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ORIGINAL PAPER

# New synthetic protocol for stereoselective synthesis of diethyl 1,2-dicyano-3-alkyl-(aryl)cyclopropane-1,2-dicarboxylate

**Nader Noroozi Pesyan · Saeed Golizadeh**

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**Abstract** A new, fast and straightforward method for the one-pot reaction of aromatic and aliphatic aldehydes and dialdehydes with ethyl cyanoacetate and cyanogen bromide was developed to afford stereoselectively diethyl 1,2-dicyano-3-alkyl/arylcyclopropane-1,2-dicarboxylate in excellent yields and short reaction time (about 5 s). The structures were characterized by IR, $^{1}$H NMR and $^{13}$C NMR spectroscopy. The reaction mechanism was discussed.

**Keywords** Ethyl cyanoacetate · One-pot reaction · Diethyl 1,2-dicyano-3-alkyl/arylcyclopropane-1,2-dicarboxylate · Cyanogen bromide

## Introduction

The cyclopropyl group is an important structural motif in many herbal compounds, displaying antibacterial, antiviral and some enzyme inhibition activities [1–7]. The first synthesis of 1,1,2,2,3-pentasubstituted cyclopropane was described by Mariella and Roth [8]. In this reaction, at first the simple condensation reaction of aldehyde and malononitrile affords alkylidenemalononitriles; then, reaction with the second malononitrile affords the Michael adduct. Subsequently, bromination of this product with bromine and finally intramolecular nucleophilic attack of a C-atom to the C-atom containing the Br-atom produces pentasubstituted cyclopropane.

The use of alkylidenemalononitriles is common in organic synthesis. Direct transformation of benzylidenemalononitriles and malononitrile into 3-aryl-1,1,2,2-tetracyanocyclopropanes in basic alcohol solution has been described by Elinson et al. [9]. On the other hand, a one-pot cascade assembling of 3-substituted tetracyanocyclopropanes from alkylidenemalononitriles and malononitrile by the only bromine direct reaction has also been reported by the same group [10, 11]. Previously, Kawai et al. [12] reported the cyclopropanation mediated by lithium iodide of electron-deficient alkenes with activated dibromomethylene compounds. Recently, we have developed the one-pot synthesis of 3-substituted tetracyanocyclopropanes in the reaction of various aldehydes, malononitrile [13] and di-spiro cyclopropanation of Meldrum's acids [14] with cyanogen bromide (BrCN) in the presence of $Et_3N$.

A search in the literature found no report about cyclopropanation of ethyl cyanoacetate via the chemical reaction route. The only report is the electrochemical cyclopropanation of this compound reported by Elinson et al. [15]. The electrochemical transformation of malononitrile and various ketones to 3,3-dialkyl tetracyanocyclopropanes have also been reported by the same author(s) [16].

Owing to these concepts, in this research, we have developed the chemical synthetic stereoselective cyclopropanation of ethyl cyanoacetate in the reaction with various aldehydes and BrCN under alkali condition.

## Experimental

### General

The drawing and nomenclature of compounds were done by ChemDraw Ultra 8.0 version software. Melting points

**Electronic supplementary material** The online version of this article (doi:10.1007/s13738-015-0590-3) contains supplementary material, which is available to authorized users.

N. Noroozi Pesyan (✉) · S. Golizadeh
Faculty of Chemistry, Urmia University, 57159 Urmia, Iran
e-mail: n.noroozi@urmia.ac.ir; nnp403@gmail.com

were measured with a digital melting point apparatus (Electrothermal) and were uncorrected. IR spectra were determined in the region 4,000–400 $cm^{-1}$ on a NEXUS 670 FT IR spectrometer by KBr pellets. The $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker 400 FT-NMR at 400 and 100 MHz, respectively (Isfahan University, Isfahan, Iran). $^1H$ and $^{13}C$ NMR spectra were obtained on solution in DMSO-$d_6$ and/or $CDCl_3$ as solvent 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. The $^1H$ and $^{13}C$ NMR spectra were opened and analyzed via MestReC software from original spectra files. Cyanogen bromide was synthesized based on reported references [17]. Aliphatic and aromatic (di)aldehydes, $Et_3N$ and solvents were purchased from Merck and Aldrich without further purification.

General procedure for the synthesis of diethyl 1,2-dicyano-3-alkyl-(aryl)cyclopropane-1,2-dicarboxylate

In a 10 mL Teflon-faced screw cap tube equipped with a magnetic stirrer and an ice bath, dissolved formaldehyde (1.0 mmol), ethyl cyanoacetate (2.0 mmol) in 5 ml EtOH added the appropriate base (1.33 mmol, see Table 1), and then (1.2 mmol) cyanogen bromide was added to the solution at 0 °C to r.t. The Teflon-faced screw cap tube prevents the evaporation of cyanogen bromide. A cream color solid was precipitated immediately after 5 s, after about 2 min it was filtered off, washed with cool EtOH (3 × 3 ml), recrystallized in minimum hot EtOH, filtered off and dried as a colorless crystalline solid (0.236 g, 100 % yield).

*Triethylammonium 1-bromo-1-cyano-2-ethoxy-2-oxoethan-1-ide (**4a′**)*

Colorless crystalline powder; mp 280–282 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H, NH), 4.22–4.25 (m, 8H, –$NC\underline{H}_2$–$CH_3$ and –O $C\underline{H}_2$–$CH_3$), 1.25–1.30 (m, 12H, –$NCH_2$–$C\underline{H}_3$ and –$OCH_2$–$C\underline{H}_3$), $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 14.1, 14.4, 59.3, 61.4, 117.5, 128.8, 141.2; IR (KBr, $cm^{-1}$): 3,739, 3,425, 2,983, 2,212, 1,680, 1,506, 1,256, 1,138, 1,025, 685, 571, 444.

*Diethyl 1,2-dicyanocyclopropane-1,2-dicarboxylate (**3a**)*

Colorless crystalline solid; mp 78.5–79.5 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 5.29 (s, 2H, cyclopropane-$\underline{H}$), 4.36 (qd, $J$ = 7.2, $J$ = 2 Hz, 4H, diastereotopic –$OC\underline{H}_2$–$CH_3$), 1.34 (t, $J$ = 7.2 Hz, 6H, –$OCH_2$–$C\underline{H}_3$), $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 14.0, 25.3, 29.7, 65.1, 112.2, 161.4; IR (KBr, $cm^{-1}$): 3,138, 3,047, 2,984, 2,940, 2,256, 1,737, 1,416, 1,375, 1,325, 1,271, 1,190, 1,160, 1,100, 995, 918, 859, 818, 859, 825, 747, 604, 557, 471, 438.

*Diethyl 1,2-dicyano-3-phenylcyclopropane-1,2-dicarboxylate (**3c**)*

Colorless crystalline solid; mp 94–95 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 7.39 (m, 5H, Ar–$\underline{H}$), 4.25–4.33 (m, 4H, –$OC\underline{H}_2$–$CH_3$), 3.87 (s, 1H, cyclopropane-$\underline{H}$), 1.30 (t, $J$ = 7.2 Hz, 6H, –$OCH_2$–$C\underline{H}_3$),$^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 13.9, 34.2, 39.0, 64.7, 111.7, 127.8, 129.0, 129.3, 129.8, 161.2; IR (KBr, $cm^{-1}$): 3,062, 3,014, 2,983, 2,937, 2,250, 1,758, 1,652, 1,503, 1,452, 1,394, 1,265, 1,202, 1,081, 1,006, 859, 751, 702, 655, 511.

