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ORIGINAL PAPER

Synthesis of various cyclopropyl methyl bromide and its derivatives from ketones and/or aldehydes and some β-dicarbonyl compounds in the presence of BrCN and Et_3N

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Abstract
The ultimate goal in this paper has been developed for the synthesis of structurally various bromomethyl cyclopropane via an α-bromoketone and/or aldehydes with ethyl cyanoacetate or malononitrile and cyanogen bromide (BrCN) in the presence of Et_3N to give products in excellent yields within about 3 s. All structures were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy techniques. The reaction mechanism was discussed.

Keywords Ethyl cyanoacetate · One-pot reaction · 3-Alkyl-3-(bromomethyl)-1,2-dipropionylcyclopropane-1,2-dicarbonitrile · 3-(4-(Bromomethyl)phenyl)cyclopropane-1,1,2,2-tetracarbonitrile · Cyanogen bromide · *N*-Bromosuccinimide · Photochemical · Bromonium ion

Introduction

The α-bromination of carbonyl compounds is an important transformation in organic synthesis chemistry [1–4]. Several more common reagents have been already applied to synthesis α-bromo carbonyl derivatives [4, 5]. Halogenation of ketones has been reported widely in organic syntheses. Therefore, many methods developed for this purpose. Classical methods for the bromination of ketones include the use of molecular bromine [6] and copper(II) bromide [7]. The harvests of these halogenations have long been valued as useful synthetic intermediates [8]. For example, each year new metabolites containing chiral halogens are isolated from several biological sources [9, 10].

In recent years, a central purpose in organic synthesis chemistry has been to develop suitable and economically competitive processes for the impressive synthesis of biologically active compounds. The cyclopropyl group is influential in biological systems [11], for example, as antibacterial in many herbal compounds, in antiviral and some enzyme inhibition activities [12, 13]. The first synthesis of 1,1,2,2,3-penta-substituted cyclopropane described by Mariella et al. [14]. In this reaction, at first, the simple condensation reaction of aldehyde and malononitrile affords alkylidenemalononitriles, then reaction with the second malononitrile provides Michael adduct. Then bromination of this product with bromine was done, and finally, intramolecular nucleophilic attack of a carbon atom to the other carbon-containing bromine atom (shoving the bromide ion out) produces penta-substituted cyclopropane [14]. There are several routes for the synthesis of cyclopropane ring frame in organic compounds, such as cyclopropanation of an aldehyde in the presence of BrCN and Et_3N with β-dicarbonyl compound as malononitrile [15], ethyl cyanoacetate [16], Meldrum's acid in the presence of NaOEt by ball-milling [17], *bis*-spiro cyclopropanes based on Meldrum's acid by ball-Milling technique [18], in the presence of I_2/DMAP [19] and so on.

A search in the literature found no story about cyclopropanation of α-bromo carbonyl compounds via ethyl cyanoacetate and/or malononitrile the chemical reaction route. Owing to these concepts, in this research, we have developed the chemical synthesis stereoselective cyclopropanation of ethyl cyanoacetate and malononitrile in the reaction with various α-bromo ketones and aldehydes with BrCN in the presence of Et_3N.

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Results and discussion

In this article, the first goal is to synthesize α-bromination from various ketones and aldehydes (**1a–1n**) with *N*-bromosuccinimide (NBS) in the presence of UV–Vis irradiation (180 nm) [20]. These substrates were converted at 30 ± 2 °C to the corresponding α-brominated products in excellent yields within a few minutes (Fig. 1). The results of these studies have been summarized in (Table 1). A new one-pot reaction of α-bromomethyl ketones and aldehydes (**2a–2r**) with ethyl cyanoacetate and malononitrile in the presence BrCN has been done to afford diethyl 3-alkyl-1,2-dicyano-3-(bromomethyl) cyclopropane-1,2-dicarboxylate and/or 3-(4-(bromomethyl)phenyl)cyclopropane-1,1,2,2-tetra carbonitrile under Et_3N in excellent yields with short reaction time (3 s) (Scheme 1). The reaction of aldehydes among excellent results have been reported [15]. Instead, aliphatic ketones do not react easily due to hindrance effect and congestion on intermediate stops Knoevenagel condensation [20] (Scheme 2). However, the reaction in the presence of bromine was proceeded in the allyl position on the intermediate Knoevenagel and the creation of intermediate bromonium ion (**12z**) as well (Scheme 3). The reaction of (**1**) with (**3**) afforded (**11z**) (the mixture of E and Z isomers). Previously, the reaction mechanism for the formation of salts (**6**) [16] and (**8**) [15] have been reported (Schemes 4 and 5). The salt of (**6**) plays the major role and its nucleophilic attack on the C-atom of (**11z**) as an α,β-unsaturated C=O compound which afforded intermediate triethylammonium (4-bromo-3-(bromomethyl)-4-cyano-5-ethoxy-2-(ethoxy carbonyl)-5-oxo-3-alkyl-pent-1-en-1-ylidene)amide (**14z**). The (**11z**) can isomerize to (**12z**) and (**13z**). 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 3-alkyl-3-(bromomethyl)-1,2-dicyano cyclopropane-1,2-dicarboxylate (**5a–5n**) (scheme 3).

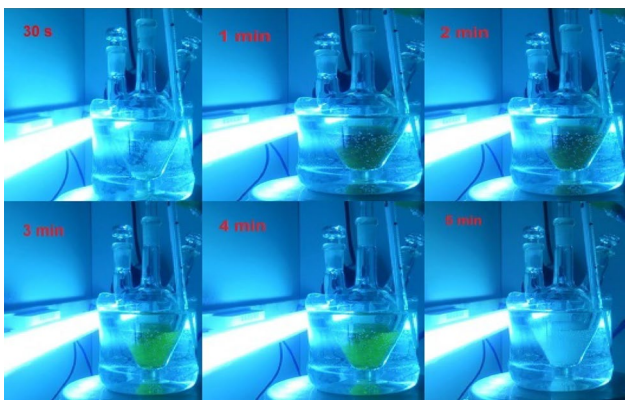


Fig. 1 Photograph representation of the reaction progress in the UV-cabinet

Unfortunately, all attempts failed to separate or characterize intermediates **3a, 3b, 4a** and **4b**, other evidence for the formation and confirmation of **6** (the existence of bromine atom in this salt structure) performed by Beilstein test and the wet silver nitrate test (precipitate of pale yellow silver bromide).

Representatively, the reaction mechanism for the formation of **5b** is shown in (scheme 3). First, the reaction of α-bromoketones with ethyl cyanoacetate **3** afforded the mixtures of two geometrical isomers (*E*) and (*Z*) ethyl 4-bromo-2-cyano-3-alkyl-but-2-enoate (**12b**) then nucleophilic attacking **6** to the β-carbon position of **12b** as an α,β-unsaturated carbonyl compound afforded intermediate triethylammonium diethyl-3-alkyl-2-bromo-3-(bromomethyl)-2,4-dicyano-3-pentane dioate-4-ide (**14b**) intermediate. Intramolecular C-attack of carbanion to carbon atom containing bromine atom (path a) as an electrophile pushing the bromide ion out produced diethyl-3-alkyl-3-bromomethyl-1,2-dicyano-3-phenyl cyclopropane-1,2-dicarboxylate (**5**). All attempts to separate and characterize the intermediates **12b** and **14b** failed. This observation that the C-attack of **6** to C-atom in the allyl position did not occur (path b).

As mentioned above, the reaction of **2** and **3** exclusively also obtained the mixtures of two geometrical (*E*)- and (*Z*)-isomers **12b** in the presence of triethylamine in absence of BrCN. It has been shown that the salt of **6** and **8** plays the major character in these reactions. First, it is a nucleophile in the reaction with **12b** then it has an electrophilic character (carbon atom containing bromine atom) in the intermediate **14b** to form **5b** (Scheme 6). On the other hand, the probable compounds (**13b**), (**15b**), (**19b**) and (**17b**) were not created through paths b, d, e, and f, respectively (Scheme 6). The reaction condition, time and yields are outlined in Tables 2 and 3.

