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ORIGINAL ARTICLE

New full-substituted cyclopropanes derived from the one-pot reaction of Meldrum's acid with aldehydes and BrCN in the presence of Et_3N

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Abstract Reaction of 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) with various aldehydes in the presence of cyanogen bromide and triethylamine leads to the selective and efficient formation of full-substituted cyclopropanes at room temperature. The products were obtained in good to excellent yields. Structure elucidation is carried out by ^1H, ^{13}C NMR, FT-IR spectroscopy and mass analysis techniques. A possible mechanism for the formation is discussed.

1. Introduction

Numerous Meldrum's acid derivatives are a highly interesting class of compounds, and research directed to their biological and pharmaceutical properties is continuously attracting great interest in the scientific community (Emtenäs et al., 2000; Snider et al., 2001; Dudinov et al., 2009; Lipson et al., 2008; Song et al., 2003). 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 (Pita et al., 2000).

They are well-documented reactions (Mudhar and Witty, 2010) and are useful reactive intermediates, such as 1,4-addition, (Wilsily and Fillion, 2009; Knöpfel et al., 2005; Ziegler et al., 1980) acting as activated dienophiles in Diels–Alder reactions (Paasz et al., 2007; Borah et al., 2005) and for the preparation of heterocyclic molecules such as benzofurans, indoles (Baxter et al., 1974) and coumarins (Mahulikar and Mane, 2006).

First synthesis of 3-substituted cyclopropane has been described by Mariella and Roth (1957). The methods for cyclopropane synthesis have been divided into two main groups: intramolecular cyclization and interaction of alkenes and carbenes (Faust, 2001; Donaldson, 2001). On the other hand, Michael Initiated Ring Closer (MIRC) is an important synthesis method for cyclization (Caine, 2001). Reaction of halogenated acid anion with the activated alkene followed by cyclization with elimination of halogen has generated

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tetramethyl 3,3-dialkylcyclopropane-1,1,2,2-tetracarboxylates (McCoy, 1964).

The cyclopropanation of Meldrum's acid has been reported by the reaction of Meldrum's acid with an aldehyde and thiophenol in the presence of catalytic amount of piperidinium acetate (Eberle and Lawton, 1988). Cyclopropanation of Meldrum's acid has also been reported by treatment of bismuthonium ylides with aldehydes (Ogawa et al., 1988). 1,1,2,2-Cyclopropanetetracarboxylate and its derivatives have been prepared by treating the sodium salt of 5-alkylidene Meldrum's acid with iodine or bromine (Hedge et al., 1961).

As part of our research program concerning the use of cyanogen bromide (BrCN) and triethylamine (Et_3N), we have investigated the one-pot condensation reaction of Meldrum's acid, aldehydes and BrCN in the presence of Et_3N for the synthesis of full substituted spiro cyclopropanes based on Meldrum's acid at room temperature.

2. Experimental

The drawing and nomenclature of compounds were done by ChemBioDraw Ultra 12.0 and 8.0 versions software. Melting points were measured with a digital melting point apparatus (Electrothermal) and were uncorrected. IR spectra were determined in the region 4000–400 cm^{-1} on a NEXUS 670 FT IR spectrometer by preparing KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on Bruker 300 FT-NMR at 300 and 75 MHz, respectively (Urmia University, Urmia, Iran). ^1H and ^{13}C NMR spectra were obtained on solution in DMSO-d_6 or in $CDCl_3$ as solvents using TMS as internal standard. The data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, bs = broad singlet, coupling constant(s) in Hz, integration). All reactions were monitored by TLC with silica gel-coated plates (EtOAc: n-hexane/8:10/v:v). The mass analysis was 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). Cyanogen bromide was synthesized based on reported references (Hartman and Dreger, 1943). Compounds **1**, **2a–u**, triethylamine and used solvents were purchased from Merck and Aldrich without further purification.

2.1. General procedures for the preparation of 3a–3q and 8r–8u

In a 25 mL round bottom flask equipped by a magnetic stirrer, was dissolved 0.05 g (0.48 mmol) cyanogen bromide (BrCN) in 2 mL methanol at 0 °C. Then separately, 0.14 g (0.96 mmol) Meldrum's acid and 0.014 g (0.48 mmol) formaldehyde were dissolved in 10 mL methanol in an Erlenmeyer, 0.04 g (0.63 mmol) triethylamine was added into the solution and then was transferred into a separatory funnel, then it was added drop wise into the solution of BrCN in a round bottom flask at 0 °C to room temperature (*Caution! The cyanogen bromide is toxic. Reactions should be carried out in a well-ventilated hood*). The progression of reaction was monitored by thin layer chromatography (TLC). After outstanding 24 h, the crystalline solid precipitate, filtered off, washed with few mL of methanol and dried.

