Synthesis of Novel Pyrindine Derivatives from a Facile Reaction of 2,5-Bisarylidenecyclopentanone and Malononitrile

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Starting from 2,5-bisarylidenecyclopentanone and malononitrile (1:1) several novel pyrindine derivatives were synthesized by a facile and convenient one-pot reaction using sodium ethoxide in absolute ethanol at room temperature. The structure of the reaction products was unambiguously deduced ftom their infrared, ^{1}H-nuclear magnetic resonance spectroscopy, elemental analysis and single crystal X-ray crystallography.

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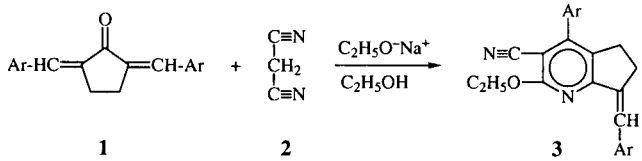
Several approaches [1-3] have been employed for the synthesis of pyridine derivatives. For example, 5*H*-[1]-Benzopyrano[4,3-*b*]pyridine derivatives were prepared by starting from salicylaldehyde and 3-acylchromones [4] or 4-hydroxycoumarines [5]. 2-Amino-4-aryl-3-cyano-pyndines were simply synthesized by the condensation of malononitrile with aromatic aldehyde and alkyl ketones in the presence of ammonium acetate [6]. Pentaphenyl-pyridines were obtained by the condensation of α-phenylchalcones with aryl benzyl ketones, methyl benzyl ketones, acetylacetone, ethyl phenylacetate, *p*-chlorobenzyl cyanide and malononitrile in the Michael reaction to give adducts which undergoes ring closure in boiling acetic acid in the presence of ammonium acetate [7]. In addition, the reactions of unsaturated ketones with malononitrile and ethyl cyanoacetate in the presence of ammonium acetate to give pyridine derivatives were first reported by Sakurai and Midorikawa [8,9]. Their process was studied by other authors [10,11]. Several pyridine derivatives have shown important biological activities as pharmaceuticals and potential agrochemicals such as herbicides [12]. Some other pyridines possess fluorescent properties and have been used in liquid-crystal industries. For example, the molecular design of liquid crystalline 2,5-disubstituted pyridine derivatives for twisted nematic and super twisted nematic liquid crystal displays and the correlations between the molecular structure of pyridine derivatives and their physico-chemical properties have been reported [13].

There are great number of references for the synthesis of various pyridine derivatives, but essentially no references for the synthesis of pyrindines. Because of our continued interest in the condensation reaction of α,β-unsaturated Michael acceptors with active methylene compounds [14-20], we expanded this study to cover the reaction of 2,5-bisarylidenecyclopentanone **1** with malononitrile **2** using sodium ethoxide in absolute ethanol. The two starting materials were mixed and stirred at room temperature. As a result of this reaction, 2-ethoxy-6,7-dihydro-4-phenyl-7-(phenylmethylene)-5*H*-1-pyridine-3-carbonitriles **3** were obtained as shown in Scheme I. Although we have not undertaken a mechanistic investigation of the reaction, a possible mechanism is shown in Scheme II. In addition, it was reported previously [21] that when 2,5-bisbenzylidenecyclopentanone was mixed with malononitrile using basic catalyst under reaction conditions similar to ours, cycloalka[*b*]pyrans were obtained. However, when they further treated those cycloalka[*b*]-pyrans with a basic catalyst, rearrangement to the corresponding pyrindine derivatives occurred. To the best of our knowledge this is the only reference in the literature describing the synthesis of this pyrindine derivative. On the other hand, we obtained the pyrindines directly without isolating the pyran intermediates.

As shown in Scheme II, we suggest that the reaction could begin with a Michael addition of the malononitrile carbanion to the 2,5-bisarylidenecyclopentanone to yield adduct **i**, followed by cyclization to the cyclohexapyran **ii** through a nucleophilic attack by the carbonyl oxygen on one of the cyano groups. The next step would be a Dimroth