We performed the reaction of **2** with ethyl cyanoacetate **3** in the presence of BrCN following Et_3N as a model reaction. The structure of **5b** characterized by IR, ^1H and ^{13}C NMR spectroscopy. The ^1H NMR spectrum of **5b** consists of a multiplet at δ 1.38, a doublet–doublet at δ 3.14, a quartet at δ 4.32 and a quartet at δ 4.51 ppm corresponding to aliphatic methyls, bromomethyl and methylene protons of **5b**. ^{13}C NMR spectrum of this compound shows eleven distinct peaks (Figs. 2, 3, respectively).

Representatively, in ^1H NMR spectrum (**5a**) with hydrogen in an axial position, show a doublet–doublet at *δ* 3.14 ppm, and bromine atoms are in the central place (Figs. 4, 5).

We also obtained the reaction of pentane-2,4-dione **1d** and 5,5-dimethyl cyclohexane-1,3-dione **1e** with **3** in the

Table 1 The structure of ketones and aldehydes **1**, brominated products **2** and reaction time

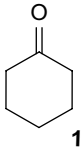
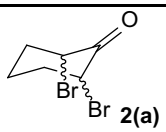
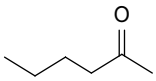
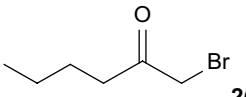
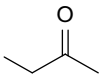
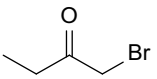
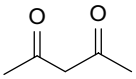
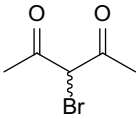
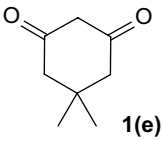
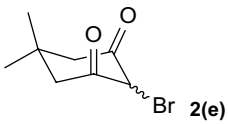
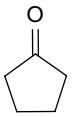
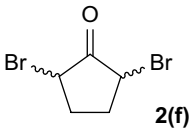
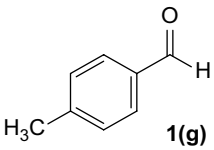
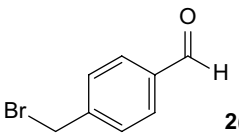
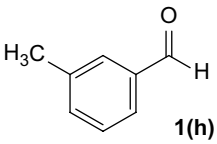
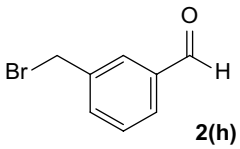
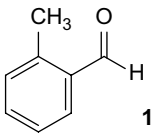
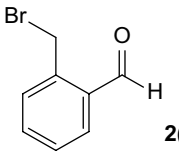
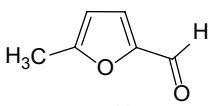
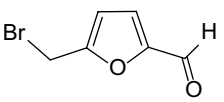
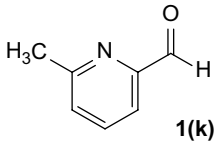
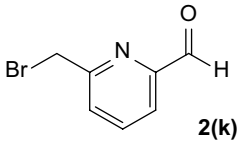
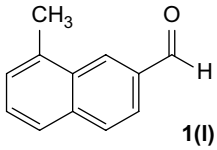
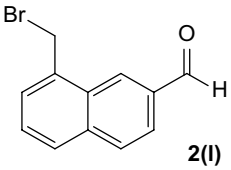
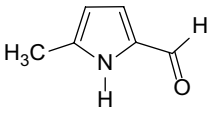
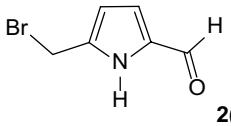
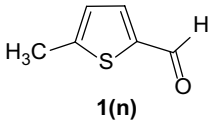
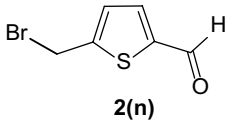
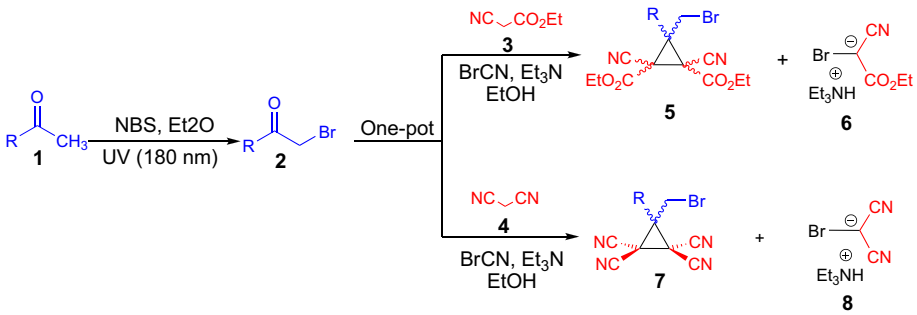
Entry	Substrate (**1**)	Product (**2**)	Time (min)
1	 **1(a)**	 **2(a)**	0.5
2	 **1(b)**	 **2(b)**	0.5
3	 **1(c)**	 **2(c)**	3
4	 **1(d)**	 **2(d)**	3
5	 **1(e)**	 **2(e)**	3
6	 **1(f)**	 **2(f)**	3
7	 **1(g)**	 **2(g)**	3
8	 **1(h)**	 **2(h)**	3
9	 **1(i)**	 **2(i)**	3
10	 **1(j)**	 **2(j)**	3

Table 1 (continued)

Entry	Substrate (**1**)	Product (**2**)	Time (min)
11	 **1(k)**	 **2(k)**	3
12	 **1(l)**	 **2(l)**	3
13	 **1(m)**	 **2(m)**	3
14	 **1(n)**	 **2(n)**	3



Scheme 1 Representatively, proposed afforded diethyl 3-alkyl/aryl-1,2-dicyano-3-(bromomethyl) cyclopropane-1,2-dicarboxylate **5** and 3-(4-(bromomethyl)alkyl/aryl)cyclopropane-1,1,2,2-tetracarbonitrile **7** under Et_3N in excellent yields with short reaction time

presence of BrCN and Et_3N (Scheme 7). In this feedback, the reaction of **1d** was comfortable, and the reaction of **1d** and **1e** with **3** and BrCN following Et_3N were furnished **5d** and **5e**, respectively (Figs. 6, 7, 8 and Scheme 8).

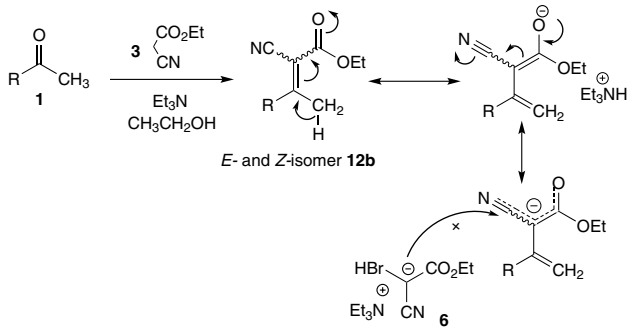
Conclusions

In conclusion, we have a reaction of α-bromo ketones with ethyl cyanoacetate and cyanogen bromide in essential media afforded stereoselectively diethyl 3-alkyl-1,2-dicyano- 3 (bromomethyl) cyclopropane-1,2-dicarboxylate in excellent yields and short reaction times. Some α-bromo ketones gave the cis and some others gave the trans cyclopropane stereoisomer. The aliphatic ketones with any bromide atom possessing strong electron donor and bulky hindered substituents exclusively afforded Knoevenagel adducts. We shall investigate this possibility and discuss our results in future communications. These observations were found in the results of ^1H and ^{13}C NMR spectroscopy analysis in detail.

