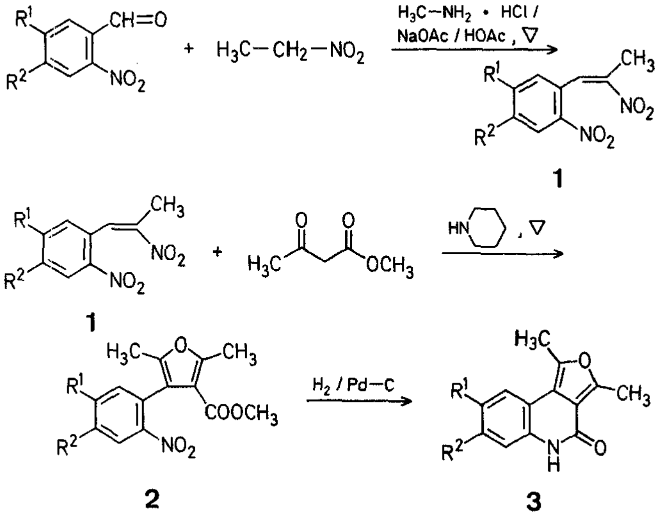
A Synthesis of 1,3-Dimethylfuro[3,4-*c*]quinolin-4-ones[1]

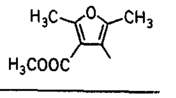
Shri Niwas, Shiv Kumar, A. P. Bhaduri*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226001, India

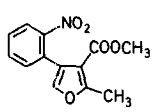
Syntheses of 1,3-dimethylfuro[3,4-*c*]quinolin-4-ones have not been reported so far. The earlier reports concerning furo[3,4-*c*]quinoline ring systems relate either to the preparation of the anhydride of the quinoline-3,4-dicarboxylic acid[2] or to the synthesis of 3-methyl-3,5-dihydrofuro[3,4-*c*]quinolin-1,4-dione[3]. We report here the first synthesis of 1,3-dimethylfuro[3,4-*c*]quinolin-4-ones **3** as well as a convenient one pot synthesis of the intermediate furans **2** required.

Reaction of 2-nitro-1-(2-nitroaryl)-propenes **1** with methyl acetoacetate in the presence of piperidine in methanol yielded the 2,5-dimethyl-3-methoxycarbonyl-4-(2-nitroaryl)-furans **2** in 70–80% yield. The synthesis of the only known example of this class of compounds, namely 2,5-dimethyl-3-ethoxycarbonyl-4-phenylfuran involved[4,5] elaborate reaction conditions with only 50% yield. Compounds **1** used in this work were prepared by the condensation of nitroethane with appropriately substituted 2-nitrobenzaldehydes[6,7]. Catalytic hydrogenation of **2** in the presence of palladium on charcoal yielded the substituted 1,3-dimethylfuro[3,4-*c*]quinolin-4-ones **3** in more than 90% yield (Table).

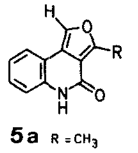


2,3	R¹	R²
a	H	H
b	—O—CH₂—O—	
c	OCH₃	OCH₃
d	H	

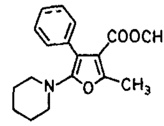
Attempts to extend the method for preparing the unsubstituted quinolinones **5a, b** failed, as shown by a model study. Thus, the reaction of 1-phenyl-2-nitroethene with methyl acetoacetate in the presence of piperidine gave the piperidine-containing product **6** instead of the expected furan derivative **4**.



