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A new type of cascade reaction: direct conversion of carbonyl compounds and malononitrile into substituted tetracyanocyclopropanes

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ABSTRACT

A new type of chemical cascade reaction was found: the direct formation of cyclopropanes from carbonyl compounds and C–H acid. The action of free halogen or active halogen containing compounds on a mixture of 1 equiv of carbonyl compound and 2 equiv of malononitrile in a basic alcohol solution results in the formation of substituted 1,1,2,2-tetracyanocyclopropanes in 15–80% yield. The latter are well-known precursors for the different bicyclic heterosystems, among them compounds containing a cyclopropane ring and possessing different types of pharmacological activity. Thus, the new, simple and efficient 'one-pot' way to substituted tetracyanocyclopropanes in 50–80% yield was found directly from such simple and reasonable starting compounds as aldehydes, or some cyclic ketones, or substituted cyclohexanones and malononitrile.

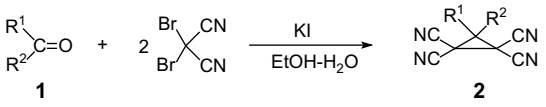
1. Introduction

The discovery of new synthetic methodologies to facilitate the preparation of organic compounds is a pivotal focal point of research activity in the field of modern organic, bioorganic and medicinal chemistry.[1]

The cyclopropyl group is a vital structural unit in many synthetic and naturally occurring compounds, exhibiting a wide spectrum of biologic properties ranging from enzyme inhibition to herbicidal, antibiotic, antitumour and antiviral activities.[2–4] Thus, the prevalence of cyclopropane containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis.

Though methods of cyclopropane synthesis have long been documented, so far, all of them consist of two main groups: (1) intramolecular cyclization or (2) interaction of two different molecules (addition of carbenes to olefins or Michael initiated ring closure (MIRC) are the most known examples of this type).[2,4]

Nevertheless there are some special famous methods of cyclopropane ring construction. One of them is well-known Wideqvist reaction, namely the interaction of two molecules of bromomalononitrile with carbonyl compounds **1** in the presence of a stoichiometric quantity of potassium iodide with the formation of the corresponding substituted tetracyanocyclopropanes **2** (Scheme 1).[5]



Scheme 1.

Later, in the electrochemical variant of Wideqvist reaction, bromomalononitrile was replaced by malononitrile and a catalytic amount of sodium bromide.[6,7] In the electrochemical variant for the reaction of aldehydes a low temperature (0 °C) is necessary;[7] whereas for ketones a three- to four-fold excess of ketone is needed to obtain tetracyanocyclopropanes **2** in good yields.[6,7] Additionally, in the case of cyclohexanone, the electrochemical process cannot be stopped on the formation of the corresponding tetracyanocyclopropane; co-electrolysis of cyclohexanone and malononitrile in ethanol in the presence of sodium bromide under these conditions furnishes 2-amino-1,5-dicyano-4,4-diethoxy-6,6-pentamethylene-3-azabicyclo[3.1.0]-hex-2-ene in 62% yield (Scheme 2).[6]

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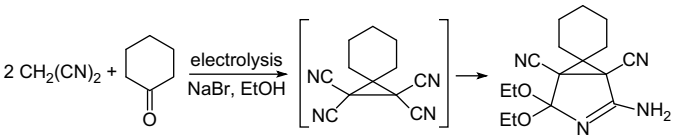
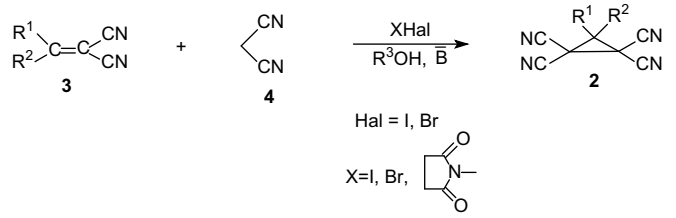


Scheme 2.

Recently we suggested a new strategy of chemical route to the cyclopropane structure: the direct transformation of benzylidenemalononitriles **3** and malononitrile **4** into 1,1,2,2-tetracyanocyclopropanes **2** (Scheme 3).[8]



Scheme 3.

Cascade reactions have been utilized as powerful method to construct molecular complexity from readily available starting materials by combining two or more reactions into a single transformation.[9] As such, cascade reactions are of increasing importance in modern organic chemistry. This is not only due to the need for the more efficient and less labour-intense methodologies for the synthesis of organic compounds, but also a consequence of the increasing importance of the environmental considerations in chemistry. Thus, cascade reactions have significant economical and ecological benefits when one performs several synthetic steps in one operation without isolating the reaction intermediates. From this point of view the best route to the substituted 1,1,2,2-tetracyanocyclopropanes **2** could be the 'one-pot' chemical cascade process starting directly from carbonyl compounds and malononitrile.

