

Microwave Assisted Selective Synthesis of four Chromanones Via Biscyclization Method in the Presence of Polyphosphoric Acid and Crystal Structure Determination of Their Dicarboxylic Acids

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ABSTRACT: Microwave irradiation is used in the synthesis of four tricyclic chromanones 11-14. The chromanone 14 and 12 are selectively formed thermally and under microwave in the presence of polyphosphoric acid (PPA) from the same dicarboxylic acid 9, respectively. The crystal structures of the two diacids are also reported. The corresponding ortho and meta isomers of diacids crystallize in the space group *Pbca* of the orthorhombic system and *C₂/c* of the monoclinic system respectively, with 8 and 4 molecules in the unit cells of dimensions $a = 4.9955(1) \text{ \AA}$ and $4.8092(4) \text{ \AA}$; $b = 19.177(4) \text{ \AA}$ and $11.5609(1) \text{ \AA}$; $c = 25.885(5) \text{ \AA}$ and $21.247(2) \text{ \AA}$; $\alpha = 90^\circ$ and $\beta = 91.214(3)^\circ$ respectively. The structures have been refined to final values for the crystallographic *R* factors of 0.0401 and 0.0247, based on 2146 and 1030 observed independent reflections, respectively.

KEY WORDS: Chromanone, Dicarboxylic Acid, Biscyclization, Microwave, Crystal Structure.

INTRODUCTION

Chromanones are the important synthetic intermediates for the synthesis of chromanes, chromenes, anti- convulsants and anti- microbials, etc. The "biscyclization" method has been used for the synthesis of different classes of organic compounds [1-5].

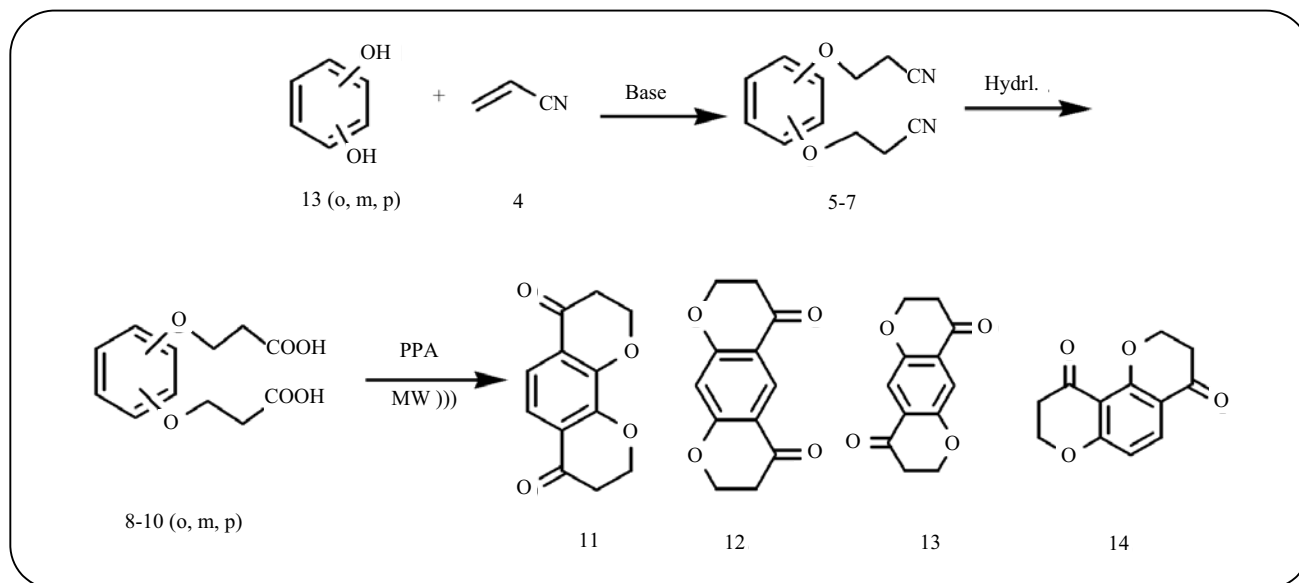
We have taken the advantage of this method for the synthesis of 1,8-dihydroxy-9,10-anthraquinone [6] and some other biologically active potential compounds [7-8]. The general procedure for the synthesis of the 4-chromanones involves the intramolecular acylation of the