Scheme I



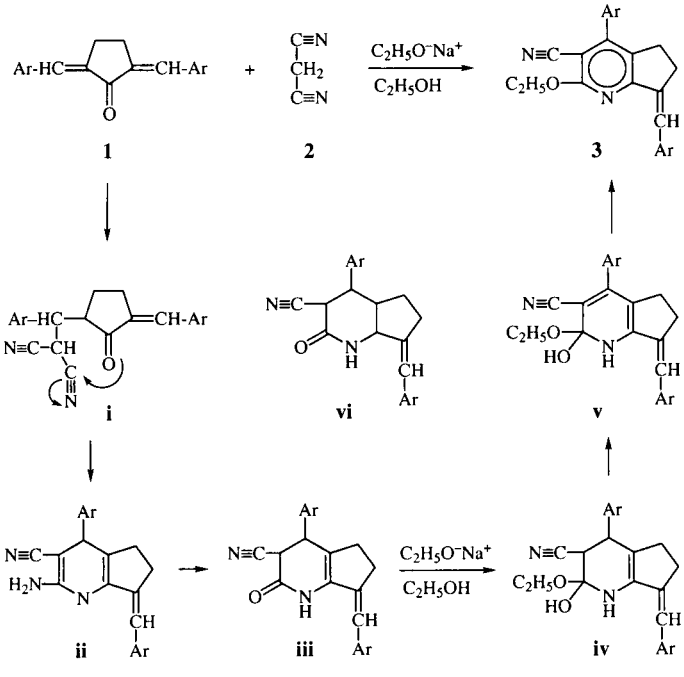
1 **2** **3**

3	Ar
a	*m*-BrC_6H_4-
b	*o*-ClC_6H_4-
c	*m*-ClC_6H_4-
d	*p*-ClC_6H_4-
e	C_6H_5-

rearrangement [22] to give the adduct **iii**. A subsequent nucleophilic attack by the alkoxide anion to the lactam carbonyl group of **iii** gives adduct **iv**, which in turn undergoes a disproportionation to give **v** and the not isolated pyrindine derivatives **vi**. A final dehydration of adduct **v** leads to the aromatic pyrindine derivatives **3**.

Using this simple reaction, five novel pyrindine derivatives were prepared, isolated, purified and characterized. The structure elucidation was based on the single crystal X-ray crystallography of **3d** (Tables 1, 2, 3 and 4) as well as on analytical and spectral data. The infrared spectra of isolated products **3** showed a peak at 2245 cm^{-1} which was assigned to the cyano group stretching frequency. The pyridine ring peaks appeared at 1605, 1570, 1500 and 1430 cm^{-1}. Another peak at 1640 cm^{-1} due to the carbon-carbon double bond was also observed. The low value of this peak is expected since this double bond is in conjugation with the aromatic ring.

Scheme II



In the proton nuclear magnetic resonance spectrum of pyrindine derivatives **3a-e**, the ethoxy group gives rise to a quartet at around 4.60 ppm and a triplet at 1.53 ppm with a J = 7.7 Hz. The aromatic proton signals appear as a multiplet at 7.25-8.10 ppm. Careful counting of the protons under this multiplet in the integrated mode concludes that the phenylmethylene proton which is highly deshielded is overlapped with aromatic protons. The signal for the four aliphatic protons of the cyclopentane ring appear as a multiplet at 2.75-3.25 ppm. Since the pyridine ring is totally substituted, no aromatic protons of this ring are expected to appear in the aromatic protons region. As shown in Figure 1, the conclusive answer for elucidation of the structure of the pyrindine derivatives came from single crystal X-ray crystallography of **3d** which shows clearly the pyridine ring, the cyclopentane ring and the substituents on these rings.

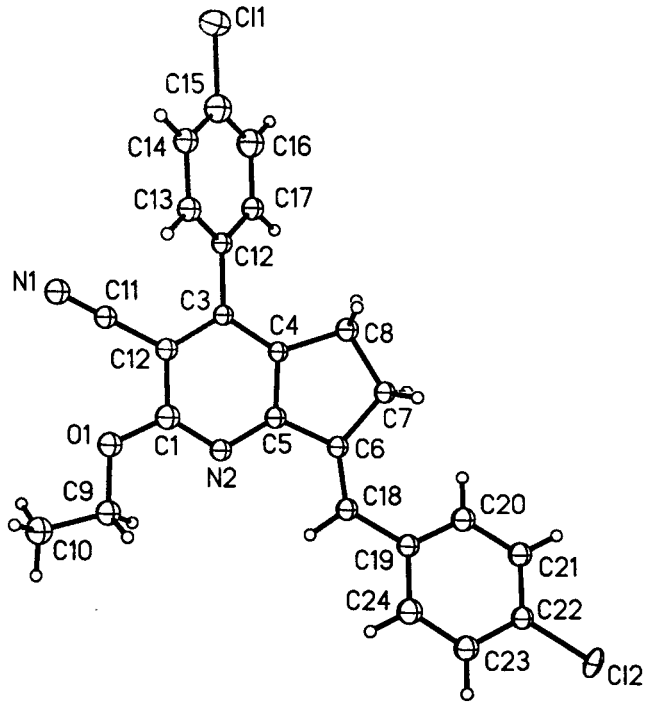


Figure 1. Single crystal X-ray plot of **3-d** ($C_{24}H_{18}Cl_2O$).

