



Tetrahedron Letters 44 (2003) 2061-2063

TETRAHEDRON LETTERS

## Novel 2-pyrone synthesis via the nucleophilic addition of active methine compounds to 2-alkynone

Iwao Hachiya, Hitoshi Shibuya and Makoto Shimizu\*

Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan Received 8 December 2002; revised 9 January 2003; accepted 17 January 2003

Abstract—Novel 2-pyrone synthesis via the nucleophilic addition of active methine compounds to 2-alkynone has been developed. The reaction of active methine compounds with 2-alkynone provided 2-pyrones in good yields. © 2003 Elsevier Science Ltd. All rights reserved.

The development of the synthetic method of functionalized 2-pyrone is important as a result of the large number of biologically active compounds containing a 2-pyrone structure<sup>1</sup> and as dienes in Diels-Alder cvcloadditions.<sup>2</sup> Many synthetic methods of 2-pyrone have been reported to date.<sup>3</sup> As a recent example, Ma reported the efficient synthesis of  $\alpha$ -pyrone derivatives by a K<sub>2</sub>CO<sub>3</sub>-catalyzed Michael addition-lactonization reaction of 1,2-allenyl ketones with substituted acetates with electron-withdrawing groups.<sup>4</sup> We have recently reported novel 2-pyridone synthesis via the nucleophilic addition of malonic esters to alkynyl imines (Scheme 1, Eq. (1)).<sup>5</sup> We found that 3,4,5,6-tetrasubstituted-2pyrones were obtained when nucleophilic additions of malonic esters were carried out with 2-alkynones instead of alkynyl imines. In this paper, we describe



Scheme 1.

novel 2-pyrone synthesis via the nucleophilic addition of active methine compounds to 2-alkynones (Scheme 1, Eq. (2)).

The effects of bases in the model reaction of diethyl methylmalonate 1 ( $R^1=Me$ ) with *tert*-butyl 2-phenylethynyl ketone 2 ( $R^2=Ph$ ,  $R^3='Bu$ ) are shown in Table 1. In every case, the reaction proceeded in 1,4-dioxane under reflux for 1 h to give 5-ethoxycarbonyl-2-pyrone 3 accompanied by its decarboxylated 2-pyrone 4. Among the bases tested, sodium hydride and sodium ethoxide were effective (entries 1 and 2).

Next, we investigated the effect of the substituent  $R^3$  of 2-alkynone 2. The reaction of methyl 2-phenylethynyl ketone 2 ( $R^2 = Ph$ ,  $R^3 = Me$ ) gave only the 1,4-adduct 5 ( $R^1 = Me$ ,  $R^2 = Ph$ ,  $R^3 = Me$ ) in 58% yield (entry 4). On the other hand, ethyl and isopropyl ketones afforded 2-pyrones 3, their decarboxylated 2-pyrones 4, and 1,4-adducts 5, respectively (entries 5 and 6). In the case of *tert*-butyl and phenyl ketones, 2-pyrones 3 and their decarboxylated 2-pyrones 4 were obtained, respectively (entries 1 and 7).

Several examples of the present 2-pyrone synthesis via the nucleophilic addition of malonic esters to 2alkynones were examined.<sup>6</sup> *tert*-Butyl 2-(1-cyclohexenyl) ketone **2** ( $R^2$ =1-cyclohexenyl,  $R^3$ ='Bu) having a double bond gave 2-pyrone **3** ( $R^1$ =Me,  $R^2$ =1-cyclohexenyl,  $R^3$ ='Bu) in 87% yield (entry 8). In the case of 2-alkynone **2** ( $R^2$ =TBS(CH<sub>2</sub>)<sub>3</sub> or TBDPS(CH<sub>2</sub>)<sub>3</sub>,  $R^3$ = 'Bu), decarboxylated 2-pyrones **4** were obtained as major products (entries 9 and 10). However, the reaction of diethyl allylmalonate **1** ( $R^1$ =allyl) gave the desired 2-pyrone **3** ( $R^1$ =allyl,  $R^2$ =Ph,  $R^3$ ='Bu) in low yield (entry 11).<sup>7</sup> We next examined a  $\beta$ -ketoester as a

