SHORT PAPER

J. Chem. Research (S), 2000, 179–181

A rapid and efficient one-pot synthesis of substituted 2-(*5 H*)-furanones under focused microwave irradiations†

Liang Liao[a,b] and Didier Villemin[a]*

[a]*Ecole Nationale Supérieure d'Ingénieurs de Caen, ISMRA, UMR CNRS 6507, F-14050 Caen, Cedex, France*

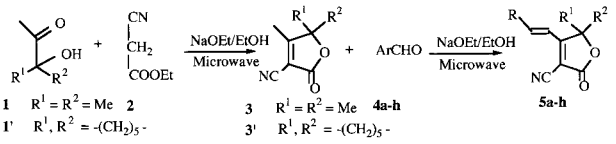
[a]*Guangxi Teachers University, Dept of Chemistry and Chemical Engineering, Guilin, 541004, Guangxi, China*

3-Hydroxy-3-methyl-2-butanone **1** reacted with ethyl cyanocetate in **2** in the presence of sodium ethoxide under focused microwave irradiations to afford 3-cyano-4,5,5-trimethyl-2-(*5H*)-furanone **3**. Furanone **3** then condensed with aromatic or heteroaromatic aldehydes **4a–h** to produce 3-cyano-4-(*trans*-aryl-vinyl)-5,5-dimethyl-2-(*5H*)-furanones **5a–h** in high overall yields (71–88%).

The 2-(*5H*)-furanone (or but-2-en-4-olide) nucleus is present in a wide variety of biologically active compounds,[1] such as vitamin C, Annonaceous acetogenins,[2] digitoxin and related cardenolides.[3] 2-(*5H*)-Furanones are also versatile synthetic intermediates.[3] Our interest in furanone derivatives and success in an one-pot efficient synthesis of Cerpegin[4] encouraged us to investigate a more efficient procedure for the synthesis of substituted 2-(*5H*)-furanones. Using focused microwave irradiation, we have developed a one-pot efficient synthesis of substituted 2-(*5H*)-furanones.

The reaction of 3-hydroxy-3-methyl-2-butone **1** with ethyl cyanocetate **2** in the presence of sodium ethoxide under focused microwave irradiation gave 3-cyano-4,5,5-trimethyl-2-(*5H*)-furanone **3**.[5] This lactone possesses an acidic methyl group and Perjéssy *et al*.[6] have reported that the condensation of lactone **3**, which has an acidic proton, and aldehyde **4b** in presence of sodium hydroxide in methanol under reflux for 4 hours gives 3-cyano-4-(thiophen-2-yl-vynyl)-5,5-dimethyl-2-(*5H*)-furanone **5b**. We have found that this condensation also takes place readily using sodium ethoxide as base. Therefore, it is possible to prepare furanones **5a–h** from 3-hydroxy-3-methyl-2-butanone **1**, ethyl cyanoacetate **2** and aromatic or heteroaromatic aldehydes **4a–h** according the Scheme 1 in two successive reactions.

Reactions under focused microwave irradiation[5] are more rapid and the yields are the same or better than those using classical heating (**5b**[6] for example). The overall yields in one-pot synthesis of **5a–h** are between 71% and 88% (Table 1). Physical data, NMR spectra and mass spectra data are listed in



Scheme 1 One-pot synthesis of furanoes **5a–h** under focused microwave irradiation

Table 1 Physical and yield data of products **5a–h**

Product	R^1	R^2	Ar	Yield (%)
5a	$-CH_3$	$-CH_3$	Furan-2-yl	82
5a′	$-(CH_2)_5-$		Furan-2-yl	85
5b	$-CH_3$	$-CH_3$	Thiophen-2-yl	82
5c	$-CH_3$	$-CH_3$	Thiophen-3-yl	98
5d	$-CH_3$	$-CH_3$	Pyridin-2-yl	74
5e	$-CH_3$	$-CH_3$	Pyridin-4-yl	74
5f	$-CH_3$	$-CH_3$	3,4-di-Cl-C_6H_3	78
5g	$-CH_3$	$-CH_3$	2,6-di-C_6H_3	86
5h	$-CH_3$	$-CH_3$	3-OH,4-OMe-C_6H_3	88

