Bioorganic & Medicinal Chemistry Letters 19 (2009) 3949–3951

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Catalyst-free tandem aldol condensation/Michael addition of 1,3-cyclohexanediones with enolizable aldehydes

Kerstin Rohr, Rainer Mahrwald *

Humboldt-University Berlin, Institute of Chemistry, Brook-Taylor Street 2, 12489 Berlin, Germany

ARTICLE INFO

Article history:
Received 3 February 2009
Accepted 9 March 2009
Available online 16 March 2009

Keywords:
Tandem aldol condensation/Michael addition
Enolizable aldehydes
1,3-Cyclohexanediones
Catalyst-free

ABSTRACT

An efficient tandem aldol condensation/Michael addition process of unactivated aldehydes and 1,3-cyclohexanedione is described. This transformation proceeds without any catalyst at room temperature with high isolated yields. By a fine-tuning of reaction conditions an access to both the aldol condensation/Michael addition products or to the dehydrated cyclized 9-substituted 1,8-dioxo-xanthenes is given.

Introduction. Xanthenes are important compounds with antibactericide-activities in agriculture,[1] with anti-inflammatory effects[2] and even with antiviral activities.[3] They are being developed to act as new clinical agents in cancer therapy.[4] In addition, substituted xanthenes are structural key-units in several natural products.[5] Many procedures exist for the synthesis of 1,8-dioxo-xanthenes.[6] However, many of these methods include strong acidic reaction conditions,[7] long reaction times,[8] high temperatures[9] or they are dedicated only to the application of aromatic aldehydes.[10] The important aldol reaction/Michael addition intermediates could not be isolated under these reaction conditions. To avoid these restrictions we have tested the scope of a new aldol addition developed in our laboratories. Herein, we describe results of these investigations.

Results and discussion. Recently, we have reported a solvent- and catalyst-free aldol addition of activated aldehydes to 1,3-dicarbonyl compounds. Aldol condensation does not occurred under these reaction conditions. This unexpected aldol reaction could be extended successfully to a variety of acyclic and cyclic β-dicarbonyl compounds.[11] In order to explore the scope and limitations of this new aldol addition we have also used 1,3-cyclohexanediones as substrates. In initial studies we were able to isolate xanthene-adduct **4h** from reaction of choroacetaldehyde with 1,3-cyclohexanedione **1** with 43% yield after 24 h at room temperature. When CH_2Cl_2 was applied as solvent **4h** was isolated with 73%. This increasing of yield is caused by homogeneity of the reaction mixture. Further studies revealed that a variety of even unactivated enolizable aldehydes **2a–h** react with 1,3-cyclohexanedione **1** to give aldol condensation/Michael addition compounds **3a–g**. Under these catalyst-free reaction conditions we obtained the 2:1 adducts **3a–g** at room temperature within 24 h in good to high isolated yields (Table 1). When used with (*R*)- or (*S*)-configured menthylglyoxylates an access to optically active products **3f** and **3g** is given. Dehydrations were accomplished by addition of catalytic amounts of pyridinium *p*-toluenesulfonate to the reaction mixtures. Also isolated aldol/Michael adducts **3a–g** were dehydrated under these catalytic conditions; the corresponding 1,8-dioxo-xanthenes **4a–g** were obtained in quantitative yields within 30 min (Scheme 1, Table 1).

It is reasoned that by an initial aldol condensation 2-arylidene- or 2-alkylidene substituted 1,3-cyclohexandiones **5a–h** were formed. These Knoevenagel products are highly reactive Michael

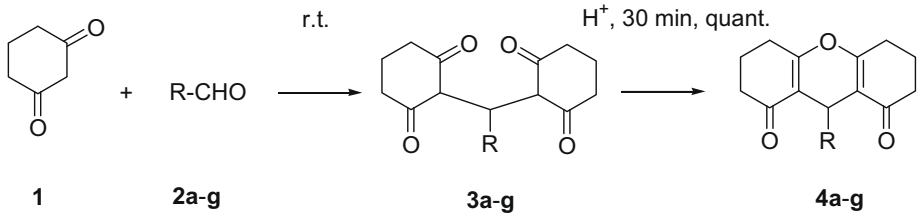
Table 1
Reactions of aldehydes with 1,3-cyclohexanedione

