Article

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Synthesis of Bis-spiro Cyclopropanes Based on Meldrum's Acid by Milling

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Reaction of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) with various solid aldehydes in the presence of cyanogen bromide and solid sodium ethoxide (EtONa) leads to the selective and efficient formation of bis-spiro cyclopropanes based on Meldrum's acid at the range of 0 °C to room temperature. The products were obtained in good to excellent yields. Structure elucidation is carried out by ^{1}H NMR, ^{13}C NMR, FT-IR spectroscopy, mass analyses and X-ray crystallography techniques. A possible mechanism for the formation of products is also discussed under solvent-free condition.

Keywords: Meldrum's acid; Aldehyde; Cyanogen bromide; Bis-spiro cyclopropanes; Milling; Solid sodium ethoxide.

INTRODUCTION

The cyclopropyl group is an important structure in many herbal compounds which displays antifungal,[1] antibacterial, antiviral, and some enzyme inhibition activities.[2-4] For example, bicifadine and its analogs.[5]

Nowadays, the development of solvent-free reaction is one of the advantages in organic synthesis. There are several reports in the literature about cyclopropanation under solvent-free condition such as microwave assisted solvent-free cyclopropanation of some β-dicarbonyls via K_2CO_3,[6] stereoselective synthesis of *cis*-1-carbomethoxy-2-aryl-3,3-dicyanocyclopropanes by grinding,[7] reactions of C_{60} with active methylene compounds in the presence of a base under high-speed vibration grinding (HSVM)[8] and rhodium(II)-catalyzed enantioselective cyclopropanation.[9]

Ball milling as a solvent-free technique has been extensively used as a new synthetic route e.g. Suzuki-Miyaura coupling,[10a] Suzuki reaction,[10b] Aldol condensation,[10c] asymmetric organocatalytic Aldol reaction,[10d] solid phase synthesis of 2,2′-dihydroxy-1,1′-binaphthyl (BINOL)[10e] and oxidation reaction.[10f] In addition to this, ball milling is a useful method to produce ferrite nanoparticles,[11a] Chevrel phase superconductor[11b] and etc. Attrition or mechanical milling is a typical top-down method in preparing nanoparticles.[12] Therefore, this technique should be considered as a potentially attractive solution for solvent-free synthesis. Of course, the reaction of aldehyde with Meldrum's acid in the presence of stabilized bismuthonium ylides afforded Meldrum's acid based cyclopropane in presence of solvent like benzene and dichloromethane, and four compounds were obtained.[13]

Recently, we have reported the cyclopropanation of some β-dicarbonyls such as malononitrile[14] and Meldrum's acid[15] in the reaction of aliphatic and aromatic aldehydes and BrCN in the presence of triethylamine under solvent condition. More recently, we also have reported the cyclopropanation of malononitrile under solvent-free condition by milling.[16] Nevertheless, the reaction of (thio)barbituric acids as a symmetrical barbituric acids,[17a,b] unsymmetrical barbituric acids,[17c] and dimedone[17d] with aldehydes, dialdehydes[17e] and ketones[17f,g] gave spiro dihydrofurans in the presence of BrCN and triethylamine under the same condition (Fig. 1).

On the other hand, Meldrum's acid is a highly interesting class of compounds, and it possesses biological and pharmaceutical properties. Also it performs as a source of geminal dicarboxylic acid which gets a lot of attention in the chemistry and pharmacology.[18] 5-Arylidene and/or 5-alkylidene derivatives of Meldrum's acid are useful intermediates for cycloaddition reaction and for the synthesis of heterocyclic compounds with potential pharmaceutical activity.[19] There are some reports about the hydrolysis of Meldrum's acid ring in some organic compounds including Meldrum's acid ring moiety for the formation of corresponding di- and/or mono-carboxylic acid derivatives.[20]

Despite our research in related studies, no report was found about the cyclopropanation of Meldrum's acid via BrCN under solvent-free condition (ball milling) in the

