Tetrahedron Letters 55 (2014) 2908–2911

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile synthesis of highly substituted 2-pyrone derivatives via a tandem Knoevenagel condensation/lactonization reaction of β-formyl-esters and 1,3-cyclohexadiones

Firouz Matloubi Moghaddam [a,*], Zohreh Mirjafary [b], Marjan Jebeli Javan [a], Sara Motamen [a], Hamid Saeidian [c]

[a] Laboratory of Organic Synthesis and Natural Products, Department of Chemistry, Sharif University of Technology, PO Box 11155-9516, Tehran, Iran
[b] Department of Chemistry, Tehran Science and Research Branch, Islamic Azad University, Tehran, Iran
[c] Department of Science, Payame Noor University (PNU), PO Box 19395-4697, Tehran, Iran

ARTICLE INFO

Article history:
Received 2 November 2013
Revised 8 February 2014
Accepted 25 February 2014
Available online 4 March 2014

Keywords:
2-Pyrone derivatives
β-Formyl-esters
Knoevenagel condensation
Lactonization
ZnO nanoparticles

ABSTRACT

A mild and efficient tandem process for the synthesis of new highly substituted 2-pyrones starting from commercially available 2-arylacetic acids has been developed. The synthesis is based on the Knoevenagel condensation of 1,3-cyclohexadiones with various β-formyl-esters, followed by lactonization in the presence of nano ZnO (20 mol %). Moderate to high yields and readily available cheap starting materials are the key features of the present method.

2-Pyrone derivatives are versatile and valuable building blocks for a number of biologically and pharmaceutically active compounds.[1] They serve as conjugated dienes for the synthesis of complex compounds in Diels–Alder cycloaddition reactions and as precursors to other heterocyclic systems.[2] This moiety is found in a large number of biologically active compounds, which exhibit a wide range of activities such as pheromonal,[3] antifungal,[4] antitumor,[5] antileukemia,[6] antimicrobial[7] and neurotoxic effects.[8] Figure 1 shows some important representatives of this heterocyclic system.

The synthesis of such compounds has been the subject of several reports which show the high importance of these pyrones.[11] However, limited attention has been given to the synthesis of 3-aryl-2-pyrone derivatives.[12] Wolfbeis et al. reported a two-step method for the synthesis of 3-aryl-substituted 2-pyrone derivatives via condensation of cyclohexane-1,3-dione derivatives with triethoxymethane and various ureas to afford compounds **I** (Scheme 1). The reaction of **I** with activated acetonitriles in the presence of a strong base in DMF gave the title compounds in moderate yields.[12a]

It is evident that the need for the development of new and flexible protocols is required to access 3-aryl-substituted 2-pyrone derivatives without using toxic reagents and avoiding harsh conditions. Ethyl 2-formyl-2-aryl acetates have been found to be very effective 1,3-dielectrophiles reacting with a variety of nucleophiles, and have been used mainly for the synthesis of five- and six-membered heterocyclic compounds.[13]

The literature has highlighted the importance of nanosized materials in several scientific and technological areas, and many research councils have increased investments in nanotechnology.[14] In any metal oxide, surface atoms make a distinct contribution to catalytic activity. Nano zinc oxide is a very interesting metal oxide, because it has special surface properties, which suggests that a wide scope of organic chemistry may occur there. High yields, selectivity and recyclability have been reported for a variety of nanocatalyst-based organic reactions using ZnO.[15] During our studies on the preparation of ZnO nanoparticles by controlled microwave heating and their promising applications in *O*-acylation of alcohols[16a] and the synthesis of β-acetamido ketones/esters[16b] via a multicomponent reaction, we became interested in the synthesis of highly substituted 2-pyrones using nano ZnO as a nanocatalyst. In the context of our general interest in the synthesis of heterocyclic compounds,[17] herein, we report an efficient tandem reaction of commercially available 1,3-cyclohexadiones and

* Corresponding author. Tel.: +98 2166165309.
E-mail address: Matloubi@sharif.edu (F.M. Moghaddam).