Entry	R	Compound	Yield (%)
1	Cy	**3a**	81
2	*i*Pr	**3b**	75
3	Ph	**3c**	69
4	PhCH=CH	**3d**	85
5	$PhCH_2$–CH_2	**3e**	87
6	(*R*)-Menthyl-CO_2	**3f**	69
7	(*S*)-Menthyl-CO_2	**3g**	78
8	$ClCH_2$	**4h**[a]	43[b], 73[c]

[a] In this reaction only xanthene-product **4b** was detected.
[b] Neat, chloroacetaldehyde—50% solution in water.
[c] Reactions were conducted in CH_2Cl_2.

* Corresponding author. Tel.: +49 30 2093 8397, fax: +49 30 2093 5553.
E-mail address: rainer.mahrwald@rz.hu-berlin.de (R. Mahrwald).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.03.040



Scheme 1. Reactions of aldehydes with 1,3-cyclohexanedione.

acceptors capable for further reactions 1,3-cyclohexanedione **1** to yield compounds **3a**–**h**. Subsequent dehydration yield 1,8-dioxo-xanthenes **4a**–**h**. In no case were we able to detect Knoevenagel products **5a**–**h** (Scheme 2).

This behaviour concurs with reports found in the literature.[12] Since 2-arylidene or 2-alkylidene adducts **5a–h** of 1,3-cyclohexanedione are not attainable by aldol methodologies so far, there are only a few other methods for the synthesis of these compounds.[13]

Also, these findings strongly contrast the results we described in Ref. 11. When used with 1,3-dicarbonyl compounds of the acyclic series we have detected exclusively aldol adducts (e.g., 2,4-pentanedione, 1,3-diphenyl-1,3-propanedione, ethyl acetoacetate or ethyl 2-cyclohexanonecarboxylate). In addition, only aldol adducts of activated aldehydes and 1,3-dicarbonyl compounds were formed in those transformations. No reactions were observed when used with unactivated aldehydes as they were applied in these reactions with 1,3-cyclohexanedione **1** (Table 1, entries 1–5).

Similar results were obtained when extending this method to other substrates. Using with 5,5-dimethyl-substituted 1,3-cyclohexanedione **6** we were able to obtain aldol/Michael adducts **7a** and **7b** with good to high yields (Scheme 3). Dehydrations to the corresponding 1,8-dioxo-xanthenes **8a** and **8b** were carried out in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate as described above. In this reaction we were able to isolate highly differently substituted and functionalized xanthene **8a** in high yields—a valuable intermediate for further transformations to higher-substituted xanthenes.

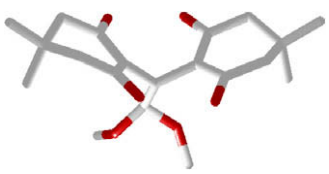
In conclusion, the non-catalysed aldol addition of 1,3-cyclohexanedione with enolizable and unactivated aldehydes has been investigated. Under catalyst-free reaction conditions we were able to isolate aldol addition/Michael adducts of 1,3-cyclohexanediones with high yields. This catalyst-free method should be of great interest especially for natural product synthesis, since no comparably mild access to aldol/Michael adducts of 1,3-dicarbonyl compounds exists.

Experimental. General experimental procedures: NMR spectra were recorded at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) in $CDCl_3$, respectively, using an AC-300 spectrometer. Chemical shifts are given in ppm. Purification of products was accomplished by flash chromatography. Thin layer chromatography was performed with Merck Silica Gel 60 F_{254} TLC plates. Melting points were determined in open capillary tubes on a Sanyo Gallenkamp melting point apparatus and are uncorrected. Mass spectra were obtained using a Hewlett–Packard GCMS 5995-A mass spectrometer operating at 70 eV.