*Diethyl 1,2-dicyano-3-(2-nitrophenyl) cyclopropane-1,2-dicarboxylate (**3d**)*

Colorless crystalline solid; mp 100 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.17 (d, $J$ = 8.4 Hz, 1H, Ar–$\underline{H}$), 7.69 (t, $J$ = 7.6 Hz, 1H, Ar–$\underline{H}$), 7.57 (t, $J$ = 9.2 Hz, 2H, Ar–$\underline{H}$), 4.44 (qd, $J$ = 7.2, 5.6 Hz, 2H, diastereotopic –$OC\underline{H}_2$–$CH_3$), 4.32 (s, 1H, cyclopropane-H), 4.14 (qd, $J$ = 7.2, 5.6 Hz, 2H, diastereotopic –$OC\underline{H}_2$–$CH_3$), 1.41 (t, $J$ = 7.2 Hz, 3H, –$OCH_2$–$C\underline{H}_3$), 1.18 (t, $J$ = 7.2 Hz, 3H, –$OCH_2$–$C\underline{H}_3$), $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 13.7, 14.0, 39.3, 64.9, 65.6, 110.8, 112.4, 124.0, 125.7, 130.5, 131.3, 134.2, 161.4; IR (KBr, $cm^{-1}$): 2,992, 2,931, 2,258, 1,749, 1,639, 1,579, 1,526, 1,462, 1,346, 1,300, 1,248, 1,209, 1,181, 1,098, 1,041, 985, 855, 793, 725, 661, 610.

*Diethyl 1,2-dicyano-3-(3-nitrophenyl) cyclopropane-1,2-dicarboxylate (**3e**)*

Colorless crystalline solid; mp 133–134 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.64 (s, 1H, Ar–$\underline{H}$), 8.34 (t, $J$ = 7.2 Hz, 1H, Ar–$\underline{H}$), 8.25 (s, 1H, Ar–$\underline{H}$), 7.68 (t, $J$ = 8 Hz, 1H, Ar–$\underline{H}$), 4.35 (q, $J$ = 7.2 Hz, 4H, –$OC\underline{H}_2$–$CH_3$), 1.35 (t, $J$ = 7.2 Hz, 6H, –$OCH_2$–$C\underline{H}_3$), $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 14.1, 63.3, 106.6, 114.6, 125.9, 127.1, 130.6, 132.9, 135.2, 148.6, 151.9, 161.5; IR (KBr, $cm^{-1}$): 3,097, 3,031, 2,989, 2,949, 2,906, 2,869, 2,225, 1,721, 1,606, 1,572, 1,528, 1,474, 1,355, 1,315, 1,267, 1,203, 1,094, 1,015, 971, 807, 763, 668, 587, 524.

*Diethyl 3-(4-nitrophenyl)-1,2-dicyanocyclopropane-1,2-dicarboxylate (**3f**)*

Colorless crystalline solid; mp 135–136 °C. $^1H$ NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, $J$ = 8.8 Hz, 2H, Ar–$\underline{H}$), 7.52 (d, $J$ = 8.8 Hz, 2H, Ar–$\underline{H}$), 4.39–4.52 (m, 2H, diastereotopic –$OC\underline{H}_2$–$CH_3$), 4.16–4.24 (m, 2H, diastereotopic –$OC\underline{H}_2$–$CH_3$), 4.10 (s, 1H, cyclopropane-$\underline{H}$), 1.41 (t, $J$ = 7.2 Hz, 3H, –$OCH_2$–$C\underline{H}_3$), 1.19 (t, $J$ = 7.2 Hz, 3H, –$OCH_2$–$C\underline{H}_3$), $^{13}C$ NMR (100 MHz, $CDCl_3$) δ: 13.8, 14.0, 31.6, 32.4, 39.3, 65.0, 65.8, 110.5, 112.3, 124.2, 129.9, 134.5, 148.3, 159.3,

**Table 1** The structure of aldehydes **1**, products **3**, used base and reaction time and yields

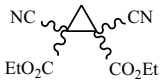
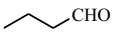
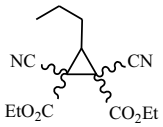
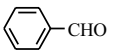
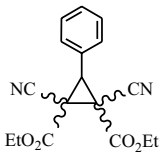
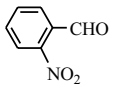
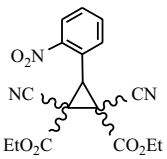
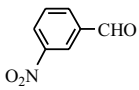
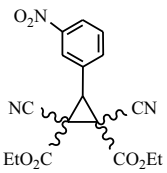
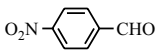
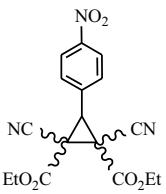
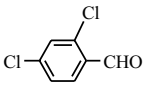
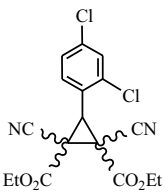
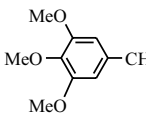
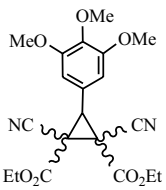
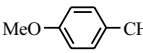
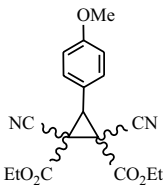
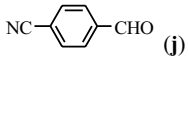
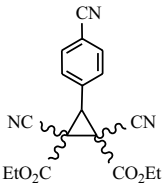
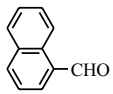
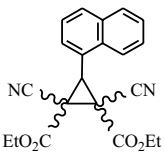
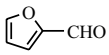
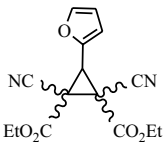
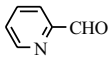
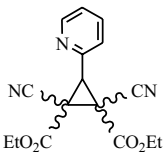
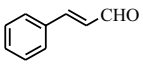
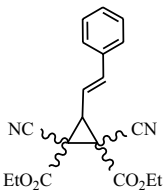
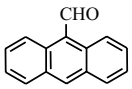
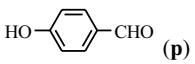
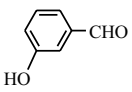
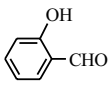
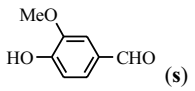
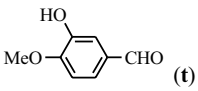
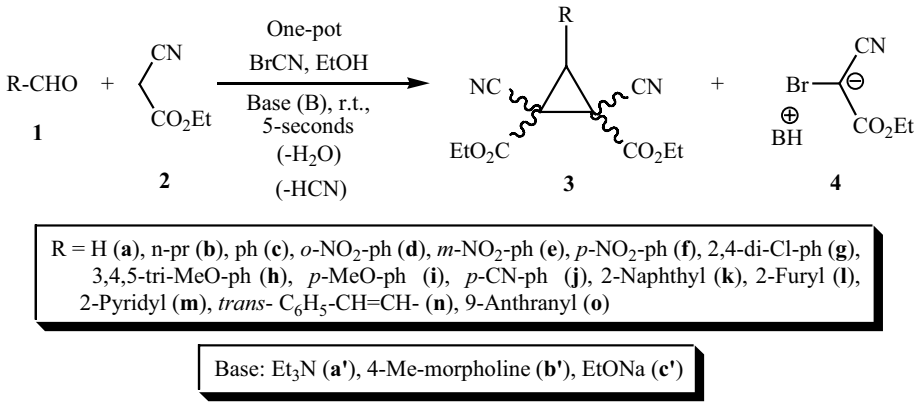
| Entry | Aldehyde (**1**) | Product (**3**) | Base (mmol) | Reaction time (sec.),Yield (%)[a] |
|---|---|---|---|---|
| 1 |  (**a**) |  | EtONa (1.33) | 5, 100 |
| 2 |  (**b**) |  | EtONa (1.33) | 5, 80 |
| 3 |  (**c**) |  | EtONa (1.33) | 5, 85 |
| 4 |  (**d**) |  | $Et_3N$ (1.33) | 5, 100 |
| 5 |  (**e**) |  | $Et_3N$ (1.33) | 5, 100 |
| 6 |  (**f**) |  | $Et_3N$ (1.33) | 5, 100 |
| 7 |  (**g**) |  | EtONa (1.33) | 5, 100 |
| 8 |  (**h**) |  | $Et_3N$ (1.33) | 5, 85 |
| 9 |  (**i**) |  | $Et_3N$ (1.33) | 5, 80 |