Table 1
Selected Bond Lengths [Å] for $C_{24}H_{18}Cl_2N_2O$

Cl(1)-C(15)	1.739(10)	N(1)-C(11)	1.138(13)
N(2)-C(5)	1.352(13)	C(1)-C(12)	1.432(14)
C(3)-C(4)	1.388(13)	C(4)-C(5)	1.391(12)
C(4)-C(8)	1.542(14)	C(5)-C(6)	1.465(13)
C(6)-C(18)	1.323(13)	C(6)-C(7)	1.521(13)
C(7)-C(8)	1.545(13)	C(11)-C(12)	1.44(2)
C(18)-C(19)	1.484(14)	C(20)-C(21)	1.39(2)
C(21)-C(22)	1.38(2)	C(22)-C(23)	1.395(14)
C(23)-C(24)	1.37(2)		

Table 2
Selected Bond Angles [°] for $C_{24}H_{18}Cl_2N_2O$

C(1)-O(1)-C(9)	117.6(8)	C(1)-N(2)-C(5)	117.1(8)
N(2)-C(1)-O(1)	122.0(9)	C(6)-C(18)-C(19)	128.5(9)
O(1)-C(1)-C(12)	115.2(9)	C(12)-C(3)-C(4)	115.4(8)
C(5)-C(4)-C(8)	110.0(8)	C(3)-C(4)-C(8)	128.7(8)
N(2)-C(5)-C(6)	124.8(8)	C(4)-C(5)-C(6)	112.1(8)
C(18)-C(6)-C(5)	122.8(9)	C(18)-C(6)-C(7)	130.6(9)
C(5)-C(6)-C(7)	106.4(8)	C(4)-C(8)-C(7)	103.5(7)

EXPERIMENTAL

Melting points were determined on a Electrothermal melting point apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets on a Matteson, Poans TM FT IR spectrometer. The ^{1}H-nmr spectra were measured on a Bruker WP 80-SY spectrometer using deuteriochloroform solutions containing TMS as internal standard. Compounds were analyzed at the Chemistry Department, University of Bahrain, State of

Table 3
Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$ x 10^3) for $C_{24}H_{18}Cl_2N_2O$- U(eq) is defined as one third of the trace of the orthogonalized U_{ij} *tensor*

	x	y	z	U(eq)
Cl(1)	10533(5)	1803(3)	7326(1)	37(1)
C1(2)	103(4)	7138(3)	-143(1)	33(1)
O(1)	12672(10)	45(9)	2607(4)	26(2)
N(1)	14202(13)	-669(11)	4401(5)	28(2)
N(2)	9690(12)	487(11)	2468(4)	20(2)
C(1)	11146(15)	798(14)	2886(6)	26(2)
C(3)	9807(13)	1601(12)	4027(5)	17(2)
C(4)	8242(13)	2285(13)	3570(5)	17(2)
C(5)	8244(14)	2239(14)	2809(5)	20(2)
C(6)	6528(14)	3109(13)	2432(5)	20(2)
C(7)	5278(14)	3712(13)	3030(5)	20(2)
C(8)	6456(14)	3302(14)	3780(5)	23(2)
C(9)	12576(15)	-95(15)	1812(6)	27(2)
C(10)	14430(16)	-1012(16)	1651(6)	33(3)
C(11)	12902(15)	-9(13)	4079(5)	21(2)
C(12)	9960(13)	646(13)	4851(5)	19(2)
C(12)	11262(14)	824(13)	3673(5)	21(2)
C(13)	11687(15)	2303(14)	5244(5)	23(2)
C(14)	11898(15)	2350(13)	5997(5)	24(2)
C(15)	10325(16)	1773(15)	6370(6)	33(3)
C(16)	8559(17)	1138(15)	5996(6)	35(3)
C(17)	8384(15)	1106(13)	5238(5)	23(2)
C(18)	6319(14)	3345(14)	1713(5)	21(2)
C(19)	4736(14)	4270(13)	1268(5)	21(2)
C(20)	2834(15)	4560(14)	1492(6)	25(2)
C(21)	1413(15)	5449(14)	1060(6)	25(2)
C(22)	1893(14)	6033(13)	396(5)	22(2)
C(23)	3783(15)	5707(14)	144(6)	26(2)
C(24)	5163(15)	4831(15)	580(6)	27(3)