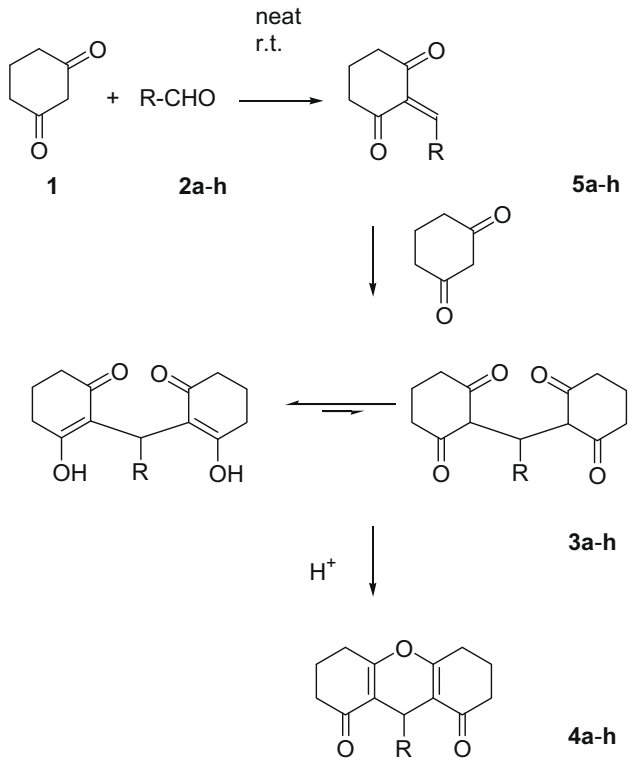
*General procedure of 1,8-dioxo-xanthenes **4a**–**h** and **8a**,**b**. (1) Aldol condensation/Michael addition*: 2.5 mmol of appropriate aldehydes and 5.0 mmol of 1,3-cyclohexane-dione were stirred for 24 h at room temperature in 2.0 ml CH_2Cl_2. The reactions were completed after that time (DC-control) and the reaction mixture was purified by column chromatography without any further extraction procedures.

(2) Cyclization: 0.5 g of corresponding Michael adducts **3a**-**h** or **7a**,**b** were stirred in 2.0 ml CH_2Cl_2 at room temperature in the presence of 5 mg pyridinium *p*-toluenesulfonate. After 30′ the reaction mixtures were extracted three times with saturated aq $NaHCO_3$-solution. The organic layers were separated, dried (Na_2SO_4), filtrated and evaporated i. vac.

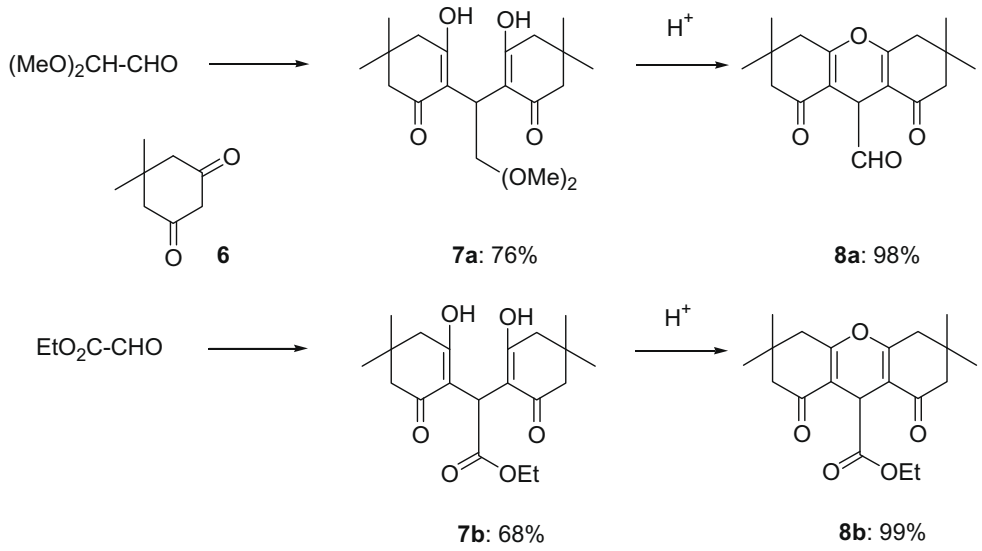
*2,2′-(2,2-Dimethoxyethane-1,1-diyl)bis(3-hydroxy-5,5-dimethyl-cyclohex-2-enone) (**7a**)*. Yield 76%; mp 104 °C (hexane/ethyl acetate); ^{1}H NMR: δ = 12.16 (br, 2H, OH), 5.58 (d, 1H, J = 9.1 Hz, CH), 4.14 (d, 1H, J = 9.5 Hz, CH), 3.27 (s, 6H, CH_3), 2.28 (s, 8H, CH_2), 1.06 (s, 12H, CH_3); ^{13}C NMR: δ = 190.0, 114.2, 100.6, 53.2, 46.4, 33.3, 31.3; HRMS: calcd for $C_{20}H_{30}O_6 + H^+$: 367.2115; found: 367.2114.