**Table 1** continued

| | | | | |
|---|---|---|---|---|
| 10 |  (**j**) |  | $Et_3N$ (1.33) | 5, 90 |
| 11 |  (**k**) |  | $Et_3N$ (1.33) | 5, 90 |
| 12 |  (**l**) |  | 4-MM[b] (1.33) | 5, 85 |
| 13 |  (**m**) |  | $Et_3N$ (1.33) | 5, 80 |
| 14 |  (**n**) |  | $Et_3N$ (1.33) | 5, 70 |
| 15 |  (**o**) | -[c] | [d] | 80[e] |
| 16 |  (**p**) | -[c] | [d] | 75[e] |
| 17 |  (**q**) | -[c] | [d] | 77[e] |
| 18 |  (**r**) | -[c] | [d] | 75[e] |
| 19 |  (**s**) | -[c] | [d] | 80[e] |
| 20 |  (**t**) | -[c] | [d] | 80[e] |

[a] Yield refers to isolated product
[b] 4-Methyl morpholine
[c] Knoevenagel *E* and *Z* adducts were obtained
[d] All used bases were examined
[e] Yield of conversion to Knoevenagel adducts




**Scheme 1** Synthesis of diethyl 1,2-dicyano-3-alkyl-(aryl) cyclopropane-1,2-dicarboxylate (**3**) in the reaction of aldehydes (**1**) with ethyl cyanoacetate (**2**) in the presence of BrCN under alkali condition

161.4,; IR (KBr, $cm^{-1}$): 3,489, 3,113, 3,082, 2,989, 2,940, 2,742, 2,678, 2,491, 2,258, 2,218, 1,753, 1,604, 1,522, 1,471, 1,352, 1,297, 1,243, 1,179, 1,105, 1,043, 993, 856, 758, 725, 697, 641, 593, 509, 471, 413.

*Diethyl 3-(2,4-dichlorophenyl)-1,2-dicyanocyclopropane-1,2-dicarboxylate (**3g**)*

Colorless crystalline solid; mp 95–96.5 °C. $^1$H NMR (400 MHz. $CDCl_3$) δ: 7.50 (dd, $J$ = 8.4, 1.2 Hz, 1H, Ar–H), 7.41 (s, 1H, Ar–H), 7.42 (dd, $J$ = 8.4, 1.2 Hz, 1H, Ar–H), 7.33 (dd, $J$ = 8.4, 2 Hz, 0.06H, Ar–H), 7.28 (dd, $J$ = 8.4, 2 Hz, 1H, Ar–H), 4.37–4.49 (m, 2H, diastereotopic –OC$H_2$–$CH_3$), 4.32 (q, $J$ = 7.2 Hz, 0.33H, diastereotopic –OC$H_2$–$CH_3$), 4.15–4.24 (m, 2H, diastereotopic –OC$H_2$–$CH_3$), 3.84 (s, 1H, cyclopropane-H), 3.80 (s, 0.07H, cyclopropane-H), 1.31 (t, $J$ = 7.2 Hz, 0.5H, –$OCH_2$–C$H_3$), 1.26 (t, $J$ = 7.2 Hz, 0.25H, –$OCH_2$–C$H_3$), 1.19 (t, $J$ = 7.2 Hz, 3H, –$OCH_2$–C$H_3$), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 13.7, 13.96, 14.04, 32.5, 32.9, 37.0, 38.4, 64.6, 64.9, 65.6, 110.8, 112.5, 124.9, 127.8, 128.0, 129.7, 130.4, 130.6, 130.8, 135.4, 136.1, 159.6, 161.4 (Mixtures of three stereoisomers); IR (KBr, $cm^{-1}$): 3,482, 3,093, 2,988, 2,258, 1,752, 1,590, 1,559, 1,474, 1,375, 1,301, 1,249, 1,211, 1,182, 1,100, 1,044, 981, 909, 855, 822, 779, 754, 677, 602, 569, 454.

*Diethyl 1,2-dicyano-3-(3,4,5-trimethoxyphenyl) cyclopropane-1,2-dicarboxylate (**3h**)*

Colorless crystalline solid; mp. 151–152 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ: 6.65 (s, 2H, Ar–H), 3.87 (s, 6H–OC$H_3$), 3.83 (s, 3H, –OC$H_3$), 3.80 (q, $J$ = 7.2 Hz, 4H, –OC$H_2$–$CH_3$), 3.79 (s, 1H, cyclopropane-H), 1.2 (t, $J$ = 7.2 Hz, 6H, –$OCH_2$–C$H_3$), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 29.7, 31.9, 39.7, 55.0, 56.3, 60.9, 106.0, 111.7, 122.6, 139.2, 153.7, 161.7; IR (KBr, $cm^{-1}$): 3,087, 3,061, 3,005, 2,264, 1,622, 1,590, 1,492, 1,401, 1,072, 1,014, 844, 785, 732, 491.

*Diethyl 1,2-dicyano-3-(furan-2-yl)cyclopropane-1,2-dicarboxylate (**3l**)*

Colorless crystalline solid; mp 94–95 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.95 (s, 1H, Ar–H), 7.69 (s, 1H, Ar–H); 7.32 (d, $J$ = 3.6 Hz, 1H, Ar–H), 6.60 (d, $J$ = 3.6 Hz, 1H, Ar–H), 4.29 (qd, $J$ = 7.2, 0.8 Hz, 4H, –OC$H_2$–$CH_3$), 1.31 (td, $J$ = 7.2, 0.8 Hz, 6H, –$OCH_2$–C$H_3$), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 14.2, 62.6, 98.6, 113.9, 115.4, 121.8, 139.5, 148.3, 148.7, 162.6; IR (KBr, $cm^{-1}$): 3,417, 3,129, 3,041, 2,988, 2,938, 2,221, 1,915, 1,717, 1,620, 1,532, 1,463, 1,390, 1,366, 1,263, 1,210, 1,090, 1,019, 965, 932, 877, 843, 760, 701, 587.

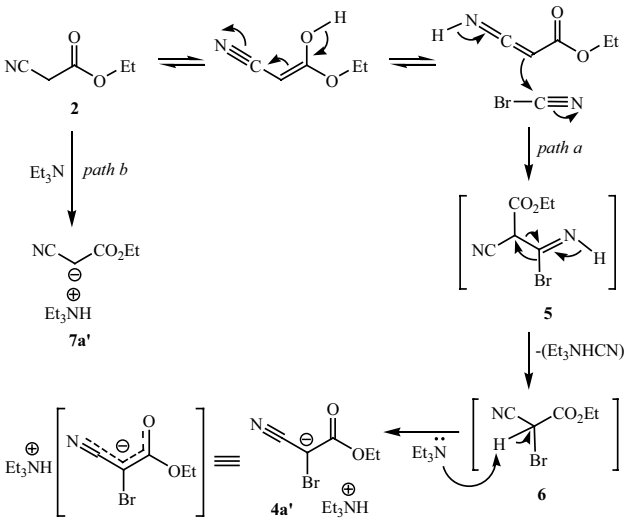
*Tetraethyl 3,3′-(1,4-phenylene) bis(1,2-dicyanocyclopropane-1,2-dicarboxylate) (**9c″**)*

Colorless crystalline solid; mp 230–231 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ: 7.57 (s, 4H, Ar–H), 4.36 (qd, $J$ = 6.8, 2.8 Hz, 8H, –OC$H_2$–$CH_3$), 3.89 (s, 2H, cyclopropane-H), 1.32 (t, $J$ = 7.2 Hz, 12H, –$OCH_2$–C$H_3$), $^{13}$C NMR (100 MHz, $CDCl_3$) δ: 13.9, 29.7, 38.4, 64.9, 111.5, 129.7, 130.0, 160.9; IR (KBr, $cm^{-1}$): 3,050, 2,996, 2,900, 2,249, 1,760, 1,473, 1,389, 1,266, 1,201, 1,081, 1,009, 860, 625.

