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Full Paper

Interaction of tetracyanoethylene (TCE) with active methylene compounds: synthesis, reactions and spectral characterization of some novel 2-pyrazoline-5-one compounds. Computational studies on the synthesized molecules by DFT

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Abstract

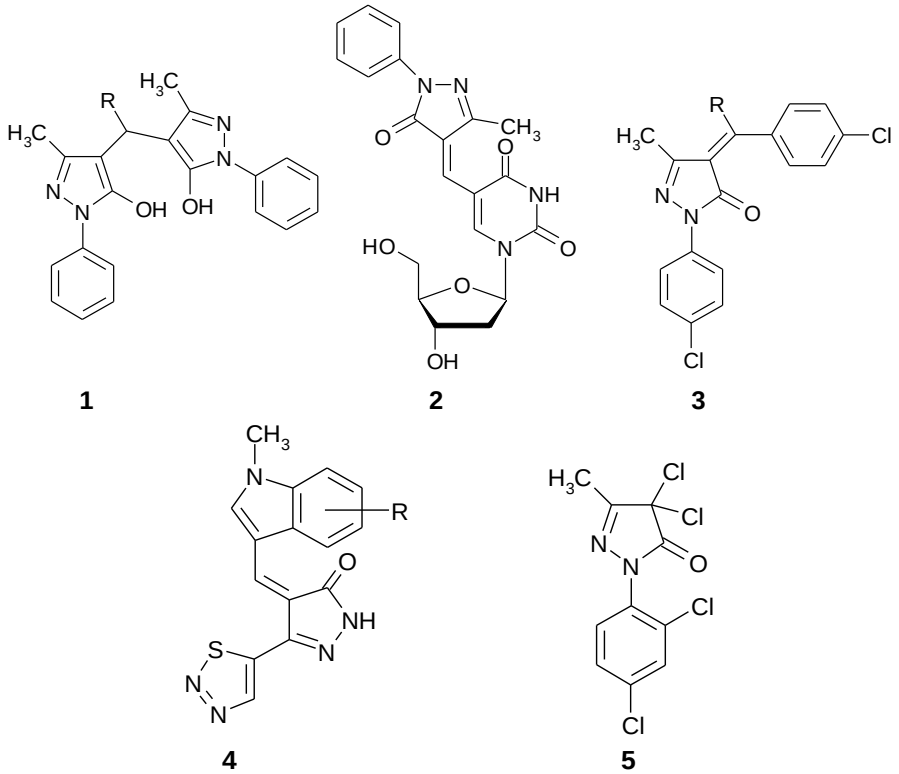
Tetracyanoethylene(TCE) (6) was reacted with 3-methyl-1-(3-bromophenyl)-2-pyrazolin-5-one (7) to give 1-(3-bomophenyl)-4-dicyanomethylene-3-methyl-2-pyrazolin-5-one (8). Also, TCE compound 6 was reacted with diethyl malonate, malonic acid dihydrazide, and ethyl acetoacetate and ethyl cyanoacetate to afford carbon acids 10a-d, respectively. Compound 8 was heated at reflux with aniline to give compound 13. Compound 8 was treated with N, N-dimethyl aniline to give the very stable violet compound 15. Also compound 8 was refluxed with glycine to yield the pyrazolone derivative 16 which reacted with N-phenyl malimide to give the adduct 17. The molecular structure of 1-(3-bromophenyl 4-dicyanomethylene-3-methyl-2-pyrazolin-5-one molecule 8 in the ground state was computed by density functional theory (DFT) using 6-311G basis set and B3LYP level of theory.

Keywords: Carbon acids, Benzimidazolylpyrazole derivative, Benzothiazolylpyrazole derivative, Benzoxazolylpyrazole derivative, DFT calculations.

1. Introduction

Pyrazolones have all found wide use in many fields. Their greatest utility resides in pharmaceuticals [1-17], dyes (textile and photography) [18-20], lesser extent in plastics [21], and agrochemicals [22]. Pyrazolones exhibit a wide range of biological properties [1]: analgesic, antibacterial, antifungal agrochemicals [22], and, antagonists, anti-inflammatory, antimicrobial, antidiabetic, antihyperglycemic and anxiolytic. The following are some of the most important ones: phenazone (Antipyrin), aminopyrin (Pyramidon), propyphenazone (Isopropylphenazone), noraminopyrine