Product	Colour	MP(°C)	Yield[a](%)	Formula(fw)	Calculated(%)	Found(%)
5a	Yellow	195	82	$C_{13}H_{11}NO_3$	C 68.12 H 4.84	C 68.23 H 4.67
5a′	Yellow	250	88	$C_{16}H_{15}NO_3$	C 71.36 H 5.61	C 72.40 H 5.35
5b	Green	156[b]	82	$C_{13}H_{11}NO_2S$	C 63.66 H. 4.52	C 63.42 H 4.70
5c	Brown	150	86	$C_{13}H_{11}NO_2S$	C 63.66 H 4.52	C 63.55 H 4.65
5d	Yellow	239	74	$C_{14}H_{12}N_2O_2$	C 69.99 H 5.03	C 70.11 H 4.99
5e	Yellow	153	74	$C_{14}H_{12}N_2O_2$	C 69.99 H 5.03	C 70.07 H 5.01
5f	Yellow	206	78	$C_{15}H_{11}Cl_2NO_2$	C 58.46 H 3.60	C 58.26 H 3.55
5g	Yellow	150	86	$C_{15}H_{11}Cl_2NO_2$	C 58.46 H 3.60	C 58.32 H 3.58
5h	Orange	250	88	$C_{16}H_{15}NO_4$	C 67.36 H 5.30	C 67.02 H 5.45

[a]In a focussed microwave cavity (cavity EO13 of MES), 60 W 10 min and 60 W 10 min

[b]Lit[6] 153–154 °C.

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

Table 2 NMR spectral data of products **5a–h**[a]