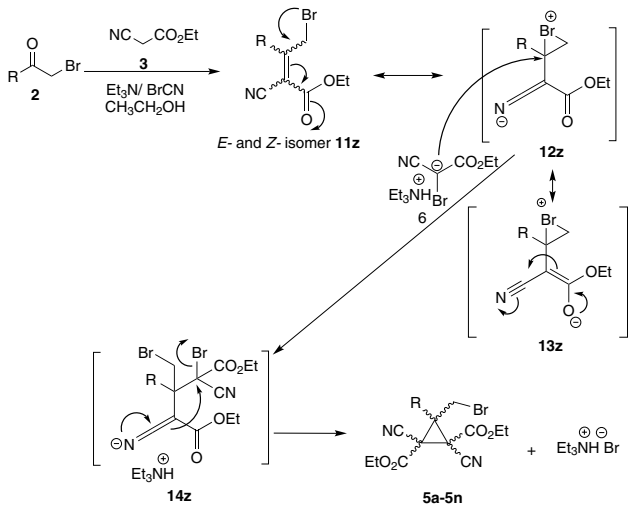
Experimental section

General

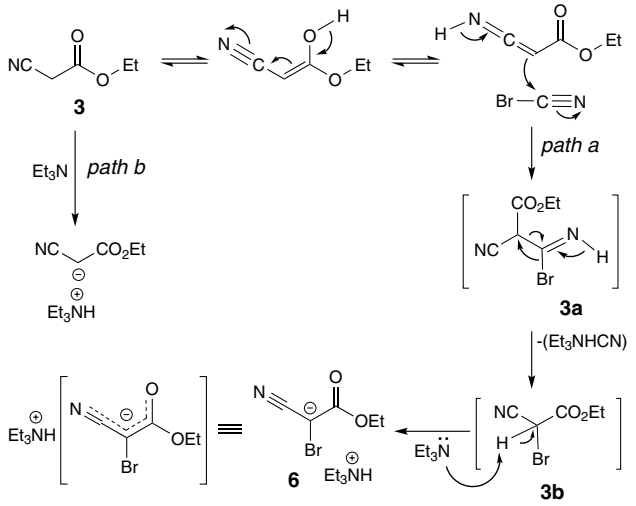
ChemDraw Ultra 8.0 version software was used for the drawing and nomenclature of compounds. Melting points were measured with a digital melting point apparatus (Electrothermal) and were uncorrected. IR spectra was determined in the region 4000–400 cm^{-1} on a NEXUS 670 FT-IR spectrometer by KBr pellets. The ^1H and ^{13}C NMR spectra was recorded on Bruker 300 FT-NMR at 300 and 75 MHz, respectively (Imam Khomeini International



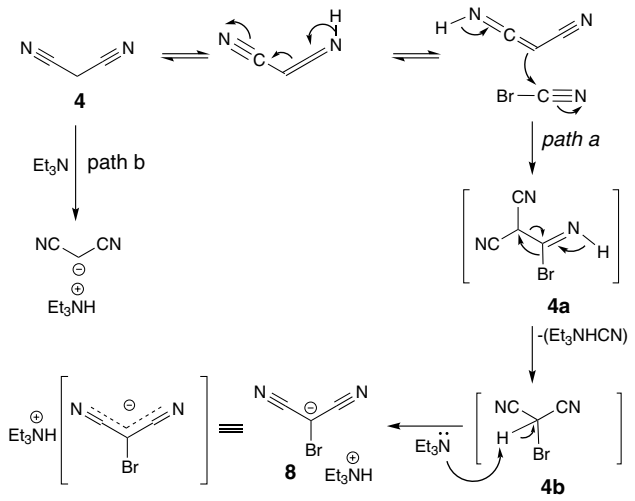
Scheme 2 Proposed mechanism for unfavored ketones without bromine



Scheme 3 Representatively, a proposed mechanism for the synthesis of **5a–5n** by the intermediate bromonium ring **12z–13z**



Scheme 4 Representatively, a proposed mechanism for the synthesis **6** [16]

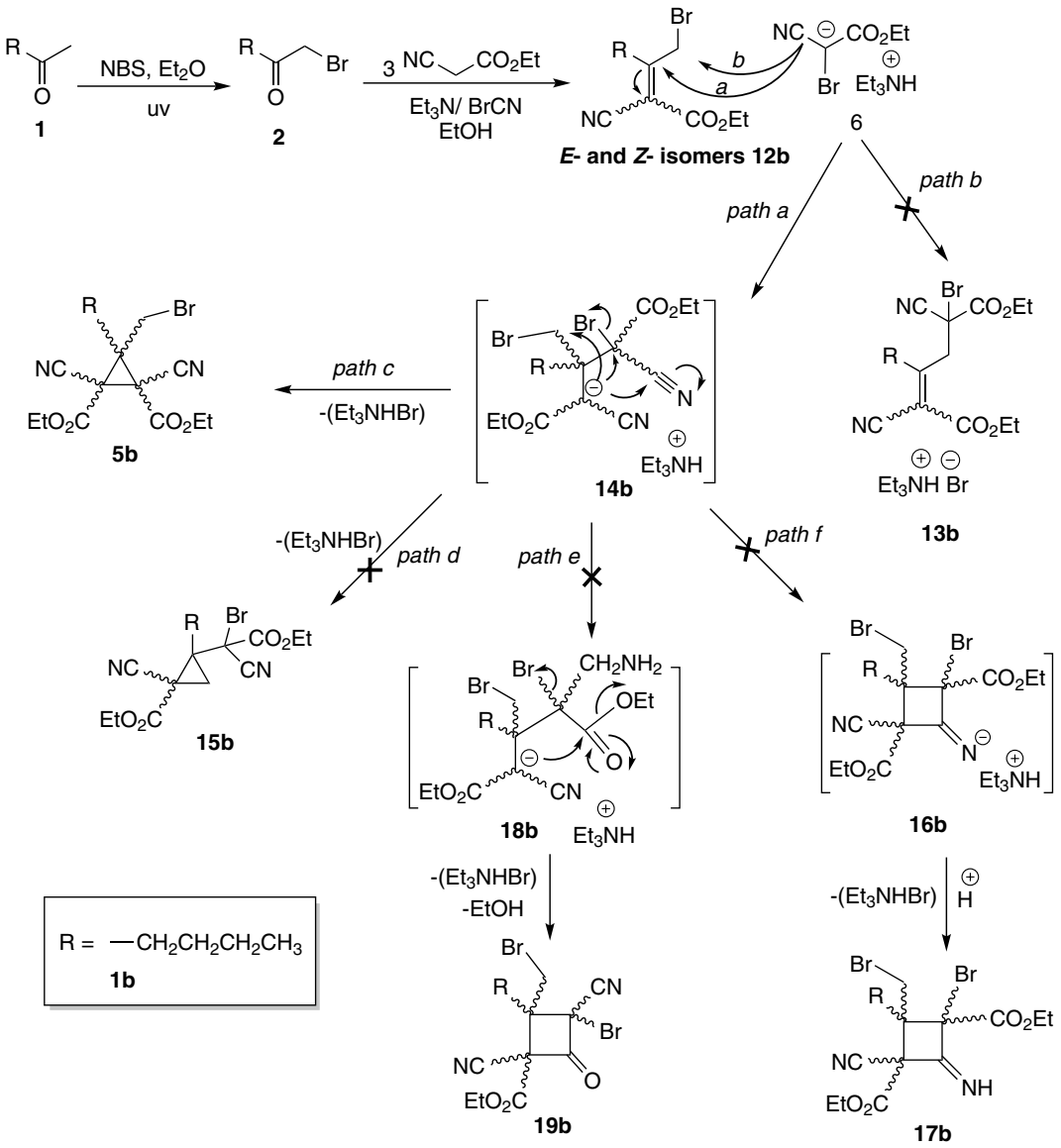


Scheme 5 Representatively, the proposed mechanism for the synthesis **8** [15]

University, Qazvin, Iran). ^{1}H and ^{13}C-NMR spectra were obtained on a solution in DMSO-d_6 and/or $CDCl_3$ as solvent using TMS as an 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 ^{1}H and ^{13}C-NMR spectra were opened and analyzed via MestReC software from original spectra files. TLC monitored all reactions 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). Cyanogen bromide was synthesized based on reported references [21]. Compounds (**1**), all ketones, all Aldehydes, triethylamine and used solvents were purchased from Merck and Aldrich without further purification.