Table 4
Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters($Å^2$ x 10^3) for $C_{24}H_{18}Cl_2N_2O$

	x	y	z	U(eq)
H(7A)	3908	3219	2984	24
H(713)	5097	4851	2984	24
H(8A)	6970	4251	4044	28
H(813)	5576	2719	4093	28
H(9A)	12590	946	1582	32
H(9B)	11308	-640	1617	32
H(10A)	14357	-1230	1122	49
H(10B)	14471	-1994	1924	49
H(10C)	15670	-411	1801	49
H(13)	12738	2726	4983	28
H(14)	13098	2769	6259	29
H(16)	7498	737	6259	42
H(17)	7171	709	4977	27
H(18)	7312	2858	1446	25
H(20)	2490	4150	1946	30
H(21)	109	5654	1221	30
H(23)	4106	6084	-319	31
H(24)	6450	4597	410	33

Bahrain. The X-ray measurements were carried out at the Deparment of Chemistry, University of California, Davis, CA 95616, U. S. A.

General Procedure.

To a freshly prepared sodium ethoxide solution (0.017 mole of sodium metal in 100 ml of absolute ethanol), 0.017 mole of malononitrile was added with stirring. To this mixture 0.017 mole of 2,5-bisarylidenecyclopentanone was added with continuous stirring for 15-45 minutes at room temperature. A solid separated, was collected by suction filtration, washed with cold ethanol and recrystallized from glacial acetic acid. Specific details on each product are as follows:

2-Ethoxy-6,7-dihydro-4-(*m*-bromophenylmethylene)-5*H*-1-pyrindine-3-carbonitrile (**3a**).

Product **3a** (63%) was recrystallized from acetic acid, mp 168-170°; ir (potassium bromide): 1145, 1430, 1500, 1580, 1595, 1640, 2245, 2995, 3065; ^{1}H nmr: δ 1.58 (t, 3H), 3.05 (m, 4H), 4.66 (q, 2H), 7.32-7.65 (m, 9H).

Anal. Calcd. for $C_{24}H_{18}N_2OBr_2$: C, 56.50; H, 3.56; N, 5.49. Found: C, 56.28; H, 3.71; N, 5.56.

2-Ethoxy-6,7-dihydro-4-(*o*-chlorophenylmethylene)-5*H*-1-pyrindine-3-carbonitrile (**3b**).

Product **3b** (69%) was recrystallized from acetic acid-water, mp 159-161°; ir (potassium bromide) 1145, 1435, 1500, 1585, 1595, 1640, 2240, 2995, 3065; ^{1}H nmr: δ 1.51 (t, 3H), 2.85 (m, 4H), 4.65 (q, 2H), 7.19-7.89 (m, 9H).

Anal. Calcd. for $C_{24}H_{18}N_2OCl_2$: C, 68.42; H, 4.31; N, 6.65. Found: C, 68.29; H, 4.25; N, 6.78.

2-Ethoxy-6,7-dihydro-4-(m-chlorophenyhnethylene)-5*H*-1-pyrindine-3-carbonitrile (**3c**).

Product **3c** (70%) was recrystallized from acetic acid, mp 162-164°; ir (potassium bromide) 1145, 1430, 1505, 1585, 1590, 1635, 2240, 2985, 3075; ^{1}H nmr: δ 1.50 (t, 3H), 2.87 (m, 4H), 4.61 (q, 2H), 7.25-7.49 (m, 9H).

Anal. Calcd. for $C_{24}H_{18}N_2OCl_2$: C, 68.42; H, 4.31; N, 6.65. Found: C, 68.29; H, 4.25; N, 6.78.

2-Ethoxy-6,7-dihydro-4-(*p*-chlorophenyhnethylene)-5*H*-1-pyrindine-3-carbonitrile (**3d**).

Product **3d** (65%) was recrystallized from acetic acid, mp 191-193°; ir (potassium bromide) 1140, 1430, 1500, 1585, 1595, 1640, 2245, 2980, 3075; ^{1}H nmr: δ 1.52 (t, 3H), 3.07 (m, 4H), 4.64 (q, 2H), 7.42-7.56 (m, 914).