http://dx.doi.org/10.1016/j.tetlet.2014.02.104
0040-4039/

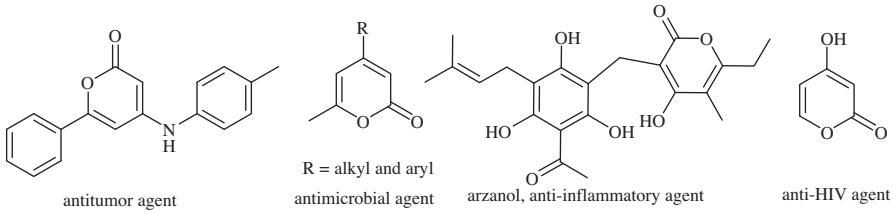
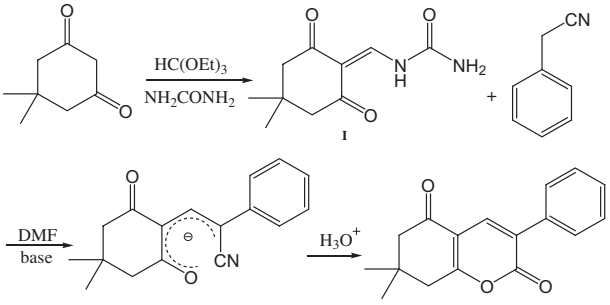
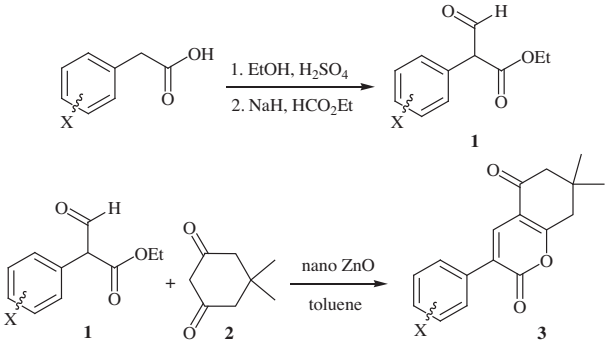


Figure 1. Examples of 2-pyrone-containing bioactive compounds.[9,10]



Scheme 1. Reported method for the synthesis of 2-pyrones.



Scheme 2. Efficient synthesis of highly substituted 2-pyrones.

β-formyl-esters in the presence of ZnO nanoparticles, which leads to highly substituted 2-pyrones in moderate to high yields (Scheme 2).

2-Formyl-2-aryl acetates **1** were synthesized in-house by an existing method.[18] The ZnO nanoparticles were prepared according to our previously reported procedure. [16a] Initially we set out to investigate the effect of solvents and bases on the reaction of ethyl 2-formyl-2-(4-methoxyphenyl)acetate (**1b**) and dimedone (**2**) as simple model substrates (see Table 2, entry 2). At room temperature, only a trace amount of the desired 2-pyrone was observed. However, the desired product was obtained in a good overall yield when conducted at higher temperatures. The results showed that the presence of a catalyst was required to achieve the synthesis of the desired products. During optimization of the reaction conditions, toluene and 20 mol % of ZnO nanoparticles were found to be the best solvent and catalyst, respectively (Table 1, entry 12). Under the optimized conditions, commercially available ZnO was also evaluated for the synthesis of the title compounds. Using ZnO nanoparticles as the catalyst, the reaction time was reduced, producing the product in higher yields, than when bulk ZnO was employed (98% vs 70%).

Using the optimized procedure, the reactions of 1,3-cyclohexadiones with various β-formyl-esters proceeded smoothly at 110 °C in the presence of 20 mol % of ZnO to afford highly substituted 2-pyrones. All the substrates consistently furnished the desired 2-pyrones in moderate to high yields and were not limited to ethyl 2-formyl-2-phenylacetate; ethyl 2-formyl-2-(naphthalen-3-yl)acetate also afforded the desired products **3d** and **3h** in good yields (Table 2, entries 4 and 8).[19]

The structures of the products were confirmed by EI-MS, ^{1}H NMR and ^{13}C NMR spectroscopy, and CHN analysis. It should be mentioned that the structure of **3a** was confirmed by a comparison with an authentic sample prepared by a reported method.[12a]

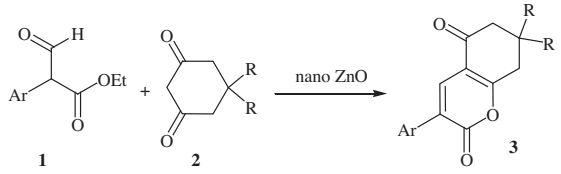
The characteristic signals for **3b** in the ^{1}H NMR spectrum were a singlet for the protons of the methoxy group at 3.87 ppm, a singlet for the methyl protons of the dimedone ring at 1.22 ppm, two singlets for the methylene protons at 2.46 and 2.78 ppm, and another singlet for the aromatic proton of the pyrone ring at 7.90 ppm.