General procedure for the synthesis of α-bromo ketones and 4-(bromomethyl)benzaldehyde

A mixture of the ketone(1 mmol) and NBS (1.0–1.5 mmol) was stirred under a nitrogen atmosphere in 5 ml of diethyl ether in one necked round bottom flask under a Philips HPL-N (250 W, k = 200–600 nm) lamp fitted with a water circulation arrangement at room temperature (30 ± 2 °C). To achieve the best yield of the product, NBS was added in four portions, each portion containing 0.25 equiv. The reaction product was filtered, diluted with diethyl ether and washed with water. The organic layer was separated and dried over sodium sulfate. The product was analyzed by GC (HP 5890) using a capillary column (HP-5). GC mass spectra



Scheme 6 Representatively, the proposed mechanism for the synthesis of **5b** (paths a–c) and others unflavored paths

were taken on a Shimadzu GC–MS–QP5050A spectrometer equipped with a DB-5 column to identify the products [20].

General procedure for the synthesis of diethyl 3-(bromomethyl)-3-butyl-1,2-dicyanocyclopropane-1,2-dicarboxylate

In a 10 mL Teflon-faced screw cap tube was equipped with a magnetic stirrer and an ice bath, dissolved 1-bromohexan-2-one (1.0 mmol), ethyl cyanoacetate (2.0 mmol) in 5 ml EtOH added the appropriate base (1.33 mmol) 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 3 s, after about 2 min it was filtered off washed with cold EtOH (3 × 3 mL), recrystallized in minimum hot EtOH, filtered off and dried as a colorless crystalline solid (0.305 g, 100% yield).

General procedure for the synthesis of 3-(4-(bromomethyl)phenyl)cyclopropane-1,1,2,2-tetracarbonitrile

In a 10 mL Teflon-faced screw cap tube equipped with a magnetic stirrer and an ice bath, dissolved 4-(bromomethyl)benzaldehyde (1.0 mmol), malononitrile (2.0 mmol) in 5 ml EtOH added the appropriate base (1.33 mmol) and then (1.2 mmol) cyanogen bromide was added to the solution

Table 2 The structure of α-bromomethyl ketones and aldehydes **2** in the reaction with **3** obtained products **5**, used base and reaction time and yields

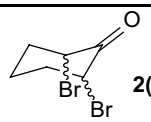
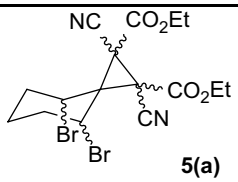
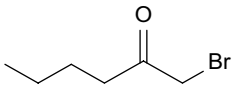
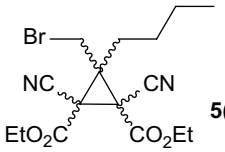
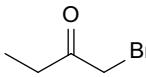
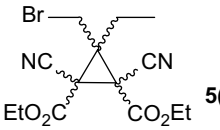
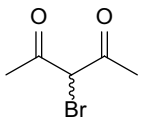
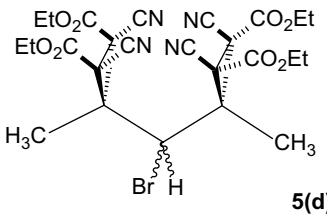
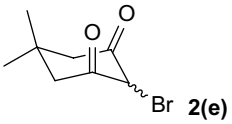
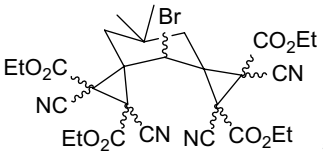
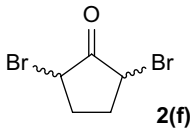
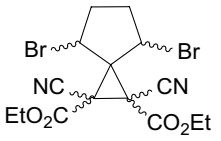
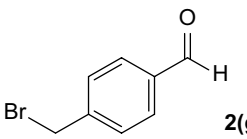
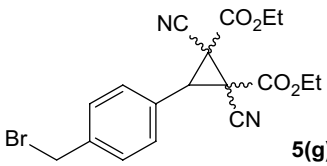
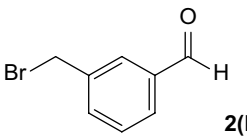
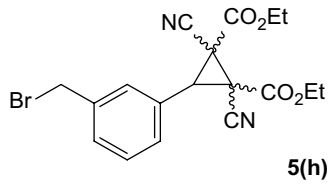
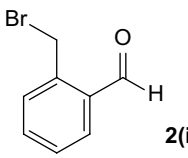
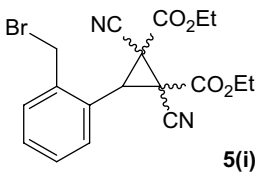
Entry	Substrate (**2**)	Product (**5**)	Base (mmol)	Reaction time (sec),Yield (%)
1	 **2(a)**	 **5(a)**	Et_3N (1.33)	5, 100
2	 **2(b)**	 **5(b)**	Et_3N (1.33)	5, 100
3	 **2(c)**	 **5(c)**	Et_3N (1.33)	5, 100
4	 **2(d)**	 **5(d)**	Et_3N (1.33)	5, 100
5	 **2(e)**	 **5(e)**	Et_3N (1.33)	5, 100
6	 **2(f)**	 **5(f)**	Et_3N (1.33)	5, 100
7	 **2(g)**	 **5(g)**	Et_3N (1.33)	5, 80
8	 **2(h)**	 **5(h)**	Et_3N (1.33)	5, 100
9	 **2(i)**	 **5(i)**	Et_3N (1.33)	5, 100

Table 2 (continued)

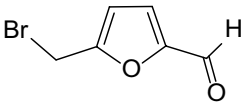
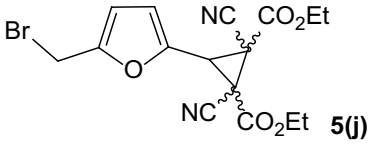
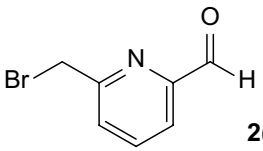
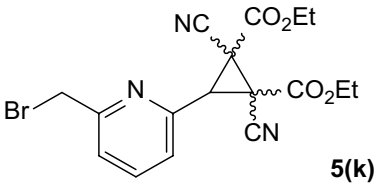
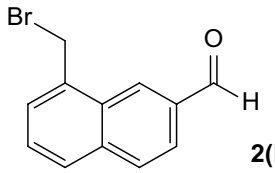
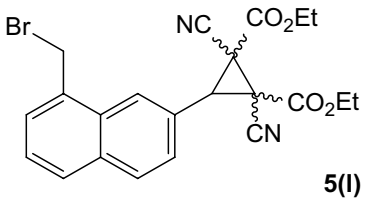
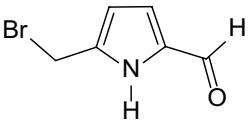
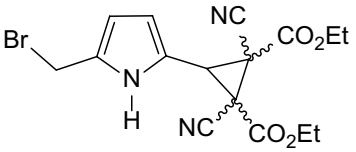
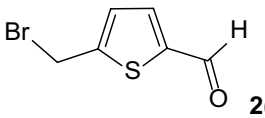
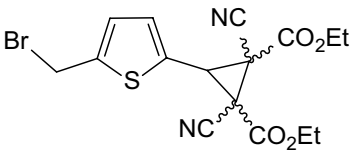
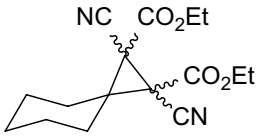
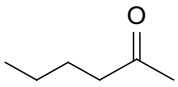
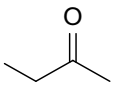
Entry	Substrate (**2**)	Product (**5**)	Base (mmol)	Reaction time (sec),Yield (%)
10	 **2(j)**	 **5(j)**	Et_3N (1.33)	5, 100
11	 **2(k)**	 **5(k)**	Et_3N (1.33)	5, 100
12	 **2(l)**	 **5(l)**	Et_3N (1.33)	5, 100
13	 **2(m)**	 **5(m)**	Et_3N (1.33)	5, 100
14	 **2(n)**	 **5(n)**	Et_3N (1.33)	5, 100
15	 **1(a)**	 **5(a)**	Et_3N (1.33)	5, 100
16	 **1(b)**	N.R		
17	 **1(c)**	N.R		