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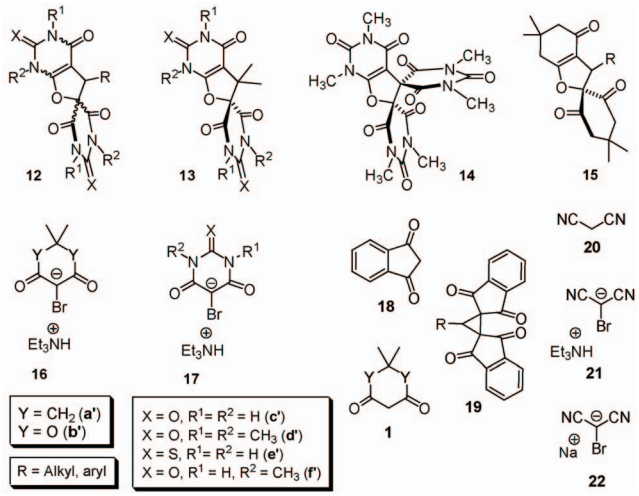


Fig. 1. Structures of some spiro heterocyclic compounds (**12-14**),[17a-d] **15**, triethylammonium-2-bromo-5,5-dimethylcyclohexane-1,3-dione-2-ide (**16a′**),[17f] triethylammonium 5-bromo-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ide (**16b′**),[15] triethylammonium-5-bromo barbiturate salts (**17**),[17a-c] dimedone (**1a′**), 1,3-indandione (**18**), full substituted cyclopropanes based on indandione (**19**),[21] malononitrile (**20**), triethylammonium bromodicyanomethanide (**21**)[14] and sodium bromodicyanomethanide (**22**).[16]

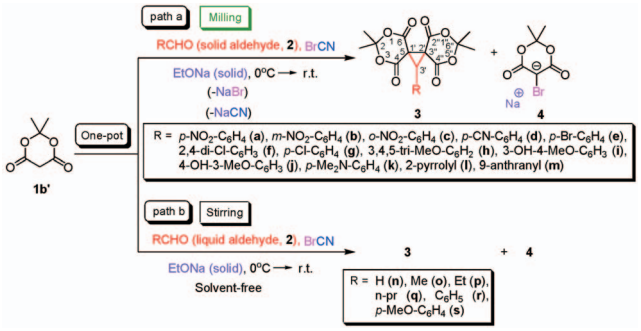
presence of solid EtONa at room temperature. Based on these concepts, herein, we have accomplished the new methodology transformation of aldehydes and Meldrum's acid to bis-spiro cyclopropanes based on Meldrum's acid in the presence of BrCN and solid EtONa by milling.

RESULTS AND DISCUSSION

This paper describes the one-pot reaction of Meldrum's acid (**1b′**) with various solid aldehydes and cyanogen bromide (BrCN) in the presence of solid EtONa that afforded full-substituted bis-spiro cyclopropanes based on Meldrum's acid ring moieties (**3**). This reaction also provided new salt of sodium 5-bromo-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ide (**4**) in moderate to good yield at room temperature by milling (Scheme 1 and Table 1, entries 1-8).

In the present research work, we found that the salt of **4** play the major rule for the formation of **3** according to our previous works that we proposed a plausible mechanism for each of the salt formation (Fig. 1).[14,16,17a-f] The mechanism of the formation of **4** is shown in Scheme 2 under solvent-free condition. It was assumed that the Meldrum's acid **1b′** reacted with EtONa as a base which captured

Scheme 1 Reaction of Meldrum's acid (**1b′**) with various solid aldehydes (**2a-m**) and with liquid aldehydes (**2n-s**) in the presence of BrCN and solid EtONa (see also Table 1)



methylene proton of **1b′**, and after that it formed sodium 2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ide (**5**), and finally EtONa converted to ethanol. The nucleophilic attack of **5** to BrCN formed an intermediate **6**. Intramolecular rearrangement of **6** formed 5-bromo-2,2-dimethyl-1,3-dioxane-4,6-dione (**7**) followed by the loss of HCN. The EtONa as a base captured the proton of active methylene in **7** formed salt **4** (Scheme 2, *path a*). In this reaction, the reaction mixture became moist when mixed and milled in a Teflon-faced screw cap tube vessel. This observation indicated the ethanol releasing in reaction. Unfortunately, all attempts failed to separate or characterize **5**, **6** and **7**. In this reaction, no 2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-carbonitrile (**8**)

Scheme 2 Proposed mechanism for the formation of **4** under solvent-free condition (ball milling)

