Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2015, **25**, 185–187
Mendeleev Communications

Non-catalytic solvent-free synthesis of 5,6,7,8-tetrahydro-4*H*-chromenes from aldehydes, dimedone and malononitrlie at ambient temperature

Michail N. Elinson,*[a] Fedor V. Ryzhkov,[a] Tatiana A. Zaimovskaya[b] and Mikhail P. Egorov[a]

[a] *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*
[b] *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation.*

DOI: 10.1016/j.mencom.2015.05.008

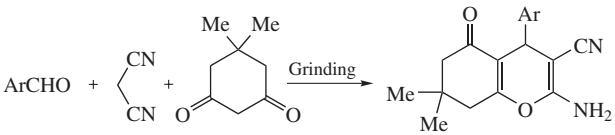
Non-catalytic solvent-free assembling of aldehydes, dimedone and malononitrile at ambient temperature affords substituted 5,6,7,8-tetrahydro-4*H*-chromenes in 88–98% yields.

Multicomponent reactions (MCRs) became the efficient strategy in the sustainable and diversity oriented synthesis of heterocycles.[1–3] The application of high-throughput screening in biomedical studies has sufficiently increased the demand for substances to test for new drug-like molecules.[4,5] In recent years, the synthesis of small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.[6]

Among the heterocycles, functionally substituted 4*H*-chromenes have received considerable attention due to their spasmolytic, diuretic, anti-coagulant, anti-cancer and anti-anaphylactic activities.[7–9] Chromene fragment constitutes the structural unit of a series of natural products.[10,11] The current interest to 4*H*-chromenes bearing nitrile functionality and especially to 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles arises from their potential application to the treatment of human neurodegenerative disorders, including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome.[12]

The known multicomponent procedures for the synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles employ the assembling of aromatic aldehydes, cyclic 1,3-diketones and malononitrile. Piperidine,[13] piperidine/ammonium acetate system[14] or triethylamine[15] used as catalysts provide 70–85% yields of the products. The second set of methods offers the catalysis with alkyl ammonium salts in water,[16,17] (*S*)-proline in water or water–ethanol mixtures,[18] potassium phthalimide-*N*-oxyl[19] or nanozeolite clinoptilolite 1,[20] as well as non-catalytic process in glycerol as a solvent.[21] Although these MCRs afford the products in higher (75–95%) yields, they significantly suffer from prolonged reaction times and high reaction temperatures (up to 90 °C). Electrochemical[22] and electrocatalytic[23] methods to initiate this process are also known. The solid state technique in the presence of sodium bromide under microwave irradiation[24] was performed at 70–85 °C in a special reactor, and further recrystallization of crude reaction mixture from ethanol was required.[24] Two-step solvent-free protocol comprises the Knoevenagel condensation of aldehyde with malononitrile (150 °C, 1 h) followed by the reaction of the adduct with dimedone (100–150 °C, 1 h).[25]

Obviously, any new, facile and highly efficient synthetic multicomponent approach to the 5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile system is an object of considerable interest. Moreover, taking into consideration the basic principles of 'green chemistry' especially both solvent-free and non-catalytic procedures are particularly welcome.[26] We have already found a series of



1a–i **2a–i**

a Ar = Ph
b Ar = 4-MeC_6H_4
c Ar = 4-EtC_6H_4
d Ar = 4-$MeOC_6H_4$
e Ar = 3-BrC_6H_4
f Ar = 4-BrC_6H_4
g Ar = 4-ClC_6H_4
h Ar = 4-$O_2NC_6H_4$
i Ar = 2,6-$Cl_2C_6H_3$

Scheme 1

solvent-free cascade and multicomponent reactions of aldehydes and C–H acids.[27] Recently we have also revealed some non-catalytic multicomponent transformations of carbonyl compounds and C–H acids.[28] Taking into consideration the above results we have developed a convenient fast and efficient solvent-free multicomponent transformation of aromatic aldehydes **1a–i**, malononitrile and dimedone into substituted 5,6,7,8-tetrahydro-4*H*-chromenes **2a–i** (Scheme 1, Tables 1, 2).†

