Synthesis of Polysubstituted α-Pyrones Using Zinc-Catalyzed Addition–Cyclization Reactions

Wei-Bing Liu,[a]* Cui Chen,[a] Qing Zhang,[a] and Zhi-Bo Zhu[b]*

[a]School of Chemistry and Life Science, Guangdong University of Petrochemical Technology, 2 Guangdu Road, Maoming 525000, China

[b]College of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515, China

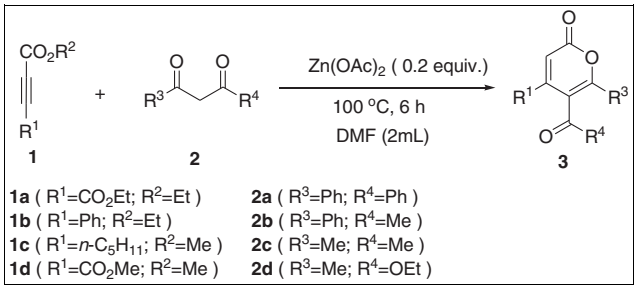
*E-mail: lwb409@yahoo.com.cn

Additional Supporting Information may be found in the online version of this article.

Received February 8, 2012

DOI 10.1002/jhet.1698

Published online 18 February 2014 in Wiley Online Library (wileyonlinelibrary.com).



Various polysubstituted α-pyrone derivatives have been directly synthesized via a hydroalkylation of Michael additional reaction following a cyclized process catalyzed by the Lewis acid of $Zn(OAc)_2$. This protocol provides a new convenient and step-economical route to construct heterocycles. Fourteen examples are obtained from easily available materials with moderate to good yields.

J. Heterocyclic Chem., **51**, 1541 (2014).

INTRODUCTION

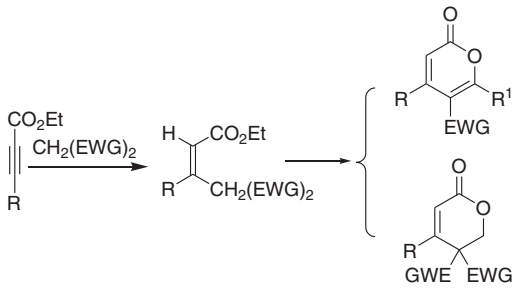
α-Pyrones and their analogs are found in numerous natural products that display important biological activities [1–10] and are also widely used as intermediates in organic and pharmaceutical synthesis [11–15]. Therefore, they have attracted much attention by researchers for the design and synthesis of polysubstituted and highly functionalized α-pyrones [16–24]. On the basis of our research, the various polysubstituted α-pyrones and their analogs were obtained by the reaction of alkynoates with activated methylene compounds in the presence of NaOH at a certain temperature (Scheme 1) [25]. In continuation of our studies, we became interested in exploring catalysts for addition–cyclization of alkynes by 1.3-dicarbonyl compounds, on which we report herein (Scheme 2).

RESULTS AND DISCUSSION

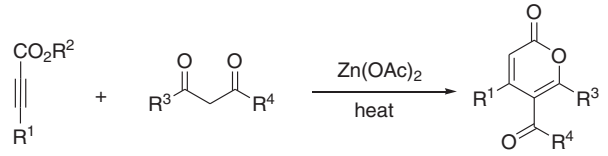
We initiated our studies by optimizing reaction conditions for the addition–cyclization of diethyl acetylenedicarboxylate (**1a**) by dibenzoylmethane (**2a**) (Table 1). As shown in Table 1, $Zn(OAc)_2$ proved to be more effective than the other tested Lewis acids or without any catalyst in dioxane at 100°C for 4 h (entries 1–7). Yet, among a set of representative solvents, dimethylformamide was chosen as the most effective solvent for the reactions (entries 8–12). It is noteworthy that 6 h proved to be the optimal reaction time (entries 13–14). Furthermore, 0.2 equivalent of $Zn(OAc)_2$ turned out to be the sacrificial amount of choice (entries 13 and 15). Increasing the amount of $Zn(OAc)_2$ cannot enhance the yield obviously.

Subsequently, we investigated the scope of the reaction substrates under the optimized conditions, as shown in Table 2. From the results, we can see that the electron-deficient internal alkynes with two strong electron-withdrawing groups were the good partners of alkynes and proved to be more suitable for this protocol than the alkynes with one strong electron-withdrawing group. For example, diethyl but-2-ynedioate (**1a**) and dimethyl but-2-ynedioate (**1d**) were the better substrates than ethyl 3-phenylpropiolate (**1b**) and methyl oct-2-ynoate (**1c**) for this transformation (Table 2 entries 1–14). This implied electron-deficient effect of alkynes had a positive influence on the reaction. As well as, the symmetrical 1,3-dicarbonyl compounds were the better substrates for this addition–cyclization reaction than asymmetrical 1,3-dicarbonyl compounds, as was verified with their corresponding yields. For instance, benzoylacetate (**2b**) and ethyl acetoacetate (**2d**) both gave lower yield to the corresponding product than dibenzoylmethane (**2a**) and acetylacetone (**1c**) (Table 2 entries 1–14). Finally, the experimental results suggested that this synthetic route includes the zinc(II)-catalyzed addition of activated methylenes of 1,3-dicarbonyl compounds to alkynoates to give the enolic adduct **5** [26,27],

Scheme 1. Synthesis of six-membered heterocycles based on alkynoates.