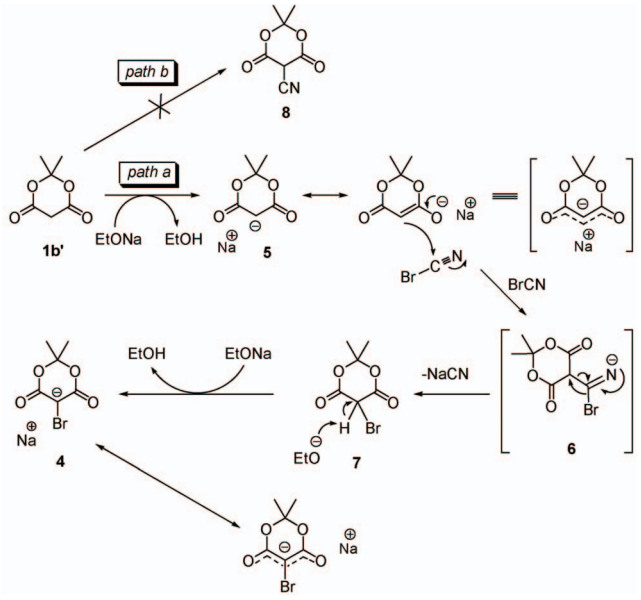


Table 1. One-pot reaction of Meldrum's acid **1b'** with various solid aldehydes (**2a-2m**)[a] and liquid aldehydes (**2n-2s**)[b] mediated by BrCN in the presence of solid EtONa by milling

Entry	R	Product	M.p. (°C)	Yield (%)
1	*p*-NO_2-C_6H_4 (**2a**)	**3a**	201-203 (202–203)[15]	70
2	*m*-NO_2-C_6H_4 (**2b**)	**3b**	192-193 (192–194)[15]	65
3	*o*-NO_2-C_6H_4 (**2c**)	**3c**	197-199 (198–199)[15]	80
4	4-CN-C_6H_4 (**2d**)	**3d**	202-204 (204–205)[15]	70
5	*p*-Br-C_6H_4 (**2e**)	**3e**	193-194 (192–193)[15]	75
6	2,4-di-Cl-C_6H_3 (**2f**)	**3f**	177-179 (178–180)[15]	80
7	*p*-Cl-C_6H_4 (**2g**)	**3g**	177-180 (178–179)[15]	75
8	3,4,5-tri-CH_3O-C_6H_2 (**2h**)	[c]		50[d][15]
9	3-OH-4-CH_3O-C_6H_3 (**2i**)	**9i**		70[e][15]
10	4-OH-3-CH_3O-C_6H_3 (**2j**)	**9j**		75[e][15]
11	*p*-$(CH_3)_2N$-C_6H_4 (**2k**)	**9k**	174-176 (175–177)[15,23]	85[e]
12	2-Pyrrolyl (**2l**)	**9l**	180-182 (182–184)[15]	75[e]
13	9-Anthranyl (**2m**)	**9m**	195-197 (194–196)[15]	90[e]
14	H (**2n**)	**3n**	216-218 (decomps.) (217–218)[15]	55
15	CH_3 (**2o**)	**3o**	215–217 (216–218)[15]	60
16	CH_3CH_2 (**2p**)	**3p**	210–212 (212–214)[15]	70
17	$CH_3CH_2CH_2$ (**2q**)	**3q**	203–205 (204–205)[15]	65
18	*p*-CH_3O-C_6H_4 (**2s**)	**9s**[f]	125–127 (126–128)[15]	70

[a] Reaction mixture to become viscous and carried out by milling. [b] Liquid at 1 atmosphere and 0 °C to room temperature and reaction was carried out by stirring. [c] Mixtures of **3h** and **9h** were obtained. [d] Yield refers to **3h**. [e] Yield refers to **9i-9m**, respectively. [f] Exclusively Knoevenagel adduct was obtained.

was observed (Scheme 2, *path b*). We performed the reaction of **1b′** with BrCN and solid EtONa in the absence of aldehydes under the same condition and the **4** was obtained and isolated in moderate yield. We also performed the reaction of **1b′** with solid EtONa for obtaining of **5** and then compared the FT IR spectrum of **1b′** with those **5** and **4** together. The carbonyl stretching frequencies of **5** and **4** shifted to low frequency than that of **1b′** due to the resonance of the negative charge with carbonyl groups in **5** and **4** (Fig. 2). Compound **1b′** can exists in two tautomeric forms (keto-enol forms) while the salts of **4** and **5** can exist in some mesomeric forms (Scheme 3). In **1b′**, the peak at 3531 cm^{-1} corresponds to hydroxyl group of the enolic form. In contrast the stretching frequencies at 3549, 3477 and 3415 cm^{-1} in **5** and also stretching frequencies at 3431, 3194 cm^{-1} in **4** corresponds to hydroxyl groups of water absorbed to the salts adducts (Fig. 2). These salts have hydrophilic property. We also examined and measured the sodium ion emission by flame photometry in the salt of **4** (see

