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Convenient synthesis of 5-methylene-4-substituted-2(5*H*)-furanones

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Abstract—A synthesis of novel 4-(substituted)benzyl-5-methylene-2(5*H*)-furanones involving Stobbe condensation of substituted aldehydes with ethyl levulinate followed by treatment with acetic anhydride in the presence of sodium acetate, has been developed.

The furanone moiety is present in a number of natural products and can be an important platform for the total synthesis of various natural products as well as for the development of new asymmetric methodologies.[1] Recently, increasing attention has been given to developing new synthetic routes for polysubstituted furanones, 5-alkylidenefuranones in particular, due to their widespread occurrence and biological activity.[2]

Protoanemonin[3] **1** is the simplest representative of this class, which forms the core of several naturally occurring molecules[4a–e] (Fig. 1). In the class of 5-alkylidene furanones, it was found that the exomethylene moiety is responsible for the biological activity of these molecules.[4a] Very few methods are available for the synthesis of substituted 5-alkylidenefuranones and the utility of these methods suffers from certain drawbacks such as restricted generality,[5a] multistep sequences[5b] and the use of expensive chemicals.[5c,d] We disclose here a synthesis of novel 4-(substituted)benzyl-5-methylene-2(5*H*)-furanones, involving Stobbe condensation[6] of substituted arylaldehydes with ethyl levulinate to give the key intermediate **7** followed by cyclization (Scheme 1).

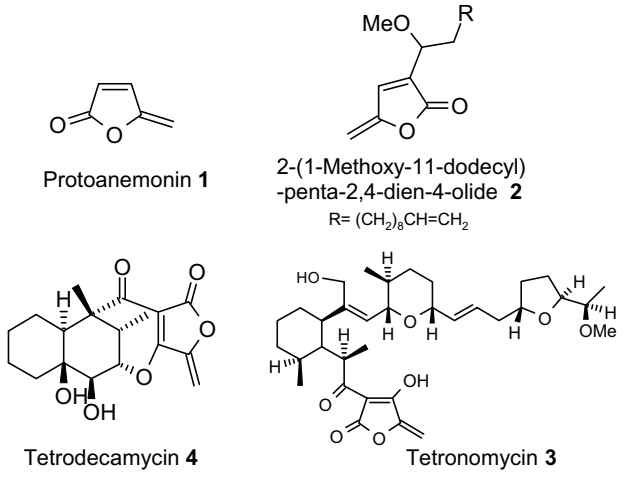

Figure 1.

The regioselectivity of the condensation was greatly dependent upon the temperature of the reaction and the substitution pattern of the aromatic aldehyde. The reaction was conducted at different temperatures for optimization of conditions to achieve a maximum yield of the desired product **7**. At room temperature the product was a mixture of **7** and **8** in equal ratio, whereas the yield of **7** could be increased when the reaction was performed at lower temperature (−10 °C). Acid **8** was obtained exclusively using DBU in refluxing dry THF.

The acid **7** was further treated with anhydrous sodium acetate and acetic anhydride to give furanone **9**. The quantity of acetic anhydride used and the reaction temperature controlled the nature of product. Formation of substituted naphthalene derivative **11** predominated (85–95%) at 110–120 °C, whereas the reaction proceeded to give furanone **9** as the major product at 80–90 °C. More than 5 equiv of acetic anhydride and high temperature resulted in a decrease in the proportion of furanone. The competing formation of *E* mixed anhydride **10** and the naphthalene derivative **11** could not be totally avoided. A plausible mechanism for the formation

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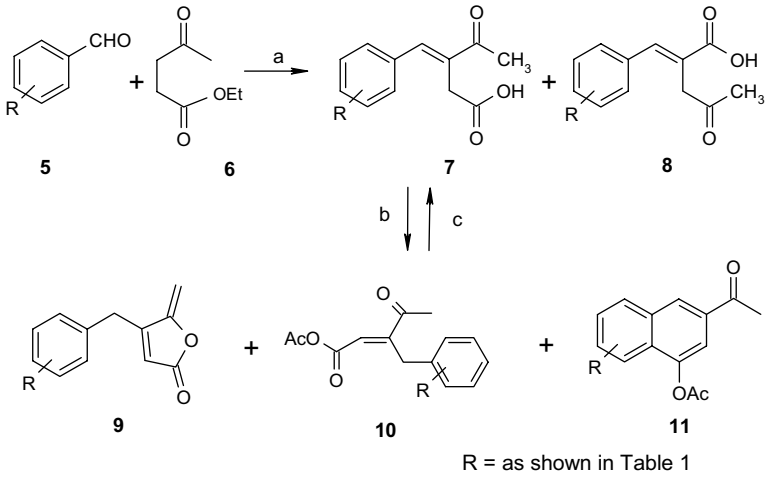
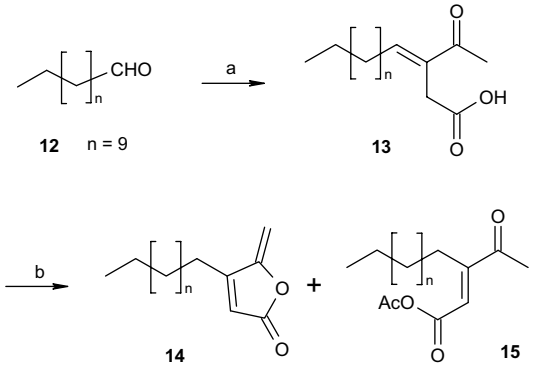