methanesulfonate sodium (Novalgin), phenylbutazone (Butazolidin), nifenazone (Nicopyron), oxyphenbutazone (Tanderil), morazone (Tarugan), isopyrin and piperylone. The parent substance of almost all these compounds is 3-methyl-1-phenyl-5-pyrazolone methylated in the 2-position (Antipyrin). The increasing interest in biological studies of pyrazol-5-ones in the last decade is a consequence of their wide use as the pharmaceutically important class of compounds [2-10]. Among them, Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, Radicut, Mitsubishi Tanabe Pharma Corporation represents an example of one of the prominent drugs which acts as a potent cerebral neuroprotectant that readily scavenges reactive oxygen species and inhibits proinflammatory responses after brain ischemia in the treatment of patients in the acute stage of cerebral infarction [12]. The derivatives of pyrazol-5-one have already been discovered as antitumor agents. For example, thiadiazole substituted pyrazol-5-ones (4) were identified as potent KDR kinase inhibitors in regulating angiogenesis which is crucial for the proliferation of tumor cells [12]. It has also been discovered that Edaravone itself enhances the antitumor effects of CPT-11 in murine colon cancer by increasing apoptosis [13] and also reacts with a pterin derivative to produce a cytotoxic substance that induces intracellular reactive oxygen species generation and cell death [14]. A new derivative of Edaravone, 4, 4-dichloro-1-(2, 4-dichlorophenyl)-3-methylpyrazol-5-one (5), was identified as a potent blocker of human telomerase and is considered to be a valuable substance for medical treatment of cancer and related diseases [15]. In spite of widely surveyed pharmacological action of series of Edaravone derivatives, antitumor screening of compounds obtained by condensation of 4-formyledaravone with primary amines has not been so far reported. The particular attention in this work is focused on introduction of the known antitumor 3-aminopyrazole pharmacophores [16, 17] at C4 position of the Edaravone moiety and their in-vitro antitumor evaluation.

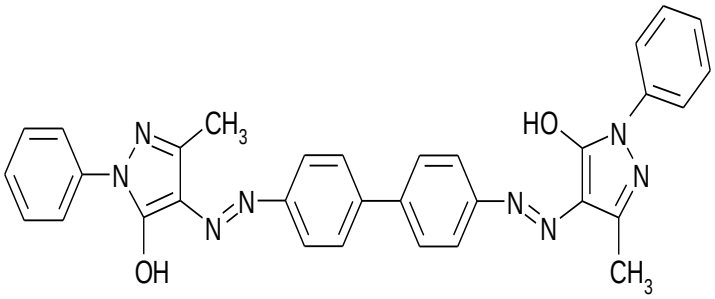


1 **2** **3**

4 **5**

Some pyrazole-5-one derivatives with pronounced biological activity

The pyrazolone pigments encompass two general structural types, arylide yellow type and the disazo type [18]. The arylide type uses the acetoacetylanilide of an arylide as a heterocycle. The disazopyrazolones are more similar in structure to diarylide pigments, but they incorporate a pyrazolone ring. Pyrazolone pigments span the color range of yellow, orange, and red. The industrially important pyrazolone dyes are almost exclusively azo dyes. The pyrazolone molecule couples with diazonium compounds in the 4-position to give azo dyes and pigments that exhibit good color strength, light fastness, and other favorable properties[19,20]. Besides their use in leather and wool dyeing (Azo Dyes) pyrazolones have also found use as precursors for cotton dyes, pigments and dyes for synthetic fibers and plastics [21]. Pyrazolones are thus found among nearly all types of dye. For wool dyes, solubilizing sulfo and carboxyl groups are used which can be substituents both in the pyrazolone and in the coupling component. The capacity of pyrazolone derivatives to form complexes with chromium is exploited in the production of chrome dyes. By introducing so-called reactive components into pyrazolones or into the coupling component, reactive dyes for cellulose fibers are obtained (Reactive Dyes).Pyrazolone derivatives without solubilizing groups are suitable as precursors for pigments. For coloring synthetic fibers, either pyrazolone pigments are used or pyrazolone dyes are dissolved in the spinning solution. Pyrazolones are gaining increasing importance as photographic dyes, particularly in sensitizer dyes and as precursors for color couplers and color filters (Photography). In addition pyrazolones and related compounds have proved to be good developing agents for black and white and Polaroid photography [21].Many pyrazolone pigments have been introduced, but only a few are commercially important today[22]. These include PO13 (21110), PO34 (21115), PR37 (21205), PR38 (21120), PR41 (21200), and PR111. Pyrazolones have good light fastness and reasonable solvent fastness. The exception is PY100, which has poor solvent fastness, and light fastness similar to the diarylide yellows. PO13 (Fig. 2), known as pyrazolone orange in the United States, is widely used in artists' paints. It was first introduced in 1910 and is used in printing inks due to its excellent solvent fastness. PO34 is also used in printing ink applications and for the coloration of plastics [18]. Pyrazolones have been tested and found useful as herbicids, fungicides and insecticides [22].The use of pyrazolones as analytical reagents has been published in numerous articles and patents. For example, derivatives are useful for the extraction and separation of various metal ions, for the determination of phenol, cyanides and ammonia, and as photographic sensitizers [23].



Structure of PO13, pyrazolone orange.

2. Materials and methods

2.1 Synthesis of 1-(3-Bromo phenyl)-1-phenyl-2-pyrazolin-5-one (7):

Compound 7 was prepared according to the literature, m.p.110 °C [24].