Table 1
Optimization of the model reaction conditions[a]

Entry	Base	Solvent	Temp (°C)	Yield (%)
1	K_2CO_3	CH_3CN	80	Trace
2	Piperidine	CH_3CN	80	Trace
3	*p*-TsOH	CH_3CN	80	Trace
4	I_2	CH_3CN	80	Trace
5	DABCO	CH_3CN	80	38
6	Piperidine	EtOH	80	Trace
7	Nano ZnO	CH_3CN	80	66
8	Et_3N	Toluene	110	36
9	Nano ZnO	Acetone	60	41
10	Nano ZnO	Solvent-free	100	73
11	ZnO	Toluene	110	70
12	Nano ZnO	Toluene	110	98

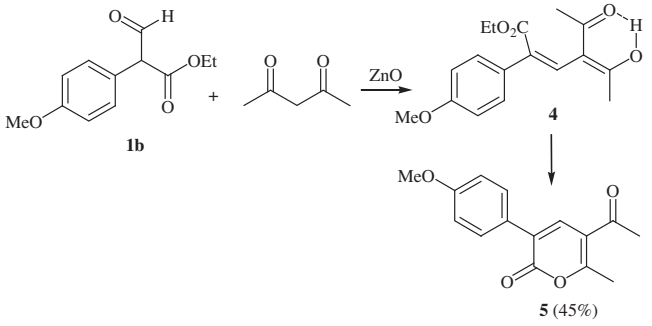
[a] Reaction conditions: solvent (5 mL), ethyl 2-formyl-2-(4-methoxyphenyl)acetate (**1b**) (1.3 mmol), dimedone **2** (1.0 mmol), catalyst (20 mol %), 15 h.

Table 2
Synthesis of highly substituted 2-pyrones

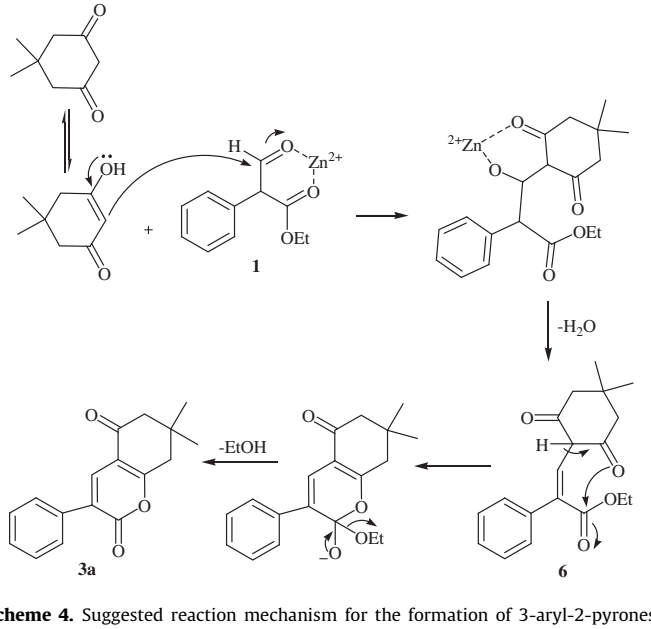


Entry	Ar	R	Product	Yield[a] (%)
1	C_6H_5	Me	**3a**	83
2	4-$MeOC_6H_4$	Me	**3b**	98
3	4-HOC_6H_4	Me	**3c**	78
4	2-Naphthyl	Me	**3d**	76
5	C_6H_5	H	**3e**	71
6	4-$MeOC_6H_4$	H	**3f**	68
7	4-HOC_6H_4	H	**3g**	70
8	2-Naphthyl	H	**3h**	61

[a] Isolated yields.



Scheme 3. Synthesis of 5-acetyl-3-(4-methoxyphenyl)-6-methyl-2*H*-pyran-2-one (**5**).



Scheme 4. Suggested reaction mechanism for the formation of 3-aryl-2-pyrones **3a–h**.

The ^{13}C NMR spectrum of **3b** showed 15 distinct resonances in agreement with the proposed structure.

When we carried out the reaction between ethyl 2-formyl-2-phenylacetate and pentane-2,4-dione, the expected 2-pyrone **5** was obtained in low yields (45%) after a long reaction time. It is thought that the intramolecular hydrogen bonding in intermediate **4** was responsible for this result (Scheme 3).