*3,3,6,6-Tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthene-9-carbaldehyde (**8a**)*. Yield 98%; mp 112 °C (hexane/ethyl acetate); ^{1}H NMR: δ = 9.90 (d, 1H, J = 0.8 Hz, CHO) 4.45 (d, 1H,

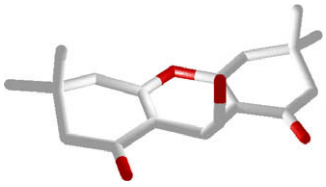


Scheme 2. Reaction mechanism.



Scheme 3. Aldol additions to 5,5-dimethyl-1,3-cyclohexanediones **6**.

J = 0.7 Hz, CH), 2.38 (s, 4H, CH_2), 2.26 (s, 6H, CH_3), 1.06 (s, 6H, CH_3); ^{13}C NMR: δ = 198.9, 196.6, 164.1, 111.0, 50.0, 40.6, 32.2, 28.9, 27.4; HRMS: calcd for $C_{18}H_{22}O_4 + H^+$: 303.1591; found: 303.1593.



Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft, Bayer-Schering Pharma AG, Bayer Services GmbH, BASF AG and Sasol GmbH. Petra Neubauer and Dr. Burhard Ziemer are gratefully acknowledged for the X-ray structure analyses.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.040.