Prd	^{1}H NMR δ *J* (Hz)	^{13}C NMR δ
5a	1.65 (6 H, s, 2 C*H*$_3$), 6.60 (1 H, q, arom), 6.74 (1 H, d, *J* 16.1 Hz, *trans* HC=C*H*), 6.86 (1 H, d, arom), 7.57 (1 H, d, *J* 16.1 Hz, C*H*=CH), 7.62 (1 H, s, arom).	25.9 (2 *C*H$_3$), 87 (-O*C*(*C*H$_3$)$_2$), 97.3 (NC-*C*=C), 112.3, 112.5 (-*C*N), 113.6, 118.7, 131.2, 147, 150.9, 166.3 (*C*=O), 176, (NC-C=*C*).
5a′	1.15-1.35 (2 H, m, CH$_2$), 1.55-1.90 (8 H, m, 4 × CH$_2$), 6.59 (1 H, dd, $^3J_{HH}$ = 1.4 Hz, $^3J_{HH}$ = 3,4 Hz, H$_{arom4}$), 66.6 (1 H, d, $^3J_{HH}$ = 16.1 Hz, *trans* HC=CH), 6.84 (1 H, d, $^3J_{HH}$ = 3,4 Hz, H$_{arom3}$), 7.61, (1 H, $^3J_{HH}$ =1.4 Hz, H$_{arom5}$), 7.72 (1 H, d, $^3J_{HH}$ =16.1 Hz, *trans* CH=CH).	1.6 (2 × **C**H$_2$), 24.2 (**C**H$_2$), 34.1 (2 × **C**H$_2$), 88.9 (**C**$_5$), 96.3 (NC-**C**=), 112.3, 112.70, (N**C**-), 113.4, 118.4, 131.03, 146.66, 150.8, 166.7 (**C**=O), 175.78 (NC-C=**C**)
5b	1.67 (6 H, s, 2 CH$_3$), 6.63 (1 H, d, *J* 16.1 Hz, C*H*=CH), 7.14–7.18 (1 H, m, arom), 7.34 (1 H, d, arom), 7.79 (1 H, t, arom), 7.90, (1 H, d, *J* 16.1 Hz, CH=C*H*).	26.1 (2 *C*H$_3$) 86.9 (-O*C*(CH$_3$)$_2$), 97.7 (NC-*C*=),112.4 (N*C* -),113.7, 129.1, 131.7, 133.6, 138.4, 140, 166.3 (*C*=O), 176 (NC-C=*C*).
5c	1.67 (6 H, s, 2 C*H*$_3$), 6.73 (1 H, d, *J* 16.3 Hz, *trans* HC=C*H*), 7.44–7.45 (2 H, m, arom), 7.71 (1 H, s, arom),7.73 (1 H, d, *J* 16.3 Hz, C*H*=CH)	26.1 (2 *C*H$_3$) 87 (-O*C*(CH$_3$)$_2$), 99.3 (NC-*C*=), 112.3 (N*C* -),114.8, 124.8, 128.2, 131.2, 137.8, 139.2, 166.2 (*C*=O), 176.7 (NC-C=*C*)
5d	1.67 (6 H, s, 2C*H*$_3$), 7.34–7.39 (1 H, m, arom), 7.51–7.53 (1 H, m, arom), 7.51 (1 H, d, *J* 16 Hz, HC=C*H*), 7.81 (1 H, d, *J* 16. Hz, C*H*=CH), 8.70–8.72 (1 H, m, arom)	25.7 (2 *C*H$_3$) 87.5 (-O*C*(CH$_3$)$_2$), 100.1 (NC-*C*=), 112.1 (N*C*-), 118.4, 125.4, 126, 137.3, 143.8, 150.6, 152, 166 (*C*=O), 176.1 (NC-C=*C*)
5e	1.71 (6 H, s, 2 C*H*$_3$), 7.08 (1 H, d, *J* 16.5 Hz, HC=C*H*), 7.46–7.49 (2 H, m, arom), 7.64 (1 H, d, *J* 16.5 Hz, HC=C*H*), 8.91 (2 H, d, arom),	25.9 (2 *C*H$_3$), 87.2 (-O*C*(CH$_3$)$_2$), 101.8 (NC-*C*=),111.6 (N*C*-),119.1, 121.8, 141.1, 142.5, 151.1, 165.4 (*C*=O), 175.1 (NC-C=*C*)
5f	1.69 (6 H, s, 2 C*H*$_3$), 6.88 (1 H, d, *J* 16.4 Hz, HC=C*H*), 7.44–7.49 (1 H, d,d, arom), 7.56 (1 H, d, arom), 7.63 (1 H, d, *J* 16.4 Hz, C*H*=CH), 7.72 (1 H, d, arom)	26 (2 *C*H$_3$) 87.1 (-O*C*(CH$_3$)$_2$), 100.3 (NC-*C*=), 111.9 (N*C*-),116.5, 127.5, 130, 131.5, 134, 134.06, 136, 142.8, 166 (*C*=O), 175.5 (NC-C=*C*)
5g	1.73 (6 H, s, 2 C*H*$_3$), 7.18 (1 H, d, *J* 16.9 Hz, HC=C*H*), 7.25–7.32 (1 H, m, arom), 7.42–7.45 (1 H, d, arom), 7.79 (1 H, d, *J* 16.9 Hz, C*H*=CH)	26 (2 *C*H$_3$) 87.2 (-O*C*(CH$_3$)$_2$, 101.5 (NC-*C*=), 111.5 (N*C*-), 123.5, 129.3, 131.1, 131.4, 135.3, 139.1, 165.6 (*C*=O), 175.9 (NC-C=*C*)
5h	1.64 (6 H, s, 2 C*H*$_3$), 3.42 (3 H, OC*H*$_3$), 6.86 (1 H, d, arom),7.00 (1 H, d, *J* 16.3 Hz, HC=C*H*), 7.30 (1 H, d, arom),7.44 (1 Hs, arom), 7.77 (II1 H, d, *J* 16.3 Hz, C*H*=CH)	25.3 (2 *C*H$_3$), 55.9 (O*C*H$_3$),87.6 (O*C*(CH$_3$)$_2$), 94.6 (NC-*C*=), 112 (N*C*-), 112.2, 113.3, 115.9, 124.6, 126.1, 146.5, 148.2, 151, 166.7 (*C*=O), 177.6 (NC-C=*C*)

[a]TMS as internal standard, and the solvent is CDCl$_3$ except **5h** which is in DMSO-d$_6$.