A plausible mechanism for the present reaction is proposed in Scheme 4. In the first step, ZnO nanoparticles are coordinated to the oxygen of the aldehyde and the ester, which activates the aldehyde carbonyl group for nucleophilic attack. Also, ZnO nanoparticles facilitate enolization of dimedone, such that it can undergo a Knoevenagel condensation with ethyl 2-formyl-2-phenylacetate in refluxing toluene to afford the intermediate **6** with the release of H_2O. Subsequently, the ring closure occurs through an intramolecular lactonization with loss of EtOH to give the desired 2-pyrones **3a–h**.

In summary, we have described a simple and efficient protocol for the synthesis of highly substituted 2-pyrones in moderate to high yields via one-pot tandem reactions. The synthesis is based on the Knoevenagel condensation of 1,3-cyclohexadiones with various β-formyl-esters, followed by lactonization using nano ZnO (20 mol %) as the nanocatalyst. Further studies on the synthesis of highly substituted 2-pyrone derivatives utilizing ZnO nanoparticles is in progress.

Acknowledgment

We gratefully acknowledge financial support from the Research Council of Sharif University of Technology. Z. M. thanks the National Elite Foundation for a scholarship.

Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR and EI-MS spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.104.

References and notes

1. McGlacken, G. P.; Fairlamb, I. J. S. *Nat. Prod. Rep.* **2005**, *22*, 369.
2. (a) Morrison, L. R.; Dickinson, J. M.; Ahmed, R.; Fairlamb, I. J. S. *Tetrahedron Lett.* **2002**, *43*, 8853; (b) Afarinkia, K.; Berna-Canovas, J. *Tetrahedron Lett.* **2000**, *41*, 4955; (c) Chen, C. H.; Liao, C. C. *Org. Lett.* **2000**, *2*, 2049; (d) Tam, T. F.; Coles, P. *Synthesis* **1988**, 383; (e) Ellis, G. P. In *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: New York, 1984, Vol. 3, Part 2B, Chapter 2.23, 647; (f) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.
3. Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71.
4. Evidente, A.; Cabras, A.; Maddau, L.; Serra, S.; Andolfi, A.; Motta, A. *J. Agric. Food Chem.* **2003**, *51*, 6957.
5. Dong, Y.; Goto, K. N.; Lai, C. Y.; Natschke, S. L. M.; Bastow, K. F.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2341.
6. Yoon, J. S.; Won, Y. W.; Kim, S. J.; Oh, S. J.; Kim, E. S.; Kim, B. K.; Cho, C. G.; Choi, J. H.; Park, B. B.; Lee, M. H.; Lee, Y. Y. *Invest. New Drug.* **2012**, *30*, 2284.
7. Fairlamb, I. J. S.; Morrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285.
8. Aytemir, M. D.; Calis, U. *Arch. Pharm.* **2010**, *343*, 173.
9. Bauer, J.; Koeberle, A.; Dehm, F.; Pollastro, F.; Appendino, G.; Northoff, H.; Rossi, A.; Sautebin, L.; Werz, O. *Biochem. Pharm.* **2010**, *81*, 251.
10. Thaisrivongs, S.; Tomich, P. K.; Watenpaugh, K. D.; Chong, K. T.; Howe, W. J.; Yang, C. P.; Strohbach, J. W.; Turner, S. R.; McGrath, J. P.; Bohanon, M. J.; Lynn, J. C.; Mulichak, A. M.; Spinelli, P. A.; Hinshaw, R. R.; Pagano, P. J.; Moon, J. B.; Ruwart, M. J.; Wilkinson, K. F.; Rush, B. D.; Zipp, G. L.; Dalga, R. J.; Schwende, F. J.; Howard, G. M.; Padbury, G. E.; Toth, L. N.; Zhao, Z.; Koeplinger, K. A.; Kakuk, T. J.; Cole, S. L.; Zaya, R. M.; Piper, R. C.; Jeffrey, P. *J. Med. Chem.* **1994**, *37*, 3200.