References and notes

1. Takeshiba, H.; Jiyoujima, T. **1981**. Japan Kokai Tokkyo Koho JP 56005480. Tokyo: Japan Patent Office.
2. Poupelin, J. P.; Saint-Ruf, G.; Foussard-Blanpin, O.; Narcisse, G.; Uchida-Ernouf, G.; Lacroix, R. *Eur. J. Med. Chem.* **1978**, *13*, 67.
3. Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J., PCT Int. Appl. WO9706178, **1997**.
4. (a) Koeller, K. M.; Haggarty, S. J.; Perkins, B. D.; Leykin, I.; Wong, J. C.; Kao, M. C. J.; Schreiber, S. L. *Chem. Biol.* **2003**, *10*, 397; (b) Dimmock, J. R.; Raghavan, S. K.; Bigam, G. E. *Eur. J. Med. Chem.* **1988**, *23*, 111; (c) Baguley, B. C.; Ching, L. M. *Biodrugs* **1997**, *8*, 119; (d) Ferlin, M. G.; Marzano, C.; Chiarelotto, G.; Baccichetti, F.; Bordin, F. *Eur. J. Med. Chem.* **2000**, *35*, 827; (e) Anonini, I.; Polucci, P.; Magnano, A.; Martelli, S. *J. Med. Chem.* **2001**, *44*, 3329.
5. Quinonoid xanthenes with antisnake venom activity: (a) Selvanayagam, Z. E.; Gnanavendhan, S. G.; Balakrishna, K.; Rao, R. B.; Sivaraman, J.; Subramanian, K.; Puri, R.; Puri, R. K. *J. Nat. Prod.* **1996**, *59*, 664; Pyridoacridine marine alkaloids: (b) Delfourne, E.; Roubin, C.; Bastide, J. *J. Org. Chem.* **2000**, *65*, 5476; Osajaxanthone: (c) Wolfrom, M. L.; Komitsky, F.; Looker, J. H. *J. Org. Chem.* **1965**, *30*, 144; Gum gamboge: (d) Yates, P.; Karmarkar, S. S.; Rosenthal, D.; Stout, G. H.; Stout, V. F. *Tetrahedron Lett.* **1963**, *4*, 1623; Morellin: (e) Kartha, G.; Ramchandran, G. N.; Bhat, H. B.; Nair, P. M.; Raghavan, V. K. V.; Ventkatamaran, K. *Tetrahedron Lett.* **1963**, *4*, 459; Ergochrysine: (f) Apsimon, J. W.; Corran, A. J.; Creasey, N. G.; Marlow, W.; Whalley, W. B.; Sim, K. Y. *Proc. Chem. Soc., London* **1963**, 313.
6. Ferric hydrogen sulfate: (a) Shatterian, H. R.; Hosseinian, A.; Ghashang, M. *Turk. J. Chem.* **2009**, *33*, 1; Montmorillonite K10: (b) Dabiri, M.; Azimi, S. C.; Bazgir, A. *Chem. Papers* **2008**, *62*, 522; Sulfuric acid: (c) Seyyedhamzeh, M.; Mirzaei, P.; Bazgir, A. *Dyes Pigments* **2008**, *76*, 836; DOWEX-50W: (d) Imani-Shakibaei, G.; Mirzaei, P.; Bazgir, A. *Appl. Catal. A: Gen.* **2007**, *325*, 188; $HClO_4$: (e) Kantevari, R.; Bantu, R.; Nagarapu, L. *J. Mol. Catal. A: Chem.* **2007**, *269*, 53; Amberlyst-15: (f) Das, B.; Thirupathi, P.; Mahender, I.; Reddy, V. S.; Rao, Y. K. *J. Mol. Catal. A: Chem.* **2006**, *247*, 233; TMSCl: (g) Kantevari, S.; Bantu, R.; Nagarapu, L. *Arkivoc* **2006**, *xvi*, 136; Cyanuric chloride: (h) Zhang, Z. H.; Tao, X. Y. *Aust. J. Chem.* **2007**, *61*, 77; $BiCl_3$: (i) Li, J. J.; Tao, X. Y.; Zhang, Z. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **2008**, *183*, 1672.
7. Nafion-H: (a) Lin, H.; Zhao, Q.; Xu, B.; Wang, X. *J. Mol. Cat. A: Chem.* **2007**, *268*, 221; Acidic ionic liquids: (b) Fang, D.; Gong, K.; Liu, Z. L. *Catal. Lett.* **2009**, *127*, 291; Sulfonic acid: (c) Jin, T. S.; Zhang, J. S.; Xiao, J. C.; Wang, A. Q.; Li, T. S. *Synlett* **2004**, 866.
8. (a) Das, B.; Thirupathi, P.; Reddy, K.; Ravikanth, B.; Nagarapu, L. *Catal. Commun.* **2007**, *8*, 535; (b) Jin, T. S.; Zhang, J. S.; Wang, A. Q.; Li, T. S. *Ultrason. Sonochem.* **2006**, *13*, 220.
9. (a) Horning, E. C.; Horning, M. *J. Org. Chem.* **1946**, *11*, 95; (b) Cremlyn, R. J.; Saunders, D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *81*, 72; (c) Singh, K.; Singh, J.; Singh, H. *Tetrahedron* **1996**, *52*, 14273; (d) Shi, D.; Wang, Y.; Lu, Z.; Dai, G. *Synth. Commun.* **2000**, *30*, 713; (e) Tonkikh, N. N.; Strakovs, A.; Petrova, M. V. *Chem. Heterocycl. Compd.* **2004**, *40*, 43.
10. Venkatesan, K.; Pujar, S. S.; Lahoti, R. J.; Srinivasan, K. V. *Ultrason. Sonochem.* **2008**, *15*, 548.
11. Rohr, K.; Mahrwald, R. *Adv. Synth. Catal.* **2008**, *350*, 2877.
12. (a) Jones, G. *Org. React.* **1967**, *15*, 204; (b) Hobel, K.; Margaretha, P. *Helv. Chim. Acta* **1989**, *72*, 975.
13. (a) Margaretha, P.; Polansky, O. E. *Monatsh. Chem.* **1970**, *101*, 824; (b) Eaton, P. E.; Bunenelle, P. H. *Tetrahedron Lett.* **1984**, *25*, 23.