Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2015, **25**, 19–20
Mendeleev Communications

Efficient non-catalytic synthesis of substituted 2,3,4,9-tetrahydro-1*H*-xanthen-1-ones from salicylaldehydes and dimedone

Michail N. Elinson,*[a] Olga O. Sokolova,[b] Ruslan F. Nasybullin,[a] Tatiana A. Zaimovskaya[c] 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] *Higher Chemical College, Russian Academy of Sciences, 125047 Moscow, Russian Federation*
[c] *A. V. Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2015.01.006

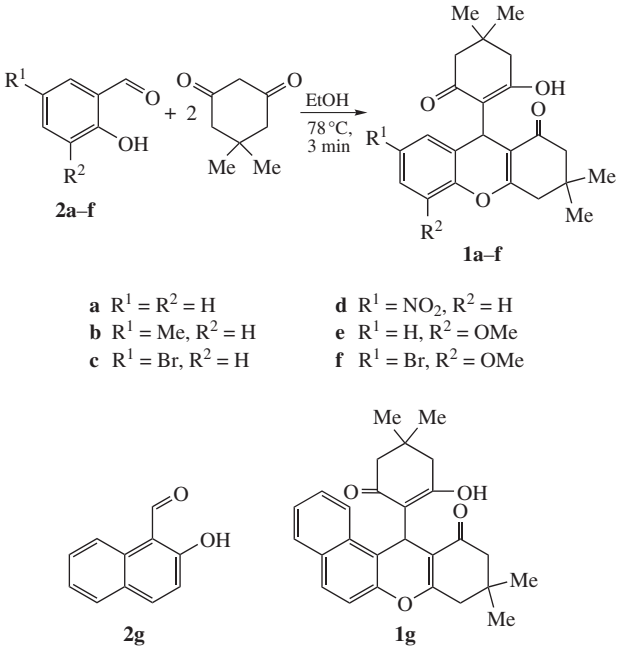
Thermally induced non-catalytic assembling of salicylaldehydes and dimedone in water or ethanol affords 9-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones in 85–95% yields as a sequence of Knoevenagel and Michael reactions.

Neuropeptide Y (NPY) is a powerful stimulant of food intake and is proposed to activate a hypothalamic 'feeding' receptor distinct from previously cloned Y-type receptors.[1] Six distinct types of G-protein-coupled NPY receptors (Y1–Y6) are known.[2] Correlations between the *in vitro* function and the binding activity of different peptide agonists and their potent stimulation of food intake have found the Y5 receptor as a major feeding receptor.[3] Recently it was revealed that 9-(2-hydroxy-4,4-dimethyl-6-oxo-1-cyclohexen-1-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones **1** (Scheme 1) are the orally active and selective Y5 antagonists.[4–6] Moreover, xanthene derivatives occur in natural products[7] and occupy a prominent position in medicinal chemistry.[8]

The usual access to tetrahydro-1*H*-xanthen-1-ones **1** is tandem Knoevenagel–Michael reaction of salicylaldehydes with two molecules of dimedone with further cyclization. For this cyclization, $CeCl_3$,[9] KF/Al_2O_3,[10] *p*-toluenesulfonic acid,[11] triethylbenzylammonium chloride[12] and Zn[(L)proline]$_2$[13] were used as catalysts. However, these catalytic methods require refluxing in different solvents (among them in water) and long reaction time (2–8 h) and often lead to insufficient yields of the products. Solvent-free method using 2,4,6-trichloro-1,3,5-triazine as catalyst also demanded heating to 120 °C for 2–3 h as well as final crystallization from ethanol.[14]

In terms of green chemistry, the 'best catalyst is no catalyst'.[15] Recently, non-catalytic synthesis of tetrahydro-1*H*-xanthen-1-ones **1** in water (reflux, 4–5 h) was suggested.[16] Among the all known tandem procedures for the synthesis of compounds **1**, the most obvious Knoevenagel–Michael one has not been well developed yet. Recently we have found that non-catalytic multicomponent assembling of isatin, cyclic C–H acids and malononitrile in alcohols (80–95 °C) gives rapidly (10 min) rise to substituted spirooxoindoles in 90–97% yields.[17]

Taking into consideration the above result, we anticipated that tetrahydro-1*H*-xanthen-1-ones **1** can be accessed by Knoevenagel–Michael tandem reaction between salicylaldehydes **2** and 2 equiv. of dimedone (Scheme 1, Tables 1, 2).†



Scheme 1

Table 1 Tandem assembling of salicylaldehyde **2a** and dimedone into tetrahydro-1*H*-xanthen-1-one **1a**.[a]

Entry	Catalyst (quantity/mmol)	Solvent (volume/ml)	*T*/°C	*t*/min	Isolated yield of **1a** (%)
1	NaOAc (3)	EtOH (2)	78	5	93
2	NaOAc (1)	EtOH (2)	78	5	91
3	NaOAc (3)	H_2O (2)	80	5	86
4	–	EtOH (2)	78	5	90
5	–	EtOH (1)	78	5	88
6	–	EtOH (2)	78	3	90
7	–	EtOH (2)	78	1	83
8	–	H_2O (2)	80	5	82
9	–	–	80	5	71
10	–	MeOH (2)	60	3	75
11	–	PrOH (2)	80	3	84

[a] Salicylaldehyde **2a** (5 mmol), dimedone (10 mmol).