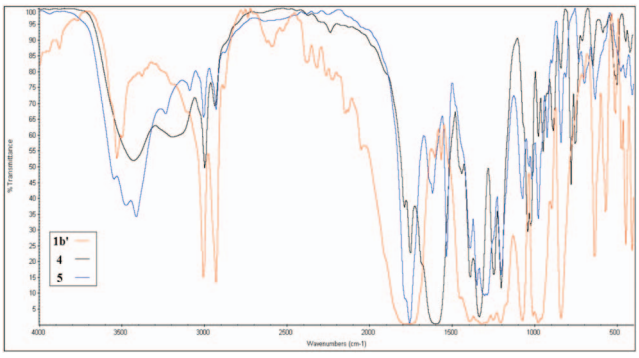
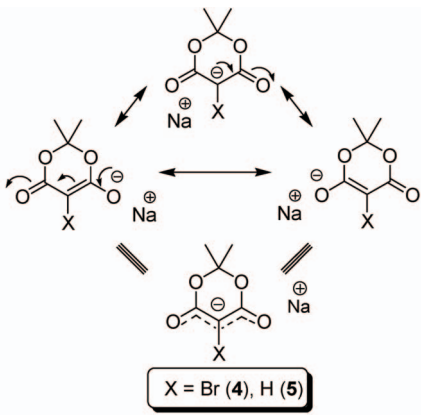


Fig. 2. Comparison of the FT IR spectra of **1b′** (red), **4** (purple) and **5** (blue).

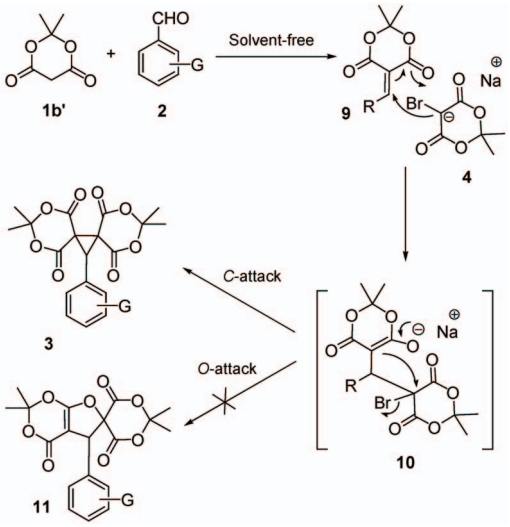
Scheme 3 Mesomeric and resonance forms of **4** and **5**



supplementary material). Other evidence for the formation of **4** (the existence of bromine atom in this molecule) was performed by Beilstein test and the wet silver nitrate test[22] (Precipitate of pale yellow silver bromide). These data are confirmed that are in good agreement with each other for the proposed structure of **4**.

Proposed mechanism for the formation of **3** is shown in Scheme 4 under solvent-free condition. First, the Knoevenagel condensation of **1b′** with equimolar of aldehydes **2** afforded the corresponding 5-arylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (**9**). The Michael addition of the compound **4** (as a nucleophile) with **9** as a key intermediate gave the intermediate **10**. In this reaction, the compound **4** plays either nucleophile or electrophile character, respectively. Finally, an intramolecular reaction of **10** (*C*-attack to the carbon atom as an electrophile containing bromine) with removal of bromide ion afforded **3** in good yield. In intermediate **10**, no *O*-attack was occurred for the formation of **11**. Two geminal oxygen atoms on carbon atom in **10** have inductive effect on each other. For this reason, the geminal oxygen atom prevents the *O*-attacking of oxygen anion to the electrophile for the formation of **11**. Therefore, the *C*-attack was favored (Scheme 4). Unfortunately, all attempts failed to separate or characterize **10**.