4



5a R = CH₃
b R = H



6

Table. Compounds **2** and **3** prepared

Product No.	Yield [%]	m.p. [°C]	Molecular formula[a]	M.S. *m/e* (M⁺)	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$) δ [ppm]
2a	80	77–78°	$C_{14}H_{13}NO_5$ (275.3)	275	1715 (COO); 1520, 1340 (NO$_2$)	2.12 (s, 3 H, 5-C$\underline{H}_3$); 2.52 (s, 3 H, 2-C$\underline{H}_3$); 3.5 (s, 3 H, OC$\underline{H}_3$); 7.19–7.3 (dd, 6'-H$_{arom}$, J_o=9 Hz, J_m=2 H); 7.4–7.59 (m, 4',5'-H$_{arom}$); 7.95–8.05 (dd, 3 H$_{arom}$, J_o=9 Hz, J_m=2 Hz)
2b	72	128–129°	$C_{15}H_{13}NO_7$ (319.3)	319	1700 (COO); 1500, 1340 (NO$_2$)	2.1 (s, 3 H, 5-C$\underline{H}_3$); 2.54 (s, 3 H, 2-C$\underline{H}_3$); 3.58 (s, 3 H, —OC$\underline{H}_3$); 6.09 (s, 2 H, C$\underline{H}_2$); 6.62 (s, 6'-H$_{arom}$); 7.58 (s, 3'-H$_{arom}$)
2c	74	104–105°	$C_{16}H_{17}NO_7$ (335.3)	335	1710 (COO); 1510, 1330 (NO$_2$)	2.1 (s, 3 H, 5-C$\underline{H}_3$); 2.53 (s, 3 H, 2-C$\underline{H}_3$); 3.54 (s, 3 H, COOC$\underline{H}_3$); 3.86, 3.9 (2s, 3 H each, OC$\underline{H}_3$); 6.62 (s, 6'-H$_{arom}$); 7.68 (s, 3'-H$_{arom}$)
2d	70	109–110°	$C_{22}H_{21}NO_8$ (427.4)	427	1720 (COO); 1525, 1325 (NO$_2$)	2.21 (s, 6 H, 5,5'-C$\underline{H}_3$); 2.6 (s, 6 H, 2,2'-C$\underline{H}_3$); 3.58 (s, 3 H, COOC$\underline{H}_3$); 3.69 (s, 3 H, COOC$\underline{H}_3$); 7.24 (d, 6'-H$_{arom}$, J_o=9 Hz); 7.45–7.55 (dd, 5'-H$_{arom}$, J_o=9 Hz, J_m=2 Hz); 7.98 (d, 3'-H$_{arom}$, J_m=2 Hz)
3a	95	235–236°	$C_{13}H_{11}NO_2$ (213.2)	213	1675 (CO)	2.24 (s, 3 H, 1-C$\underline{H}_3$); 2.3 (s, 3 H, 3-C$\underline{H}_3$); 6.85–7.0 (br. s, 4 H$_{arom}$)[b]
3b	90	>300°	$C_{14}H_{11}NO_4$ (257.2)	257	1660 (CO)	1.65 (s, 3 H, 1-C$\underline{H}_3$); 1.74 (s, 3 H, 3-C$\underline{H}_3$); 5.9 (s, 2 H, C$\underline{H}_2$); 6.42 (s, 6-H$_{arom}$); 6.8 (s, 9-H$_{arom}$)[b]
3c	92	>300°	$C_{15}H_{15}NO_4$ (273.3)	273	1675 (CO)	1.67 (s, 3 H, 1-C$\underline{H}_3$); 1.75 (s, 3 H, 3-C$\underline{H}_3$); 3.55 (br. s, 6 H, 2×OC$\underline{H}_3$); 6.4 (s, 6-H$_{arom}$); 6.84 (s, 9-H$_{arom}$)[b]
3d	95	269–270°	$C_{21}H_{19}NO_5$ (365.4)	365	1705 (COO); 1660 (CO)	1.8 (s, 3 H, 1-C$\underline{H}_3$); 2.18 (s, 3 H, 5'-C$\underline{H}_3$); 2.34 (br. s, 6 H, 2',3-C$\underline{H}_3$); 3.42 (s, 3 H, OC$\underline{H}_3$); 6.85–7.0 (m, 6,8-H$_{arom}$); 7.48–7.58 (d, 9-H$_{arom}$, J_o=9 Hz)[b]

[a] Satisfactory microanalyses obtained: C, ±0.32; H, ±0.36; N, ±0.3; exception: **2b**, N, −0.4; **3a**, N +0.43.

[b] Measured in trifluoroacetic acid solution.

In summary, we have shown that 2,5-dimethyl-3-methoxycarbonyl-4-(2-nitroaryl)-furans **2** can be prepared by an improved, one-pot synthesis in 70–80% yield and then cyclised to the novel heterocyclic system **3**. The synthetic sequence has the limitation that the parent unsubstituted system **5** could not be prepared.

