PREPARATION OF SOME NEW BENZYLIDENEMALONONITRILES BY AN S_NAr REACTION: APPLICATION TO NAPHTHO[1,2-*b*]PYRAN SYNTHESIS

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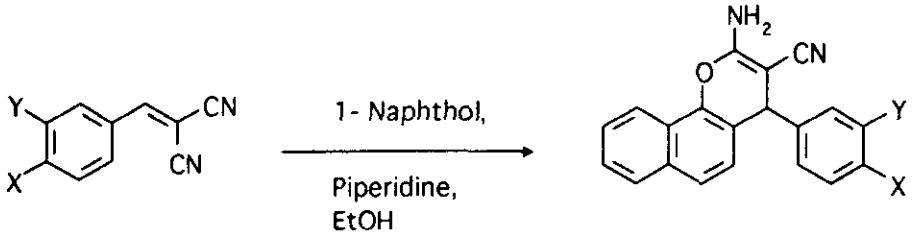
Abstract-The reaction of 4-fluoro-3-nitrobenzylidene malononitrile (**3**) with piperidine and 1-naphthol yields the addition-elimination product (**9**) rather than the expected naphtho[1,2-*b*]pyran (**7**). This reaction is extended to produce other 3,4-disubstituted benzylidenemalononitriles (**10**)-(**13**). These compounds are then reacted with 1-naphthol and 4-methylmorpholine producing the naphtho[1,2-*b*]pyrans (**14**)-(**17**).

The reaction of 1-naphthol with benzylidenemalononitriles and piperidine is known[1,2] to produce 2-amino-4-aryl-4*H*-naphtho[1,2-*b*]pyran 3-carbonitriles. This interesting reaction presumably proceeds *via* a carbon-centred Michael type attack of the naphthol onto the unsaturated nitrile, followed by cyclisation of the naphthol oxygen onto the nitrile and imine-enamine isomerisation. Our interest in the biological activity[3] of this series prompted us to investigate this reaction with the intention of preparing some close analogues of naphthopyran (**5**). We were particularly interested in compounds possessing a substituent adjacent to the nitro group. The first starting material examined was 4-chloro-3-

nitrobenzylidenemalononitrile (2). This smoothly reacted with 1-naphthol and piperidine in ethanol producing the naphtho[1,2-*b*]pyran (6) in 81% yield (Scheme 1). Spectral parameters were fully in accord with the assigned structure: the pyran 4-H singlet appearing at 5.19 ppm and the enamine NH_2 singlet at 7.39 ppm in the ^{1}H-nmr spectrum, the nitrile seen at 2194 cm^{-1} in the ir and ions seen at 395 ($[M+NH_4]^+$), 378 ($[M+H]^+$) and 221 ($[M-C_6H_3ClNO_2]^+$) in the mass spectrum.



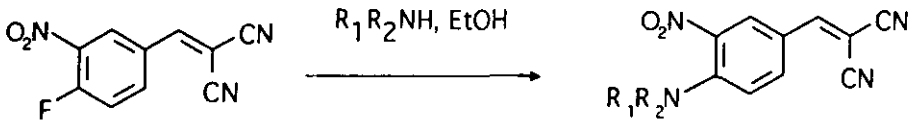
1-4 5-8

	X	Y
1, 5	H	NO_2
2, 6	Cl	NO_2
3, 7	F	NO_2
4, 8	F	F

Scheme 1

However, when the corresponding fluorinated starting material (**3**) was treated with 1-naphthol under similar conditions, the reaction took a different course. The bright orange, grossly insoluble solid which precipitated from the reaction mixture was obviously not the desired pyran (**7**), this was clear from the absence of the 4-H proton in the ^{1}H-nmr spectrum. The latter appeared very simple: there were four protons in the aromatic region and broad singlets at 1.73 and 3.29 ppm, integrating for six and four protons respectively. No signal for the NH_2 group was seen in the ir, only the characteristic nitrile band at 2223 cm^{-1}. The mass spectrum showed a parent ion at 283. All this evidence pointed towards the

product being compound (**9**), where the fluorine of (**3**) had simply been displaced by piperidine in a nucleophilic aromatic substitution (S_NAr) reaction.[4] This interesting experience prompted further work- benzylidenemalononitrile (**3**) was treated with a number of other cyclic amines to provide further examples of this displacement reaction (Scheme 2). It is of note that the nitro group appears to be necessary to facilitate the displacement as reaction of 3,4-difluorobenzylidenemalononitrile (**4**) with piperidine and 1-naphthol provides naphtho[1,2-*b*]pyran (**8**) in 66% yield.