Scheme 4 Proposed mechanism for the formation of **3** under solvent-free condition



Representatively, in ^{1}H NMR spectrum of **3n** (derived from formaldehyde), two geminal methyl groups on Meldrum's acid moieties show two singlets at δ 1.84 and 1.91 ppm and methylene show a singlet at δ 2.92 ppm, respectively. ^{13}C NMR spectrum of this compound shows six distinct peaks. The presence of two plane of symmetry in **3n**, in ^{13}C NMR spectrum of this molecule, the four carbonyl groups of C4, C6, C2″ and C4″ have equivalent chemical shifts and show a peak at δ 160.3 ppm (Fig. 3). Other cyclopropane derivatives **3a-3r** (with exception **3n**) shows two distinct peaks for carbonyl groups because of a plane of symmetry (Fig. 3). These observations are the best evidence for supporting the cyclopropanation and the structure of **3n** as a representative under solvent-free condition (solid aldehydes by milling and liquid aldehydes by stirring). Other evidences for the cyclopropanation is the chemical shift value of cyclopropane CH proton that appeared in high field (a singlet at δ 2.92 ppm for **3n**, a quartet at δ 3.33 ppm for **3o** and a distinct singlet derived from aromatic aldehydes as representative) and the X-ray crystallographic data for **3g** (see later).

As mentioned above, the reason of the unsuccessful intramolecular *O*-attack in **10** was because of inductive effect of oxygen atoms on Meldrum's acid ring moiety in intermediate **10** and decreased the nucleophile ability of oxygen anion in this intermediate. In contrast, in the similar intermediates derived from (thio)barbituric acids (**24a′-24c′**) and dimedone (**25**) forced *O*-attack and resulted in spiro dihydrofuranes (**12a′-12c′** and **15**), respectively. Like Meldrum's acid **1b′**, the *C*-attack, in the intermediate (**23**) derived from 1,3-indandione **18**, also occurred[21] and formed full-substituted cyclopropane based on 1,3-indandione (**19**) in the presence of I_2/DMAP system (Figure 1 and Scheme 5). It seems that the reason of *C*-attack was arisen from inductive effect of fused phenyl ring moiety in intermediate **23** (Scheme 5). Also the *C*-attack was occurred and 1,1,2,2,3-aryltetracyanocyclopropanes (**27**) were obtained in excellent yields via the intermediates **26a″** and **26b″** by interfering of the salts of **21**[14] and **22**,[16] respectively (Scheme 5).

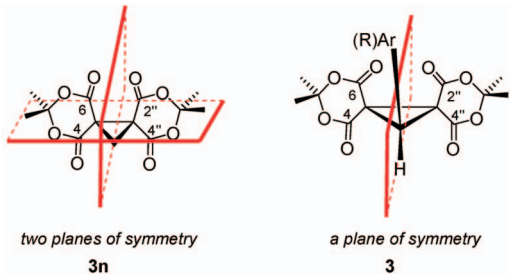
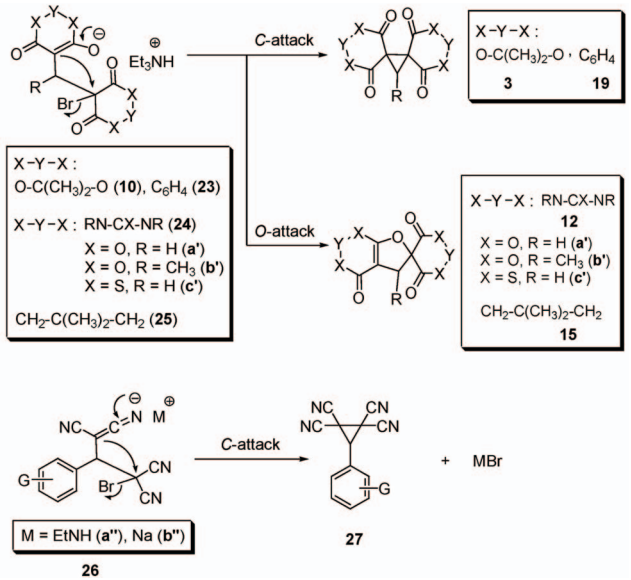


Fig. 3. Representatively, two planes of symmetry and equivalency of four carbonyl groups in **3n** and a plane of symmetry in **3** (except **3n**).