2.2. Reaction of Tetracyanoethylene with Active Methylenes:

A)Active methylenes with pKa < 10; Formation of 3-methyl-1-(3-Bromo phenyl-4-dicyanomethylene- -2-pyrazolin-5-one (8)

A solution of tetracyanoethylene (10 mmol) in acetonitrile (25 ml) was added to the active methylene derivative (7) (5 mmol) in acetonitrile (25 ml) at 60°C. The mixture was stirred for 30 minutes and filtered. The filtrate was diluted with water with stirring and the solid formed was filtered, washed thoroughly with water and dried. It was crystallized from dioxane. Black flakes; yield: 53%; m.p.:196°C ; $C_{13}H_7BrN_4O$ (324/316); Calc.: C, 49.50; H, 2.2; N, 17.7%; Found: C, 48.47; H, 2.2; N, 17.8%;IR: υ (cm^{-1}): 3093 (CH aromatic), 2220 (C≡N), 1711 (C=O), 1590 (C=N), 1478, 1367, 1312, 1160, 1073, 973, 793, 727 and 677; ^{1}H NMR($CDCl_3$), δ , ppm: 2.56 (s, 3H, CH_3), 7.49 (m, 4H , Ar-H) ppm ; ^{13}C NMR ($CDCl_3$) , δ , ppm: 157.48, 145.0, 134.0, 130.0, 122.0, 116, 110, 14.95; MS, m/z (*I*,%): 314[M^+] (96.2) , 316[M^+] (100), doubly charged ion at 154.75 (54.2%), 156.79 (53.4%) indicating the high stability of compound 8 under electron impact.

B) Active methylenes with pKa ≥ 10; Synthesis of Carbon Acids (10a-d):

General Method:

Acetonitrile solution (25 ml) of tetracyanoethylene (10 mmol) at 60 °C was added dropwise to the solution of the titled active methylene derivative (9) (5 mmol) in acetonitrile (25 ml). The reaction mixture was stirred for 30 minutes then added to ice-cold water to give the corresponding C-acid. The results are summarized as follows:

a) Carbon Acid from Tetracyanoethylene and Diethyl Malonate (10a):

Brown solid from ethanol; yield: 90%, m.p.: 147 °C; $C_{13}H_{12}N_4O_4$(288), Calc.: C, 54.17; H, 4.20; N, 19.44 %; Found :C, 54.22; H, 4.36; N, 19.46%;IR: υ (cm^{-1}): 2261, 2227(CN), 1750;^{1}H NMR(DMSO-d_6), δ , ppm: 6.035(s, 1H ,CH), 6.332 (s, 1H, CH), 4.04(q, 2H , $2CH_2$) , 2.45(t, 3H,$2CH_3$) ; ^{13} CNMR(DMSO-d_6), δ , ppm: 158.4 , 135.10 , 118.04 , 116.56 , 116.11 , 114.83 , 114.14 , 113.87 , 123.87 , 123.49 , 57.24 , 55.21 , 40.13 , 39.91 , 39.70 , 39.50 , 39.29 , 38.87 ; MS, m/z (*I*,%):288[M^+](100).

b) Carbon Acid from Malonic Acid Dihydrazide and Tetracyanoethylene(10b):

Black flakes from ethanol, yield: 69.33%, m.p.:137°C; IR: υ(cm^{-1}): 3282(NH), 2261, 2228(C≡N), 1637(C=O), 1584, 1507(C=N); ^{1}HNMR(DMSO-d_6), δ , ppm: 11.852(s, 1H, NH), 10.436(s ,1H , NH) , 6.323(s , 1H , CH) , 6.922(s , 1H , CH) , 4.085 (s , 2H , NH_2) , 3.453(s , 2H , NH_2) ; ^{13} C NMR(DMSO-d_6), δ , ppm: 158.18 , 134.89, 117.86 , 116.27 , 115.91 , 114.66 , 113.97 , 113.74 , 60.82 , 57.06 , 54.97 , 41.23 , 40.13 , 39.91 , 39.71 , 39.50 , 39.29 , 39.09 , 38.87.

C) Carbon Acid from Ethyl Acetoacetate and Tetracyanoethylene (10c):

Black amorphous solid from methanol, yield: 86%, m.p. > 300 °C; $C_{12}H_{10}N_4O_3$ (258) ,Calc.: N, 21.7; Found: N, 21.7; IR: υ (cm^{-1}): 3219 (CH aromatic), 2227 (C≡N) , 1716 (C=O) , 1592(C=N); ^{1}HNMR(DMSO-d_6) , δ , ppm: 6.345(s , 1H , CH) , 5.210(s , 1H , <u>CH</u>-OCH_3) , 4.018(q , 2H ,CH_2) , 2.549(s , 1H , CH_3) , 1.289(t , 3H , CH_3) .

d) Carbon Acid from Ethylcyanoacetate and Tetracyanoethylene(d):

Black amorphous substance from ethanol, yield :82%, m.p. 171 °C; $C_{11}H_7N_5O_2$(241) Calc.: C, 54.70 ; Found: C, 55.15 ; IR: υ (cm^{-1}): 2227 (C≡N) , 1592 (C=N) , ^{1}H NMR (DMSO-d_6) , δ , ppm: 6.033(s , 1H , CH) , 5.994(s , 1H ,

CH) , 4.64(q , 3H , CH_2) , 1.925(t , 3H , CH_3) ; ^{13}C NMR(DMSO-d_6) , δ , ppm: 158.48 , 135.18 , 118.07 , 116.59, 116.14 , 114.86 , 114.19 , 113.77 , 113.53 , 112.16 , 57.30 , 55.25 , 40.13 , 39.91 , 39.71 , 39.50 , 39.29 , 39.09 , 38.87 , 8.65.