Table 3 The structure of α-bromomethyl ketones and aldehydes **2** in the reaction with **4** obtained products **7**, used base and reaction time and yields

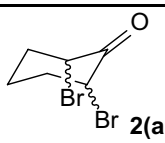
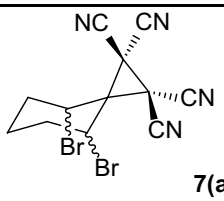
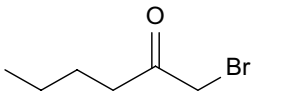
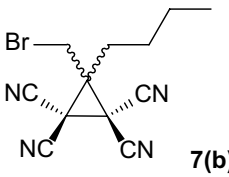
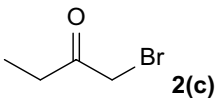
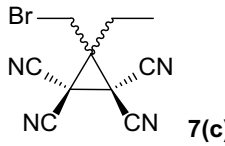
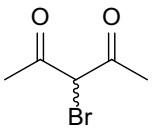
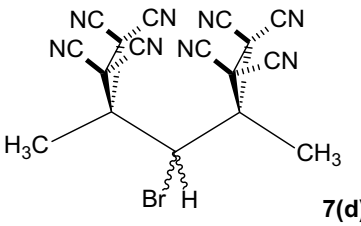
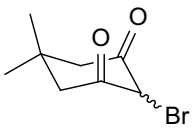
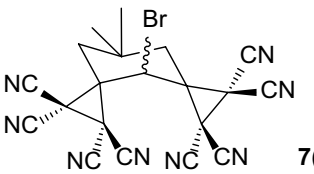
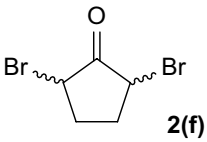
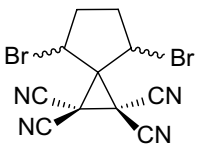
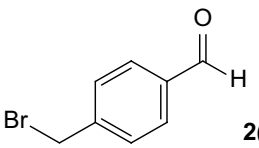
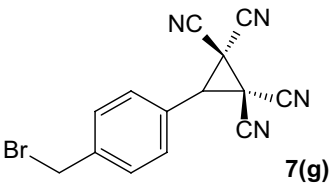
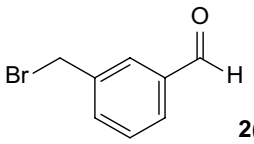
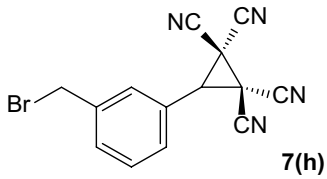
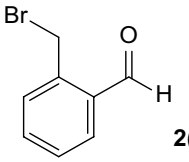
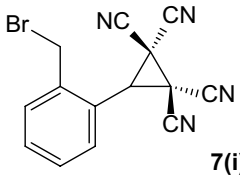
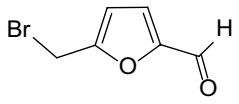
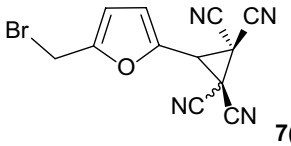
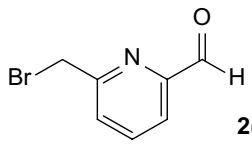
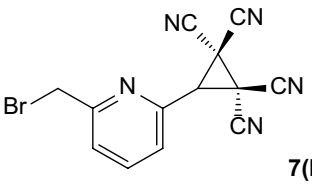
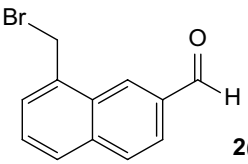
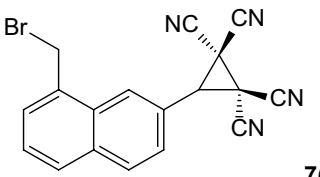
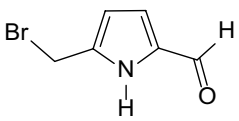
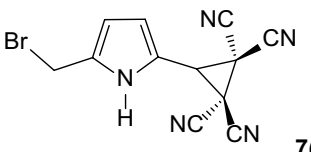
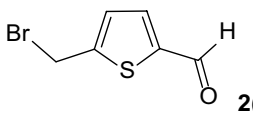
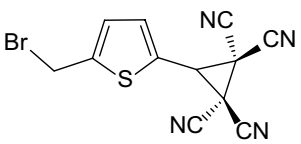
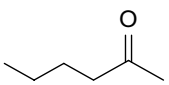
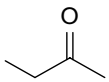
Entry	Substrate (**2**)	Product (**7**)	Base (mmol)	Reaction time (sec.),Yield (%)a
1	 **2(a)**	 **7(a)**	Et_3N (1.33)	5, 100
2	 **2(b)**	 **7(b)**	Et_3N (1.33)	5, 100
3	 **2(c)**	 **7(c)**	Et_3N (1.33)	5, 100
4	 **2(d)**	 **7(d)**	Et_3N (1.33)	5, 100
5	 **2(e)**	 **7(e)**	Et_3N (1.33)	5, 100
6	 **2(f)**	 **7(f)**	Et_3N (1.33)	5, 100
7	 **2(g)**	 **7(g)**	Et_3N (1.33)	5, 100

Table 3 (continued)

Entry	Substrate (**2**)	Product (**7**)	Base (mmol)	Reaction time (sec.),Yield (%)a
8	 **2(h)**	 **7(h)**	Et_3N (1.33)	5, 100
9	 **2(i)**	 **7(i)**	Et_3N (1.33)	5, 100
10	 **2(j)**	 **7(j)**	Et_3N (1.33)	5, 100
11	 **2(k)**	 **7(k)**	Et_3N (1.33)	5, 100
12	 **2(l)**	 **7(l)**	Et_3N (1.33)	5, 100
13	 **2(m)**	 **7(m)**	Et_3N (1.33)	5, 100
14	 **2(n)**	 **7(n)**	Et_3N (1.33)	5, 100
15	 **1(b)**	N.R		
16		N.R		
17	 **1(c)**	N.R		

