

One-pot cascade assembling of 3-substituted tetracyanocyclopropanes from alkylidenemalononitriles and malononitrile by the only bromine direct action

Anatolii N. Vereshchagin,* Michail N. Elinson,* Nikita O. Stepanov and Gennady I. Nikishin

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation.
Fax: + 7 499 135 5328; e-mail elinson@ioc.ac.ru*

DOI: 10.1016/j.mencom.2009.11.010

The new cascade reaction was found: the formation of cyclopropanes from alkylidenemalononitriles and malononitrile by the only bromine direct action; the action of aqueous bromine on the equal amounts of alkylidenemalononitriles and malononitrile in EtOH–H₂O solutions results in the formation of 3-substituted 1,1,2,2-tetracyanocyclopropanes in 55–98% yields.

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, antitumor and antiviral activities.^{1,2} Though the methods of cyclopropanes 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].^{3,4}

The well-known method of MIRC synthesis of substituted cyclopropanes involves addition of halogen-substituted CH-acid anions to the conjugated activated olefins followed by cyclization with elimination of a halogen anion.⁵

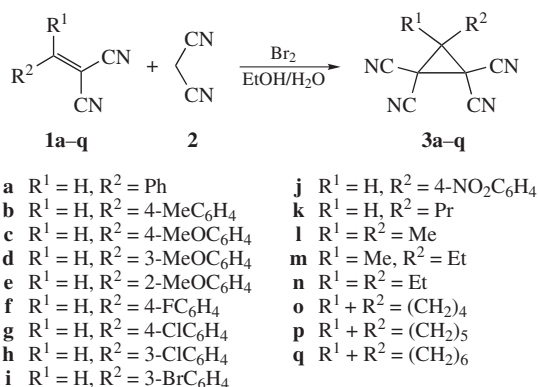
This method was used for the syntheses of tetracyano-substituted cyclopropanes from alkylidene- or benzylidenemalononitriles and bromomalononitrile^{6–10} with one exception – the base was omitted due to bromomalononitrile, which is a reasonably strong acid.^{11,12}

Nevertheless, any new one-pot easy and efficient approach to substituted 1,1,2,2-tetracyanocyclopropanes starting from simple and reasonable compounds was still welcome.

Recently, we suggested a new strategy of the chemical route to the cyclopropane structure: the one-pot transformation of alkylidenemalononitriles **1** and malononitrile **2** into 1,1,2,2-tetracyanocyclopropanes **3** in the basic alcohols by the action of free halogen.¹³ The only disadvantage of the last method was the necessity to use 1.2 equiv. of EtONa to ensure good yields of substituted 1,1,2,2-tetracyanocyclopropanes **3**. Moreover, in basic solutions both alkylidenemalononitriles **1**¹⁴ and malononitrile **2**¹⁵ undergo oligomerization reactions. Thus, a one-step simple and efficient chemical approach to substituted 1,1,2,2-tetracyanocyclopropanes starting from alkylidenemalononitriles **1** and malononitrile **2** without using a base, especially such strong base as EtONa, is still welcome.

Here we report our results on direct one-pot transformation of alkylidenemalononitriles **1** and malononitrile **2** into substituted 1,1,2,2-tetracyanocyclopropanes **3** by the action of only bromine in EtOH/H₂O solution (Scheme 1).[†]

[†] *Typical procedure.* To a mixture of olefin **1** (10 mmol) and malononitrile (0.66 g, 10 mmol) in 20 ml of ethanol in two-necked 100 ml flask, 50 ml of 0.2 M bromine in water (10 mmol) was added dropwise during 3 min. The mixture was magnetically stirred at 40 °C for 1 h. Then solid phase was filtered off, washed with 5% aqueous solution of Na₂SO₃, then with warm water and dried in desiccator over P₂O₅ to isolate pure **3a–q**.



Scheme 1

First, transformation of benzylidenemalononitriles **1a** and malononitrile **2** into 3-phenyl-1,1,2,2-tetracyanocyclopropane **3a** by the action of elemental bromine in ethanolic solution was studied (Table 1). In this case, 3-phenyl-1,1,2,2-tetracyanocyclopropane **3a** was isolated only in 15% yield, but also good conversion of starting **1a** and malononitrile **2** and the mixture of different oligomeric compounds were found under this reaction conditions.