2.3 Reactions of 1-(3-Bromophenyl)-4-dicyano-methylene-3-methyl-2-pyrazolin-5-one (8) with aniline:

The dicyano derivative 8, (10 mmol) was dissolved in ethanol (50 ml) and the aniline (30 m mol) in ethanol (50 ml) was added in portions. The mixture was heated at reflux for 2 hrs and then left to cool. The precipitated product was filtered, dried, and crystallized from ethanol as red needles, yield: 82%., m.p. 147 °C. $C_{18}H_{13}BrN_4O$ (380/382).: Calc. C, 56.71 ; H,3.44 ; N , 14.70 ; Found: C, 56.82 ; H , 3.42 ; .N , 14.81 ; IR: υ (cm^{-1}): 3030 (CH aromatic), 2910 (CH aliphatic) , 2210 (C≡N) , 1680 (C=O) , 1590 (C=N) ; ^{1}H-NMR (d_6-DMSO) , δ , ppm: 2.36(s , 3H , CH_3) , 7.1-7.9(m , 9H , Ar-H).

2.4 Reaction of 8 with N,N-Dimethy laniline(15) :

The hydrogen atom in the para position of the reacted N,N-dimethyl aniline (10 mmol) is added to the exocyclic double bond of 8 (10 mmol) giving the colorless adduct which loses hydrogen cyanide to give the stable violet product (15), violet needles from methanol, yield : 81%, m.p. 181 °C ; $C_{20}H_{17}BrN_4O$(408/410)Calc.: C,58.82 ; H , 4.14 ; N , 13.72 ; Found: C,58.87 ; H,4.24 ; N,13.81 ; IR:υ(cm^{-1}): 3150(CHaromatic) , 1610(CO) , 1429(c=c) ; ^{1}H NMR(DMSO-d_6) , δ , ppm: 2.682(s, 3H , CH3) , 2.90(s , 6H , 2CH3) , 7.367-70963(m , 8H , Ar-H).

2.2.5 Reaction of 8 with Glycine(16):

Glycine (10 mmol) dissolved in water (10 ml) was added to a solution of 8, (10 mmol) in acetonitrile (10 ml). The mixture was heated at 50 °C for 10-15 minutes and then allowed to cool to room temperature. The expected adduct(16) precipitate was collected by filtration, dried and was crystallized from ethanol/dioxane (1:1) as yellow needles ; yield : 48%, m.p. 193 °C; $C_{14}H_{11}BrN_4O_3$(362/364) Calc.: C, 46.40 ; H, 3.01 ; N , 15.47 ; Found: C, 46.52 ; H , 3.11 ; N , 15.53 ; IR : υ (cm^{-1}): 3400 (carboxylic OH) , 2900 (CH aliphatic) , 2210 (C≡N) , 1710 (C=O carboxylic) , 1635 (C=O, pyrazolone) , 1585 (C=N).

2.6 Reaction of α-amino acid adduct 16 of 8, with N-phenyl maleimide (17):

A mixture of 16 (1 mmol) and N-phenyl maleimide (1 mmol) is dissolved in acetonitrile (20 ml) and triethyl amine (1 mol) was added. The reaction mixture was stirred at room temperature for 20 minutes. The precipitate formed during this time was filtered and recrystallized from aqueous ethanol, yield: 75% of (17); $C_{23}H_{17}BrN_4O_5$(508/510) Calc.: C, 54.22 ; H, 3.34 ; N, 11.00; Found: C, 54.32 ; H, 3.48 ; N, 11.12 ; IR: υ (cm^{-1}): 3210 (NH) , 1740 and 1710 (2C=O , N-phenyl maleimide) , 1650 (C=O, pyrazolone).

Computational Details:

The molecular geometry optimization energy and vibrational frequency calculations were performed with the "GAUSSIAN O3W Software Package" using DFT B3LYP/6-311G Level. The Cartesian representation of the theoretical force constants were computed at the optimized geometry by assuming C1 point group symmetry. Scaling of the force yield was performed using 0.9613 factors. The geometry was fully optimized without any constraint with the help of analytical gradient procedure. The optimized structure is a minimum because all the frequencies are positive. By the use of GAUSIAN VIEW molecular visualization program with symmetry consideration along the available related molecules, vibrational wave number assignment were made with a high degree of accuracy.^{1}H-NMR and ^{13}C-NMR chemical shift calculations of the title compounds were using B_3LYP / 6-31G and HF / 6-31G methods.

The calculation was performed in DMSO solution using IEF-PCM model, rather than in the gas phase and the values obtained were compared with the experimental data.

3. Apparatus

Melting points were determined on a kofler melting point apparatus and are not corrected.IR spectra were recorded on a pye Unicam Sp^3-100 spectrophotometer using KBr pellets. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Jeol LA 400 instrument. Electron-impact mass spectra were taken on a JEOL JMs 600 spectrometer at an ionizing potential of 70 eV.