## Results and discussion

This paper describes a new one-pot reaction of aldehydes (**1a–1n**) with ethyl cyanoacetate (**2**) and BrCN to afford diethyl 1,2-dicyano-3-alkyl- (aryl)cyclopropane-1,2-dicarboxylate (**3a–3n**) under alkali condition in excellent yields with short reaction time (5 s) (Scheme 1).

As described in Scheme 2, in these reactions, the salt **4** plays an essential role for the synthesis of **3**. The structures of salts **4a′–4c′** are shown in Fig. 1. According to our previous reported mechanisms for the formation of the salts **10** [13] and **11** [14, 18–24], a representative proposed reaction mechanism for the formation of triethylammonium




**Scheme 2** Representative proposed mechanism for the synthesis of **4a′**

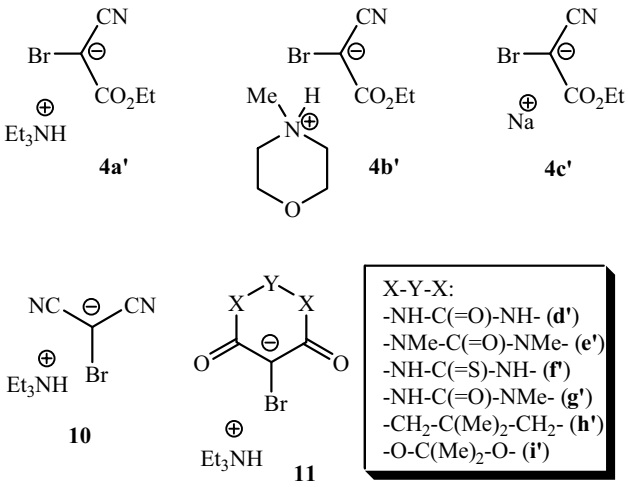



**Fig. 1** Formula structure of salts **4a′–4c′** (this work), **10** [13] and **11** [14, 18–24]

1-bromo-1-cyano-2-ethoxy-2-oxoethan-1-ide (**4a′**) is shown in Scheme 2.

On the basis of the well-established chemistry of some β-dicarbonyl compounds such as malononitrile [13], Meldrum's acid [14], barbituric acids [18–23] and dimedone [24] in the reaction with BrCN in the presence of $Et_3N$ and also the mechanism of the bromination of imidazoles by cyanogen bromide [25], it is reasonable to assume that compound **2** reacts directly with BrCN to form ethyl 3-bromo-2-cyano-3-iminopropanoate (**5**) intermediate through path *a*. Intramolecular rearrangement of **5** produces ethyl 2-bromo-2-cyanoacetate (**6**) as a new intermediate. Finally, $Et_3N$ as a base captures the acidic proton to afford **4a′** (Scheme 2). Ethyl cyanoacetate (**2**) directly reacts with

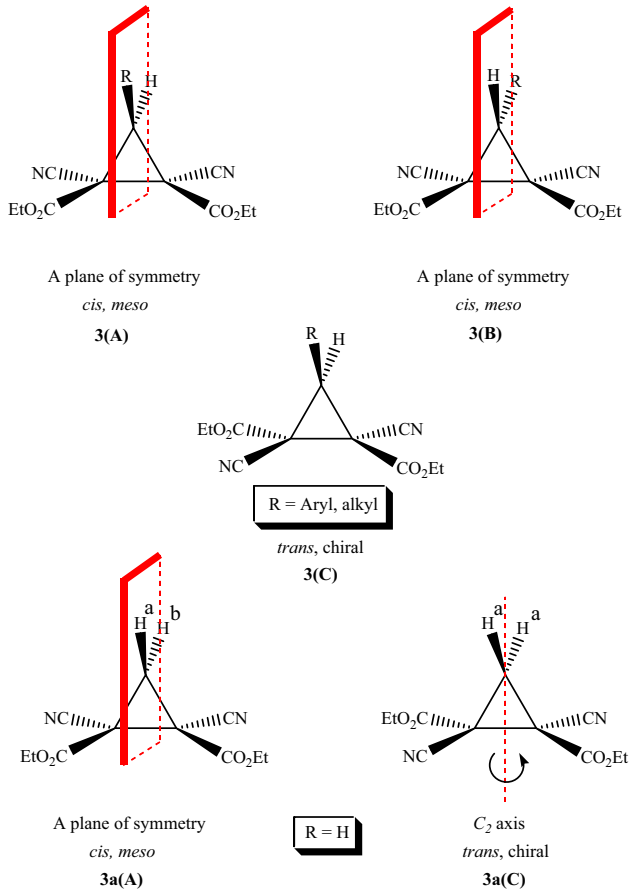
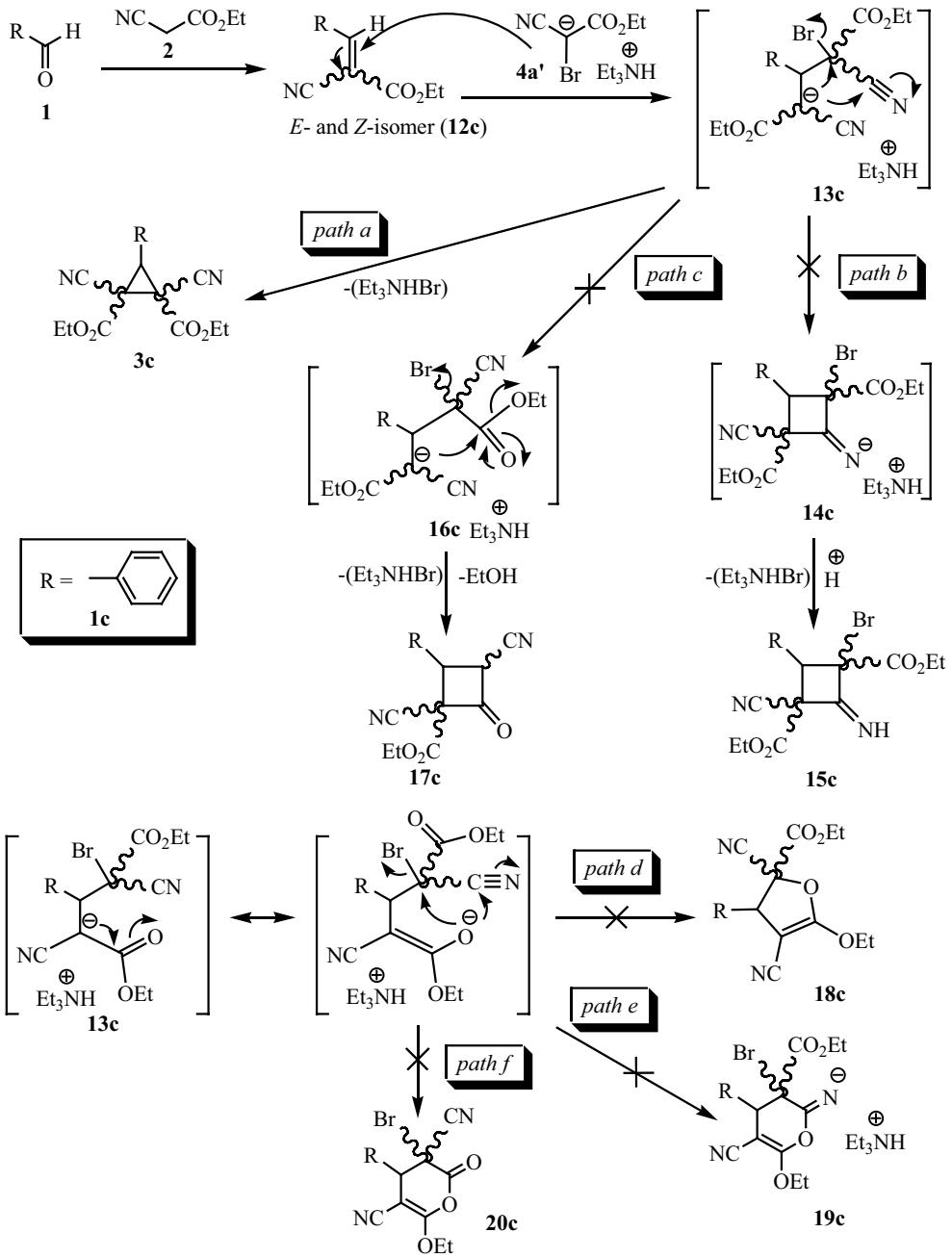