0040-4039/03/\$ - see front matter @ 2003 Elsevier Science Ltd. All rights reserved. doi:10.1016/S0040-4039(03)00211-9

<sup>\*</sup> Corresponding author. Tel.: +81-59-231-9413; fax: +81-59-231-9413; e-mail: mshimizu@chem.mie-u.ac.jp

Table 1. 2-Pyrone synthesis using malonic esters<sup>a</sup>

	$EtO_2C \xrightarrow{R^1} + EtO_2C$ 1 (2.5 equiv)	$R^{2}$ $R^{2}$ $R^{2}$ $R^{2}$ $R^{2}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{2}$ $R^{3}$ $R^{3$	$\begin{array}{c} \text{ane} \\ 1 \text{ h} \\ n \\ 1 \text{ h} \\ n \\ $	$\mathbf{\hat{R}}^{3}_{\text{Et}} + \mathbf{\hat{R}}^{1}_{\text{R}^{2}} + \mathbf{\hat{R}}^{0}_{\text{R}^{2}}$	$EtO_2C$ $EtO_2C$ $+ R^2$ $R^3$	0 R <sup>3</sup>	
Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Base	Yield (%)		
					3	4	5
1	Me	Ph	'Bu	NaH	75	9	
2	Me	Ph	<sup>t</sup> Bu	NaOEt	80	7	
3	Me	Ph	<sup>t</sup> Bu	KO <sup>t</sup> Bu	53	4	
4	Me	Ph	Me	NaOEt			58
5	Me	Ph	Et	NaOEt	19	10	25
6	Me	Ph	<sup><i>i</i></sup> Pr	NaOEt	49	13	17
7	Me	Ph	Ph	NaOEt	56	8	
8	Me	1-Cyclohexenyl	<sup>t</sup> Bu	NaOEt	87		
9	Me	TBSO(CH <sub>2</sub> ) <sub>3</sub>	<sup>t</sup> Bu	NaH	20	43	
10	Me	TBDPSO(CH <sub>2</sub> ) <sub>3</sub>	<sup>t</sup> Bu	NaH	24	50	
11	Allyl	Ph	<sup>t</sup> Bu	NaH	9		

<sup>a</sup> For reaction conditions, see Ref. 6.

nucleophile instead of malonic esters. While under the conditions reported<sup>5</sup> the reaction of  $\beta$ -ketoesters with alkynyl imines provided 2-pyridones in good yields,<sup>8</sup> that of ethyl 2-methyl-3-oxobutanoate **6** (R = Me) with *tert*-butyl 2-phenylethynyl ketone proceeded to give 5-acetyl-2-pyrone **7** (R = Me) in 60% yield along with its deacetylated 2-pyrone **8** (R = Me) in 6% yield (Table 2, entry 1). Even by increasing the steric bulk of the nucleophile with ethyl 2-(2-propenyl)-3-oxobutanoate **6** (R = allyl), 5-acetyl-2-pyrone **7** (R = allyl) was obtained in 58% yield.

Table 2. 2-Pyrone synthesis using  $\beta$ -keto esters<sup>a</sup>



<sup>a</sup> For reaction conditions, see Ref. 6.

We propose a plausible reaction mechanism as shown in Scheme 2. Metalloallenoate 11 would be generated via the 1,4-addition reaction of the active methine compound sodium salts 9 to 2-alkynone 10 and would undergo intramolecular cyclization give to cyclobutenoxide intermediate 12. The cyclobutenoxide intermediate 12 would be transformed into the metalenolate 13 via ring-opening, and the subsequent cyclization would give 2-pyrone 14 (Path A). Metalloallenoate 11 would undergo protonation to give  $\alpha,\beta$ -unsaturated ketone 15. The decarboxylated 2-pyrone 16 would be formed via the nucleophilic addition of sodium alkoxide to the carbonyl group of 15 and the subsequent cyclization (Path B).9

To obtain decarboxylated 2-pyrone, 2-methyl Meldrum's acid 17 was used as a nucleophile (Eq. (3)). The reaction of 17 with *tert*-butyl 2-phenylethynyl ketone using NaHMDS as a base gave only 2-pyrone 18 in 79% yield.