Elemental analyses were carried out using a Perkin-Elmer 240 C Micro analyzer all at Assuit Univerisity

4. Results and Discussion

Geometrical parameters:

The labeling of atoms in 4-dicyanomethylene-3-methyl-1-(3-bromophenyl)-2-pyrazolin-5-ones (8) is given in fig (1). The calculated structural parameters and ground state energy using B3LYP/6-311G Level method are collected in table (1). The Mullikan atomic charges distribution are reported in table (2).

Table 1: Listed some of the geometrically calculated parameters for compound (8).

Compound	Bond length (A°)	Bond angles(◦)	Dihedral angle(◦)	Ground stage energy	Point group	Method of calculation
Compound 8	$R_4(2,3)$ = 1.3969 $R_{14}(10,12)$ = 1.1448 $R_{15}(11,13)$ = 1.1455 $R_3(1,16)$ = 1.4152 $R_{16}(14,15)$ = 1.215 $R_{24}(19,24)$ = 1.8075	$A_2(2,1,16)$ = 119.0738 $A_3(14,1,16)$ = 129.5723 $A_{19}(10,9,11)$ = 114.1925 $A_5(2,3,4)$ = 121.5668 $A_{22}(8,14,15)$ = 127.2672 $A_{33}(17,19,24)$ = 118.2804	$D_1(14,1,2,3)$ = 0.0073 $D_9(14,1,16,17)$ = 0.0114 $D_{42}(20,17,19,24)$ = 0.0007 $D_{30}(9,8,14,15)$ = 0.0133 $D_{24}(3,8,9,11)$ = 0.0002 $D_{25}(14,8,9,10)$ = 0.0163	-1248.06744504 (a.u)	C_1	B3LYP/6-311G

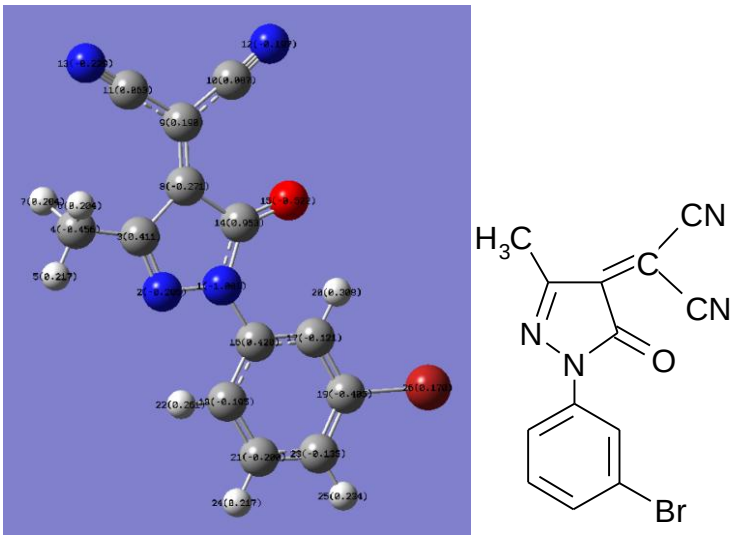


Fig.1 Optimized structure of compound (8)

Table 2: Mullikan Atomic charges of compound (8) at B3LYP/6-311G level.

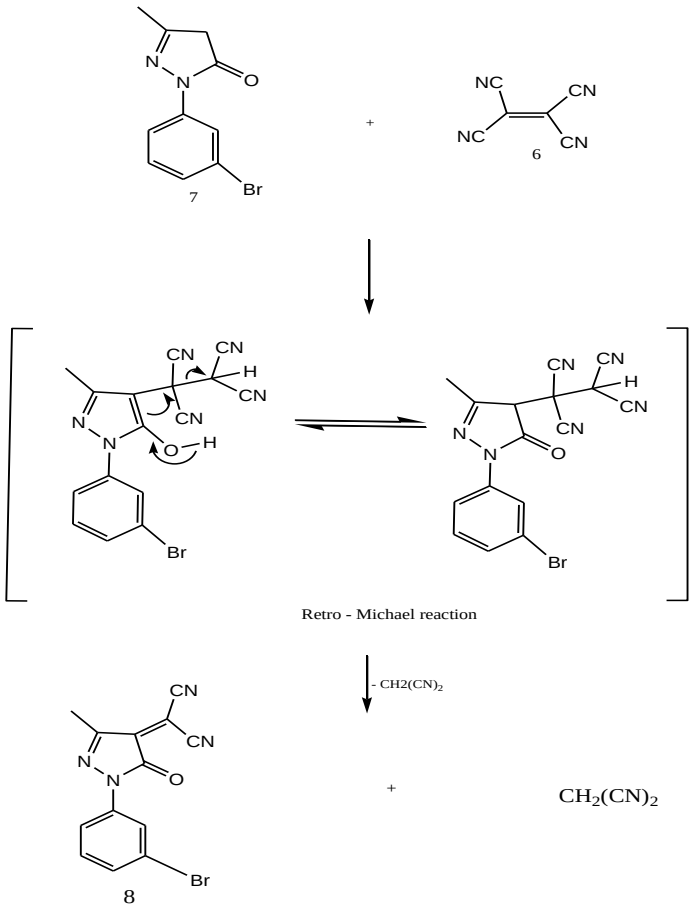
No.	Atoms	Atomic charges	Atoms	Atomic charges	Atoms	Atomic charges
1	N	-0.994878	N	-1.001694	N	-1.001101
2	N	-0.203565	N	-0.206530	N	-0.206103
3	C	0.406552	C	0.411178	C	0.410626
4	C	-0.455602	C	-0.456482	C	-0.456381
5	H	0.216143	H	0.217163	H	0.217027
6	H	0.202581	H	0.204661	H	0.204407
7	H	0.202585	H	0.204661	H	0.204409
8	C	-0.268604	C	-0.271766	C	-0.271384
9	C	0.183389	C	0.190564	C	0.189702
10	C	0.088250	C	0.086791	C	0.089702
11	C	0.063556	C	0.063039	C	0.063084
12	N	-0.201503	N	-0.196181	N	-0.196821
13	N	0.951020	N	-0.228278	N	-0.228740
14	O	0.951020	C	0.953219	C	0.952832
15	C	-0.526516	O	-0.521564	O	-0.522025