Scheme 1. Reagents and conditions: (a) aq NaOH, ethanol, −10 °C, 4–5 h, (**7**, 80–95%); or Ref. 6; (b) anhydr NaOAc, Ac_2O, 80 °C, 3 h; (c) aq NaOH, ethanol, rt, 2–3 h.



Scheme 2. (a) Reagents and conditions: **6**, aq NaOH, ethanol, −10 °C, 4–5 h, (**13**, 82%); (b) anhydr NaOAc, Ac_2O, 80 °C, 3 h, (**14**, 51%; **15**, 24%).

of furanone **9** in a single step from the corresponding intermediate **7** involves firstly isomerization of the double bond from aryl conjugation to carbonyl conjugation followed by enolization and lactonization. We believe that the double bond isomerization proceeds to give a mixture of *Z* and *E* products and then the *Z* isomer of compound **10** favors the formation of furanone **9**, while its *E* isomer remains unreacted at 80–90 °C. On the other hand, a higher temperature 110–120 °C favors the formation of the more stable *E* isomer which readily cyclizes to the naphthalene derivatives **11**.

The intermediate **7** could be recovered by hydrolysis of mixed anhydride **10** using aqueous sodium hydroxide. It was noteworthy that during hydrolysis the isomerized double bond regained its original orientation as shown in Scheme 1. This simple protocol[7] proved to be general for the synthesis of furanones **9** starting from a variety of aromatic aldehydes and dodecyl aldehyde (an example of an aliphatic aldehyde to show the versatility of the protocol Scheme 2).

Table 1. Ratio of compounds **9**:**10**:**11** in % yield

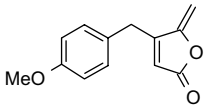
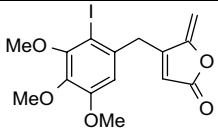
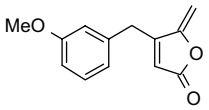
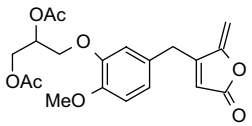
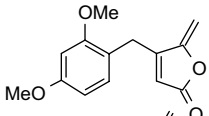
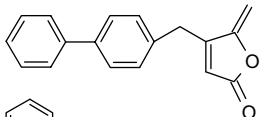
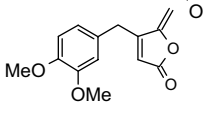
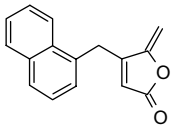
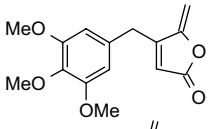
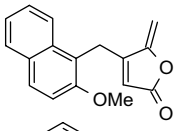
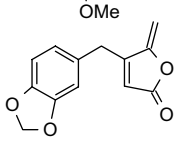
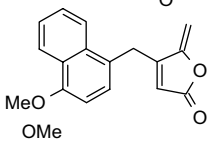
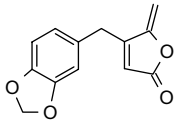
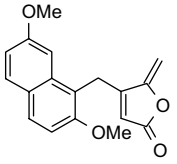
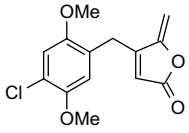
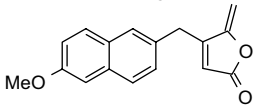
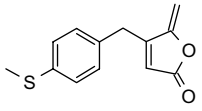
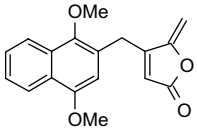
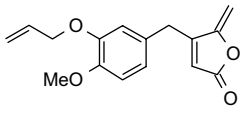
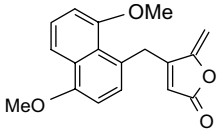
Entry	Product **9**	Yield[a] (%)			Entry	Product **9**	Yield[a] (%)		
		9	**10**	**11**			**9**	**10**	**11**
1		52	27	11	11		57	33	8
2		50	32	13	12		57	34	2
3		64	18	8	13		60	23	—
4		56	24	18	14		67	15	18

Table 1 (*continued*)

Entry	Product **9**	Yield[a] (%)			Entry	Product **9**	Yield[a] (%)		
		9	**10**	**11**			**9**	**10**	**11**
5		72	17	9	15		61	20	—
6		67	21	5	16		62	18	15
7		55	30	12	17		58	32	—
8		75	10	6	18		57	12	20
9		63	22	10	19		64	17	13
10		48	20	15	20		52	29	6

[a] Isolated yield.

