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Meldrum's Acid Catalyzed Reaction of Tetracyanoethylene and Aldehydes in Water: A Novel Approach to Arylidenemalononitrile

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Meldrum's acid catalyzed the reaction of tetracyanoethylene with aromatic, heteroaromatic, and conjugated aldehydes led to arylidenemalononitrile in water in good yields at 80 °C. The work-up of reactions is very simple and the crude products are sufficiently pure to be used without further purification. The procedure provides an alternative method for the synthesis of arylidenemalononitrile.

Key words Meldrum's acid; arylidenemalononitrile; tetracyanoethylene; water

The Knoevenagel condensation of aldehydes with activated methylene compounds is an important and widely employed method for carbon–carbon bond formation in organic synthesis[1,2] with numerous applications in the synthesis of fine chemical,[3] and in synthesis of carbocyclic as well as heterocyclic[4] compounds of biological significance. The reactions are usually catalyzed by bases[5—7] such as amines, ammonia or sodium ethoxide in organic solvents. Lewis acids,[8] surfactants,[9] zeolites,[10] and heterogeneous catalysts[11,12] have also been employed to catalyze reaction. Similarly, the use of ionic liquids[13,14] paves a new path for such organic synthesis.

The use of water as a solvent in organic chemistry was rediscovered in the 1980s by Breslow[15,16] who showed that hydrophobic effects can strongly enhance the rate of organic reactions. Previously the scant solubility of the reactants was the main reason that ruled this solvent out from studies. Further reasons that make water unique among solvents are that it is cheap, not inflammable, and more importantly, it is not toxic. Choice of solvent is one of the problems to face in order to perform eco-efficient processes. The reaction promoters also deserve to be reinvestigated, because large amounts of waste are produced in the fine-chemicals industry, mainly due to stoichiometric reactions and to organic and inorganic salt formation during the quenching procedure.[17]

Tetracyanoethylene (TCNE) is the simplest percyanoalkenes (cyanocarbons). Due to four powerful electron-withdrawing cyano groups the C–C double bond is highly electron-deficient and it is strongly electrophilic reagent. TCNE undergoes two principal types of reaction, namely, addition to its double bond and replacement of a cyano group. TCNE has received an extensive amount of study and the chemistry of this compound has been reviewed several times.[18—20)]

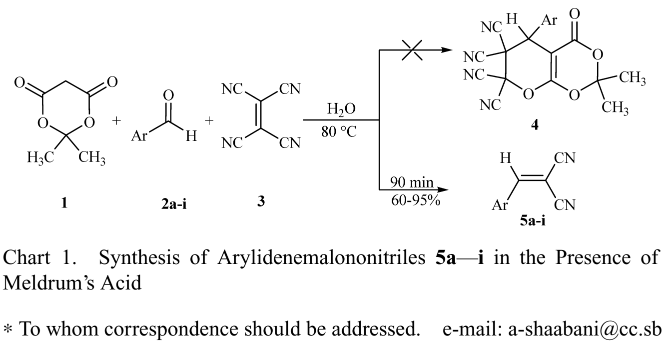

Chart 1. Synthesis of Arylidenemalononitriles **5a**—**i** in the Presence of Meldrum's Acid

As a part of our current studies on the multi component reactions (MCRs),[21—25] and our interest in chemistry of TCNE,[26—29] we have investigated the possibility of trapping the heterodiene generated from the reaction of Meldrum's acid (**1**) and aldehydes **2** with TCNE **3**. In the event we did not observe the expected MCR product **4**; instead the reaction afforded the corresponding arylidenemalononitrile **5** with Meldrum's acid playing as a catalyst role in the reaction between the TCNE and various aldehydes. To the best of our knowledge, this is the first report which shows Knoevenagel products obtained from different substrate, TCNE (Chart 1).

Experimental

Apparatus Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained on solutions in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from Merck and Fluka Chemical Company.

All the products are known compounds (except **5b**, **5c**, **5e**, and **5f**), which were characterized by elemental analyses, IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectra data, and their melting points were compared with literature reports.[30—33]

General Procedure for the Preparation of Arylidenemalononitriles 5a—i A mixture of tetracyanoethylene (0.128 g, 1.0 mmol), aldehydes **2a**—**i** (1 mmol) and Meldrum's acid (0.014 g, 10 mmol%) was successively added to a screw-capped vial containing a magnetic stirring bar in water (20 ml). The mixture was heated at 80 °C in a preheated oil bath for 90 min. After completion of the reaction, the solid residue was filtered and washed with H_2O (10 ml) to yield **5a**—**i**.