Table 2: Mullikan Atomic charges of compound (8) at B3LYP/6-311G level(Continued).

No.	Atoms	Atomic charges	Atoms	Atomic charges	Atoms	Atomic charges
16	C	0.416982	C	0.421462	C	0.420485
17	C	-0.200641	C	-0.134505	C	-0.121239
18	C	-0.203439	C	-0.192722	C	-0.194880
19	C	-0.209713	C	-0.340819	C	-0.404836
20	H	0.283245	H	0.314798	H	0.308038
21	C	-0.201452	C	-0.200125	C	-0.200048
22	H	0.252097	H	0.261353	H	0.260506
23	C	-0.190503	C	-0.144223	C	-0.135316
24	H	0.209745	H	0.0218716	H	0.217209
25	H	0.206091	H	0.240465	H	0.233895
26	H	0.206114	Cl	0.106818	Br	0.169687

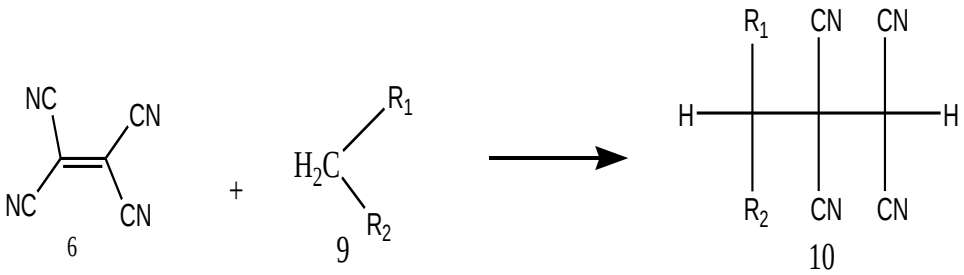
Sum of Mulliken charges = zero.

From this table it could be seen that Br in compound 8, carry more positive charge and could be easily eliminated to form Br_2 with high toxicity. Further investigations concerning the computational studies on the newly synthesized compounds reported in this work will be published in separate publications.The use of tetracyanoethelene(TCE) 6 is based on the high reactivity of this reagent which have use or potential use in organic synthesis. The twelve classical papers published in 1958 laid the foundation for the fundamental chemistry of tetracyanoethylene[25]. The formation of 4-dicyanomethylene-3-methyl-1-(3-bromophenyl)-2-pyrazolin-5-ones (8) is represented and proved by the following reaction scheme (scheme 1). The reaction conducted at 60°C in acetonitrile as a solvent whereby a tinny precipitate was formed which was filtered and identified as 4-dicyanomethylene-3-methyl-1-phenyl (3-bromo phenyl)-2-pyrazolin-ones (8). The feasibility of active methylene hydrogen at 4-position of the pyrazolone derivative (7) depend on the pKa value of such active hydrogen. To our knowledge no systematic study between tetracyanoethylene and different active methylene derivatives was previously recorded. In our present study we have found that the reaction of tetracyanoethylene with active methylenes will depend mainly on the pKa value of the later. With active methylenes of pKa values less than 10, the formation of the dicyanomethylene derivative at position 4 in 2-pyrazolin-5-one ring is favored (cf. Scheme 1). Active methylenes with pKa value 10 or higher react with tetracyanoethylene to give the tetracyano derivative adduct i.e. the corresponding carbon acid (cf. Scheme 2).



7 6 8

Scheme 1



6 9 10

a , R_1=R_2= COOEt

b , R_1=R_2= $CONHNH_2$

c , R1= COOEt , R2 = CH3CO

d , R1= COOEt , R2 = CN

Scheme 2

We record here the most recent pKa values for some active methylene derivatives[22] to be used as a guide in the reaction of tetracyanoethylene to give either the dicyanomethelene (8) or the adduct derivatives (10) (cf. Tables 3 and 4 respectively).

Table (3): Active methylene with pKa < 10[25].