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β -phenoxypropionic acid [9]. Other methods such as direct Friedel-Crafts acylation or Fries rearrangement followed by the intramolecular cyclization have been used with moderate success [10]. In an alternative approach, the γ -bromoprop-2-ynyl aryl ethers undergo thermal transformation on mercury(II)-mediated cyclization, affording good yields of 4-chromanones [11]. The effect of microwave on the rate and the yield of variety of reactions have drawn considerable attentions during the last decade [12-14]. We now report the impact of microwave irradiation on the synthesis of the tricyclic chromanones 11-14 from the corresponding diacids in the PPA condition.

The synthesis of the corresponding diacids 8-10 are performed by the condensation reactions of corresponding phenols such as catechol, resorcinol and hydroquinone with the acrylonitrile in the presence of KOH (Michael addition), Scheme 1.

EXPERIMENTAL SECTION

Apparatus

The instruments used in this work were Butane MB245 Microfer, Perkin-Elmer 843 Infrared, Hitachi Perkin-Elmer 60 MHz ^1H NMR, Bruker DRX-500 Avance NMR, Magnetic sector 8430 Mass spectrometer, Stuart scientific SMPI, and Melting point apparatus.

Biscyclization of the diacids 8-9 in the microwave and PPA conditions, General procedure

A magnetically stirred solution of concentrated phosphoric acid (4 ml) and P_2O_5 (10 g) was exposed to microwave radiation in a water bath. 100 watts power was used for one minute. After cooling the solution, the diacid (0.0045 mol) was added to it and the greasy mixture stirred by glass rod and exposed to microwave radiation again for optimum time.

The PPA in the reaction mixture was decomposed in a mixture of 50 g water and ice. The product was extracted with chloroform (3×20 ml). Then the organic phase was washed with distilled water until the aqueous phase became neutral to the litmus paper. It was dried over sodium sulphate and the product obtained after evaporation of solvent.

After this step the purified product of the para isomer was obtained. For the meta and ortho derivatives column chromatography with 40 mesh silica gel was used for the purification of the corresponding products (The solvent mixture was 1:1 ratio of the petroleum ether and ethylacetate). Table 1 shows the time interval necessary for the synthesis of each chromanone (a), and the results of the experiments in the presence of the PPA alone are also presented in this Table (b) for comparison.

Table 1: The Biscyclization of the Diacids 8-10 in the Microwave (a) and PPA Conditions and the Biscyclization of These Diacids in the PPA Conditions Alone (b)

Diacid	g ^a	Time(sec) ^a	Product ^a	g ^a	mp(°C) ^a	Temp(°C) ^b	Time (sec) ^b	Product	g ^b	Yield (%) ^b
8	1	140	11	0.69	221-2	95	120	11	0.74	75
9	1	140	14	0.59	145-9	95	120	12	0.69	70
10	1	90	13	0.69	232-5	80-85	60	13	0.85	87

[11]: [1,3-*a*, 3,2-*e*] **Dipyrano-4, 7-Dione-2,3,8,9-Tetrahydro Benzene**: ν_{\max} (KBr): 2998(w), 2920(w), 1690(s), 1580(s), 1440(s), 1040(m). ¹HNMR, δ (60MHz,CDCl₃): 2.9(t,j=5Hz,4H), 4.7(t,j=5Hz,4H), 7.5(s,2H). MS m/z(rel. int.): 218(M⁺,37.97), 190(100), 162(84.08), 149 (23.57), 134(28.02), 55(47.77).