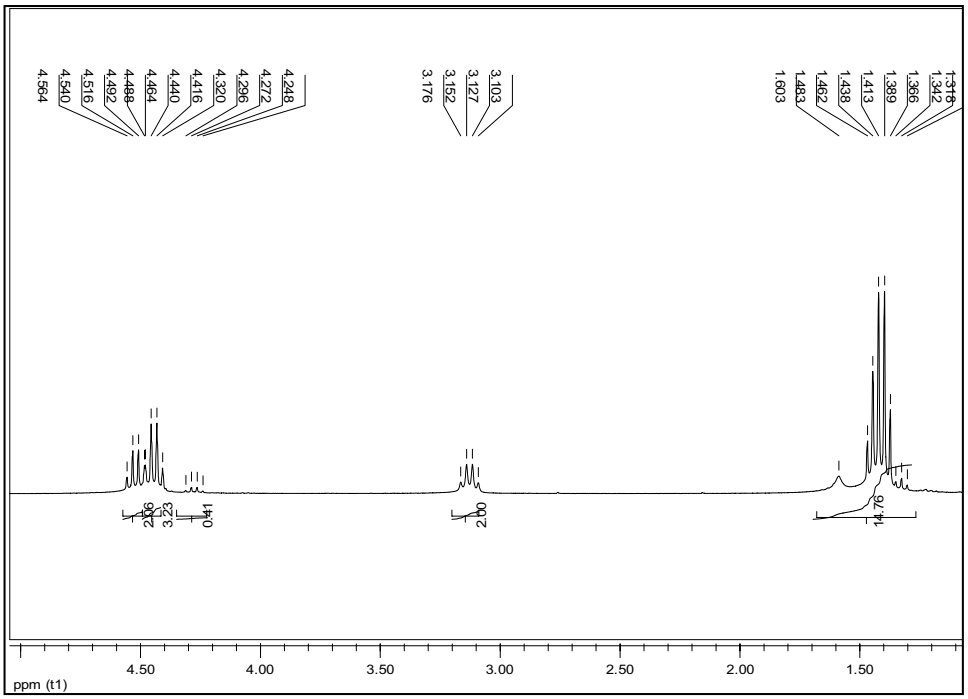


Fig. 2 ^{1}H NMR spectrum of **5b** in $CDCl_3$

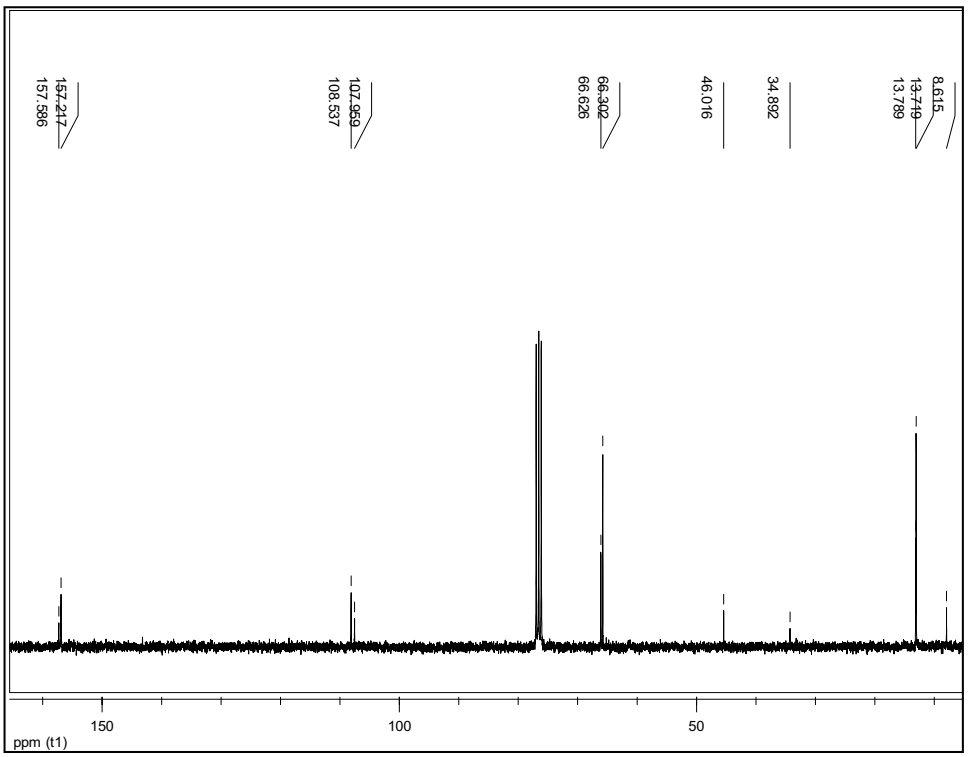


Fig. 3 ^{13}C NMR spectrum of **5b** in $CDCl_3$

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 3 s, after about 2 min it was filtered off, washed with cold EtOH (3 × 3 mL), recrystallized in minimum hot EtOH, filtered off and dried as a colorless crystalline solid (0.320 g, 100% yield).

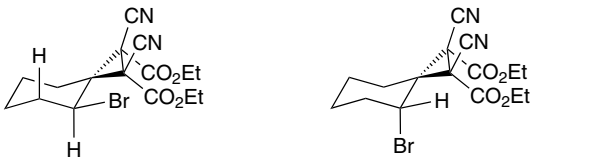


Fig. 4 Possible stereo structures of **5a** and **5a′**

Triethylammonium bromo dicyanomethanide (8)

White crystalline solid. m.p. 240–242 °C. IR (KBr, cm^{-1}): 3446, 2943, 2738, 2677, 2491, 2166, 1475, 1397, 1036. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 1.22$ (t, $J = 6$ Hz, 9H), 3.00 (m, 6H), 3.77 (s, 1H), 9.03 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = 110.1$, 46.7, 9.3, 8.7.

Triethylammonium 1-bromo-1-cyano-2-ethoxy-2-oxoethan-1-ide (6)

Orange crystalline solid. m.p. 280–282 °C. IR (KBr, cm^{-1}): 3739, 3425, 2983, 2212, 1680, 1506, 1256, 1138, 1025, 685, 571, 444.^{1}H NMR (300 MHz, (DMSO-d_6, ppm) δ 1.25–1.30 (m, 12H), 4.22–4.25 (m, 8H), 8.36 (s, 1H).^{13}C NMR (75 MHz, (DMSO-d_6, ppm): $\delta = 141.2$, 128.8, 117.5, 61.4, 59.3, 14.4, 14.1.

1,2-Di cyano-1,2-di(ethyl carboxylate) spairo(2–5) octane-2,7 di bromine (5a)

Colorless crystalline solid. m.p. 123 °C, IR (KBr, cm^{-1}): 2996, 2987, 2358, 1765, 1273, 1019, 857, 616.^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 1.42$ (m, $J = 5.1$ Hz, $J = 2.1$ Hz, 12H), 3.14 (dd, $J = 4.8$ Hz, 2H), 4.44 (dq, $J = 7.2$ Hz, $J = 1.2$ Hz, 2H), 4.52 (q, $J = 7.2$ Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = 157.59$, 157.2, 108.53, 107.95, 66.63, 66.31, 62.07, 46.1, 34.89, 14.11, 13.79, 13.72, 8.64.

Diethyl 3-(bromomethyl)-3-butyl-1,2-dicyanocyclopropane-1,2-dicarboxylate (5b)

Colorless crystalline solid. m.p. 118 °C, IR (KBr, cm^{-1}): 2996, 2989, 2359, 1765, 1469, 1274, 1019, 858, 614.^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 1.42$ (m, $J = 7.2$ Hz, 12H), 3.13 (dd, $J = 7.2$ Hz, 2H), 4.4 (q, $J = 7.2$ Hz, 2H), 4.52 (q, $J = 7.2$ Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = 157.8$, 157.5, 108.5, 107.95, 66.62, 66.3, 46.1, 34.89, 13.78, 13.71, 8.61.

Bromo bis(diethyl 1,2-dicyano-3-methyl cyclopropane-1,2-dicarboxylate) methane (5d)

Colorless crystalline solid. m.p. 122 °C, FT-IR (KBr, cm^{-1}): 2996, 2886, 2357, 1765, 1470, 1372, 1274, 1178, 1114, 1019, 858, 685, 616, 514, 419. ^{1}H NMR (300 MHz,