2-(3-Methoxybenzylidene)malononitrile (**5b**): Cream solid (0.129 g, 85%). mp 105—107 °C. IR (KBr) (ν_{max}, cm^{-1}): 2195, 1602, 1578. ^{1}H-NMR (300 MHz, CDCl$_3$) δ_H: 3.89 (s, 3H, $O\underline{CH_3}$), 7.18—7.51 (m, 4H, CH arom), 7.77 (s, 1H, CH olefin). ^{13}C-NMR (75 MHz, CDCl$_3$) δ_C: 55.5 (OCH$_3$), 82.9 (=$\underline{C}$(CN)$_2$), 112.6 and 113.7 (2CN), 114.1, 121.3, 123.9, 130.6, 132.0, 159.9, 160.1. MS, *m/z* (%): 184 (M$^+$, 100), 156 (40), 127 (70), 114 (70), 88 (25), 63 (40). *Anal.* Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.56; H, 4.31; N, 15.11.

2-(4-Methylbenzylidene)malononitrile (**5c**): Cream solid (0.123 g, 86%). mp 134—135 °C. IR (KBr) (ν_{max}, cm^{-1}): 2223, 1605, 1585. ^{1}H-NMR (300 MHz, CDCl$_3$) δ_H: 2.83 (s, 3H, $\underline{CH_3}$), 7.36 (d, 2H, $^3J_{HH}$=7.79 Hz), 7.75 (s, 1H, CH olefin), 7.83 (d, 2H, $^3J_{HH}$=7.83 Hz). ^{13}C-NMR (75 MHz, CDCl$_3$) δ_C: 22.0 (CH$_3$), 81.2 (=$\underline{C}$(CN)$_2$), 112.8 and 114.0 (2CN), 128.4, 130.4, 130.9, 146.4, 159.8. MS, *m/z* (%): 168 (M$^+$, 100), 140 (80), 114 (30), 89 (25), 63 (30). *Anal.* Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.47; H, 4.66; N, 16.55.

2-(4-Fluorobenzylidene)malononitrile (**5e**): Cream solid (0.138 g, 89%). mp 125—127 °C. IR (KBr) (ν_{max}, cm^{-1}): 2229, 1596, 1575. ^{1}H-NMR (300 MHz, CDCl$_3$) δ_H: 7.23—7.28 (m, 2H, CH arom), 7.63 (s, 1H, CH olefin), 7.96—8.00 (d, 2H, CH arom). ^{13}C-NMR (75 MHz, CDCl$_3$) δ_C: 82.4

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(=C(CN)$_2$), 112.5 and 113.6 (2CN), 117.4 (d, $^2J_{FC}$=2.20 Hz), 127.3 (d, $^4J_{FC}$=3.22 Hz), 133.4 (d, $^3J_{FC}$=9.45 Hz), 158.3, 165.8 (d, $^1J_{FC}$=238.50 Hz). MS, *m/z* (%): 172 (M$^+$, 100), 145 (90), 121 (80), 94 (25), 75 (25), 50 (50). *Anal.* Calcd for $C_{10}H_5FN_2$: C, 69.77; H, 2.93; F, 11.04; N, 16.27. Found: C, 69.65; H, 2.81; F, 11.12; N, 16.41.

2-((Pyridin-3-yl)methylene)malononitrile (**5f**): Cream solid (0.132 g, 85%). mp 162—164 °C. IR (KBr) (ν_{max}, cm^{-1}): 2223, 1605, 1585. ^{1}H-NMR (300 MHz, CDCl$_3$) δ_H: 7.42 (d of d, 1H, $^3J_{HH}$=8.18 Hz, $^3J_{HH}$=4.81 Hz), 8.51 (d, 1H, $^3J_{HH}$=8.20 Hz), 8.46 (d of d, 1H, $^3J_{HH}$=4.80 Hz, $^4J_{HH}$=1.38 Hz), 8.90 (d, 1H, $^4J_{HH}$=2.18 Hz). ^{13}C-NMR (75 MHz, CDCl$_3$) δ_C: 83.4 (=C(CN)$_2$), 121.0 and 122.8 (2CN), 124.3, 135.6, 142.2, 152.4, 154.6, 156.3. MS, *m/z* (%): 157 (M$^+$+2, 2), 79 (100), 52 (80), 39 (25). *Anal.* Calcd for $C_9H_5N_3$: C, 69.67; H, 3.25; N, 27.08. Found: C, 69.73; H, 3.18; N, 27.15.