The novel 5-methylene-4-substituted-2(5*H*)-furanones[8] described in the present communication and depicted in Table 1 were found to be more stable as compared to protoanemonin. The furanones showed characteristic IR carbonyl absorptions[9] and the ^{1}H NMR spectra were in full agreement with 5-methylenelactone moiety. The ^{13}C assignments of the furanones were made by ^{1}H decoupled and DEPT experiments. Signals obtained by ^{1}H–^{1}H COSY and NOESY spectra confirmed the structures of the corresponding furanones **9** and mixed anhydrides **10**.

In summary, we have developed an efficient two-step and conceptually novel strategy for the synthesis of 4-(substituted)benzyl/naphthylmethylene-5-methylene-2(5*H*)-furanones. Our method has the advantages of simplicity and good yields from commercially available starting materials.

Acknowledgements

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References and notes

1. Carter, N. B.; Nadany, A. E.; Sweeny, J. B. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 2324–2342.
2. (a) Manny, A. J.; Kjelleberg, S.; Kumar, N.; Nys, R. D.; Read, R. W.; Steinberg, P. *Tetrahedron* **1997**, *53*, 15813–15826; (b) Bruckner, R. *Chem. Commun.* **2001**, 141–152.
3. (a) Shaw, E. *J. Am. Chem. Soc.* **1946**, *68*, 2510–2511; (b) Gruxdmann, C.; Kober, E. *J. Am. Chem. Soc.* **1955**, *77*, 2332–2333.
4. (a) Painter, F. F.; Bauscke, G.; Kestel, M. *Tetrahedron Lett.* **2000**, *41*, 9977–9980; (b) Hori, K.; Hikage, N.; Inagaki, A.; Mori, S.; Nomura, K.; Yoshii, E. *J. Org. Chem.* **1992**, *57*, 2888–2992; (c) Lee, S.; Chang, S.; Chen, C. *J. Nat. Prod.* **2001**, *64*, 1548–1551; (d) Kwon, H. C.; Baek, N. I.; Choi, S. U.; Lee, K. R. *Chem. Pharm. Bull.* **2000**, *48*, 614–616; (e) Jacobi, P. A.; Yongkai, L. *Org. Lett.* **2003**, *5*, 701–704.
5. (a) Sorg, A.; Siegel, K.; Bruckner, R. *Synlett* **2004**, 321–325; (b) Grigg, R.; Savic, V.; Thornton-Pett, M. *Tetrahedron* **1997**, *53*, 10633–10642; (c) Tanabe, Y.; Ohino, N. *J. Org. Chem.* **1988**, *53*, 1560–1563; (d) Krafft, M. E.; Pankowski, J. *Synlett* **1991**, 865–866.
6. Swaminathan, B. V. *Ind. J. Chem.* **1976**, *14B*, 620.
7. Typical procedure for the synthesis of 5-methylene-4-benzyl (substituted)-2(5*H*)-furanones **9**. The carboxylic acid **7** (102 mmol) was mixed with anhydrous sodium acetate (204 mmol) and acetic anhydride (510 mmol) and allowed to stir at 85 °C under nitrogen for 3 h. The mixture was allowed to cool to rt when crystals of sodium acetate precipitated. The reaction mixture was poured on ice,

stirred vigorously for 30 min and extracted with ethyl acetate. The organic layer was washed repeatedly with fresh portions of water, followed by dilute sodium bicarbonate solution, then with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by column chromatography (silica gel) using petroleum ether–ethyl acetate as eluent provided the desired furanones **9** (yields 48–75%).

5-Methylene-4-(3,4,5-trimethoxybenzyl)furan-2 (5*H*)-one. Yield 72%; mp 115 °C; IR ($CHCl_3$) ν 3018, 1787, 1765, 1212 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.71 (s, 2H), 3.80 (s, 9H), 4.93 (d, J = 2.9 Hz, 1H), 5.15 (m, 1H), 5.81 (br s, 1H), 6.36 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 33.06, 56.29 (2C), 60.89, 94.67, 106.25 (2C), 118.60, 131.50, 137.68, 153.81 (2C), 155.76, 157.89, 168.44; MS (FAB) *m*/*z* (% relative intensity) 276 (M^+, 100), 261 (9), 245 (10), 217 (21), 181 (81), 166 (22). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.79%. Found: C, 65.33; H, 5.84%.

8. Our disclosure: Gurjar, M. K.; Wakharkar, R. D.; Borate, H. B.; Mahajan, V. A.; Shinde, P. D.; Bhure, M. H.; Mahajan, D. C. Indian Patent 1559/DEL/2003.
9. Winston, A.; Kemp, R. N. *Tetrahedron* **1971**, *27*, 543–548.