† *Tetrahydro-1*H*-xanthen-1-ones* **1** *(general procedure).* A solution of salicylic aldehyde (5 mmol) and dimedone (10 mmol) in ethanol (2 ml) was stirred under reflux for 3 min and cooled. The precipitated product was filtered off, rinsed with an ice-cold ethanol–water solution (1:1, 2 ml) and dried under reduced pressure. For characteristics of tetrahydro-1*H*-xanthen-1-ones **1a**–**g**, see Online Supplementary Materials.

Sodium acetate is an advantageous catalyst for a number of organic reactions.[18–21] Therefore, we used it in our initial experiments (Table 1, entries 1–3) in ethanol or water at 78–80 °C and obtained tetrahydro-1*H*-xanthen-1-one **1a** in 86–93% yields within yet 5 min. Surprisingly, in ethanol at 78 °C in the absence of sodium acetate the yield of product **1a** was as high as 90% in 3–5 min (entries 4, 6). Under solvent-free conditions (80 °C, 5 min) compound **1a** was formed in 71% yield (entry 9). Methanol and *n*-propanol were less effective solvents (entries 10, 11).

Under the optimum conditions (boiling ethanol, 3 min), the variety of tetrahydro-1*H*-xanthen-1-ones **1a–g** was prepared in excellent yields (Table 2).

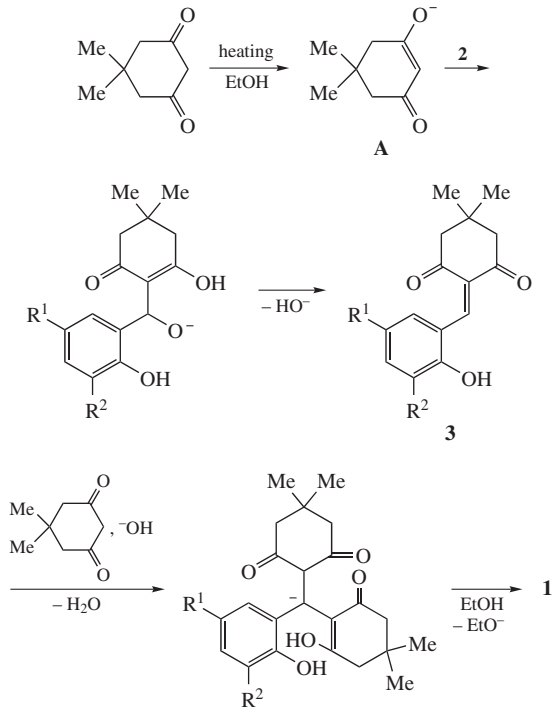
Table 2 Tandem transformation of salicylaldehydes **2a–g** and dimedone into tetrahydro-1*H*-xanthen-1-ones **1a–g**.[a]

Entry	Salicylaldehyde	Product	Isolated yield (%)
1	**2a**	**1a**	90
2	**2b**	**1b**	91
3	**2c**	**1c**	93
4	**2d**	**1d**	89
5	**2e**	**1e**	95
6	**2f**	**1f**	88
7	**2g**	**1g**	85

[a] Salicylaldehyde **2a–g** (5 mmol), dimedone (10 mmol), EtOH (2 ml), 3 min boiling.

As practically pure compounds **1a–g** were formed ultimately, the resulting precipitate was filtered off, rinsed with an ice-cold ethanol–water solution (1:1, 2 ml) and dried under reduced pressure, which provided a simple isolation operation.

Taking into consideration the above results, the data on non-catalytic multicomponent transformation of isatin, cyclic C–H acids and malononitrile into substituted spirooxoindoles[17] and the data on non-catalytic 'on water' Knoevenagel condensation of isatins with malononitrile[22] the following mechanism for the non-catalytic chain transformation of salicylaldehydes **2a–g** and dimedone into tetrahydro-1*H*-xanthen-1-ones **1a–g** was suggested (Scheme 2). As the initiation step, the thermal deprotonation of dimedone leads to dimedone anion **A**. Then Knoevenagel condensation of dimedone anion **A** with salicylaldehyde **2** occurs with elimination of hydroxide anion and formation of the adduct **3**.[23] The subsequent Michael addition of dimedone to electron deficient adduct **3** with further cyclization results in ultimate tetrahydro-1*H*-xanthen-1-one **1** and ethoxide anion.