Table 3 Mass spectral data

Product	MS
5a	229 (M$^{+\cdot}$, 90.5), 214 (14.3), 184 (38.1), 170 (14.3), 165 (14.3), 143 (100), 121 (14.3), 115 (38.1), 43 (14.3).
5a′	269 (M$^{+\cdot}$, 55.9), 143 (10.2), 115 (29.9), 114 (21.2), 89 (22.1), 88 (25.2), 81 (100), 77 (18.1), 55 (38.6), 43 (69.3), 41 (69.3).
5b	245 (M$^{+\cdot}$, 31.4), 230 (5.7), 200 (29.8), 172 (8.6), 159 (70.8), 132 (7.9), 115 (13.3), 89 (11.8), 84 (14.0), 77 (10.8), 69 (16.5), 43 (100).
5c	245 (M$^{+\cdot}$, 17.5), 230 (3.9), 200 (47.1), 186 (86.8), 174 (8.2), 159 (45.5), 132 (10), 115 (10.5), 114 (10), 88 (11.4), 77 (9.8), 43 (100).
5d	240 (M$^{+\cdot}$, 22.37), 225 (6.1), 196 (79.3), 182 (42.2), 181 (39.8), 169 (17.8), 154 (100).
5e	240 (M$^{+\cdot}$, 18.4), 225 (12.3), 210 (15.3), 195 (100), 181 (32.8), 169 (20.6), 154 (25.7), 127 (12.3), 43 (10.7).
5f	311 (C$_{15}$H$_{11}$NO$_2$ ^{37}Cl$_2^{+\cdot}$, 0.71), 309 (C$_{15}$H$_{11}$NO$_2$ ^{37}Cl^{35}Cl$^{+\cdot}$, 3.09), 307 (M$^{+\cdot}$, 4.1), 264 (5.0), 262 (6.0), 240 (7.8), 223 (9.4), 221 (14.7), 196 (26.0), 181 (18.7), 154 (47.4), 43 (100).
5g	311 (C$_{15}$H$_{11}$NO$_2$ ^{37}C1$_2^{+\cdot}$, 1.44), 309 (C$_{15}$H$_{11}$NO$_2$ ^{37}Cl^{35}Cl$^{+\cdot}$, 9.51), 307 (M$^{+\cdot}$, 15.0), 292 (3.5), 264 (9.2), 223 (15.6), 221 (28.2), 201 (7.2), 186 (19.6), 173 (8.7), 151 (14.4), 99 (11.0), 75 (15.3), 43 (100).
5h	285 (M$^{+\cdot}$, 63.0), 240 (53.4), 226 (42.5), 212 (30.1), 199 (28.8), 184 (17.8), 182 (17.8), 156 (43.8), 139 (19.2), 127 (15.1), 115 (13.7), 101 (46.6), 43 (100).

Tables 1–3. All products **5a–h** are new except for **5b**. The products were identified by their elemental analysis (C, H, N) and by spectroscopy (NMR, IR and MS). The stereochemistry of the double bond in products **5a–h** was determined using ^{1}H-NMR and showed a typical coupling constant for *trans* protons (J ~ 16 Hz).[7] Infrared was used to show the presence of a nitrile group (νCN 2225–2230 cm^{-1}) and an lactone group (νC=O 1765–1722 cm^{-1}).

In conclusion, this one-pot procedure is a rapid and efficient method for synthesising substituted 2-(*5H*)-furanones in high yields. The biological properties of products **5a–h** are presently under investigation.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded in CDC1$_3$, or in (CD$_3$)$_2$SO solution on a Bruker AC 250 (250 MHz ^{1}H, 62.6 MHz ^{13}C) spectrometer with Me$_3$Si as an internal standard. Microwave

irradiations were carried out with a focused microwave cavity (cavity EO13 of MES). The IR spectra were recorded as KBr pellets on Perkin Elmer 16 PC FT-IR spectrometer. The mass spectra were obtained on a Nermag Riber R10-10H with a 70eV electron impact ionisation.