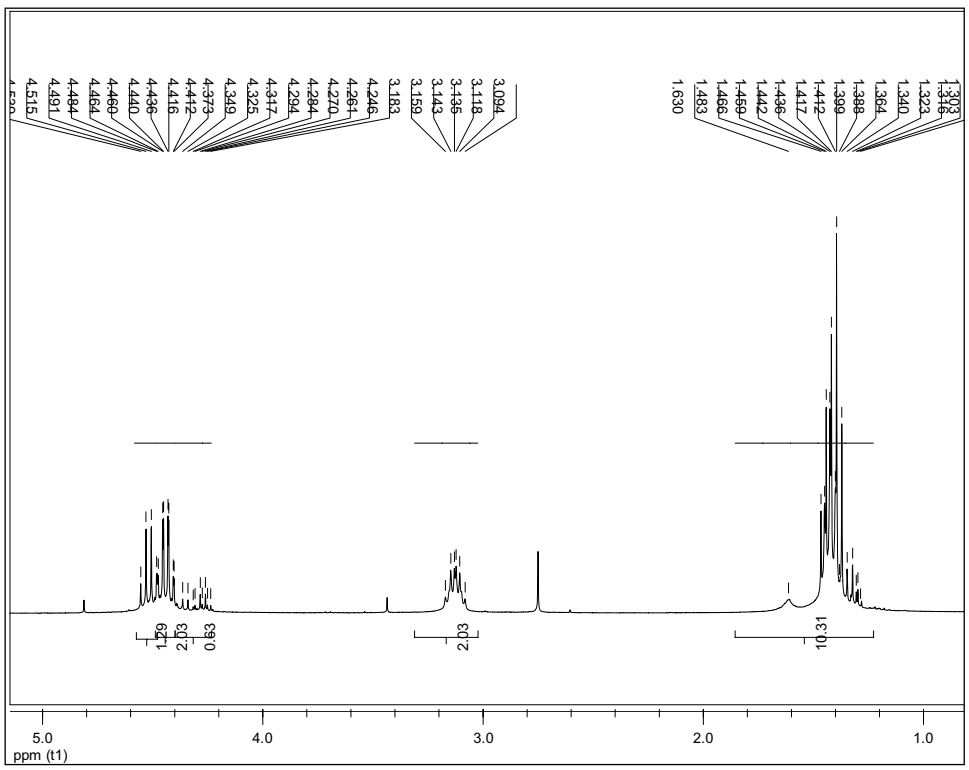


Fig. 5 Representatively, ^{1}H NMR spectrum **5a** with the hydrogen atom in axial position and for more information see supplementary data

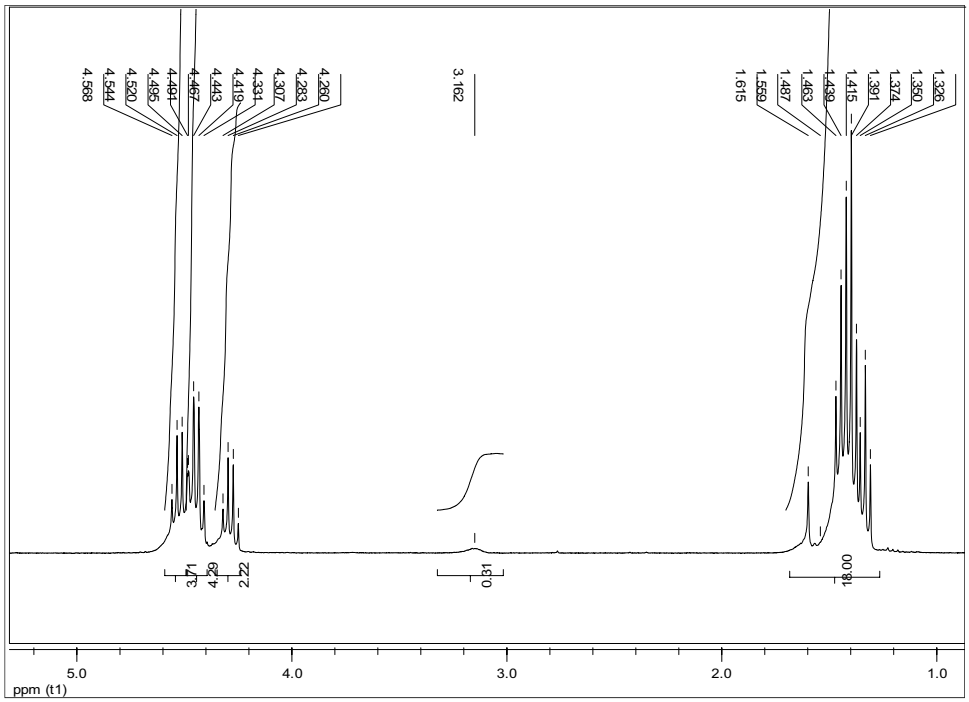


Fig. 6 ^{1}H NMR spectrum of **5d** in $CDCl_3$

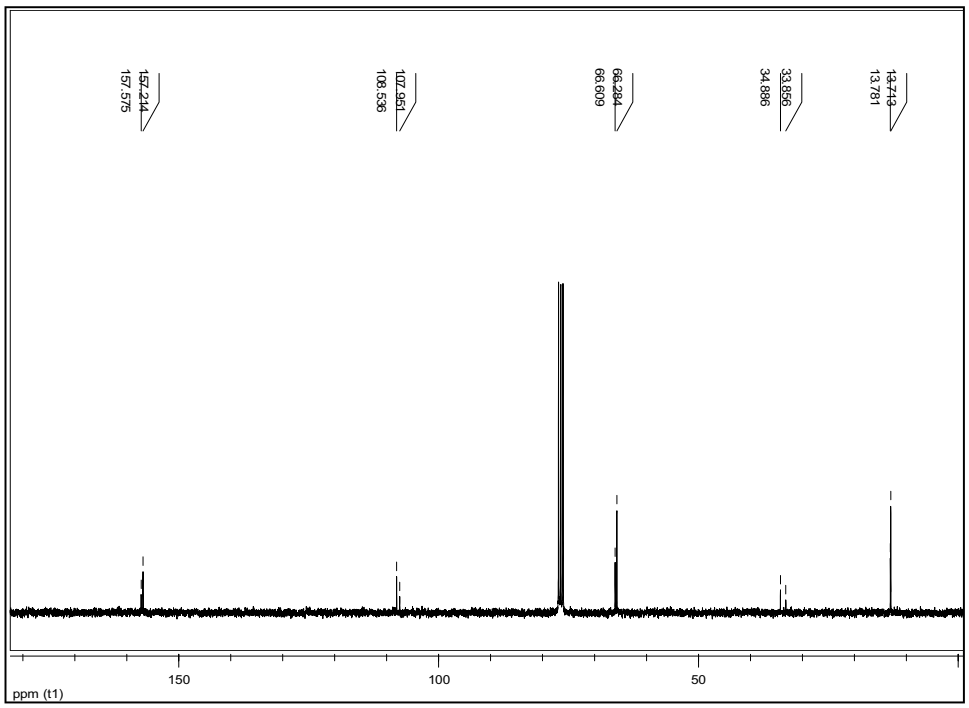


Fig. 7 ^{13}C NMR spectrum of **5d** in $CDCl_3$

$CDCl_3$, ppm): $\delta = 1.4$ (m, $J = 7.2$ Hz,18H), 3.16 (S, 1H), 4.2 (q, $J = 7.2$ Hz, 2H), 4.25 (q, $J = 7.2$ Hz, 4H), 4.5 (m, 4H, $J = 7.2$ Hz).^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = 157.6$, 157.2, 108.5, 108, 66.6, 66.2, 34.9, 33.9, 13.8, 13.7.

4-Bromo 1,2,6,7 tetra cyano 1,2,6,7-tetra ethyl carboxylate-9-di methyl di spiro(2,1,2,3) decane (5e)

Colorless crystalline solid. m.p. 120 °C, IR (KBr, cm^{-1}): 2996, 2886, 2355, 1765, 1699, 1640, 1272, 1114, 1019, 859, 675, 613, 518. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 1.42$ (m, $J = 7.2$ Hz, 18H), 3.14 (dq, $J = 4.8$ Hz, $J = 2.4$ Hz,.1H),

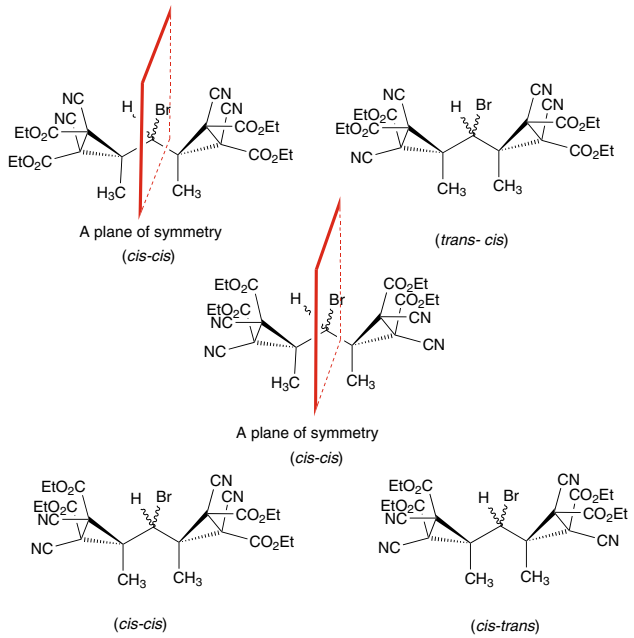


Fig. 8 Possible favored and unfavored forms of **5d** and a plane of symmetry

4.45 (dq, $J=7.2$ Hz, $J=0.6$ Hz, 4H) 4.53 (q, $J=7.2$ Hz, 4H).^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta=157.5$, 157.2, 108.5, 108.1, 107.9, 66.6, 66.2, 34.8, 33.8, 13.8, 13.7.

