	(59.45)	(4.95)	(3.15)	(18.01)
7a	195	$C_{25}H_{17}N_2O_5Br$	59.71	3.68	5.18	15.43
	(yellowish green)	(benzene)	(59.40)	(3.36)	(5.54)	(15.84)
7b	233	$C_{27}H_{21}N_2O_5Br$	60.30	4.13	5.53	15.61
	(pale yellow)	(methanol)	(60.78)	(3.93)	(5.25)	(15.00)
7c	200	$C_{27}H_{21}N_2O_5Br$	60.21	3.74	5.32	15.73
	(pale yellow)	(benzene)	(60.78)	(3.93)	(5.25)	(15.00)
8a	215	$C_{26}H_{19}N_2O_4Br$	61.83	3.80	5.72	16.31
	(yellow)	(acetic acid)	(62.02)	(3.77)	5.56	(15.90)
8b	210	$C_{28}H_{23}N_2O_4Br$	63.66	4.55	5.43	15.70
	(pale yellow)	(acetic acid)	(63.27)	(4.33)	(5.27)	(15.06)
8c	220	$C_{28}H_{23}N_2O_4Br$	63.21	3.98	5.25	14.80
	(pale yellow)	(acetic acid)	(63.29)	(4.33)	(5.27)	(15.06)
9	185	$C_{26}H_{19}N_2O_4Br$	62.10	4.0	5.64	16.30
	(yelllow)	(ethanol)	(62.02)	(3.77)	(5.56)	(15.90)
10a	220	$C_{21}H_{18}NO_3Br$	61.03	4.88	3.31	20.21
	(pale yellow)	(Benzene)	(61.16)	(4.36)	(3.39)	(19.41)
10b	185	$C_{22}H_{20}NO_3Br$	62.05	4.73	3.54	19.43
	(colourless)	(Benzene)	(61.97)	(4.69)	(3.28)	(18.77)
11a	148	$C_{21}H_{16}NO_3Br$	61.74	3.58	3.95	19.21
	(brown)	(ethanol)	(61.46)	(3.90)	(3.41)	(19.51)
11b	127	$(C_{22}H_{18}NO_3Br$	62.30	4.50	3.70	19.32
	(brown)	(ethanol)	(62.26)	(4.24)	(3.30)	(18.86)
11c	213	$C_{23}H_{20}NO_3Br$	62.67	4.70	2.95	18.78
	(brown)	(benzene)	(63.01)	(4.56)	(3.19)	(18.28)
12a	118	$C_{34}H_{30}N_3O_3Br$	67.53	4.86	7.03	13.34
	(yellowish brown)	(light pet. 60-80°)	(67.10)	(4.93)	(6.90)	(13.15)
12b	126	$C_{36}H_{34}N_3O_3Br$	68.21	5.19	6.32	13.01
	(pale yellow)	(light pet. 60-80°).	(67.92)	(5.34)	(6.60)	(12.57)

Action of Grignard reagents on 3(N-p-tolylcarbamido)-6-bromocoumarin (1): Formation of (2a-f)

The solution of Grignard reagents namely, methylmagnesium iodide, ethylmagnesium iodide, p-anisylmagnesium bromide, o-anisylmagnesium bromide, phenylmagnesium bromide or cyclohexylmagnesium bromide (prepared from 0.03 mole of alkyl or arylhalide and 0.03 atoms of magnesium) was added to a solution of 1 (0.01 mol) in dry ether. The solution obtained was refluxed for 4 hours in a boiling water bath and left overnight. The reaction mixture was then hydrolysed with saturated solution of ammonium chloride, extracted with ether, and the solvent removed to give a solid product which was crystallized from a suitable solvent to give 2a-f, respectively, in about 60-70% yield (Table 1).

Condensation of 1 with active methylene compounds or ketones at 170-180°: Formation of (3),(4a-c), (5,7a-c), (8a-c), (9),(10a-b) and (11a-c).

A mixture of (1) (3.58 g; 0.01 mol), active methylene compounds (diethyl malonate or ethyl acetoacetate) or ketones (acetone, ethylmethyl ketone, diethyl ketone, cyclopentanone or cyclohexanone) (0.01 mol) and sodium ethoxide or amines (aniline, p-toluidine or benzylamine (0.025 mol) was heated at 170-180° for 3 hours. The product was stirred with conc. HCl (20 ml) washed with water and crystallised from a suitable solvent to give (3) (4a-c) (5) (7a-c) (8a-c) (9) (10a-b) and (11a-c) (yield 40-80% except (9) yield 10%) (Table 1).

Condensation of 1 with active methylene compounds or ketones at room temperature: Formation of (6) and (12a-b).

A solution of (1) (3.58 g; 0.01 mole), diethyl ketone or acetylacetone (0.01 mol) and sodium ethoxide or amines (aniline or p-toluidine) (0.025 mol) in absolute ethanol (100 ml) was kept at room temperature for 7 days, evaporated to syrup, stirred with conc.HCl (20 ml), then with water (50 ml) and finally allowed to stand for several hr. The products was crystallized from suitable solvent to give (6) and (12a,b) respectively; yield 40-70% (Table 1).

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