**Fig. 2** A representation of plane of symmetry in **3** and a $C_2$ axis in **3a(C)**

$Et_3N$ to form the salt of **7a′** in the absence of BrCN (path *b*). We performed the reaction of **2** with BrCN in the presence of $Et_3N$ and in the absence of aldehydes **1,** so that salt **4a′** was isolated in excellent yield. These experiments confirm the major role of **4** in the synthesis of **3**.

According to our search, there is no report about compounds **4** in the literature. Salts **4** were isolated and characterized by spectroscopic techniques. Representatively, the IR spectrum of **4a′** shows the frequency of NH+ stretching at the broad range of 2,731–3,739 $cm^{-1}$ and the frequencies of C≡N, C=O and C–Br stretching at 2,212, 1,680 and 571 $cm^{-1}$, respectively. The $^1$H-NMR spectrum of this compound shows (integration in parenthesis) a multiplet at $\delta$ 1.25–1.30 (12H) and a multiplet (a quartet approximately) at $\delta$ 4.22–4.25 ppm (8H) for Me and $CH_2$ groups in $Et_3NH^+$ and ethyl 2-bromocyanoacetate moieties, respectively. A singlet at $\delta$ 8.36 ppm (1H) corresponds to $NH^+$. $^{13}$C-NMR spectrum of this salt shows seven distinct peaks that confirm the structure of **4a′** (Fig. 1, "Experimental" and supplementary data). Unfortunately, all attempts failed to separate or characterize intermediates **5** and **6**. Other evidence for the formation and confirmation of **4** (the




**Scheme 3** Representatively, proposed mechanism for the synthesis of **3c** (path *a*) and no paths *b–f* were occurred

existence of bromine atom in this salt structure) was performed by Beilstein test and the wet silver nitrate test (precipitate of pale yellow silver bromide).

Representatively, the reaction mechanism for the formation of **3c** is shown in Scheme 3. First, the reaction of benzaldehyde **1c** with ethyl cyanoacetate **2** afforded mixtures of two geometrical isomers, (*E*)- and (*Z*)-ethyl 2-cyano-3-phenylacrylate (**12c**); then the nucleophilic attack of **4a′** on the C-atom of **12c** as an α,β-unsaturated C=O compound afforded intermediate triethylammonium 4-bromo-2,4-dicyano-1,5-diethoxy-1,5-dioxo-3-phenylpentan-2-ide (**13c**). Intramolecular *C*-attack of the carbanion on carbon atom containing bromine atom (path *a*) as an electrophile (pushing the bromide ion out) resulted in diethyl 1,2-dicyano-3-phenylcyclopropane-1,2-dicarboxylate (**3c**). All attempts to separate and characterize the intermediates **12c** and **13c** failed. No **15c** was observed through intermediate **14c** (path *b*). This observation indicated that the *C*-attack of carbanion on nitrile group did not occur (Scheme 3).

**Table 2** Stereoisomers of obtained **3** and **9**

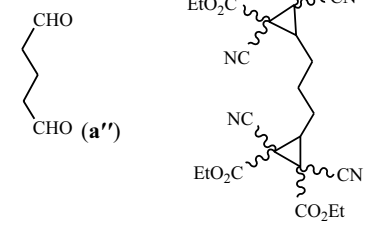
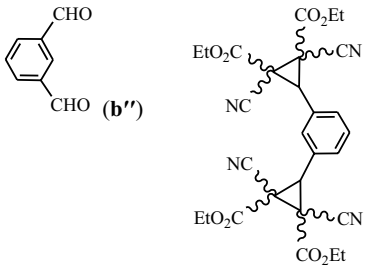
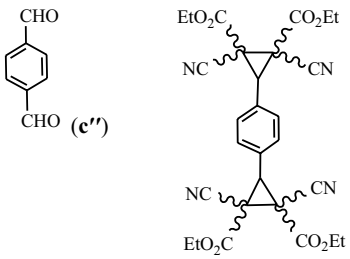
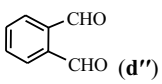
| Entry | Compound | Favored stereoisomer(s) |
|---|---|---|
| 1 | **3a** | *trans* |
| 2 | **3c** | *cis* |
| 3 | **3d** | *trans* |
| 4 | **3e** | *cis* |
| 5 | **3f** | *trans* |
| 6 | **3g** | *trans*[a] and *cis*[b] |
| 7 | **3h** | *cis* |
| 8 | **3l** | *cis* |
| 9 | **9c″** | *cis–cis* and/or *trans–trans* |

[a] Major product (88.9 %, **3gC**)

[b] Minor products (7.4 % and 3.7 %, mixtures of **3gA** and **3gB**) (Figs. 2 and 3). Percentages were obtained by $^1$H NMR spectroscopy (for more information see also supplementary data)

As mentioned above, from the reaction of **1c** and **2,** mixtures of two geometrical (*E*)- and (*Z*)-isomers **12c** were exclusively also obtained in the presence of triethylamine and absence of BrCN. It has been shown that the salt **4** plays a major role in these reactions. First, it is a nucleophile in the reaction with **12c;** then it has an electrophilic character (carbon atom containing a bromine atom) in the intermediate **13c** to form **3c** (Scheme 3). On the other hand, the probable compounds ethyl 1,3-dicyano-2-oxo-4-phenylcyclobutanecarboxylate (**17c**), ethyl 2,4-dicyano-5-ethoxy-3-phenyl-2,3-dihydrofuran-2-carboxylate (**18c**) and 3-bromo-6-ethoxy-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-3,5-dicarbonitrile (**20c**) were not formed through paths *c*, *d* and *f*, respectively (Scheme 3). The reaction condition, time and yields are outlined in Table 1.