Scheme 5 The condition of intramolecular *C*- and *O*-attacking in intermediates **10**[15] and **23-25**,[17] **26a″**[14] and **26b″**[16]



The different reactivity of variously substituted aldehydes in the reaction with β-dicarbonyl compounds could be rationalized taking into account that the reaction occurs in two steps, i.e. the nucleophilic attack and the dehydration.[20b] Electron-withdrawing substituents facilitate the first step, meanwhile electron donor substituents facilitate the loss of water giving a conjugated stabilized α,β-unsaturated carbonyl compounds. Further, in these latter cases no trace of bis adduct was observed. In contrast, aldehydes possessing electron-withdrawing substituents facilitate the formation of bis-adduct.[15]

It has been reported that only Knoevenagel condensation was occurred in aldehyde possessing strong electron-donor substituents in the reaction with barbituric acids.[23] In the reaction of **1b′** with solid aldehydes **2a-2m** in the presence of BrCN and solid EtONa, the Knoevenagel adducts (**9i-9m**) were obtained (Table 1, entries 9-13). Presumably, the hindrance effect in **2m** led to formation of **9m**. Instead, the existence of acidic NH group on **9l** and OH group upon **9i** and **9j** caused the **4** as a nucleophile to be able to capture acidic proton on NH and/or OH group prior to Michael addition to β-carbon position of Knoevenagel adducts **9i-9m**.[15]

For more generality of these reactions, we performed the reaction of some liquid aldehydes with **1b′** and BrCN in the presence of solid EtONa by stirring under solvent-free condition (Scheme 1, *path b*). The results of these reactions are summarized in Table 1, entries 14-18 (for more information see supplementary material).

X-Ray structure determination of 3g

For further study, an X-ray diffraction analysis of **3g** was undertaken (Fig. 4). Single crystal of **3g** was obtained as colorless crystal by slow evaporation from methanol at room temperature. Two spiro Meldrum's acid moieties in the molecular structure have boat conformer and have the same direction (Fig. 5 (d)). Two carbonyl oxygen atoms of each Meldrum's acid moiety have weak interactions with the second Meldrum's acid moiety in the same side and the corresponding distances are shown in parenthesis {C10 = O1·····O4 = C16 (2.838 Å) and C11 = O2·····O3 = C15 (2.854 Å)} (Fig. 5 (a and b)). These weak interactions and the boat conformations from different views are shown in Fig. 5. The torsion angle between C3-C4-C7-H7 (H7 is the hydrogen atom on cyclopropane) is equal of 48.85°. The selected bond lengths, angles and torsion angles for **3g** are summarized in Table 2.

For the crystal structure determination, the single-crystal of the compound **3g** was used for data collection on a Bruker SMART BREEZE CCD diffractometer. The graphite-monochromatized Mo K_α radiation (λ = 0.71073 Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using Bruker SAINT

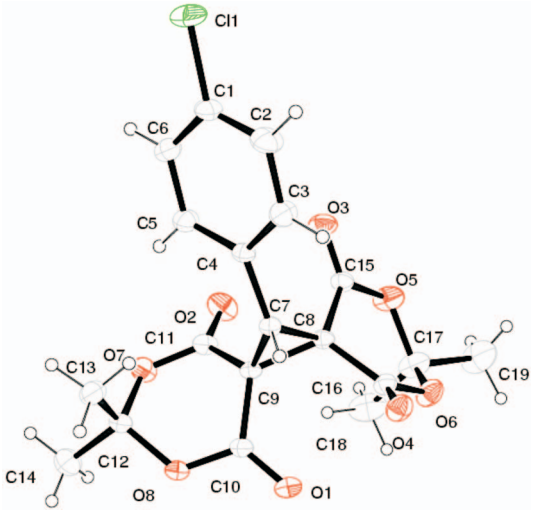


Fig. 4. *ORTEP* drawing of **3g** with the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level.

Table 2. Selected bond lengths (d, Å), angles (θ) and torsion angles (φ) for **3g**

Atom	Bond length (Å), angles (θ, °) and torsion angles (φ, °)
C7-H7	0.979
C7-C8	1.508
C7-C9	1.524
C8-C9	1.531
C4-C7	1.498
C4-C7-H7	112.02
C7-C9-C8	59.15
C7-C8-C9	60.20
C8-C7-C9	60.66
C2-C3-C4-C7	176.22
C4-C7-C8-C15	-9.98
C4-C7-C9-C11	3.37
C3-C4-C7-H7	48.85
C5-C4-C7-C9	14.93
C10-C9-C7-H7	5.40
C16-C8-C7-H7	-8.32
C12-O7-C11-C9	-3.13
C17-O5-C15-C8	4.45
C10-O1·····O4-C16	-60.60[a]
C11-O2·····O3-C15	63.96[a]

[a] See Fig. 5 (c).