[12]: [2,3-*a*, 3,2-*d*] **Dipyrano-4, 6-Dione-2,3,7,8-Tetrahydro Benzene**: ν_{\max} (KBr): 2920(m), 2850(w), 1680(s), 1620(s), 1040(m). ¹H NMR, δ (FT. 500MHz, CDCl₃): 2.83(t,j=6Hz,4H), 4.58(t,j=6Hz,4H), 6.52(s,1H), 8.6(s,1H). MS m/z(rel. int.): 218(M⁺,38.22), 190(45.86), 189(52.23), 162(59.23), 161 (100), 134(19.11), 106(9.55). mp. 236-240(°C)

[13]: [2,3-*a*, 2,3-*d*] **Dipyrano-4, 9-Dione-2,3,7,8-Tetrahydro Benzene**: ν_{\max} (KBr): 3000(w), 2880(w), 1680(s), 1470(s), 1250(s), 1030(m). ¹HNMR, δ (FT. 500MHz, CDCl₃): 2.8(t,j=6.6Hz,4H), 4.5 (t,j=6.6Hz,4H), 7(s,2H). MS m/z (rel. int.): 218(M⁺, 39.49), 189(100), 162(35.67), 134(44.58), 133 (33.12), 55 (69.43).

[14]: [2,3-*a*, 2,3-*c*] **Dipyrano-4, 8-Dione-2,3,6,7-Tetrahydro Benzene**: ν_{\max} (KBr): 3520(m), 3450(w), 1680(s), 1580(s), 1480(s), 1250(s), 1030(s). ¹HNMR, δ (60MHz,CDCl₃): 2.8(t,j=4Hz,4H), 4.6(t,j=4Hz,4H), 6.6 (d,j=8Hz,1H), 8(d,j=8Hz,1H). MS m/z (rel. int.): 218 (M⁺, 45.04), 190(60.30), 162(100), 134(21.33), 106(7.6%), 55(4.58%).

RESULTS AND DISCUSSION

Our attempts have led to the synthesis of four tricyclic chromanones 11-14 which are all identified by spectroscopic means. This work demonstrates that the use of the "biscyclization" method could be a useful alternative method for the synthesis of such compounds. Crystals of satisfactory quality have been obtained by

slow evaporation of mixture of water and ethanol solution of the ortho isomer and slow diffusion of ether through water solution of meta isomer. Perspective views and the crystal packing diagrams of the ortho and meta diacid are presented in Fig.1 and Fig. 2 respectively. The selected bond distances and angles the selected torsion angles, and intermolecular hydrogen bond distances are listed in Tables 2-4.

Examination of the ORTEP plots, clearly show that one of the most important features in the crystal structure of ortho diacid isomer is the presence of the water molecules that are connected to each other as well as to the two oxygen atoms situated at the ortho positions of phenyl rings via strong hydrogen bonding interactions (Fig.1). Therefore, ortho isomer crystallizes as a monohydrate (space group *Pbca*). The structure contains two (phenyl) O...H-O (water) hydrogen bonds, (O7W-H7WA...O₃: 2.20Å, 162°; O7W-H7WA...O₄: 2.50Å, 131°) and water-water hydrogen bonding (O7W-H6WB...O7W: 2.02Å, 166°).

Small molecule carboxylic acids in the solid state usually form centrosymmetric or pseudo-centrosymmetric cyclic hydrogen-bonded dimers via the carboxylic acid group [16] although there are examples which adopt polymeric (catemer [17]) or other arrangements [18-19]. So, another important feature in the structure of ortho and meta isomers is the presence of cyclic eight-membered hydrogen-bonded rings between adjacent carboxylic acid groups (Fig.2). This hydrogen bonding between carboxylic groups together with others mentioned above, play an important role in presenting an extended organic network.