11. (a) Sunazuka, T.; Omura, S. *Chem. Rev.* **2005**, *105*, 4559; (b) Luo, T.; Dai, M.; Zheng, S. L.; Schreiber, S. L. *Org. Lett.* **2011**, *13*, 2834; (c) Liang, Y.; Xie, Y. X.; Li, J. H. *Synthesis* **2007**, 400; (d) Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Khabazzadeh, H.; Saidi, K. *Synthesis* **2006**, 435; (e) Huang, X.; Shen, R. *Synthesis* **2006**, 2731; (f) Kim, W. S.; Lee, J. H.; Kang, J.; Cho, C. G. *Tetrahedron Lett.* **2004**, *45*, 1683.
12. (a) Trummer, I.; Ziegler, E.; Wolfbeis, S. O. *Synthesis* **1981**, 225; (b) Lyukmanov, N. F.; Kovshev, E. I. *Chem. Heterocycl. Compd.* **1985**, *21*, 1215.
13. (a) Isabelle, P.; Cedric, B.; Andre, T.; Arnaud, G.; Francisco, C.; Jean, B. A.; Solo, G. *Bioorg. Med. Chem.* **2011**, *19*, 2517; (b) Bulut, M.; Erk, C. *J. Heterocycl. Chem.* **2001**, *38*, 1291; (c) Sergey, D. L.; Tatyana, S. S.; Oleg, C. N.; Vladimir, R. L.; Zakhar, S. O.; Alexander, A. S. *J. Org. Chem.* **2010**, *75*, 8487; (d) Jiau, H. L.; Chieh, H. M.; Ming, T. C.; Hsiung, L. K.; Chu, K. S. *Bioorg. Med. Chem.* **1998**, *6*, 1657.
14. Beaudry, C.; Allaoui, S. *Res. Policy* **2012**, *41*, 1589.
15. (a) Kassaee, M. Z.; Movahedi, F.; Masrouri, H. *Synlett* **2009**, 1326; (b) Gupta, M.; Paul, S.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2005**, *46*, 4957; (c) Sharghi, H.; Hosseini-Sarvari, M. *Synthesis* **2002**, 1057; (d) Tamaddon, F.; Amrollahi, A. M.; Sharafat, L. *Tetrahedron Lett.* **2005**, *46*, 7841; (e) Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.
16. (a) Matloubi, F. M.; Saeidian, H. *Mater. Sci. Eng. B.* **2007**, *139*, 265; (b) Mirjafary, Z.; Saeidian, H.; Sadeghi, A.; Matloubi, F. M. *Catal. Commun.* **2008**, *9*, 299.
17. (a) Matloubi, F. M.; Taheri, S.; Mirjafary, Z.; Saeidian, H. *Synlett* **2010**, 123; (b) Matloubi, F. M.; Koushki, B.; Saeidian, H.; Nourian, S.; Mirjafary, Z.; Kiamehr, M. *Pure Appl. Chem.* **2011**, *83*, 709. and references cited therein.
18. Aguilar, C. A.; Llado, J. B.; Garcia, P. C.; Onrubia Miguel, M. C.; Madrid, N. S. US patent 6506941 B1, **2001**; *Chem. Abstr.* **2001**, *134*, 147402.
19. *General procedure for the synthesis of highly substituted 2-pyrones* ***3a–h****:* To a stirred suspension of nano ZnO (18 mg) in toluene (5 mL) were added 1,3-cyclohexadione (**2**) (1.0 mmol) and the β-formyl-ester (1.3 mmol). The mixture was stirred at 110 °C for 15 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was recovered by filtration. The nano ZnO can be reused in subsequent reactions without losing any significant activity. The solvent was removed under reduced pressure, and the residue was separated by flash column chromatography on silica gel with petroleum ether/EtOAc (5:1) as eluent to afford the desired pure compound **3a–h**.
Representative spectroscopic data:
7,8-Dihydro-3-(4-methoxyphenyl)-7,7-dimethyl-6H-chromene-2,5-dione (***3b***)*:* Mp: 142–144 °C. ^{1}H NMR (500 MHz, $CDC1_3$): δ = 7.90 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.78 (s, 2H), 2.46 (s, 2H),

1.22 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.1, 171.2, 170.9, 170.8, 133.9, 129.1, 125.6, 125.1, 113.7, 113.0, 55.3, 50.7, 41.9, 32.9, 28.5 ppm. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.28; H, 5.98.

5-Acetyl-3-(4-methoxyphenyl)-6-methyl-2*H*-pyran-2-one (**5**): ^{1}H NMR (300 MHz, $CDC1_3$): δ = 7.75 (s, 1H), 7.62 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 2.64 (s, 3H), 2.51 (s, 3H) ppm. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.89; H, 5.51.