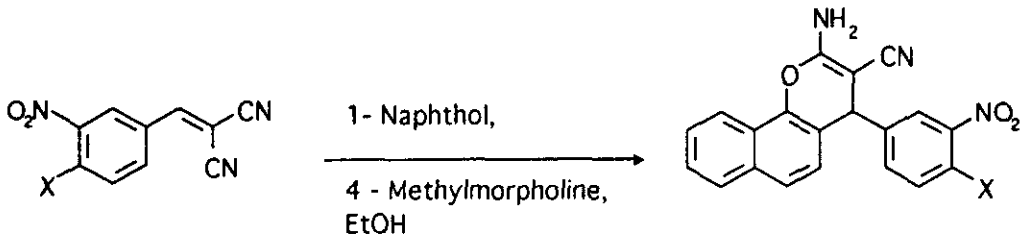


3

	R_1R_2
9	$-[CH_2]_5-$
10	$-[CH_2]_4-$
11	$-[CH_2]_2O[CH_2]_2-$
12	$-[CH_2]_2NMe[CH_2]_2-$
13	- Imidazole

Scheme 2

A logical approach to synthesise the target naphtho[1,2-*b*]pyran (**7**) was to replace the piperidine used in the unsuccessful reaction with a tertiary amine. Accordingly, treatment of (**3**) with 1-naphthol and 4-methylmorpholine in ethanol proceeded successfully, furnishing (**7**) in 69% yield. Spectral data for (**7**) were as expected with the diagnostic pyran 4-H appearing at 5.2 ppm and the enamine NH_2 at 7.36 ppm in the ^{1}H-nmr spectrum. The novel benzylidenemalononitriles (**10**)-(**13**) were treated in similar fashion. This again proved successful with the pyrans (**14**)-(**17**) being synthesised in this manner (Scheme 3), allowing access to a range of 4-aryl-4*H*-naphtho[1,2-*b*]pyrans with an interesting substituent pattern for SAR studies.



3, 10-13 7, 15-18

	X
3, 7	F
10,15	1-Pyrrolidino
11,16	4-Morpholino
12,17	4-(1-Methylpiperazinyl)
13,18	1-Imidazolyl

Scheme 3

EXPERIMENTAL

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Ir spectra were recorded on a Bruker IFS 48 instrument as KBr discs. Uv spectra were determined on a Philips PU8725 instrument as methanol solutions. Mass spectra were recorded using a VG7070E instrument. Nmr spectra were obtained on dilute solutions in $CDCl_3$, except where indicated otherwise, on a Bruker AM300 or AC300 instrument (300 MHz). Signals are reported downfield from TMS. Coupling constants are in Hertz. Microanalyses were carried out by the molecular structure research group at Eli Lilly and Company, Indianapolis.

Representative arylidenemalononitrile preparation.- A stirred solution of 4-fluoro-3-nitrobenzaldehyde[5] (14.15g, 83.7 mmol) and malononitrile (5.53g, 83.7 mmol) in ethanol (100 ml) was warmed to reflux. Piperidine (5 drops) was then

added, the solution instantly turning red in colour. Heating at reflux was continued for 30 min. The red solution was cooled in ice whereupon an orange precipitate appeared. This was filtered off, washed with ethanol and ether, leaving pale orange needles. These were dried *in vacuo* overnight providing *4-fluoro-3-nitrobenzylidenemalononitrile* **3** (11.4 g, 63%). For spectroscopic and microanalytical data, see Tables 1 and 2.

Prepared in a similar manner were **1** (91.5% yield, mp 108 °C, lit.,[6] 104.5-105 °C), **2** (94 % yield, mp 142 ° C, lit.,[7] 140 ° C) and **4** (79% yield, data: see Tables 1 and 2).

Reaction of arylidenemalononitrile **3** *with 1-naphthol and piperidine.*- 1-Naphthol (3.68 g, 25.5 mmol) was dissolved in ethanol (30 ml) with stirring. To this was added the nitrile **3** (5.54 g, 25.5 mmol) followed by piperidine (2.17 g, 25.5 mmol). A deep red colour developed instantly, there was a slight exotherm and a solid began to precipitate out. The mixture was warmed to reflux and within 10 min the contents of the flask had solidified. The mixture was cooled to room temperature, the solid broken up, filtered off, washed with ethanol and ether and dried *in vacuo*, providing *3-nitro-4-(1-piperidino)benzylidenemalononitrile* (**9**) as a bright orange solid (4.69 g, 65%). For data: see Tables 1 and 2.