Results and Discussion

In this communication, we wish to highlight our findings on the Meldrum's acid catalyzed reaction of tetracyanoethylene with aromatic, heteroaromatic, and conjugated aldehydes. The reaction conditions are mild and carried out in water as a green solvent. In a typical reaction, the reaction of 4-methoxybenzaldehyde **2a** with tetracyanoethylene (**3**) in the presence of Meldrum's acid (10 mol%) in water at 80 °C resulted in the formation of 2-(4-methoxybenzylidene)malononitrile **5a** in 95% yield within 90 min. In a similar manner, a wide range of aldehydes including aromatic, heteroaromatic, and conjugated reacted efficiently with tetracyanoethylene under the same reaction conditions to give the corresponding substituted olefins (Table 1). It is important to note that conjugated aldehyde **2g** was converted to the geometrical single isomer of *Z*-configuration,[34,35] without any side products (Table 1, Entry 7).

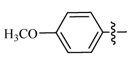
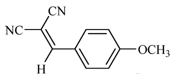
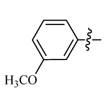
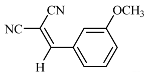
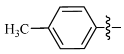
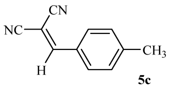
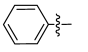
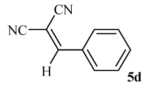
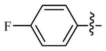
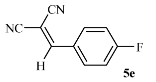
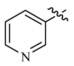
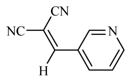
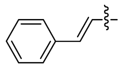
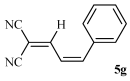
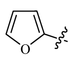
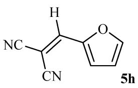
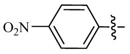
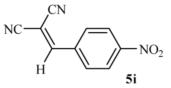
To explore the scope and limitations of this reaction, we extended our studies to the use of various activated CH-acids, organic and inorganic acids (Chart 2). As indicated in Table 2, the best yields have been obtained in the presence of Meldrum's acid (Table 2, Entry 2). However, in the presence of trifluoroacetic acid and hydrochloric acid the reaction yield after 24 h is only 10% yield (Table 2, Entries 8, 9). The other CH-acids such as barbituric acid, cyclopentanedione, 4-hydroxy-2*H*-chromen-2-one and malonic acid can not play as well as the role of Meldrum's acid and in these cases product **6** obtained as a Knoevenagel condensation side product (Table 2, Entries 3—6). In the absence of catalyst, the yield of product **5a** after 24 h is only tracing (Table 2, Entry 1). It is important to note, the reaction is completely stopped in the presence of oxalic acid (Table 2, Entry 7).

In order to obtain the best solvent, 4-methoxybenzaldehyde **2a** with tetracyanoethylene (**3**) in the presence of Meldrum's acid in various organic solvents, were allowed to react at 80 °C. As can be seen in Table 3, the best yield was selectively obtained in water (Table 3, Entry 1). In the cases of EtOH and CH_3CN both of the products **5** and **6** were obtained and in CH_2Cl_2 and $C_6H_5CH_3$ the reaction is completely stopped (Table 3, Entries 2—5).

In view of the emerging importance of the catalytic process to replace the stoichiometric reagents; we studied the optimized reaction conditions with 10 mol% of the catalyst.

Although the mechanism of the reaction between the aro-

Table 1. Synthesis of Arylidenemalononitrile in the Presence of Meldrum's Acid

Entry	Ar	Product	Yield (%)
1		 **5a**	95
2		 **5b**	85
3		 **5c**	86
4		 **5d**	92
5		 **5e**	89
6		 **5f**	85
7		 **5g**	80
8		 **5h**	92
9		 **5i**	60[a]

[a] Due to low solubility of 4-nitrobenzaldehyde in water, the reaction was carried out in EtOH under reflux conditions.