The main idea of further experiments was to decrease the reactivity of elemental bromine to ensure the more selective cascade process of 3-phenyl-1,1,2,2-tetracyanocyclopropane **3a** synthesis. Thus, bromine was added as 0.2 M solution in water rather than elemental bromine. Even in the first experiment of this type at 20 °C in 3 h, 3-phenyl-1,1,2,2-tetracyanocyclopropane **3a** was obtained in 83% yield. Increasing the temperature up to 40 °C resulted even in 1 h in 96% yield of 1,1,2,2-tetracyanocyclopropane **3a**. Further increasing the temperature up to

Table 1 Direct transformation of benzylidenemalononitrile **1a** and malononitrile **2** into 3-phenyl-1,1,2,2-tetracyanocyclopropane **3a**.^a

Solvent	Bromine	T/°C	t/h	Yield of 3a ^b (%)
EtOH	elemental	20	3	15
EtOH/H ₂ O	0.2 M (H ₂ O)	20	3	83
EtOH/H ₂ O	0.2 M (H ₂ O)	20	1	71
EtOH/H ₂ O	0.2 M (H ₂ O)	40	1	96
EtOH/H ₂ O	0.2 M (H ₂ O)	60	1	95

^a10 mmol of benzylidenemalononitrile **1**, 10 mmol of malononitrile **2**, 20 ml of EtOH, 50 ml of 0.2 M Br₂ in water (10 mmol). ^bYield of isolated product.

Table 2 Direct transformation of olefins **1a–q** and malononitrile **2** into substituted 1,1,2,2-tetracyanocyclopropanes **3a–q** by the action of bromine in EtOH/water system.^a

Olefin	R ¹	R ²	Product	Yield of 3 ^b (%)
1a	H	Ph	3a	96
1b	H	4-MeC ₆ H ₄	3b	95
1c	H	4-MeOC ₆ H ₄	3c	98
1d	H	3-MeOC ₆ H ₄	3d	96
1e	H	2-MeOC ₆ H ₄	3e	95
1f	H	4-FC ₆ H ₄	3f	94
1g	H	4-ClC ₆ H ₄	3g	91
1h	H	3-ClC ₆ H ₄	3h	90
1i	H	3-BrC ₆ H ₄	3i	96
1j	H	4-NO ₂ C ₆ H ₄	3j	94
1k	H	Pr	3k	93
1l	Me	Me	3l	63
1m	Me	Et	3m	60
1n	Et	Et	3n	55
1o		(CH ₂) ₄	3o	93
1p		(CH ₂) ₅	3p	95
1q		(CH ₂) ₆	3q	91

^a10 mmol of olefin **1**, 10 mmol of malononitrile **2**, 20 ml of EtOH, 50 ml of 0.2 M Br₂ in water (10 mmol), time of reaction 1 h. ^bYield of isolated product.

60 °C had a little effect on 1,1,2,2-tetracyanocyclopropane **3a** formation.

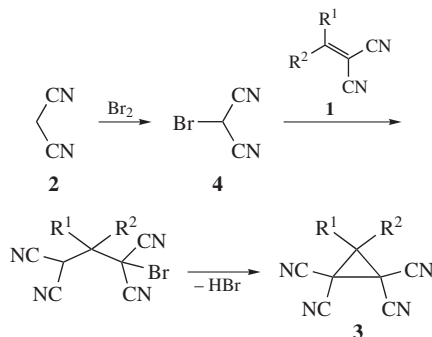
Under the optimal conditions thus found, all other experiments were carried out (Table 2).

Under the conditions of Table 2, benzylidenemalononitriles **1a–j**, propylidenemalononitrile **1k**, and cycloalkylidenemalononitriles **1o–q** in the presence of malononitrile were directly transformed into corresponding 1,1,2,2-tetracyanocyclopropanes **3a–k,o–q** in more than 90% yield by the action of only bromine.

Taking into consideration the above results, the following mechanism for the direct one-pot transformation of alkylidenemalononitriles **1** and malononitrile **2** into substituted 1,1,2,2-tetracyanocyclopropanes **3** by the action of only bromine is proposed.

The first step of the cascade process is the bromination of malononitrile with the bromomalononitrile **4** formation. The following Michael addition of bromomalononitrile **4** to alkylidenemalononitrile **1** with further ring cyclization results in the selective formation of substituted 1,1,2,2-tetracyanocyclopropanes **3** under conditions studied (Scheme 2).