Prepared in a similar manner, but omitting the 1-naphthol and using pyrrolidine, morpholine, 1-methylpiperazine and imidazole respectively in place of piperidine, were **10** (81% yield),**11** (83% yield), **12** (63% yield) and **13** (82% yield). For data, see Tables 1 and 2.

Representative 4-aryl-4H-naphtho[1,2-b]pyran preparation.- A stirred mixture of 1-naphthol (1.44 g, 10 mmol) and **3** (2.17 g, 10mmol) in ethanol (30 ml) was treated with 4-methylmorpholine (1.01 g, 10 mmol). A slight red colour appeared. The mixture was warmed to reflux, yielding a red solution. Copious quantities of a pink solid precipitated out within 5 min of attaining reflux. The mixture was

cooled to room temperature and the solid filtered off, washed with ethanol and ether and dried *in vacuo* providing *2-amino-4-(4-fluoro-3-nitrophenyl)-4H-naphtho[1,2-b]pyran 3-carbonitrile*(7)as a flesh coloured powder (2.49 g, 69%). For data, see Tables 1 and 2.

Table 1: Microanalytical and Spectral Data

Compound	mp/ °C	Found/% (Required)				ν_{max}(CN)/ cm^{-1}	λ_{max}/ nm
		C	H	N	Hal		
3	117	55.3	1.9	19.3	8.75	2230	292
		(55.3	1.9	19.2	8.5)		
4	69	63.3	2.3	14.7	20.3	2233	304
		(63.2	2.1	14.7	20.0)		
5	214.5-216	69.7	4.0	12.1		2195	228
		(70.0	3.8	12.2)			
6	249-251	63.5	3.4	11.1	9.8	2194	230
		(63.6	3.2	11.1	9.4)		
7	218-220	66.8	3.3	11.3	5.0	2191	228
		(66.5	3.35	11.6	5.3)		
8	210.5-211	71.9	3.6	8.4	11.2	2196	226
		(71.9	3.6	8.4	11.4)		
9	154	63.8	5.0	19.85		2223	432
		(63.6	4.9	19.6)			
10	188-190	62.7	4.5	20.9		2223	405
		(62.6	4.6	20.9)			
11	187-189	59.2	4.3	19.7		2214	398
		(59.4	4.1	19.9)			
12	157	60.6	5.1	23.6		2225	398
		(60.4	5.2	23.8)			

13	151-153	59.2	2.6	26.1	2229	300
		(58.9	2.7	26.4)		
14	138-139	69.7	4.8	13.75	2190	225
		(69.9	4.9	13.6)		
15	236-238	67.2	4.7	13.1	2198	225
		(67.3	4.7	13.1)		
16	177-178	67.7	5.5	15.8	2184	225
		(68.0	5.25	15.9)		
17	240-242	67.6	4.0	16.7	2192	226
		(67.5	3.7	17.1)		

Table 2: Spectroscopic Data.

Compound	*m/z* (%)	δ_H / ppm
3	235 (100) and 217 (6)	8.55 (1H, dd, *J* 7 and 2), 8.30 (1H, m), 7.83 (1H, s) and 7.57 (1H, t, *J* 8).
4	208 (4), 190 (100) and 142 (33)	7.85 (1H, m), 7.73 (1H, s), 7.70 (1H, m) and 7.37 (1H, q, *J* 8).
5	361 (45), 344 (60) and 221 (55).	8.20 (1H, dd, *J* 8 and 0.8), 8.13 (1H, m), 8.08 (1H, t, *J* 2), 7.81 (1H, dd, *J* 7 and 2), 7.66-7.55 (3H, m), 7.54 (1H, d, *J* 8), 7.52 (1H, t, *J* 8), 6.96 (1H, d, *J* 8), 5.03 (1H, s) and 4.91 (2H, s).
6*	395 (70), 378 (64) and 221 (100)	8.28 (1H, *J* 8), 8.07 (1H, d, *J* 2), 7.93 (1H, d, *J* 8), 7.75 (1H, d, *J* 8), 7.70-7.58 (4H, m), 7.39 (2H, s), 7.16 (1H, d, *J* 8) and 5.19 (1H, s).
7*	379 (90), 362 (64), 296 (20) and 221 (100)	8.26 (1H, d, *J* 8), 8.09 (1H ,dd, *J* 5 and 1.5), 7.92 (1H, d, *J* 8), 7.71-7.53 (5H, m), 7.36 (2H,s), 7.16 (1H, d, *J* 8) and 5.20 (1H, s).