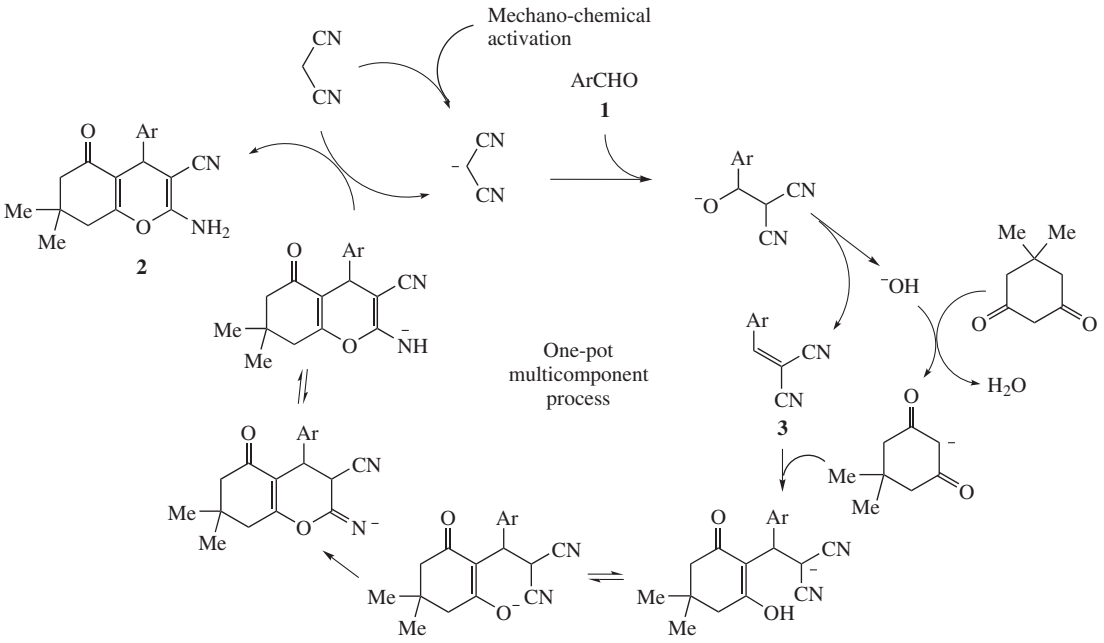
Sodium acetate, an inexpensive, non-toxic and readily available substance, was used as mild base catalyst for aldol condensation of aromatic aldehydes and acid anhydrides (Perkin reaction)[29] and

Table 1 Solvent-free multicomponent transformation of aldehyde **1a**, malononitrile and dimedone into 5,6,7,8-tetrahydro-4*H*-chromene **2a**.[a]

Entry	Base (mol%)	Time/min	Isolated yield of chromene **2a** (%)
1	AcONa (10)	15	74
2	AcONa (5)	15	79
3	AcONa (2)	15	85
4	KF (10)	15	77
5	KF (5)	15	82
6	KF (2)	15	88
7	—	15	96
8	—	10	92

[a]Aldehyde **1a** (3 mmol), malononitrile (3 mmol), dimedone (3 mmol) and sodium acetate or potassium fluoride (0.3 mmol), or without catalyst were grinded with the pestle in mortar at room temperature for 10 to 15 min.

† *General (typical) procedure*. Aldehyde **1** (3 mmol), malononitrile (3 mmol, 0.20 g) and dimedone (3 mmol, 0.42 g) were grinded with a pestle in a mortar at ambient temperature for 15 min. After the reaction was finished, the material was dried in air to afford practically pure substituted 5,6,7,8-tetrahydro-4*H*-chromene **2**. For characteristics of products **2a–i**, see Online Supplementary Materials.



Scheme 2

for Knoevenagel condensation of carbonyl compounds.[30] Earlier we used sodium acetate to catalyze multicomponent cyclization of aldehydes, malononitrile and acetone into *cis*-4-dicyanomethylidene-2,6-diarylcyclohexane-1,1-dicarbonitrile.[31] Thus, initially the reaction between aldehyde **1a**, malononitrile and dimedone was carried out under solvent-free base catalytic conditions with sodium acetate (Table 1, entries 1–3).

Surprisingly we have found that yields of 5,6,7,8-tetrahydro-4*H*-chromene **2a** increased from 74 to 85% with lowering quantity of sodium acetate from 10 to 2 mol%. The same tendency has been observed for potassium fluoride (Table 1, entries 4–6): increasing the yields of **2a** from 77 up to 88% with the same decreasing quantity of potassium fluoride. The best results were achieved without any catalyst, when product **2a** was obtained in 92 and 96% yields in 10 and 15 min reaction time period, respectively. Under optimum non-catalytic solvent-free conditions thus found (ambient temperature grinding, 15 min reaction time), substituted 5,6,7,8-tetrahydro-4*H*-chromenes **2a–i** were obtained in excellent 88–98% yields (Table 2). The final crude materials were the practically pure products.