The chromanone 14 was formed selectively when the microwave irradiation and PPA were used together, while the chromanone 12 was the selective product when the PPA was used alone. Another important conclusion is that biscyclizations take place in very short times

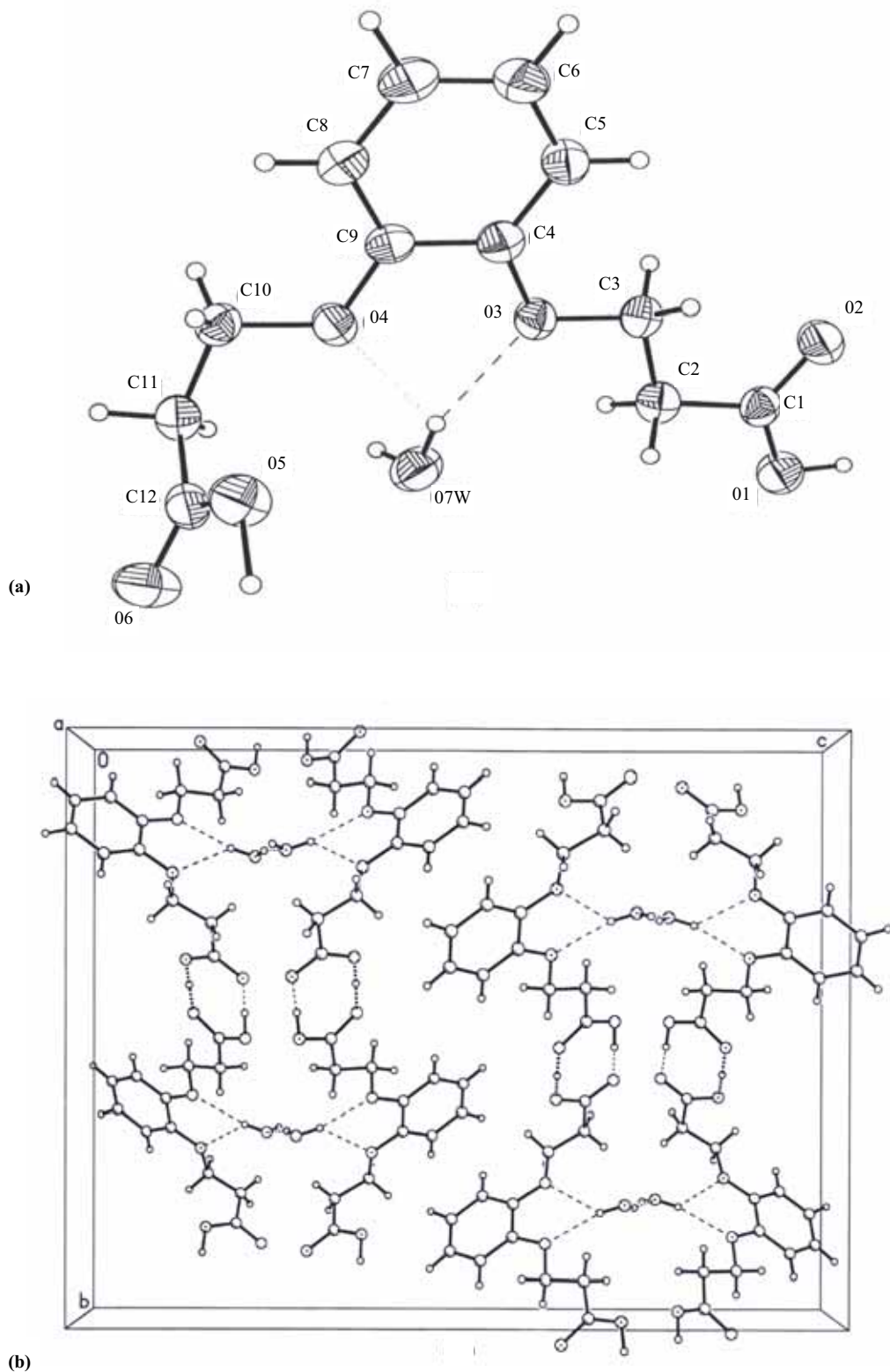


Fig. 1: (a) ORTEP drawing of the ortho isomer of diacid 1 (b) Unit cell packing diagram of ortho isomer of diacid 1