8*	352 (4), 335 (100) and 221 (16)	8.29 (1H, d, *J* 8), 7.92 (1H, d, *J* 8), 7.67 (1H, t, *J* 7), 7.64 (1H, d, *J* 7), 7.60 (1H, t, *J* 8), 7.5-7.3 (2H, m), 7.32 (2H, s), 7.15 (2 X 1H, overlapping pair of doublets, *J* 8) and 5.02 (1H, s).
9	283 (100), 265 (31), 249 (30) and 235 (10)	8.15 (1H, dd, *J* 8 and 2), 8.15 (1H, s), 7.55 (1H, s), 7.13 (1H, d, *J* 8), 3.29 (4H, br s) and 1.73 (6H, br s).
10	269 (100), 251 (18), 235 (17) and 221 (26)	8.15 (1H, dd, *J* 8 and 2), 8.10 (1H, d *J* 2), 7.52 (1H, s), 6.95 (1H, d, *J* 8), 3.37 (4H, m) and 2.05 (4H, m).
11	285 (100), 267 (4) and 251 (4)	8.20 (1H, d, *J* 2), 8.18 (1H, dd, *J* 8 and 2), 7.60 (1H, s), 7.14 (1H, d, *J* 8), 3.87 (4H, m) and 3.30 (4H, m).
12	298 (100), 267 (15) and 250 (31)	8.18 (1H, d, *J* 2), 8.15 (1H, dd, *J* 8 and 2), 7.58 (1H, s), 7.14 (1H, d, *J* 8), 3.34 (4H, m), 2.57 (4H, m) and 2.37 (3H, s).
13*	266 (100), 236 (4) and 218 (10).	8.73 (1H, s), 8.70 (1H, d, *J* 2), 8.36 (1H, dd, *J* 8 and 2), 8.05 (1H, d, *J* 0.8), 7.99 (1H, d, *J* 8), 7.54 (1H, s) and 7.15 (1H, d, *J* 0.8).
14*	413 (100), 383 (16) and 347 (19)	8.23 (1H, d, *J* 8), 7.90 (1H, d, *J* 8), 7.67-7.56 (4H, m), 7.30 (1H, dd, *J* 8 and 2), 7.22 (2H, s), 7.14 (1H, d, *J* 8), 7.02 (1H, d, *J* 8), 4.94 (1H, s), 3.09 (4H, m) and 1.89 (4H, m).
15*	429 (100), 363 (11) and 221 (40).	8.24 (1H, d, *J* 8), 7.90 (1H, d, *J* 8), 7.75 (1H, d, *J* 2), 7.63 (1H, d, *J* 8), 7.62 (1H, t, *J* 9), 7.59 (1H, t, *J* 9), 7.47 (1H, dd, *J* 8 and <1), 7.30 (1H, d, *J* 8), 7.27 (2H, s), 7.14 (1H, d, *J* 8), 5.03 (1H, s), 3.66 (4H, m) and 2.95 (4H, m).

16*	442 (100), 376 (15) and 221 (9)	8.24 (1H, d, *J* 8), 7.90 (1H, d, *J* 8), 7.72 (1H, d, *J* 0.2), 7.63 (1H, d, *J* 8), 7.62 (1H, t, *J* 8), 7.59 (1H, t, *J* 8), 7.44 (1H, dd, *J* 8 and <1), 7.27 (1H, d, *J* 8), 7.26 (2H, s), 7.14 (1H, d, *J* 8), 5.01 (1H, s), 2.96 (4H, m), 2.39 (4H, m) and 2.19 (3H, s).
17*	410 (100), 380 (70), 316 (29) and 221 (14)	8.26 (1H, d, *J* 8), 8.12 (1H, d, *J* <1), 7.93 (1H, d, *J* 8), 7.92 (1H, br s), 7.76 (1H, dd, *J* 8 and 1.5), 7.69-7.59 (4H, m), 7.44 (1H, d, *J* 1), 7.40 (2H, s), 7.21 (1H, d, *J* 8), 7.07 (1H, br s) and 5.26 (1H, s).

(Nmr spectra on asterisked samples were run in methyl sulfoxide-d_6)

Naphthopyrans (**5**), (**6**) and (**8**) were prepared in a similar manner,starting from the appropriate benzylidenemalononitrile, using piperidine as the base (yields 66-86%). Using 4-methylmorpholine, naphthopyrans (**14**)-(**17**) were also prepared (yields 60-85%). For these last four compounds, the reactions were markedly slower than for the preparations of **5** - **8** . The rate could be enhanced by adding an equivalent of pyrrolidine (for **14**), morpholine (for **15**) *etc.*, the choice of base here merely removing any chance of amine exchange.

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