Scheme 2. Synthesis of α-pyrones.



which served as precursor to form the ethyl 5-acetyl-6-methyl-2-oxo-2*H*-pyran-4-carboxylate (**3ac**) by dealcoholic reaction (Scheme 3).

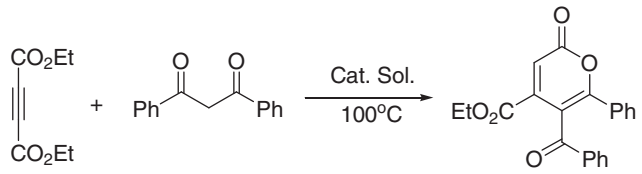
CONCLUSION

In conclusion, we have developed an efficient method for the synthesis of polysubstituted and highly functionalized α-pyrones using $Zn(OAc)_2$ as the catalyst. This protocol provides a convenient and step economical route to construct α-pyrones from easily available 1,3-dicarbonyl compounds and electron-deficient internal alkynes via a sequential addition–cyclization process.

Acknowledgments. The authors are grateful to the Guangdong University of Petrochemical Technology of China for financial support of this work.

Table 1

Optimization of reaction conditions.[a]



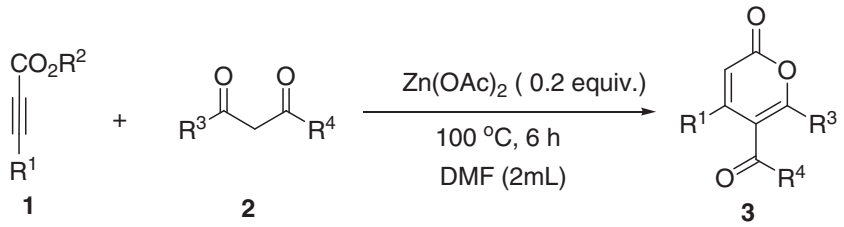
1a **2a** **3a**

Entry	Catalyst (0.2 equiv)	Solvent	Yield (%)[b]
1	$FeCl_3$	Dioxane	59
2	$CuCl_2$	Dioxane	51
3	$ZnCl_2$	Dioxane	68
4	ZnO	Dioxane	65
5	$Zn(OAc)_2$	Dioxane	75
6	$ZnBr_2$	Dioxane	70
7	None	Dioxane	42
8	$Zn(OAc)_2$	CH_3CN	74
9	$Zn(OAc)_2$	DMF	79
10	$Zn(OAc)_2$	DMSO	66
11	$Zn(OAc)_2$	THF	71
12	$Zn(OAc)_2$	Toluene	62
13[c]	$Zn(OAc)_2$	DMF	85
14[d]	$Zn(OAc)_2$	DMF	85
15[c,e]	$Zn(OAc)_2$	DMF	85

[a]Unless otherwise specified, all the reactions were carried out using 0.25 mmol of **1a**, 0.25 mmol of **2a** in 2.0 mL of solvent at 100°C for 4 h.
[b]GC yield.
[c]Reactional time: 6 h.
[d]Reactional time: 8 h.
[e]$Zn(OAc)_2$: 1.0 equiv.

Table 2

$Zn(OAc)_2$-induced domino synthesis of polysubstituted α-pyrones.[a]

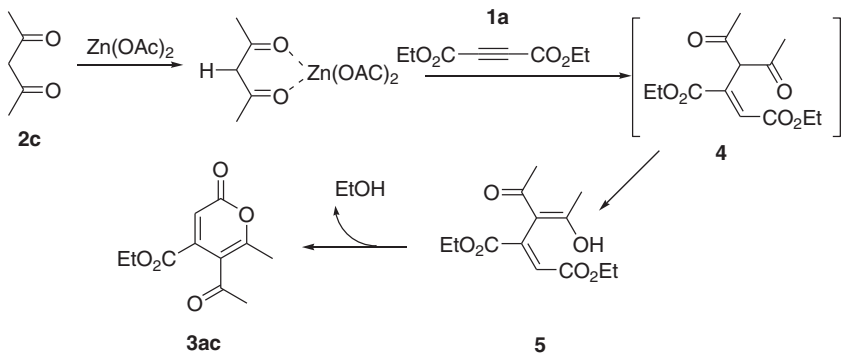


1a (R^1=CO_2Et; R^2=Et) **2a** (R^3=Ph; R^4=Ph)
1b (R^1=Ph; R^2=Et) **2b** (R^3=Ph; R^4=Me)
1c (R^1=*n*-C_5H_{11}; R^2=Me) **2c** (R^3=Me; R^4=Me)
1d (R^1=CO_2Me; R^2=Me) **2d** (R^3=Me; R^4=OEt)