(Bruker AXS Inc, 2012) software.[24] The structure was solved by direct methods using SHELXS-97[25] and refined by a full-matrix least-squares procedure using the program

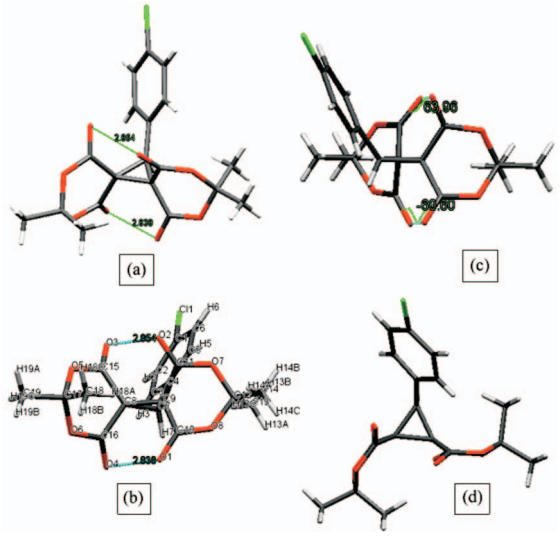
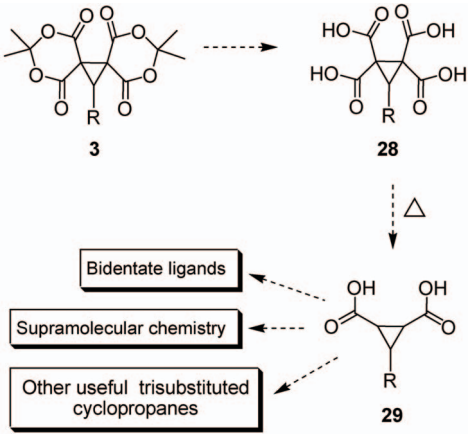


Fig. 5. Two weak interactions, corresponding distances (O·····O) between two carbonyl groups of Meldrum's acid moieties (a, b) and dihedral angles between two carbonyls (c) and boat conformer of Meldrum's acid rings (d) in **3g** from different view sides.

SHELXL-97.[25] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* **3g**: $C_{19}H_{17}O_8Cl$; crystal system, space group: monoclinic, $P2_1/n$ (no:14); unit cell dimensions: a = 11.206(3), b = 10.092(3), c = 18.414(5) Å, α = 90, β = 90.363(2), γ = 90°; volume: 2082.4(10) Å^3; Z = 2; absorption coefficient: 0.232 mm^{-1}; θ range for data collection 2.1 – 28.6°; refinement method: full-matrix least-square on F^2; data/parameters: 4344/290; goodness-of-fit on F^2: 1.048; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0583$, $wR_2 = 0.171$; R indices (all data): $R_1 = 0.071$, $wR_2 = 0.185$; largest diff. peak and hole: 461 and -0.486 e Å^{-3}. Crystallographic data for the compound **3g** (excluding structure factors) have been deposited with the Cambridge Crystallographic data Centre as the supplementary publication No. CCDC-996329. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif and also from CCDC, 12 Union Road, Cambridge, UK (fax: +44-1223-336033, *e-mail*: *deposit@ccdc.cam.ac.uk*).

As mention above in introduction section, compounds 3 are useful and applicable compounds in different study fields as an advantage. For instance, these compounds can hydrolyze to produce tetracarboxylic acids (**28**), vicinal dicarboxylic acids (**29**) that the later compound is the starting material for the preparation of various organic compounds such as; bidentate ligands, supramolecules and other useful trisubstituted cyclopropanes (Scheme 6).