**Table 3** The structure of dialdehydes **8** and products (**9a″–c″** and **9d″**), and reaction time and yields

| Entry | Dialdehyde (**8**) | Product (**9**) | Base (mmol) | Reaction time (sec.), Yield (%)[a] |
|---|---|---|---|---|
| 1 |  (**a″**) | | $Et_3N$ (2.66) | 20, 70 |
| 2 |  (**b″**) | | 4-MM (2.66) | 5, 100 |
| 3 |  (**c″**) | | 4-MM (2.66) | 5, 100 |
| 4 |  (**d″**) | | 4-MM (2.66) | 10, 80 |

[a] Yields refer to isolated product

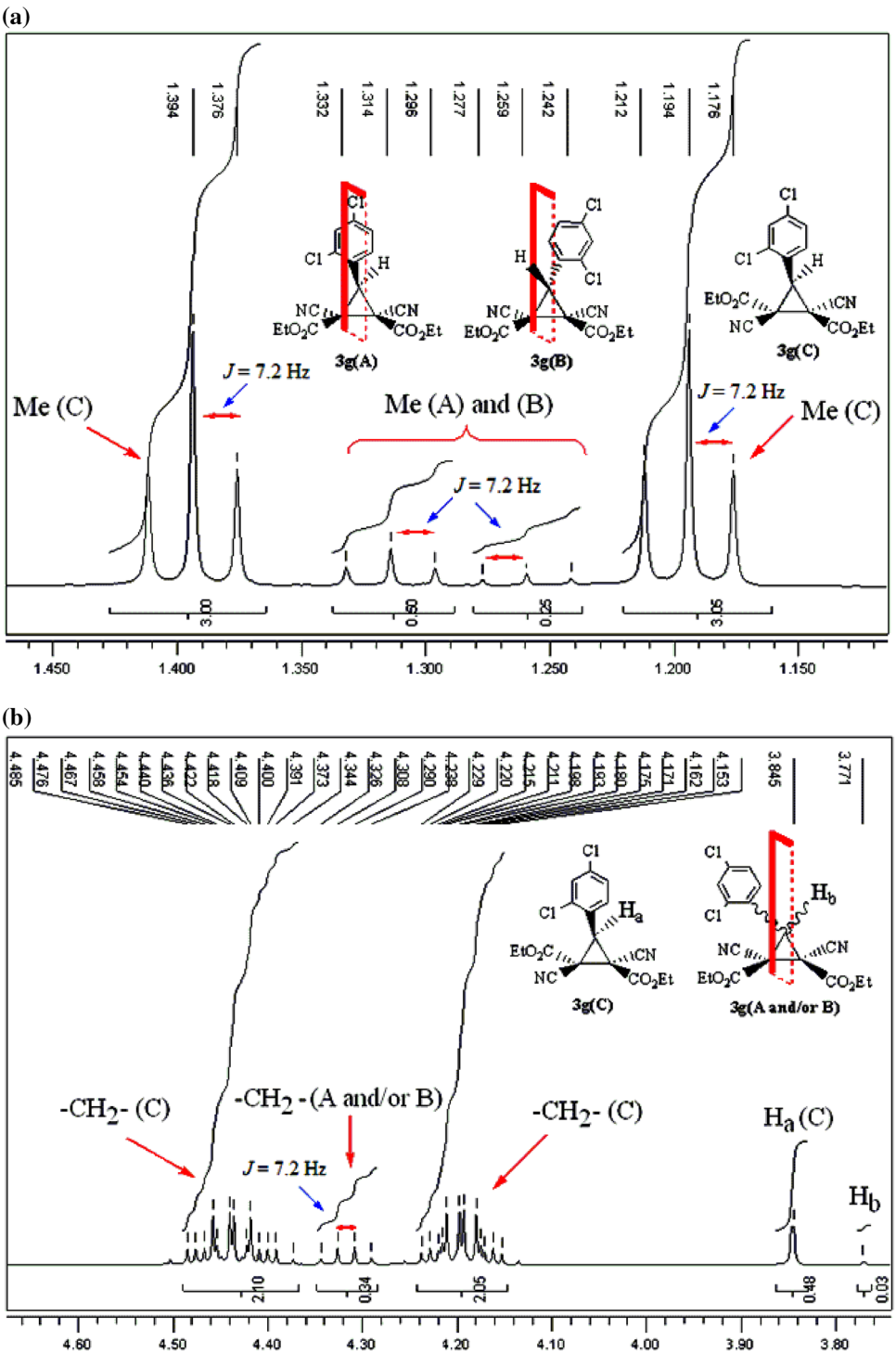
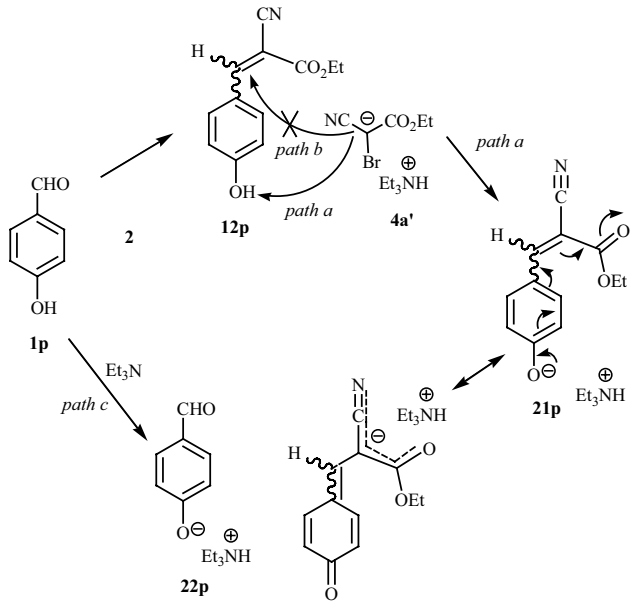



**Fig. 3** Representative $^{1}$H NMR spectrum of the mixtures of stereoisomers of **3g** at aliphatic regions [Me (**a**) and $CH_2$ (**b**) regions; for more information see supplementary data]

Representatively, IR spectrum of **3c** shows stretching frequencies at 2,250 and 1,758 $cm^{-1}$ for the C≡N and C=O groups, respectively. By comparison of the C≡N and C=O stretching frequencies of **4a′** with **3a**, it is obvious that the resonance of the negative charge with C≡N and C=O groups in **4a′** caused the stretching frequencies of these functional groups to shift to low frequency ($(_{N}\equiv C-\overset{O}{\overset{\|}{C}}-C\equiv O_{)}$). $^{1}$H NMR spectrum of **3c** shows a triplet at $\delta$ 1.31 ppm for methyl groups and a multiplet at $\delta$ 4.25–4.33 ppm for methylene groups (two H-atoms of $CH_2$ groups are diastereotopic due to the neighbor being a chiral center). A singlet at $\delta$ 3.87 ppm corresponds to cyclopropyl proton and a multiplet at $\delta$ 7.30–7.43 ppm to



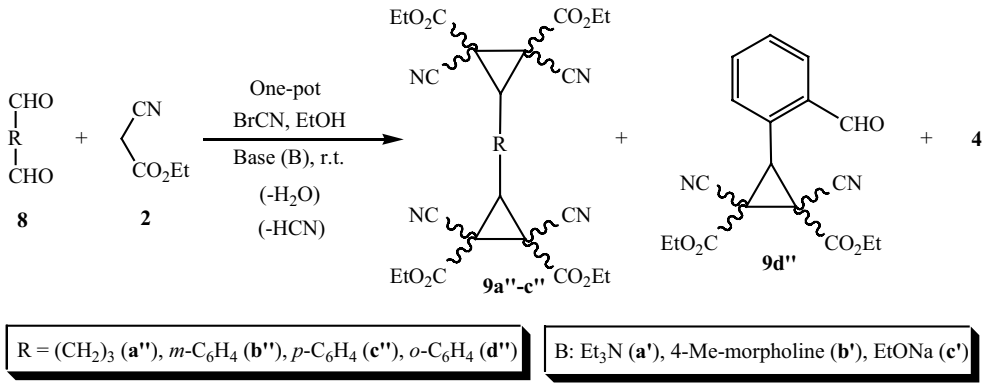

**Scheme 4** The proposed mechanism for the favored path *a* and unfavored path *b*

phenyl group. The $^{13}$C NMR spectrum of this compound shows ten distinct peaks and confirms the assigned structure (see "Experimental" and also supplementary data). Compound **3c** was found to be stereoselectively *cis* form (**3cA** and/or **3cB** forms), due to having a triplet at $\delta$ 1.31 ppm and also a distinct carbonyl peak at $\delta$ 161.2 ppm in $^{1}$H and $^{13}$C NMR spectroscopies, respectively (Fig. 2; Table 2).