Table 2 Solvent-free multicomponent transformation of aldehydes **1a–i**, malononitrile and dimedone into 5,6,7,8-tetrahydro-4*H*-chromenes **2a–i**.[a]

Entry	Starting aldehyde	Time/min	Obtained chromene	Isolated yield (%)
1	**1a**	15	**2a**	96
2	**1b**	15	**2b**	93
3	**1c**	15	**2c**	95
4	**1c**	10	**2c**	83
5	**1c**	5	**2c**	79
6	**1d**	15	**2d**	88
7	**1e**	15	**2e**	90
8	**1f**	15	**2f**	95
9	**1g**	15	**2g**	97
10	**1h**	15	**2h**	98
11	**1h**	10	**2h**	85
12	**1h**	5	**2h**	83
13	**1i**	15	**2i**	93

[a]Aldehydes **1a–i** (3 mmol), malononitrile (3 mmol), dimedone (3 mmol) were grinded with a pestle in a mortar at ambient temperature for 5 to 15 min.

Taking into consideration the above results, the data on non-catalytic multicomponent transformation of carbonyl compounds and C–H acids[28] as well as solvent-free cascade and multicomponent reactions of aldehydes and C–H acids[27] the following mechanism for the non-catalytic solvent-free transformation of aldehydes **1a–i**, malononitrile and dimedone into substituted 5,6,7,8-tetrahydro-4*H*-chromenes **2a–i** was suggested (Scheme 2).

At the first step, the formation of malononitrile anion occurs as the result of mechano-chemical activation by grinding in the mortar. Then Knoevenagel condensation of malononitrile anion with aldehyde **1** occurs with elimination of hydroxide anion and formation of the corresponding arylidenemalononitrile **3**.[32] The subsequent hydroxide-promoted Michael addition of cyclic 1,3-diketone to electron deficient Knoevenagel adduct **3** followed by intramolecular cyclization leads to the corresponding 5,6,7,8-tetrahydro-4*H*-chromene **2** with regeneration of malononitrile anion at the last step, which continues the catalytic process by the interaction with the next molecule of aldehyde **1** (see Scheme 2). Thus, the generation of even single malononitrile anion is theoretically sufficient for total conversion of equimolar quantities of aldehyde, malononitrile and cyclic 1,3-diketone into the corresponding 5,6,7,8-tetrahydro-4*H*-chromene system under conditions studied.

In conclusion, simple grinding as mechanochemical activation can induce assembling of aromatic aldehydes, dimedone and malononitrile into chromenes in the absence of solvent and catalyst at ambient temperature. The developed efficient non-catalytic solvent-free approach to the 5,6,7,8-tetrahydro-4*H*-chromene system is beneficial from the viewpoint of diversity-oriented large-scale processes and represents a new example of the ecologically benign synthetic concept for not only non-catalytic but also solvent-free 'domino' reactions strategy at ambient temperature. Our findings bring us a step closer to the notion of 'ideal synthesis'.[26]

This work was supported by the Russian Foundation for Basic Research (project no. 13-03-00096a).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.05.008.