Anal. Calcd. for $C_{24}H_{18}N_2OCl_2$: C, 68.42; H, 4.31; N, 6.65. Found: C, 68.52; H, 4.48; N, 6.78.

2-Ethoxy-6,7-dihydro-4-(phenylmethylene)-5*H*-1-pyrindine-3-carbonitrile (**3e**).

Product **3e** (67%) was recrystallized from acetic acid-water, mp 132-134°; ir (potassium bromide) 1145, 1435, 1505, 1580, 1590, 1635, 2245, 2990, 3085; ^{1}H nmr δ 1.52 (t, 3H), 3.03 (m, 4H), 4.65 (q, 2H), 7.33-7.51 (m, 11H).

Anal. Calcd. for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.65; H, 5.76; N, 8.03.

X-ray Crystallography.

Crystals of compound **3d** were extremely thin with a tendency to twin. The crystal selected for data collection was mounted in the cold nitrogen stream (130 K) on a Siemens P4 diffractometer equipped with a LT-2 low temperature apparatus. The radiation employed was Ni filtered CuKα from a Siemens rotating anode

source operating at 15 kW. A 3% decay in the intensifies of two standard reflections was observed during the data collection. The structure was solved using direct methods [23]. Hydrogens were included by use of a riding model with isotropic U equal to 1.2 (1.5 for methyl) times that of bonded carbons. Refinement was by full-matrix least-squares methods. based on F^2, using all data and with only thermal parameters for chlorine atoms. The stereo enantiomeric isomer was determined by use of the Flack x parameter [24]. The largest peaks in the final difference map were less than 0.72 e $Å^{-3}$. θ range for data collection, 2.43 to 56.01°; scan type, 2θ-ω; index ranges, $-7 \leq -9 \leq 1$, $0 \leq -1 \leq 19$; reflection collected, 2363. Independent reflections, 1658 ($R_{int.}$ = 0.1200); standard reflections, 2. We assume the larger R value and the limited number of observed data are due to the small crystal.

Crystal Data for $C_{24}H_{18}Cl_2N_2O$.

Empirical formula, $C_{24}H_{18}Cl_2N_2O$; formula weight, 421.30; crystal size; 0.32 x 0. 1 x 0.02 mm; crystal habit, plate; crystal color, pale yellow; crystal system, monoclinic; space group, P2 1; unit cell dimensions, a = 6.5653 (9) Å, b = 8.6042 (8) Å, c = 18.270 (3) Å, α = 90°; β = 95.809 (11)°, γ = 90°; volume, 1026.8(2) $Å^3$ density (calculated), 1.363 $Mg•m^{-3}$; absorption coefficient, 2.980 mm^{-1}; F(000), 436; absorption correction [25], XABS2; max. and min transmission, 0.96 and 0.78.

Solution and Refinement of $C_{24}H_{18}Cl_2N_2O$ [26-28].

System for solution, SHELXTL v. 5.03 (Sheldrick, 1994); structure solution, direct; system for refinement, SHELXTL v. 5.03 (Sheldrick, 1994); refinement method, full-matrix least-squares on F^2; hydrogen atoms, riding; data / restraints / parameters, 1658 / 1 / 128; Goodness-of-fit on F^2, 1.081; weighting scheme, $w^{-1} = \sigma^2(Fo^2) + (0.1643)^2 + 2.7287P$, where $P = (Fo^2 + 2Fc^2)/3$; R indices (all data), R1 = 0.0989, wR2 = 0.2453; R indices calcd. from observed data, R1 = 0.0895, wR2 = 0.2318; observed data (>2sigma (I)), 1467; absolute structure parameter, 0.04(5); largest diff. peak and hole, 0.716 and 0.989 e$Å^{-3}$.

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[26] $R1 = \Sigma||Fo-Fc||/\Sigma|Fo|$; $wR2 = [\Sigma[w(Fo^2-Fc^2)]/\Sigma(Fo^2)^2||^{1/2}$.

[27] Goodness-of-Fit = $[\Sigma(Fo^2-Fc^2)^2]/(M-N)^{1/2}$; where M is the number of reflections and N is the number of parameters refined.

[28] Refinement is based on F^2 for ALL reflections except for those with very negative F^2 or flagged by the user for potential systematic errors. Weighted R-factors wR and all goodnesses of fit S are based on F^2, conventional R-factors R are based on F, with F set to zero for negative F^2. The observed criterion on $F^2 > 2\sigma(F^2)$ is used only for calculating R indices for observed data and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on All data will be even larger.