Scheme 2

In conclusion, the herein developed facile and efficient procedure provides very fast (neutral conditions, 3 min) and selective multicomponent assembling of salicylaldehydes and dimedone into tetrahydro-1*H*-xanthen-1-ones **1** (85–95% yields), which are the orally active and selective Y5 antagonists[4] and seem promising for other biomedical applications. The procedure is valuable from the viewpoint of environmentally benign diversity-oriented large-scale processes.

This work was supported by the Russian Foundation for Basic Research (project nos. 14-03-31918 and 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.2015.01.006.

References

1 C. Wahlestedt and D. J. A. Reis, *Rev. Pharmacol. Toxicol*., 1993, **32**, 309.
2 A. G. Blomqvist and H. Herzog, *Trends. Neurosci*., 1997, **20**, 294.
3 C. Gerald, M. W. Walker, L. Criscione, T. L. Gustafson, C. Batzl-Hartmann, K. E. Smith, P. Vaysse, M. M. Durkin, T M. Laz, D. L. Linemeyer, A. O. Schaffhauser, S. Whitebread, K. G. Hofbauer, R. I. Taber, T. A. Branchek and R. L. Weinshank, *Nature*, 1996, **382**, 168.
4 A. Kanatani, A. Ishihara, H. Iwaasa, K. Nakamura, O. Okamoto, M. Hidaka, J. Ito, T. Fukuroda, D. J. MacNeil, L. H. T. Van der Ploeg, Y. Ishii, T. Okabe, T. Fukami and M. Ihara, *Biochem. Biophys. Res. Commun*., 2000, **272**, 169.
5 S. Mashiko, A. Ishihara, H. Iwaasa, H. Sano, Z. Oda, J. Ito, M. Yumoto, M. Okawa, J Suzuki, T. Fukuroda, M. Jitsuoka, N. R. Morin, D. J. MacNeil, L. H. T. Van der Ploeg, M. Ihara, T. Fukami and A. Kanatani, *Endocrinology*, 2003, **144**, 1793.
6 A. Ishihara, A. Kanatani, S. Mashiko, T. Tanaka, M. Hidaka, A. Gomori, H. Iwaasa, N Murai, S. Egashira, T. Murai, Y. Mitobe, H. Matsushita, O. Okamoto, N Sato, M. Jitsuoka, T. Fukuroda, T. Ohe, X. Guan, D. J. MacNeil, L. H. T. Van der Ploeg, M. Nishikibe, Y. Ishii, M. Ihara and T. A. Fukami, *Proc. Natl. Acad. Sci. U.S.A.*, 2006, **103**, 7154.
7 O. Thoison, E. Hnawia, F. Gueritte and T. Sevenet, *Phytochemistry*, 1992, **31**, 1439.
8 H. K.Wang, S. L. Morris-Natschke and K. H. Lee, *Med. Res. Rev.*, 1997, **17**, 367.
9 G. Sabitha, K. Arundhathi, K. Sudhakar, B. S. Sastry and J. S. Yadav, *Synth. Commun*., 2008, **38**, 3439.
10 Y.-L. Li, H. Chen, Z.-S. Zeng, X.-S. Wang, D.-Q. Shi and S.-J. Tu, *Chin. J. Org. Chem*., 2005, **25**, 846.
11 L. Nagarapu, S. Karnakani, R. Bantu and B. Sridhar, *Synth. Commun.*, 2012, **42**, 967.
12 X.-S. Wang, D.-Q. Shi, Y.-L. Li, H. Chen, X.-Y. Wie and Z.-M. Zong, *Synth. Commun*., 2005, **35**, 97.
13 M. Kidwai and A. Jain, *Appl. Organomet. Chem*., 2012, **26**, 528.
14 P. Zang, Y.-D. Yu and Z.-H. Zang, *Synth. Commun*., 2008, **38**, 4474.
15 R. A. Sheldon, *J. Mol. Catal. A*, 1996, **107**, 75.
16 D. M. Pore, T. S. Shaikh, K. A. Undale and D. S. Gaikwad, *C. R. Chimie*, 2010, **13**, 1429.
17 M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, T. A. Zaimovskaya and G. I. Nikishin, *Mendeleev Commun*., 2012, **22**, 143.
18 T. Rosen, *Comp. Org. Syn*., 1991, **2**, 395.
19 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).
20 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.
21 W.-B. Liu, H.-F. Jiang, S.-F. Zhu and W. Wang, *Tetrahedron*, 2009, **65**, 7985.
22 D. V. Demchuk, M. N. Elinson and G. I. Nikishin, *Mendeleev Commun*., 2011, **21**, 224.
23 S. Patai and Y. Israeli, *J. Chem. Soc*., 1960, 2025.

Received: 2nd April 2014; Com. 14/4342