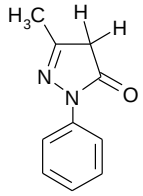
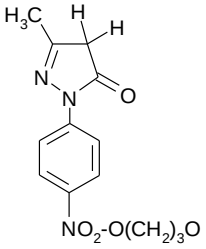
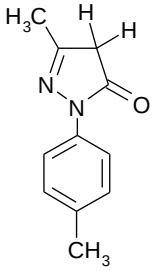
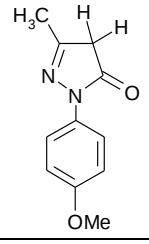
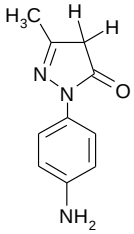
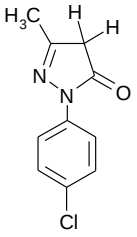
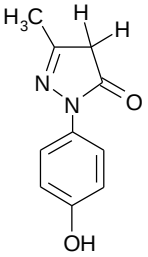
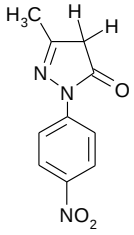
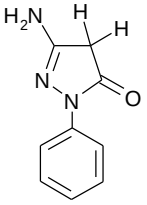
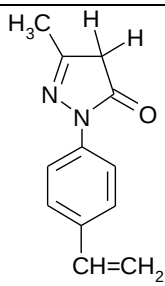
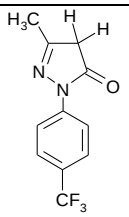
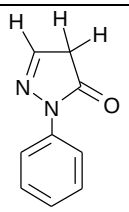
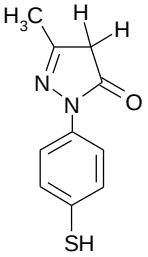
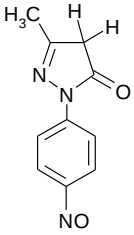
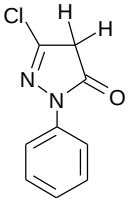
Active methylene	pKa	Active methylene	pKa	Active methylene	pKa
	6.90		7.18		7.31
	7.54		7.32		6.57
	7.40		5.48		9.52
	6.67		5.88		5.17
	7.12		5.71		3.00

Table (3): Active methylene with pKa < 10[25](Continued).

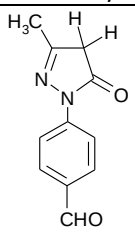
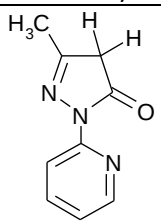
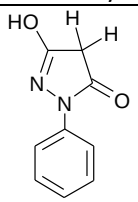
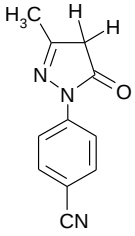
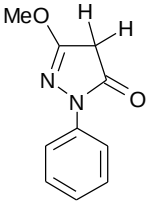
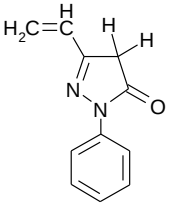
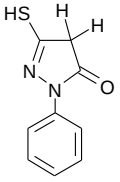
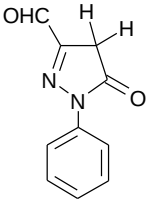
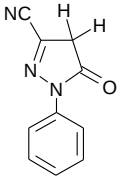
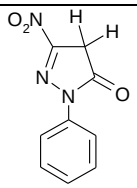
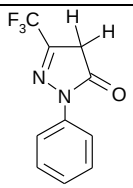
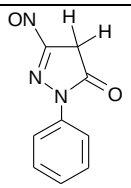
Active methylene	pKa	Active methylene	pKa	Active methylene	pKa
	6.14		6.64		5.82
	5.85		6.19		6.26
	4.8		2.39		0.27
	2.60		0.47		0.31

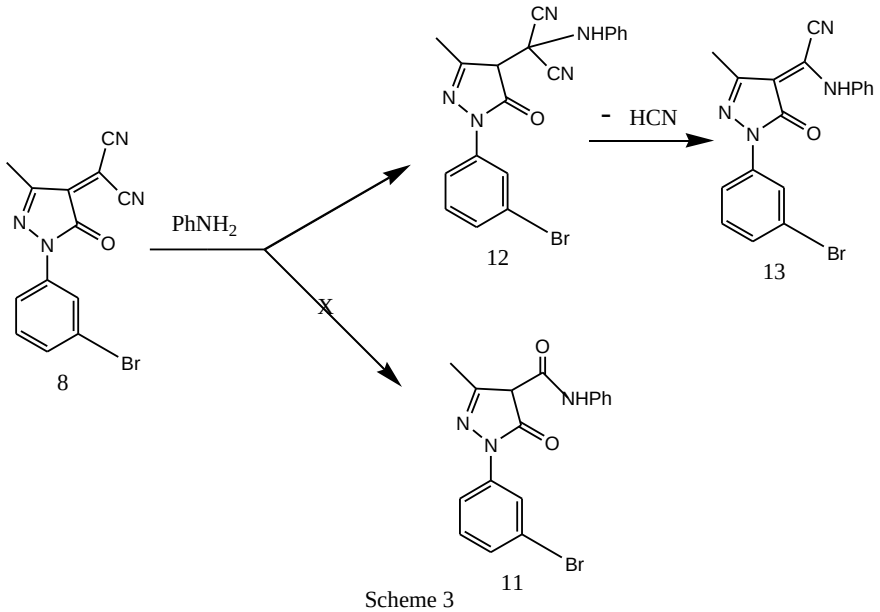
Table (4): Active methylenes with pKa ≥ 9[25].