We suggest a possible reaction mechanism as shown in Scheme 3. Metalloallenoate **20** would be generated via the 1,4-addition reaction of 2-methyl Meldrum's acid sodium salts **19** to *tert*-butyl 2-phenylethynyl ketone. Metalloallenoate **20** would undergo protonation to give  $\alpha,\beta$ -unsaturated ketone **21**. The decarboxylated 2pyrone **18**, acetone and carbon dioxide would be formed via the thermolysis of  $\alpha,\beta$ -unsaturated ketone **21** and the subsequent cyclization.



Scheme 2.





In summary, we have found a novel method for 2pyrone synthesis by the 1,4-addition of active methine compounds to 2-alkynone. Although numerous methods for the synthesis of 2-pyrones are available, in the present reactions, 3,4,6-trialkyl-5-ethoxycarbonyl or 5acetyl-2-pyrones can be easily obtained via a novel reaction mechanism including cyclobutenoxide intermediates because 2-alkynones and active methine compounds such as malonic esters and  $\beta$ -ketoesters, respectively, are readily available. The synthetic application of 2-pyrones is now in progress.

## References

 For examples, see: (a) Chen, K. K.; Kovarikova, A. J. *Pharm. Sci.* **1967**, *56*, 1535; (b) Kupchan, S. M.; Moniot, J. L.; Sigel, C. W.; Hemingway, R. J. J. Org. Chem. **1971**, *36*, 2611; (c) Hayashi, Y.; Yuki, Y.; Matsumoto, T.; Sakan, T. *Tetrahedron Lett.* **1977**, *18*, 3637; (d) Prasad, J. V. N. V.; Para. K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B., Jr.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. M. A.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. J. Am. Chem. Soc. **1994**, 116, 6989.

- Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* 1992, 48, 9111.
- Staunton, J. In *Comprehensive Organic Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1979; Vol. 4, pp. 629–658.
- 4. Ma, S.; Yin, S.; Li, L.; Tao, F. Org. Lett. 2002, 4, 505 and references cited therein.
- 5. Hachiya, I.; Ogura, K.; Shimizu, M. Org. Lett. 2002, 4, 2755.
- 6. A typical experimental procedure of the reaction of 2-alkynone with an active methine compound: To 60% NaH or sodium ethoxide (0.400 mmol) was added a solution of an active methine compound (0.500 mmol) in 1,4-dioxane (2.0 mL) and a solution of 2-alkynone (0.200 mmol) in 1,4-dioxane (2.0 mL) successively at room temperature. The reaction mixture was stirred under reflux for 1 h and then cooled to room temperature. Brine (10 mL) was added to quench the reaction. The mixture was extracted with dichloromethane (15 mL×3). The combined organic layers were dried over sodium sulfate. The solvents were evaporated in vacuo, and then the residue was purified by preparative TLC on silica gel to give 2-pyrone and decarboxylated 2-pyrone.
- 7. When dimethyl allylmalonate was used instead of diethyl allylmalonate, the desired 2-pyrone and its decarboxylated 2-pyrone were obtained in 24 and 6% yields, respectively.
- For example, the reaction of ethyl 2-methyl-3-oxobutanoate
   6 (R = Me) with the imine derived from 3-phenyl-2-propynal and 4-methoxyaniline gave *N*-(4-methoxyphenyl)-5-acetyl-3-methyl-4-phenyl-2-pyridone in 64% yield. The details of the 2-pyridone synthesis via nucleophilic addition of β-ketoesters to alkynyl imines will be reported in a full paper.
- 9. In the case of malonic esters as a nucleophile, it would be possible to generate cyclobutenone **22**. See Ref. 5.