Synthesis of 4,5,5-trimethyl-2-oxo-2, 5-dihydro-furan-3-carbonitrile **3**: 3-Hydroxy-3-methyl-2-butanone (3 mmol) **1** and ethyl cyanoacetate (3 mmol) **2** were added simultaneously in a solution of sodium ethoxide (0.45 mmol) in ethanol (0.25 ml). The mixture was then irradiated by focused microwave in Pyrex tube (internal diameter 10 mm) 1 at 20 W for 10 minutes. The solvent was removed under reduced pressure; the residue was acidified by aqueous HCl (18%, 0.6 ml) and extracted by diethyl ether (3 × 7.5 ml). The organic phase was washed by saturated aqueous sodium chloride (NaCl), dried over $MgSO_4$, and the solvent was removed under reduced pressure to give an oil. Recrystalization of the oil from ethanol affords product **3a** ($R^1 = R^2 =$ Me, yield 96%).

*Example procedure for the condensation of **3a**: synthesis of 5,5-dimethyl-2-oxo-4-(2-furan-2-yl-vinyl)-2,5-dihydro-furan-3-carbonitrile **5a***: A mixture of furanone **3a** (3 mmol), furan-2-carboxaldehyde (3 mmol) and a solution of sodium ethoxide (0.4 mmol) in ethanol (0.25 ml) was irradiated by microwave at 75 W for 8 minutes. The reaction mixture was cooled to 0 °C for 10 hours. The solid was collected and recrystallized from ethanol to give produce **5a** (yield 85%).

Example of one-pot synthesis: A mixture of 3-hydroxy-3-methyl-2-butanone **1** (3 mmol), ethyl cyanoacetate **2** (3 mmol), and a solution of sodium ethoxide (0.4 mmol) in ethanol (0.25 ml) was irradiated by focused microwave at 60 W for 10 minutes. Then furan-2-carboxaldehyde (3 mmol) was added, and the mixture was irradiated by focused microwave at 60 W for another 10 minutes. The purification was the same as above and product was obtained **5a** in 82% overall yield. All products **5a–h** were prepared by this one-pot method and the results are listed in Table 1.

Thanks go to the région Basse at Haute-Normandie (Rincof) for their generous financial support (grant L.L.).

Received 10 February 2000; accepted 21 March 2000
Paper 99/150

References

1 (a) D.K. Knight, *Contemporary Org. Synth*., 1994 **1**, 287–315; (b) T. Laduwahetty, *Contemporary Org. Synt*., 1995, **2**, 133–149; (c) I. Collins, *Contemporary Org. Synth*., 1996, **3**, 295–321.
2 (a) J.K. Rupprecht, Y.-H Hui and J.L. McLaughlin, *J. Nat. Prod*., 1990, **53**, 237–258; (b) Z.M. Gu, G.X. Zhao, N.H. Oberlies, L. Zeng and J.L. McLaughlin, In *Recent Adv. Phytochem*., ed., J.T. Arnason, R. Mata and J.R. Romeo, Plenum Press, New York, 1995, Vol. **29**, pp 249–310; (c) L. Zeng, Q. Ye, N.H. Oberlies, G. Shi, Z.-M Gu, K. He and J.L. McLaughlin, *J. Nat. Prod. Rep*., 1996, **13**, 275–306.
3 (a) Y.S. Rao, *Chem. Rev*., 1964, **64**, 353–388; (b) Y.S. Rao, *Chem. Rev*., 1976, **76**, 625–694; (c) A.A. Avetisyan and M.T. Dangyan, *Russ. Chem. Rev*., 1977, **46**, 643–656.
4 D. Villemin and L. Liao, *Tetrahdreon Lett*., 1996, **37**, 8733–8734.
5 For a review on focused microwave action: A Loupy, A. Petit, A. Hamelin, J. TexierBoullet, F. Jacquault, P. Mathe, D. *Synthesis*, 1998, 1213–1234.
6 A. Perjéssy, A.A. Avetisyan, A.A. Aknazaryan, and G.S. Melikyan, *Collect. Czech. Chem. Commun*. 1989, **54**, 1666–74.
7 A.J. Gordan and R.A. Ford, *The Chemist's Companion – A Handbook of Practical Data, Techniques, and References*, John Wiley, New York, 1972, p 275.
8 Although results were obtained with a cavity EO13 of MES described previously,[9] we recently obtained similar results with a Prolabo Synthewave 402 and with a tube of internal diameter of 10 mm as reactor.
9 D. Villemin and B. Martin, *Synth. Commun*., 1995, **25**, 2319–2326.