One of the interesting situations in these compounds is the stereostructure of these compounds (Fig. 2). Many of these compounds (**3A** and **3B** forms) have a plane of symmetry ($\sigma$), so that the two ethyl groups are equivalent in chemical shift (Fig. 2). The structure of **3C** form (with exception of the products derived from formaldehyde (**3a**)) has neither plane of symmetry nor $C_2$ axis. For instance, the structure of **3aA** has a plane of symmetry ($\sigma$) and so does the *meso* form; however, **3aC** has a $C_2$ axis and is a chiral form. The $^{1}$H NMR spectrum of **3a** shows a triplet for methyl groups at $\delta$ 1.34 ppm, a quartet–doublet at $\delta$ 4.35 ppm ($J$ = 7.2 Hz, $J$ = 5.2 Hz) for diastereotopic methylene protons and a singlet at $\delta$ 2.52 ppm for cyclopropane methylene protons. On the other hand, in **3aA** form, $H^a$ and $H^b$ protons are diastereotopic, while these protons in **3aC** are homotopic. According to the $^{1}$H NMR data for **3a**, and the equivalency of two protons on the cyclopropane ring moiety (a singlet at $\delta$ 2.52 ppm), we conclude that this compound was formed as **3aC** (*trans* form). The $^{13}$C NMR spectrum of this compound shows six distinct peaks at $\delta$ 161.4 (for C=O), 112.2 (for CN), 65.1 (for CO–**C**H$_2$–CH$_3$), 29.7 (cyclopropane-**C**H$_2$), 25.3 (cyclopropane-**C**–CO) and 14.0 ppm (for CO–CH$_2$–**C**H$_3$). These observations confirm the formation of distinct **3aC** form (see also "Experimental" and supplementary data). All these spectroscopic explanation results for stereostructures of **3** are summarized in Table 2.

For instance, the $^{1}$H NMR spectrum of compound **3g** shows three stereoisomers (Table 2; Fig. 3). The main stereoisomer (**3gC**) is *trans* form (88.9 % yield, obtained from $^{1}$H NMR spectrum). Owing to the two different chemical shifts for Me groups (also two multiplets for methylene groups), the **3gC** isomer was found to be a major product. This isomer (**3gC**) has neither plane of symmetry nor a $C_2$ axis. In contrast, the *cis* isomers (**3gA** and **3gB**) have a plane of symmetry and are *meso* forms. According to $^{1}$H NMR spectrum of **3g**, there are two main distinct triplets for methyl groups of **3gC**. The two *meso* forms were obtained in 7.4 and 3.7 % yields (Fig. 3).

The reaction of bulky aldehyde such as 9-anthracene carbaldehyde (**1o**) and aldehydes containing exchangeable protons (**1p–1t**) with **2** and BrCN afforded a mixture of *E*- and *Z*- Knoevenagel adducts (**12p–12t**) under the same condition and did not yield cyclopropanes (**3p–3t**).




**Scheme 5** Stereoselective synthesis of tetraethyl bis(1,2-dicyanocyclopropane-1,2-dicarboxylate) (**9**) in the reaction of dialdehydes (**8**) with **2** in the presence of BrCN and in alkali condition

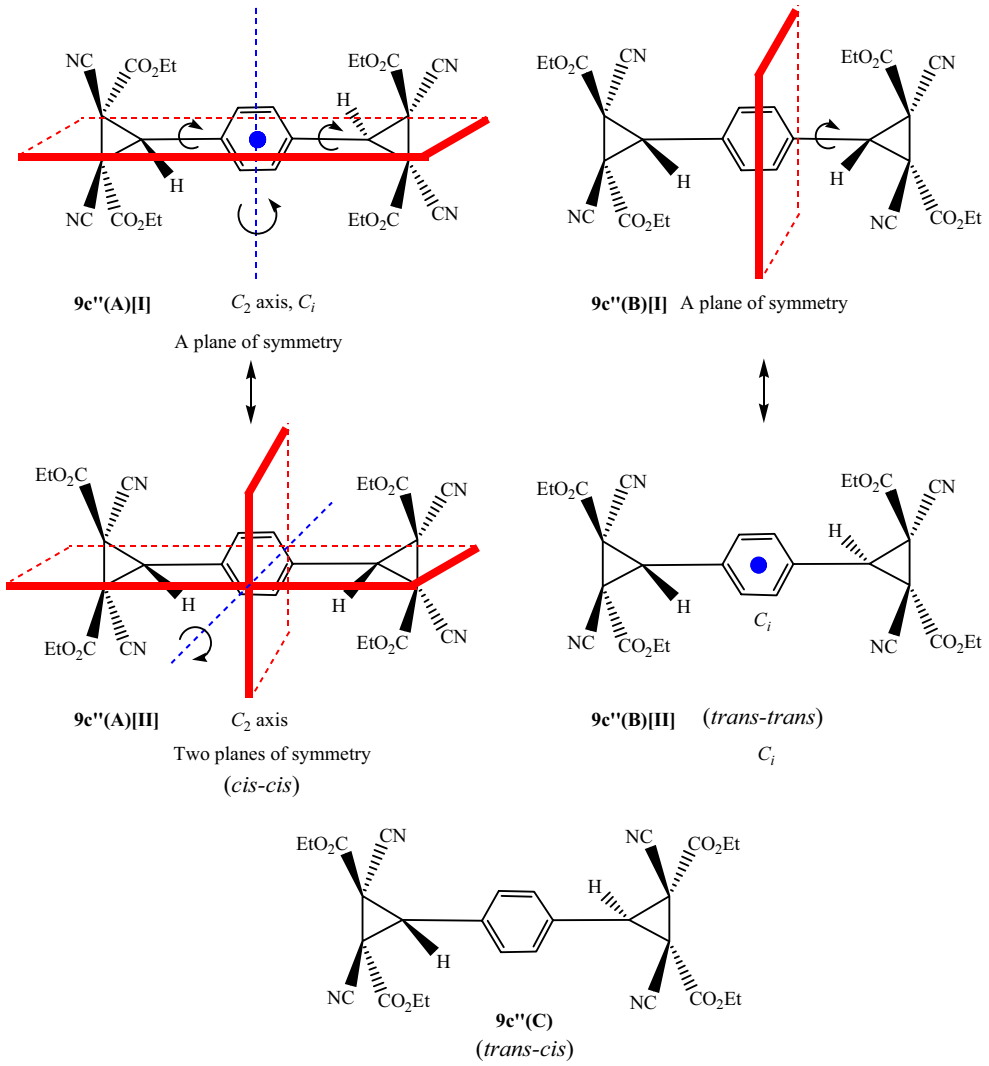



**Fig. 4** Possibly favored forms **9c″A** and **9c″B** and unfavored form **9c″C**. A plane of symmetry, a $C_2$ axis and $C_i$ in **9c″A[I]** equal two planes of symmetry and $C_2$ axis in **9c″A[II],** and a plane of symmetry in **9c″B[I]** also equals a $C_i$ symmetry in **9c″B[II]** [$C_i$ is assigned a *blue dot*]

Presumably, the hindrance effect in **1o** led to the formation of **12o** (mixture of *E*- and *Z*- isomers). Instead, the existence of acidic OH group upon **12p–12t** caused **4** as nucleophile to be able to capture acidic proton on the OH group (path *a*) prior to Michael addition to β-carbon position of Knoevenagel adducts **12p–12t** (path *b*) (Scheme 4). Therefore, the path *a* is more favored than path *b*. It seems that the existence of exchangeable proton having acidic nature on Knoevenagel adducts prevented the Michael addition of **4** and made the path *a* more favorable to form **21p** (Scheme 4). Another possible pathway can be path *c*. For instance, triethylamine as a base can attack acidic proton on phenol derivative (4-hydroxy benzaldehyde **1p** as representative) to form triethylammonium 4-formylphenolate **22p** (Scheme 4, path *c*). Our attempt to separate and characterize **12p**, **21p** and **22p** failed. These results demonstrated the reason for the unsuccessful cyclopropanation of aromatic aldehydes possessing exchangeable proton.