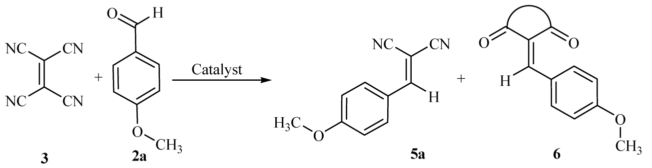
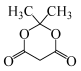
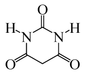
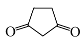
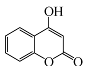


Chart 2. Reaction of 4-Methoxybenzaldehyde (**2a**) with Tetracyanoethylene (**3**) in the Presence of Various Catalyst

Table 2. Synthesis of 2-(4-Methoxybenzylidene)malononitrile **5a** in the Presence of Various Activated CH-acids, Organic and Inorganic Acids[a]

Entry	Acid	Time	Yield (%)	
			5a	**6**
1	None	24 h	Trace	—
2		90 min	95	—
3		300 min	50	10
4		120 min	30	45
5		120 min	25	40
6	$CH_2(CO_2H)_2$	180 min	45	5
7	$(CO_2H)_2$	24 h	—	—
8	CF_3CO_2H	24 h	10	—
9	HCl	24 h	10	—

[a] Tetracyanoethylene (1.0 mmol), 4-methoxybenzaldehyde (1.0 mmol) at 80 °C in H_2O.

Table 3. Effect of Solvent on the Reaction Times, Yields and Molar Ratio of Products **5a** and **6**[a)]

Entry	Solvent		Yield (%)	
			5a	**6**
1	H_2O	90 min	95	0
2	EtOH	12 h	50	10
3	CH_3CN	12 h	40	20
4	CH_2Cl_2	12 h	0	0
5	$C_6H_5CH_3$	12 h	0	0

a) Tetracyanoethylene (1.0 mmol), 4-methoxybenzaldehyde (1.0 mmol), and Meldrum's acid (10 mol%) at 80 °C in various organic solvents.

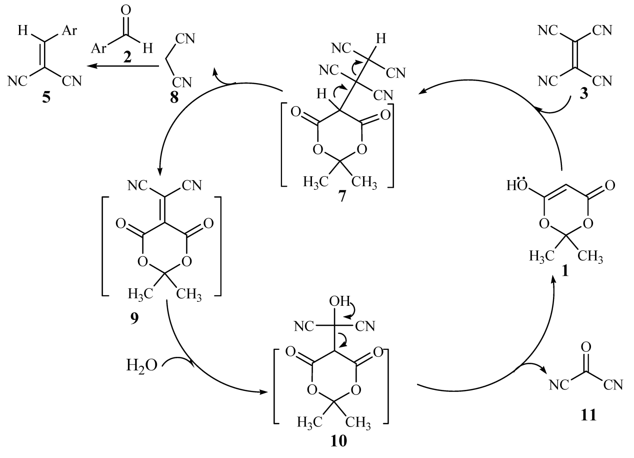


Chart 3. Proposed Mechanism

matic aldehydes with tetracyanoethylene in the presence of Meldrum's acid has not yet been established experimentally, a possible explanation is proposed in Chart 3. It is reasonable to assume that intermediate **7** is formed from the initial attack of the Meldrum's acid on the tetracyanoethylene. Intermediate **7** rearranges to generate malononitrile **8** and intermediate **9**, which condensation of malononitrile **9** with arylbenzaldehyde to produce the product **5**. Intermediate **9** in the presence of water is converted to intermediate **10**, then, eliminating of 2-oxomalononitrile **11** from it to regenerate the Meldrum's acid under the reaction conditions.

Conclusions

In conclusion, we have demonstrated a very simple and highly efficient approach for the condensation of aromatic, heteroaromatic, and conjugated aldehydes with tetracyanoethylene in water to give Knoevenagel products in good yields within 90 min at 80 °C. The work-up procedure is very simple. To the best of our knowledge this is the first report on the synthesis of arylidenemalononitrile using Meldrum's acid as a catalyst. Further on reactivity studies and synthetic application of this methodology are in progress in our laboratory.

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