Entry	1	2	3	Yield (%)[b]
1	**1a**	**2a**	**3aa**	78
2	**1a**	**2b**	**3ab**	75
3	**1a**	**2c**	**3ac**	82
4	**1a**	**2d**	**3ad**	73
5	**1b**	**2a**	**3ba**	75
6	**1b**	**2b**	**3bb**	71
7	**1b**	**2c**	**3bc**	80
8	**1b**	**2d**	**3bd**	66
9	**1c**	**2a**	**3ca**	71
10	**1c**	**2b**	**3cb**	65
11	**1c**	**2c**	**3cc**	72
12	**1c**	**2d**	**3cd**	67
13	**1d**	**2b**	**3db**	82
14	**1d**	**2d**	**3dd**	83

[a]All the reactions were carried out using 1.0 mmol of **1**, 1.0 mmol of **2**, 0.2 equivalent of $Zn(OAc)_2$ in 2.0 mL of DMF at 100°C for 4 h.
[b]Isolated yield.

Scheme 3. Hypothesized reaction pathway.



REFERENCES AND NOTES

[1] Vara Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. A. M.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. J Am Chem Soc 1994, 116, 6989.

[2] Kanai, A.; Kamino, T.; Kuramochi, K.; Kobayashi, S. Org Lett 2003, 5, 2837.

[3] Barrero, A. F.; Oltra, J. E.; Herrador, M. M.; Sanchez, J. F.; Quilez, J. F.; Rojas, F. J.; Reyes, J. F. Tetrahedron 1993, 49, 141.

[4] Abraham, W. R.; Arfmann, H. Phytochemistry 1988, 27, 3310.

[5] Evidente, A.; Cabras, A.; Maddau, L.; Serra, S.; Andolfi, A.; Motta, A. J Agric Food Chem 2003, 51, 6957.

[6] Evidente, A.; Conti, L.; Altomare, C.; Bottalico, A.; Sindona, G.; Segre, A. L.; Logrieco, A. Natural Toxins 1999, 7, 133.
[7] Chen, K. K.; Kovarikova, A. J. J Pharm Sci 1967, 56, 1535.
[8] Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. Tetrahedron Lett 1995, 36, 71.
[9] Schlingmann, G.; Milne, L.; Carter, G. T. Tetrahedron 1998, 54, 3013.
[10] Sato, H.; Konoma, K.; Sakamura, S. Agric Biol Chem 1981, 45, 1675.
[11] Joerg, T. B.; Stefan, F. K.; Stefan, F. K. Chem Com 2007, 4164.
[12] Gardner, S. C.; Kwon, O. Org Lett 2008, 10, 429.
[13] Lin, L. L.; Chen, Z. L.; Yang, X.; Liu, X. H.; Feng, X. M. Org Lett 2008, 10, 1311.
[14] Frébault, F.; Oliveira, M. T.; Wöstefeld, E.; Maulide, N. J Org Chem 2010, 75, 7962.
[15] Rosso, H.; Paolis, M. D.; Collin, V. C.; Dey, S.; Hecht, S. M.; Prandi, C.; Richard, V.; Maddaluno, J. J Org Chem, 2011, 76, 9429.
[16] Komiyama, T.; Takaguchi, Y.; Tsuboi, S. Tetrahedron Lett 2004, 45, 6299.
[17] Zhu, X. F.; Schaffer, A. P.; Li, R. C.; Kwon, O. Org Lett 2005, 7, 2977.
[18] Fukuyama, T.; Higashibeppu, Y.; Yamaura, R.; Ryu, I. Org Lett 2007, 9, 587.
[19] Yoshikawa, T.; Shindo, M. Org Lett 2009, 11, 5378.
[20] Dombray, T.; Blanc, A.; Weibel, J. M.; Pale, P. Org Lett, 2010, 12, 5362.
[21] Battenberg, O. A.; Nodwell, M. B.; Sieber, S. A. J Org Chem, 2011, 76, 6075.
[22] Fu, P.; Liu, P. P.; Qu, H. J.; Wang, Y.; Chen, D. F.; Wang, H.; Li, J.; Zhu, W. M. J Nat Prod, 2011, 74, 2219.
[23] Luo, T. P.; Dai, M. J.; Zheng, S. L.; Schreiber, S. L. Org Lett, 2011, 13, 2834.
[24] Majumdar, K. C.; Ansary, I.; Samanta, S.; Roy, B. Synlett 2011, 694.
[25] Liu, W. B.; Jiang, H. F.; Qiao, C. L. Tetrahedron 2009, 65, 2110.
[26] Zuo, W. X.; Hua, R.; Qiu, X. Synth Commun 2004, 34, 3219.
[27] Zhao, W. G.; Hua, R. M. Tetrahedron 2007, 63, 11803.