Scheme 6 Conversion of **3** to some useful and applicable trisubstituted cyclopropanes as an advantage



EXPERIMENTAL

General: The drawing and nomenclature of compounds were done by ChemDraw Ultra 8.0 and ChemBioDraw Ultra 12.0 version softwares, respectively. IR spectra were recorded in the region 4000- 400 cm^{-1} on a NEXUS 670 FT IR spectrometer by using KBr disks. The ^{1}H and ^{13}C NMR spectra were measured on Bruker 300 FT-NMR at 300 and 75 MHz, respectively. ^{1}H and ^{13}C NMR spectra were obtained on solution in $CDCl_3$ as solvent using TMS as internal standard. The ^{1}H NMR data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, coupling constant(s) in Hz). The reaction completion were monitored by TLC with silica gel-coated plates (EtOAc: n-hexane/ 8:10/ v:v). The mass analysis performed using mass spectrometer (Agilent Technology (HP) type, MS Model: 5973 network Mass selective detector Electron Impact (EI) 70 eV), ion source temperature was 230 °C (Tehran University, Tehran, Iran). The flame photometry analyzing of Na^{+} in 4 was recorded on CORNING 410 flame photometer (Urmia University, Urmia, Iran). Melting points were determined with a digital melting point apparatus (Electrothermal) and were uncorrected. Cyanogen bromide was synthesized based on reported references.[26] Solid EtONa was prepared with dissolving of freshly metal sodium in appropriate absolute ethanol and then remained ethanol was evaporated. Solid EtONa was kept in vacuumed desiccator. Compounds **1b′**, **2a-s** and used solvents purchased from Merck and Aldrich without further purification.

General procedures for the preparation of 3 under solvent-free condition by milling: Representatively, in a 10 mL with Teflon-faced screw cap tube equipped with an ice-bath the mixtures of 0.05 g (0.48 mmol) cyanogen bromide (BrCN), 0.14 g (0.96 mmol) Meldrum's acid and 0.072 g (0.48 mmol) 3-nitrobenzaldehyde and 0.14 g (2.0 mmol) solid EtONa are mixed, milled by a magnetically stirrer and homogenized at 0 °C to room temperature. Teflon-faced screw cap tube prevents the evaporation of cyanogen bromide (*Caution! The cyanogen bromide is toxic. It is better that the milling should be carried out in a well-ventilated hood*). After 5 minutes the homogenized mixture perturbed to be viscously by milling (indicating the releasing of EtOH). The reaction progression was monitored by thin layer chromatography (TLC) every ten minutes and the TLC solvent was the mixture of EtOAc and n-hexane (EtOAc: n-hexane/ 8:10/ v:v). Initially, the reaction mixture was extracted by water (2 × 5 mL) twice to remove the residue of EtONa and 4, then residue 3-nitrobenzaldehyde and Meldrum's acid was removed by extraction with fresh ethanol (2 × 5 mL). The solvent evaporated by reduced pressure and dried. Spectroscopic data and physical properties of obtained 3b were compared with their reported reference data (Table 1).[15]

General procedures for the preparation of 3 under solvent-free condition by stirring: Representatively, in a 10 mL with Teflon-faced screw cap tube equipped with an ice-bath the mixtures of 0.11 g benzaldehyde (1.0 mmol), 0.29 g Meldrum's acid (2.0 mmol) and 0.13 g cyanogen bromide (1.2 mmol) and 0.14 g solid EtONa (2.0 mmol) are mixed, stirred by a magnetically stirrer and homogenized at 0 °C to room temperature. Teflon-faced screw cap tube prevents the evaporation of cyanogen bromide. The reaction progression was monitored by thin layer chromatography (TLC). After completion of reaction, similar to the milling reaction work-up initially, the reaction mixture was extracted by water (2 × 5 mL) twice to remove the residue of EtONa and 4, then residue benzaldehyde and Meldrum's acid was removed by extraction with fresh ethanol (2 × 5 mL). Spectroscopic data and physical properties of obtained 3 were compared with their reported reference (Table 1).[15]

CONCLUSIONS

In summary, we have presented and developed a versatile one-pot reaction of Meldrum's acid with aliphatic and aromatic aldehydes and cyanogen bromide to selectively afforded bis-spiro cyclopropanes based on Meldrum's acid in the presence of solid EtONa by milling at room temperature in good yields. The experimental results indicated that the aromatic aldehydes are more reactive than that of aliphatic. The aromatic aldehydes possessing electron-withdrawing substituent are more reactive than that of electron-donating substituent. The aromatic aldehydes possessing strong electron-donating substituent gave exclusively Knoevenagel adducts. Similarly, the reaction of Meldrum's acid with liquid aldehydes and cyanogen bromide in the presence of solid EtONa was also afforded bis-spiro cyclopropanes based on Meldrum's acid by stirring at room temperature in good yields.

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