Compound	pKa	Compound	pKa
$(NC)C\underline{H}_2CO_2C_2H_5$	9	$CH_3COC\underline{H}_3$	20
$C\underline{H}_2(COCH_3)_2$	9	$CH_3SO_2C\underline{H}_3$	~23
$C\underline{H}_3NO_2$	10	$CH_3CO_2C_2H_5$	~24
$CH_3COC\underline{H}_2CO_2C_2H_5$	11	$C\underline{H}_3CN$	~25
$C\underline{H}_2(CO_2C_2H_5)_2$	13	$C_6H_5N\underline{H}_2$	~30
$CH_3O\underline{H}$	16	$(C_6H_5)_3C\underline{H}$	~40
$C_2H_5O\underline{H}$	18	$CH_3SOC\underline{H}_3$	~40
$(CH_3)_3CO\underline{H}$	19		
$C_6H_5COC\underline{H}_3$	19		

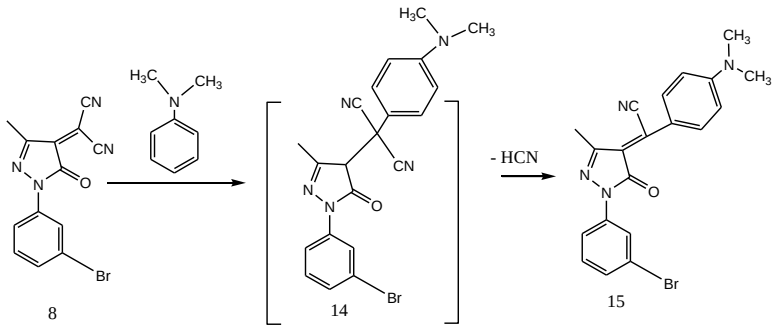
Acidic hydrogen atoms are underline.

Structure 8 was confirmed using elemental analysis and spectroscopic techniques (FT IR, ^{1}H NMR, ^{13}C NMR and MS). Compound 8 condenses readily with primary aniline by hydrogen cyanide elimination. Two structures seemed possible for the condensation product. Thus attack of the amine at the cyclic amide carbonyl function should afford 11 by ring opening and recyclization. Alternately, attack at C-α of the dicyanomethylene moiety would afford 12 which then loses hydrogen cyanide yielding the aryl aminocyanomethylene derivatives (13) (cf. Scheme 3). Structure 13 was established based on the fact that the reaction products are intensely colored. The pyrazole carboxamide derivatives (11) are expected to be almost colorless products.

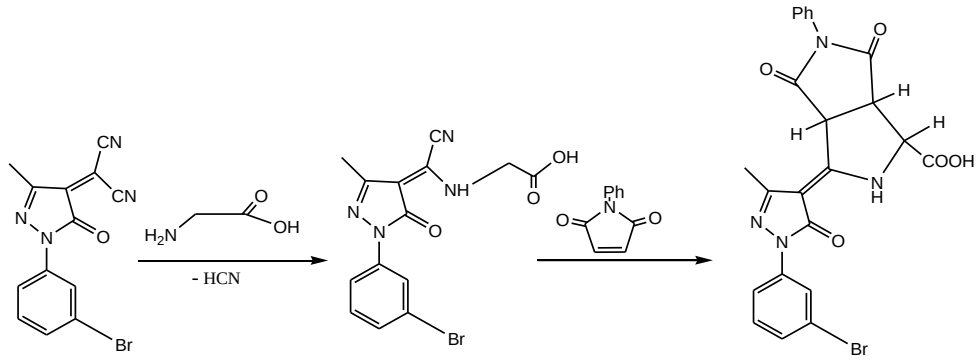
Compound 8 also reacts with N, N-dimethylaniline or N, N-diethylaniline to give the colorless adduct (14) which turns violet on standing or thermal treatment to give the violet product (15) by elimination of hydrogen cyanide (cf. Scheme 4). Compound 8 reacts readily with glycine to give the expected adducts in 40-45% yield (16). It seemed to us that compounds 16 might serve as precursors of azomethine ylides which are formed In this case potential 1,3-dipoles (16) are generated as intermediate which could be trapped by N-phenylmaleimide to give the corresponding 1,3-cycloaddition adduct (17) (cf. Scheme 5).



Scheme 3



Scheme 4



8 16 17

Scheme 5

Conclusion

The previously discussed reactions described a simple facile synthetic procedure to prepare carbon acids, benzimidazolylpyrazole derivative, benzothiazolylpyrazole derivative, and benzoxazolylpyrazole derivative which might have important biological applications.

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