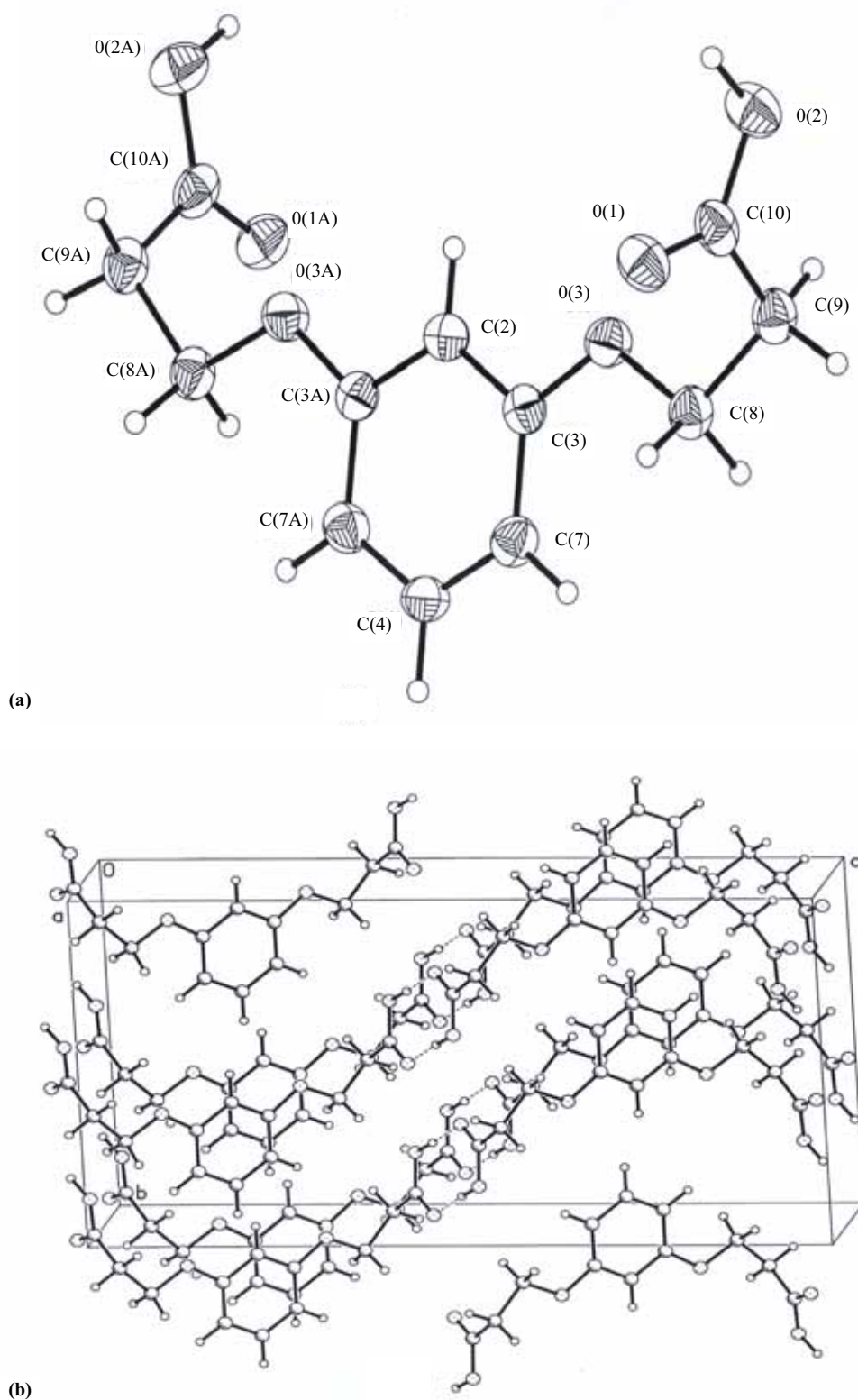


Fig. 2: (a) ORTEP drawing of the meta isomer of diacid 2 (b) Unit cell packing diagram of meta isomer of diacid 2.