*2.1.1. Triethylammonium 5-bromo-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ide (**4**)*

White crystalline solid, mp 252–253 °C; IR (KBr) 3448 (OH), 2995, 2944, 2738, 2678 (CH-aliph.), 1752 (C=O), 1033 (C–O), 752 (C–Br) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.10 (bs), 3.09 (q, 6H), 1.54 (s, 6H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.0, 102.2, 46.4, 27.5, 25.6, 8.7.

*2.1.2. Dispiro[(2,2-dimethyl-1,3-dioxan)-5,1′-cyclopropane-2′,5″-(2,2-dimethyl-1,3-dioxan)]-4,4″,6,6″-tetrone (**3a**)*

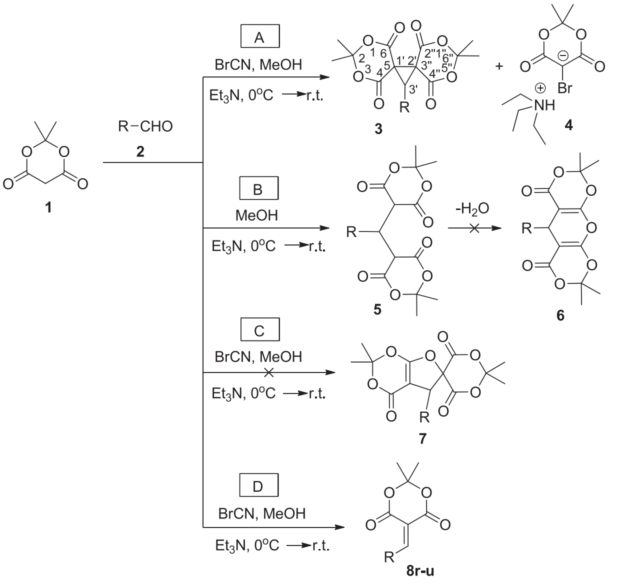
White crystalline solid (45%), mp 218 °C (decomps.); IR (KBr) 3112, 3021, 2924, 1804, 1762, 1396, 1290, 1204, 1056, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.92 (s, 2H), 1.91 (s, 6H), 1.84 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.3, 106.6, 39.5, 27.6, 27.1, 26.1.

*2.1.3. 3′-Methyl-dispiro[(2,2-dimethyl-1,3-dioxan)-5,1′-cyclopropane-2′,5″-(2,2-dimethyl-1,3-dioxan)]-4,4″,6,6″-tetrone (**3b**)*

White crystalline solid (55%), mp 216–218 °C; IR (KBr) 3022, 2953, 1769, 1392, 1278, 1205, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.33 (q, 1H, J = 6.6 Hz), 1.85 (s, 6H), 1.81 (s, 6H), 1.79 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.5, 159.4, 106.0, 42.3, 36.1, 27.9, 27.0, 9.3.

*2.1.4. 3′-Ethyl-dispiro[(2,2-dimethyl-1,3-dioxan)-5,1′-cyclopropane-2′,5″-(2,2-dimethyl-1,3-dioxan)]-4,4″,6,6″-tetrone (**3c**)*

White crystalline solid (60%), mp 212–214 °C; IR (KBr) 3023, 2970, 2943,2880, 1801, 1766, 1395, 1357, 1283, 1205, 1026, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.2 (t, 1H, J = 7.8 Hz), 2.1 (quin, 2H), 1.86 (s, 6H), 1.80 (s, 6H), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7,



R=
H (**a**), Me (**b**), Et (**c**), n-pr (**d**), C_6H_5 (**e**), *p*-NO_2-C_6H_4 (**f**), *m*-NO_2-C_6H_4 (**g**) *o*-NO_2-C_6H_4 (**h**), *p*-CN-C_6H_4 (**i**) , *p*-Br-C_6H_4 (**j**) , 2,4-di-Cl-C_6H_3 (**k**), *p*-Cl-C_6H_4 (**l**) 3-OH-4-MeO-C_6H_3 (**m**), 4-OH-3-MeO-C_6H_3 (**n**), *o*-MeO-C_6H_4 (**o**), 1-naphthyl (**p**) 3,4,5-tri-MeO-C_6H_2 (**q**), *p*-MeO-C_6H_4 (**r**), *p*-Me_2N-C_6H_4 (**s**), 2-pyrrolyl (**t**), 9-anthranyl (**u**)

Scheme 1

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