Diethyl 3-(4-(bromomethyl)phenyl)-1,2-dicyanocyclopropane-1,2-dicarboxylate (5 g)

Colorless crystalline solid. m.p. 122 °C, IR (KBr, cm^{-1}): 2998, 2880, 2355, 1765, 1465, 1272, 1019, 869. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta=1.42$ (m, $J=7.2$ Hz, 6H), 2.1 (s, 1H), 4.19 (q, $J=7.2$ Hz, 2H), 4.27 (q, $J=7.2$ Hz, 2H), 6.6 (s 1H), 6.95(d, $J=8.1$ Hz, 2H), 7.15 (d, $J=8.1$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta=157.5$, 157.2, 129.4, 127.7, 108.5, 108.1, 107.9, 77.4, 77, 76.6, 66.6, 66.2, 34.89, 33.85, 21.52, 13.75, 13.71.

3-(4-(Bromomethyl)phenyl)cyclopropane-1,1,2,2-tetracarbonitrile (7g)

Colorless crystalline solid. m.p. 136 °C, IR (KBr, cm^{-1}): 3004, 2987, 2354, 1519, 1482, 1020, 666. ^{1}H NMR (300 MHz, (DMSO-d_6, ppm): $\delta=2$ (s, 1H), 2.1 (s, 1H), 4.96 (s, 1H), 7.03 (d, $J=8.1$, 2H), 7.41(d, $J=8$, 12H).^{13}C NMR (75 MHz, (DMSO-d_6, ppm): $\delta=140.1$, 129.9, 122.8, 124.3, 111.4, 109.9, 42, 23.6, 21.2.

3-(3-(Bromomethyl)phenyl)cyclopropane-1,1,2,2-tetracarbonitrile (7h)

Colorless crystalline solid. m.p. 138 °C, IR (KBr, cm^{-1}): 3004, 2928, 2355, 2253, 1628, 1514, 1412, 1186, 1127, 767. ^{1}H NMR (300 MHz, (DMSO-d_6, ppm): $\delta=2.24$ (s, 1H), 2.27 (s, 1H), 4.99 (s, 1H), 7 (t, $J=7.8$, 1H), 7.1 (t, $J=7.8$, 1H).7.33 (t, $J=7.33$, 2H). ^{13}C NMR (75 MHz, (DMSO-d_6, ppm): $\delta=138.8$, 131, 130.4, 129.3, 127.2, 126.9, 111.4, 109.8, 42.2, 23.5, 21.2.

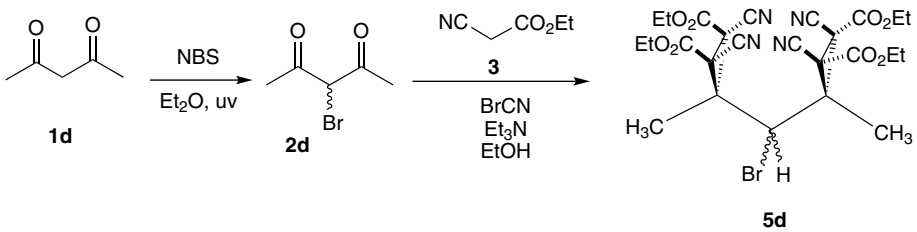
3-(5-(bromomethyl)furan-2-yl)cyclopropane-1,1,2,2-tetracarbonitrile (7j)

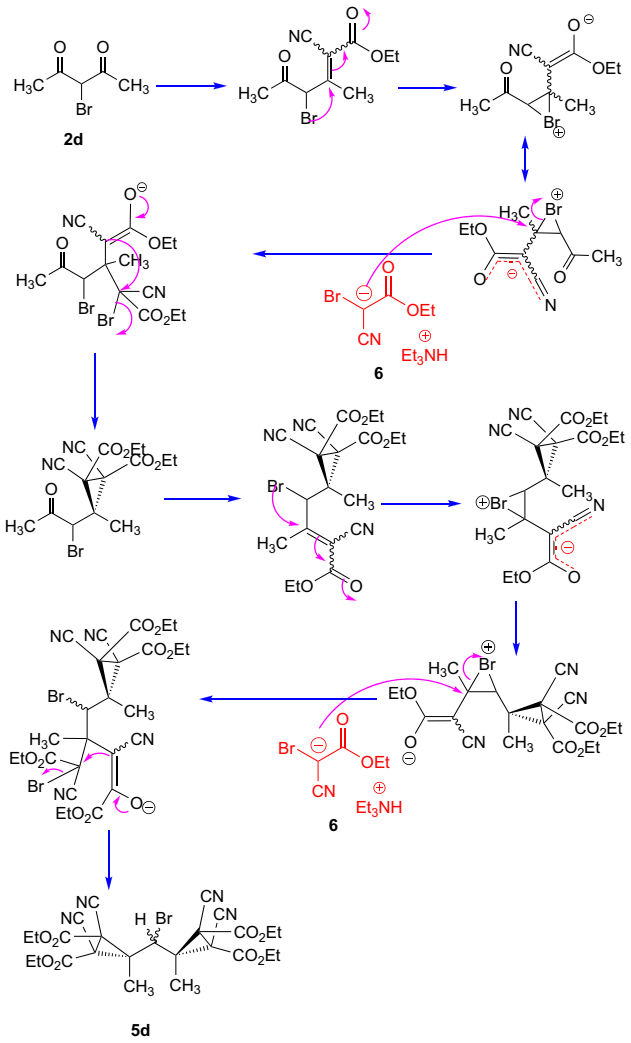
Colorless crystalline solid. m.p. 128 °C, IR (KBr, cm^{-1}): 2925, 2352, 1620, 1456, 1369, 1271, 1175, 1109, 993, 799, 604. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta=2.37$ (s, 2H), 2.04 (s, 1H), 3.74 (s, 1H), 6.62 (d, $J=3.3$ Hz,1H),.5.92(d, $J=3.3$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta=157.1$, 134.7, 115, 108.5, 108.1, 106.7, 37.6, 20.1, 13.6.

Diethyl 1,2-dicyanospiro[2.5]octane-1,2-dicarboxylate (5a)

Colorless crystalline solid. m.p. 105 °C, IR (KBr, cm^{-1}): 2995, 2358, 1764, 1629, 1471, 1369, 1276, 1170, 1021, 859, 615. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta=1.44$ (m, $J=6.9$ Hz,16H), 4.45 (dq, $J=7.2$ Hz, $J=0.9$ Hz, 4H), 4.53 (q, $J=7.2$ Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta=157.52$, 157.5, 108.5, 107.9, 66.6, 66.3, 36.3, 34.9, 23.4, 22.5, 13.8, 13.72.

Scheme 7 Representatively, the reaction of **1d** with NBS then followed by the reaction with **3** and BrCN in the presence of Et_3N





Scheme 8 Representatively, the proposed mechanism for the synthesis of **5d**

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