Table 2: Selected Bond Distances (Å) and Bond Angles (°) for Ortho 1 and Meta 2 Diacids

1				2			
O1-C1	1.271(3)	O3-C4	1.373 (3)	C3-O3	1.370(3)	C9-C10	1.493(3)
O5-C12	1.281(3)	O4-C9	1.370(3)	C8-O3	1.432(3)	C10-O1	1.224(3)
O2-C1	1.262(3)	O3-C3	1.431(3)	C2-C3	1.388(3)	C10-O2	1.317(3)
O6-C12	1.243(3)	O4-C10	1.433(3)	C8-C9	1.508(3)		
C4-O3-C3	116.87(2)	O1-C1-C2	117.2(2)	O3-C8-C9	105.99(2)	O2-C10-C9	114.41(2)
C9-O4-C10	116.94(2)	O5-C12-C11	118.2(2)	C10-C9-C8	112.37(2)	C3-O3-C8	117.45(2)
O2-C1-O1	123.3(2)	C3-C2-C1	112.6(2)	O1-C10-O2	122.7(2)		
O6-C12-O5	122.5(2)	C10-C11-C12	115.1(2)				

Table 3: Selected Torsion Angles (°) for Ortho 1 and Meta 2 Diacids

1				2			
O1-C1-C2-C3	177.4(2)	C3-O3-C4-C5	0.0(3)	C3A-C2-C3-O3	-179.32(2)	C8-C9-C10-O1	40.3(3)
C10-C11-C12-O5	-5.9(4)	C10-O4-C9-C8	5.8(3)	C2-C3-O3-C8	179.48(1)	C8-C9-C10-O2	-141.61(2)
O2-C1-C2-C3	-3.2(3)	C4-O3-C3-C2	177.7(2)	C9-C8-O3-C3	177.50(2)		
C10-C11-C12-O6	173.3(2)	C9-O4-C10-C11	-177.6(2)	O3-C8-C9-C10	65.0(2)		

Table 4: Hydrogen Bond Distance for Ortho 1 and 2 Diacids

D-H... A	d (H...A)	d(D...A)	<(DHA)
1			
O(7W)-H(7WA)...O(3)	2.20(4)	3.060(3)	162(2)
O(7W)-H(7WA)...O(4)	2.50(4)	3.159(3)	131(2)
O(7W)-H(7WB)...O(7W) [x-½, y, -z+½]	2.02(4)	2.818(3)	166(2)
O1-H1O...O6 [-x+¾, y-½, z]	1.66(5)	2.675(3)	168(3)
O5-H5O...O2 [-x+¾, y+½, z]	1.04(5)	2.633(3)	178(2)
2			
O2-H8...O1 [-x+½, -y+¾, -z+1]	1.613	2.638	175.33

Table 5: Cyanoethylation of the Phenol Derivatives

Phenol	Product
Catechol 1	1,2 Bis(2'- cyanoethoxy) benzene 5 : ν_{\max} (KBr) , 2260s ,1580s, 1520m, 1240s, 1060; $^1\text{H NMR}$, δ (60MHz, CDCl_3), 2.83 (t, j=6.5,4H) , 4.23 (t, j=6.5,4H) , 6.97 (s,4H). (6g, mp. 122-3°C, yeild 30%)
Resorcinol 2	1,3 Bis(2'- cyanoethoxy) benzene 6 : ν_{\max} (KBr) , 2250s , 1610s, 1580s, 1500s, 1230m, 1060s; $^1\text{H NMR}$, δ (60MHz, CDCl_3), 2.85 (t, j=6.5,4H), 4.2 (t, j=6.5,4H), 6.5 (m,3H), 7.3(m,1H).(10g, mp.106-11°C, yeild 60%)
Hydroquinone 3	1,4 Bis(2'- cyanoethoxy) benzene 7 : ν_{\max} (KBr) , 2260s , 1510s, 1230s, 1050s; $^1\text{H NMR}$, δ (60MHz, CDCl_3), 2.8 (t, j=6.5,4H), 4.16 (t, j=6.5,4H), 6.87 (s,4H). (9g, mp.140-2°C, yield 45.5%)