This process is a typical cascade reaction, which combines in the one-pot process three reactions, *i.e.*, (1) bromination of malononitrile, (2) Michael addition of bromomalononitrile to alkylidenemalononitrile and (3) cyclization of substituted 1-bromo-1,1,3,3-tetracyanopropane into corresponding substituted 1,1,2,2-tetracyanocyclopropane **3** (Scheme 2).

**Scheme 2**

As compared to the earlier known method of the transformation of alkylidenemalononitriles **1** and malononitrile **2** into substituted 1,1,2,2-tetracyanocyclopropanes **3** in the basic alcohol solutions,¹³ this new method of the action of aqueous bromine on alkylidenemalononitriles and malononitrile in EtOH–H₂O system results in the formation of 1,1,2,2-tetracyanocyclopropanes **3** in the yields being 10–25% higher, eliminates the necessity to use 1.2 equiv. of EtONa as a base and the time of this new cascade process is three times shorter (1 h instead of 3 h). This sufficient yield increase is partly a result of noticeably lower solubility of 3-substituted 1,1,2,2-tetracyanocyclopropanes **3** in EtOH–H₂O mixtures in comparison with the pure EtOH solutions.

Thus, the new cascade reaction was found, namely: the formation of cyclopropanes from activated olefins and CH acids by the direct action of the only bromine. The action of aqueous bromine on the equal amounts of alkylidenemalononitriles and malononitrile in EtOH–H₂O solution results in the formation of 3-substituted 1,1,2,2-tetracyanocyclopropanes in 55–98% yields. The procedure utilises inexpensive reagents, it is easily carried out and the work up is not complicated. 3-Substituted 1,1,2,2-tetracyanocyclopropanes are crystallized directly from the reaction mixture, consequently, the isolation includes only filtration and washing with 5% aqueous solution of Na₂SO₃ and warm water.

This work was supported by the Russian Foundation for Basic Research (project no. 09-03-00003a) and the Presidential Scholarship Programme for the State Support of Leading Scientific Schools of the Russian Federation (project no. 5022.2006.3).

References

- 1 Z. Rappoport, *The Chemistry of the Cyclopropyl Group*, Wiley, New York, 1996.
- 2 (a) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi and Y. Takemoto, *J. Org. Chem.*, 2001, **66**, 81; (b) D. L. Boger, T. V. Hughes and M. P. Hedrick, *J. Org. Chem.*, 2001, **66**, 2207; (c) S. Yoshida, T. C. Rosen, O. G. J. Meyer, M. J. Sloan, S. Ye, G. Haufe and K. L. Kirk, *Bioorg. Med. Chem.*, 2004, **12**, 2645.
- 3 W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589.
- 4 (a) R. D. Little and J. R. Dawson, *J. Am. Chem. Soc.*, 1978, **100**, 4607; (b) H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, 1015.
- 5 G. Bonavent, M. Causse, M. Guitard and R. Fraisse-Julien, *Bull. Soc. Chim. Fr.*, 1964, 2462.
- 6 H. Hart and Y. C. Kim, *J. Org. Chem.*, 1966, **31**, 2784.
- 7 Y. C. Kim and H. Hart, *Tetrahedron*, 1969, **25**, 3869.
- 8 H. Horf and M. Kreutzer, *Angew. Chem.*, 1990, **102**, 425.
- 9 O. E. Nasakin, P. M. Lukin and A. V. Sadovoi, *Zh. Org. Khim.*, 1993, **29**, 1917 (*Russ. J. Org. Chem.*, 1993, **29**, 1598).
- 10 O. V. Kayukova, Ya. S. Kayukov, E. S. Lapteva, I. N. Bardasov, O. V. Ershov and O. E. Nasakin, *Zh. Org. Khim.*, 2006, **42**, 1427 (*Russ. J. Org. Chem.*, 2006, **42**, 1414).
- 11 R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 1953, **75**, 2439.
- 12 R. P. Mariella and A. J. Roth, *J. Org. Chem.*, 1957, **22**, 1130.
- 13 M. N. Elinson, S. K. Feducovich, N. O. Stepanov, A. N. Vereshchagin and G. I. Nikishin, *Tetrahedron*, 2008, **64**, 708.
- 14 A. J. Fatiadi, *Synthesis*, 1978, 165.
- 15 F. Freeman, *Chem. Rev.*, 1980, **80**, 329.
- 16 M. N. Elinson, S. K. Feducovich, T. L. Lizunova and G. I. Nikishin, *Tetrahedron*, 2000, **56**, 3063.

Received: 17th April 2009; Com. 09/3324