2. Results and discussion

In the present study we report our results on the direct 'one-pot' cascade transformation of carbonyl compounds and malononitrile into the substituted 1,1,2,2-tetracyanocyclopropanes **2** (Scheme 4).

First, to evaluate the synthetic potential of the proposed procedure and to optimize the general conditions, the cascade transformation of benzaldehyde **1a**, and malononitrile **4** into the corresponding 3-phenyl-1,1,2,2-tetracyanocyclopropanes **2a** was studied (Table 1).

Excellent conversions of starting compounds were obtained under all conditions studied. The best yield of cyclopropane **2a** (75%) was achieved when the reaction was carried out in ethanol by the action of bromine in the presence of 1 equiv of EtONa (entry 10, Table 1). The second step was devoted to the careful evaluation of EtONa quantity needed for the reaction (Table 2).

The best yield of cyclopropane **2a** (83%) was obtained when 1.2 equiv of EtONa was used (entry 3, Table 2). The increase of EtONa quantity beyond 1.2 equiv (entries 4 and 5, Table 2) resulted in a sufficient decrease of the reaction yield, that may be connected with the activation of undesired base induced oligomerization processes of malononitrile.[10]

Under the optimal conditions thus found, i.e., bromine as active halogen compound, 1.2 equiv of EtONa as base, and ethanol as solvent, the substituted carbonyl compounds **1a–o** and malononitrile **4** were transformed into corresponding substituted 1,1,2,2-tetracyanocyclopropanes **2a–o** in 61–83% yields (Table 3).

In the case of aldehydes **1d** and **1i** (entries 4 and 9, Table 3) the quantity of EtOH was increased up to 40 mL because of the lower

Table 1
Cascade transformation of benzaldehyde **1a** and malononitrile **4** into 3-phenyl-1,1,2,2-tetracyanocyclopropane **2a**[a]

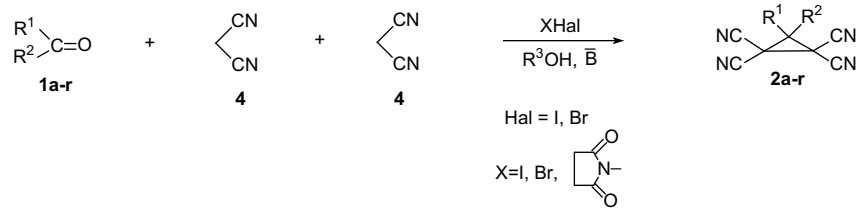
Entry	Alcohol	XHal	Base	Yield of **2a**[b] (%)
1	MeOH	I_2	NaOH	25
2	MeOH	I_2	KOH	31
3	EtOH	I_2	KOH	38
4	EtOH	I_2	NaOEt	45
5	MeOH	NBS	KOH	32
6	EtOH	NBS	KOH	43
7	EtOH	NBS	NaOEt	56
8	MeOH	Br_2	KOH	39
9	EtOH	Br_2	KOH	62
10	EtOH	Br_2	EtONa	75

[a] Benzaldehyde **1a** (10 mmol), 20 mmol of malononitrile **4**, 10 mmol of halogen or NBS, 10 mmol of base, 20 mL of alcohol, time of the reaction—3 h.
[b] Isolated yield (isolated by filtration of the reaction mixture).

Table 2
Influence of EtONa quantity on the 3-phenyl-1,1,2,2-tetracyanocyclopropane **2a** yield[a]

Entry	Quantity of EtONa (equiv)	Yield of **2a**[b] (%)
1	0.5	55
2	1.0	75
3	1.2	83
4	1.5	57
5	2.0	32

[a] Benzaldehyde **1a** (10 mmol), 20 mmol of malononitrile **4**, 10 mmol of bromine, 20 mL of alcohol, time of the reaction—3 h.
[b] Isolated yield (isolated by filtration of the reaction mixture).



a R^1 = H, R^2 = Ph; **b** R^1 = H, R^2 = 4-MeC_6H_4; **c** R^1 = H, R^2 = 4-$MeOC_6H_4$; **d** R^1 = H, R^2 = 2-$MeOC_6H_4$;

e R^1 = H, R^2 = 4-FC_6H_4; **f** R^1 = H, R^2 = 2-ClC_6H_4; **g** R^1 = H, R^2 = 3-ClC_6H_4; **h** R^1 = H, R^2 = 4-ClC_6H_4;

i R^1 = H, R^2 = 2,4-$Cl_2C_6H_3$; **j** R^1 = H, R^2 = 3-BrC_6H_4; **k** R^1 = H, R^2 = 3-$NO_2C_6H_4$; **l** R^1 = H, R^2 = 4-$NO_2C_6H_4$;

m R^1 = H, R^2 = naphth-1-yl; **n** R^1 = H, R^2 = Et; **o** R^1 = H, R^2 = *n*-Pr; **p** R^1 = Me, R^2 = Me; **q** R^1 = Me, R^2 = Et;

r R^1 = Et, R^2 = Et

Scheme 4.