Table 6: Hydrolysis of Cyanoethylated Products

Diacid
1,2- Bis (2'- carboxy ethoxy) benzene 8: ν_{\max} (KBr) 3600-2400(s,broad), 1700s, 1600s, 1200-1300 (s,broad), 1030s; $^1\text{H NMR}$, δ (60MHz, $\text{DMSO}-d_6$), 2.57 (t,j=6,4H), 4.06 (t,j=6,4H), 6.83 (s,4H). (0.867 g, mp 155-7 °C, yield 85%)
1,3- Bis (2'- carboxy ethoxy) benzene 9: ν_{\max} (KBr) 3600-2400(s,broad), 1700s, 1600s, 1580-1160s, 1050s; $^1\text{H NMR}$, δ (60MHz, $\text{DMSO}-d_6$), 2.7 (t,j=6,4H), 4.17 (t,j=6,4H), 6.5 (m,3H), 7.15(s,1H). (0.867 g, mp 177-9 °C, yield 85%)
1,4- Bis (2'- carboxy ethoxy) benzene 10: ν_{\max} (KBr) 3600-2400(s,broad), 1700s, 1510s, 1480s-1210s, 1040s; $^1\text{H NMR}$, δ (60MHz, $\text{DMSO}-d_6$), 2.63 (t,j=6,4H), 4.06 (t,j=6,4H), 6.8 (s,4H). (0.785 g, mp 202-204°C, yield 77%)

Table 7: Crystallographic Data for ortho 1 and meta 2 Dicarboxylic Acids

	1	2		1	2
Empirical Formula	$\text{C}_{12}\text{H}_{16}\text{O}_7$	$\text{C}_{12}\text{H}_{14}\text{O}_6$	β , deg	90°	91.214(3)
Fw	272.25	254.23	V , \AA^3	2479.8(8)	1181.05(2)
Space Group	Pbca	C_2/c	Z	8	4
T, K	200(2)	110(2)	D_{calcld} , gcm^{-3}	1.458	1.430
Λ Mo(k_α), \AA	0.71073	0.71073	μ , mm^{-1}	0.121	0.116
a, \AA	4.9955(1)	4.8092(4)	R1 / wR2 (obs data) ^a	0.0476 / 0.1105 ^b	0.0524 / 0.1255 ^c
b, \AA	19.177(4)	11.5609(1)	R1 / wR2 (all data) ^a	0.0801 / 0.1247 ^b	0.0718 / 0.1364 ^c
c, \AA	25.885(5)	21.247(2)			

compared to the conditions in which the PPA is used alone. To the best of our knowledge this is not reported in the literature before.

The results of the cyanoethylated products via Michael addition in the presence of KOH are illustrated in Table 5 and the results of the hydrolysis processes of dicyanides 5-7 to obtain the diacids 8-10 are illustrated in Table 6.

Further attempts are being made for the synthesis of variety of their derivatives in our laboratory using the microwave and PPA together.

X-ray Structure Analysis

Analysis on single crystals of ortho and meta isomer of corresponding dicarboxylic acids were carried out on a Bruker SMART CCD area detector diffractometer at 200(2) and 110(2) K, respectively, using graphite monochromated Mo K α radiation ($\lambda=0.71073\text{\AA}$).

Diffraction data were corrected for absorption using the SADABS program. Some softwares [15] including SMART (data collection), SAINT⁺ (cell refinement and data reduction), SHELXTL (structure solution & refinement; molecular graphics and publication material) were used. Crystals of dimensions $0.3 \times 0.1 \times 0.05 \text{ mm}^3$, ortho isomer, and $0.1 \times 0.1 \times 0.3 \text{ mm}^3$, meta isomer, were mounted and the data were collected in the range $2.12 \leq \theta \leq 24.99^\circ$ (ortho) and $1.92 \leq \theta \leq 25.01^\circ$ (meta) with $-5 \leq h \leq 5$, $-22 \leq k \leq 11$, $-30 \leq l \leq 28$ (ortho) and $-5 \leq h \leq 5$, $-6 \leq k \leq 13$, $-25 \leq l \leq 24$ (meta). The structures were solved by direct method and refined by full-matrix least squares based on F^2 . The crystallographic data are listed in Table 7.

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