References

1 *Multicomponent Reactions*, eds. J. Zhu and H. Bienayme, Wiley-VCH, Weinheim, 2005.
2 D. M. D'Souza and T. J. J. Müller, *Chem. Soc. Rev*., 2007, **36**, 1095.
3 *Synthesis of Heterocycles via Multicomponent Reactions I*, eds. R. V. A. Orru and E. Ruijter, Springer, New York, 2010.
4 L. Weber, *Drug Discovery Today*, 2002, **7**, 143.
5 A. Dömling, *Curr. Opin. Chem. Biol*., 2002, **6**, 306.
6 *Drug Design*, ed. G. Klebe, Springer, Berlin, 2013.
7 J. Skommer, D. Wlodkowic, M. Mättö, M. Eray and J. Pelkonen, *Leukemia Res*., 2006, **30**, 322.
8 N. Yu, J. M. Aramini, M. W. Germann and Z. Huang, *Tetrahedron Lett*., 2000, **41**, 6993.
9 L. Bonsignore, G. Loy, D. Secci and A. Calignano, *Eur. J. Med. Chem.*, 1993, **28**, 517.
10 V. S. Parmar, S. C. Jain, K. S. Bisht, R. Jain, P. Taneja, A. Jha, O. D. Tyagi, A. K. Prasad, J. Wengel, C. E. Olsen and P. M. Boll, *Phytochemistry*, 1997, **46**, 597.
11 V. V. Polyakov, *Chem. Nat. Compd. (Engl. Transl.)*, 1999, **35**, 21 (*Khim. Prir. Soedin*., 1999, 27).
12 C. S. Konkoy, D. B. Fick, S. X. Cai, N. C. Lan and J. F. W. Keana, *PCT Int. Appl. WO 0075123*, 2000 (*Chem. Abstr*., 2001, **134**, 29313a).
13 F. F. Abdel-Latif, M. M. Mashaly and E. H. El-Gawish, *J. Chem. Res. Miniprint*, 1995, 1220.
14 A. A. Hassanien, M. A. Zahran, M. S. A. El-Gaby and M. M. Ghorab, *J. Indian Chem. Soc*., 1999, **76**, 350.
15 A. M. Shestopalov, Yu. M. Emelianova and V. N. Nesterov, *Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 1164 (*Izv. Akad. Nauk, Ser. Khim*., 2003, 1103).
16 T.-S. Jin, A.-Q. Wang, X. Wang, J.-S. Zhang and T.-S. Li, *Synlett*, 2004, 871.
17 S. Gao, C. H. Tsai, C. Tseng and C.-F. Yao, *Tetrahedron*, 2008, **64**, 9143.
18 S. Balalaie, M. Bararjanian, A. M. Amani and B. Movassagh, *Synlett*, 2006, 263.
19 M. G. Dekamin, M. Eslami and A. Maleki, *Tetrahedron*, 2013, **69**, 1074.
20 S. M. Baghbanian, N. Rezaeia and H. Tashakkorian, *Green Chem.*, 2013, **15**, 3446.
21 H. R. Safaei, M. Shekouhy, S. Rahmanpur and A. Shirinfeshan, *Green Chem*., 2012, **14**, 1696.
22 L. Fotouhi, M. M. Heravi, A. Fatehi and K. Bakhtiari, *Tetrahedron Lett*., 2007, **48**, 5379.
23 M. N. Elinson, A. S. Dorofeev, S. K. Feducovich, S. V. Gorbunov, R. F. Nasybullin, F. M. Miloserdov and G. I. Nikishin, *Eur. J. Org. Chem.*, 2006, 4335.
24 A. I. Devi and P. J. Bhuyan, *Tetrahedron Lett.*, 2004, **45**, 8625.
25 G. Kaupp, M. R. Naimi-Jamal and J. Schmeyers, *Tetrahedron*, 2003, **59**, 3753.
26 P. A. Wender, *Nat. Prod. Rep.*, 2014, **31**, 433.
27 (*a*) M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, A. O. Chizhov, P. A. Belyakov and G. I. Nikishin, *Tetrahedron*, 2010, **66**, 4043; (*b*) M. N. Elinson, M. G. Medvedev, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya and G. I. Nikishin, *Mendeleev Commun*., 2013, **23**, 94; (*c*) M. N. Elinson, R. F. Nasybullin, F. V. Ryzhkov, T. A. Zaimovskaya and M. P. Egorov, *Monatsh. Chem*., 2014, **145**, 605; (*d*) M. N. Elinson, R. F. Nasybullin, F. V. Ryzhkov and M. P. Egorov, *C. R. Chimie*, 2014, **17**, 437; (*e*) M. N. Elinson, F. V. Ryzhkov, V. M. Merkulova, A. I. Ilovaisky and G. I. Nikishin, *Heterocycl. Commun*., 2014, **20**, 281; (*f*) M. N. Elinson, R. F. Nasybullin, F. V. Ryzhkov, T. A. Zaimovskaya and G. I. Nikishin, *Monatsh. Chem*., 2015, **146**, 631.
28 (*a*) M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, P. A. Belyakov, F. Barba and B. Batanero, *Tetrahedron*, 2012, **68**, 5833; (*b*) M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya and G. I. Nikishin, *Mendeleev Commun*., 2012, **22**, 143; (*c*) M. N. Elinson, O. O. Sokolova, R. F. Nasybullin, T. A. Zaimovskaya and M. P. Egorov, *Mendeleev Commun*., 2015, **25**, 19.
29 T. Rosen, *Comp. Org. Syn*., 1991, **2**, 395.
30 M. N. Elinson, S. K. Feducovich, T. A. Zaimovskaya, A. N. Vereshchagin and G. I. Nikishin, *Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 673 (*Izv. Akad. Nauk, Ser. Khim*., 2005, 663).
31 M. N .Elinson, A. N. Vereshchagin, S. K. Feducovich, T. A. Zaimovskaya, Z. A. Starikova, P. A. Belyakov and G. I. Nikishin, *Tetrahedron Lett.*, 2007, **48**, 6614.
32 S. Patai and Y. Israeli, *J. Chem. Soc.*, 1960, 2025.

Received: 22nd October 2014; Com. 14/4490