We also performed the reaction of glutaraldehyde (**8a″**), isophthalaldehyde (**8b″**), terphthalaldehyde (**8c″**) and phthalaldehyde (**8d″**) with **2** in the presence of BrCN under the same conditions (Scheme 5). In these reactions, the reaction of **8a″** was crucial, while those of **8b″–8c″** were easy. The reaction of **8d″** with **2** and BrCN under alkali condition afforded diethyl 1,2-dicyano-3-(2-formylphenyl)cyclopropane-1,2-dicarboxylate (**9d″**) due to *ortho* formyl hindrance effect. In contrast, with **8a″–8c″**, both aldehyde groups in each compound reacted with **2** and tetraethyl 3,3′-(propane-1,3-diyl)bis(1,2-dicyanocyclopropane-1,2-dicarboxylate) (**9a″**), tetraethyl 3,3′-(1,3-phenylene)bis(1,2-dicyanocyclopropane-1,2-dicarboxylate) (**9b″**) and tetraethyl 3,3′-(1,4-phenylene)

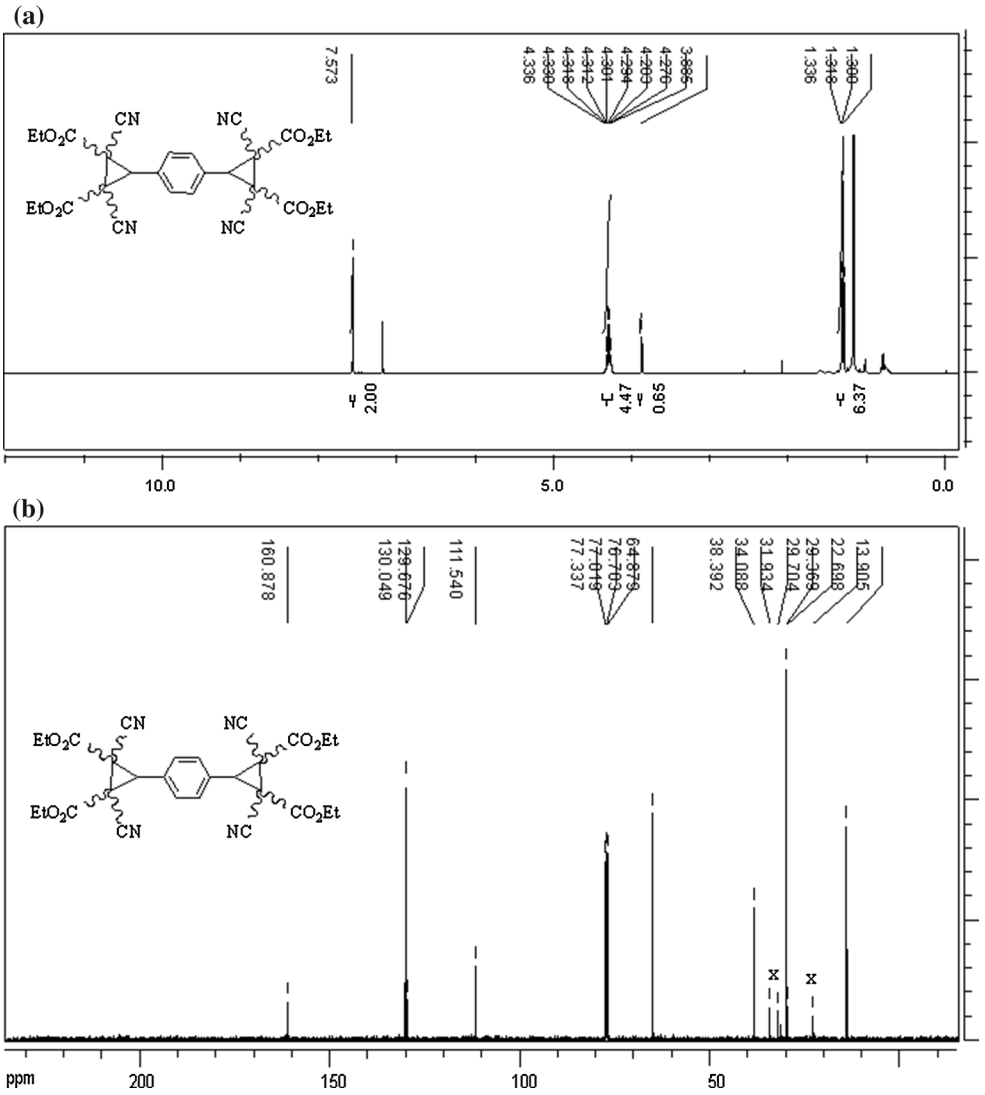



**Fig. 5** $^{1}$H NMR (**a**) and $^{13}$C NMR spectra of **9c″** (**b**) in $CDCl_3$

bis(1,2-dicyanocyclopropane-1,2-dicarboxylate) (**9c″**) were obtained, respectively (Scheme 5; Table 3).

Representatively, $^{1}$H NMR spectrum of **9c″** shows a triplet and a multiplet for four equivalent Me and diastereotopic methylene protons at $\delta$ 1.30 and 4.31 ppm, respectively. This compound also shows two singlets for Ph and cyclopropyl protons at $\delta$ 7.57 and 3.89 ppm, respectively. The $^{13}$C NMR spectrum of **9c″** shows eight distinct peaks. Peaks at $\delta$ 160.9 (C=O), 130.0, 129.7 (Ph ring), 111.5 (CN), 64.9 (–O–$CH_2$–), 38.4 (cyclopr.–**C–**C=O), 29.4 (cyclopr.–**C–**H) and 13.9 (Me) confirm the assigned structure (Figs. 4, 5). Both structures of **9c″A** (*cis–cis*) and **9c″B** (*trans–trans*) confirms the $^{1}$H and $^{13}$C NMR spectral data. The **9c″A[I]** form has a plane of symmetry ($\sigma$), $C_2$ axis and a center of symmetry ($C_i$). The rotamer of **9c″A[I]** is the **9c″A[II]** form, due to the free rotation about single bonds between phenyl and both cyclopropyl rings. In fact, the **9c″A[II]** form has two perpendicular $\sigma$ and a $C_2$ axis. On the other hand, the **9c″B[I]** form has a $\sigma$ and can convert to the rotamer of **9c″B[II]** that consists of a $C_i$ symmetry. No unfavored form of **9c″C** (*trans–cis*) was observed (Figs. 4, 5).

## Conclusions

In summary, the reaction of various mono- and di-aldehydes with ethyl cyanoacetate and cyanogen bromide in basic media afforded stereoselectively diethyl 1,2-dicyano-3-alkyl-(aryl)cyclopropane-1,2-dicarboxylate in excellent yields and short reaction times. Some aldehydes gave the *cis* and some others gave the *trans* cyclopropane stereoisomer. These observations were found in the results of $^{1}$H and $^{13}$C NMR spectroscopy analysis in detail.

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