2-Nitro-1-(2-nitroaryl)-propenes 1; General Procedure:

To a solution of the 2-nitro-3,4-substituted benzaldehyde (0.11 mol) in nitroethane (33 g, 0.44 mol) is added glacial acetic acid (9 g, 0.15 mol), methylamine hydrochloride (2.97 g, 0.044 mol), and sodium acetate (3.61 g, 0.044 mol). The mixture is stirred at 100°C for 1.5 h, allowed to cool to room temperature, water (150 ml) is added, and the stirring is continued for 30 min. The precipitated solid is filtered, washed thoroughly with water, and then crystallised either from chloroform/hexane (**1a–c**) or from ether (**1d**):

1a (R^1=R^2=H); yield: 73%; m.p. 74°C (Ref.[6], m.p. 69–70°C);

1b (R^1–R^2=O—CH$_2$—O); yield: 80%; m.p. 153–154°C;

$C_{10}H_8N_2O_6$	calc.	C 47.62	H 3.20	N 11.10
(252.2)	found	48.00	3.60	10.83

1c (R^1=R^2=OCH$_3$); yield: 74%; m.p. 132–132°C (Ref.[7], m.p. 133°C).

1d [R^1=H, R^2=—CH=C(CH$_3$)NO$_2$]; yield: 85%; m.p. 104–105°C.

$C_{12}H_{11}N_3O_6$	calc.	C 49.15	H 3.78	N 14.33
(293.2)	found	49.03	3.59	14.21

2,5-Dimethyl-3-methoxycarbonyl-4-(2-nitroaryl)-furans 2; General Procedure:

To a solution of **1** (0.02 mol) in methanol (30 ml) is added piperidine (1.7 g, 0.02 mol) under stirring followed by the dropwise addition of methyl acetoacetate (2.32 g, 0.02 mol). The mixture is stirred at room temperature for 1 h and then refluxed for 2 h. The solvent is removed under reduced pressure and the residue treated with water (100 ml). To this mixture, concentrated hydrochloric acid (5 ml) is added and then extracted with chloroform (2×80 ml). The organic layer is separated, washed with water (2×60 ml), and dried with sodium sulfate. The residue obtained after removal of solvent is filtered through a column of silica gel using either chloroform/hexane (1:1; **2a–c**) or chloroform (**2d**) as the eluent. These products are recrystallised from chloroform/hexane.

Substituted 1,3-Dimethylfuro[3,4-*c*]quinolin-4-ones (3a–d); General Procedure:

A solution of **2** (1 g) in methanol (20 ml) is hydrogenated over 10% palladium on charcoal (100 mg) at 2.5 kg/cm^2 for about 5 h. The solution is filtered and the solvent removed from the filtrate under reduced pressure. The separated solid is filtered and recrystallised from ethyl acetate.

3-Methoxycarbonyl-2-methyl-4-phenyl-5-piperidylfuran (6):

To a solution of 1-phenyl-2-nitroethene (2.98 g, 0.02 mol) in methanol (25 ml) is added piperidine (1.70 g, 0.02 mol) under stirring followed by the dropwise addition of methyl acetoacetate (2.32 g, 0.02 mol). The reaction is allowed to continue at room temperature for 1 h, then the solid which separates out is filtered, washed with water (3×25 ml), and dried. It is then recrystallised three times from chloroform/hexane; yield: 4.18 g (70%); m.p. 179–180°C.

$C_{18}H_{21}NO_3 \cdot H_2O$	calc.	C 68.12	H 7.30
(317.4)	found	68.07	6.94

I.R. (KBr): ν=1715 cm^{-1} (C=O).

^{1}H-N.M.R. (CDCl$_3$+DMSO-d_6): δ=1.43 (br. s, 6 H, CH$_2$); 1.68 (s, 3 H, CH$_3$); 3.00 [br. s, 4 H, N(CH$_2$)$_2$]; 3.58 (s, 3 H, OCH$_3$); 7.30 ppm (br. s, 5 H$_{arom}$).

M.S.: *m/e*=299 (M⁺).

Thanks are due to D. A. E., Bombay, for Junior Research Fellowship (S. N.) and C.S.I.R., New Delhi for Postdoctoral Research Fellowship (S. K.).

Received: November 8, 1982
(Revised form: June 13, 1983)

---

* Address for correspondence.

[1] CDRI Communication No. 3298.

[2] W. Lawson, W. H. Perkin, R. Robinson, *J. Chem. Soc.* **125**, 634 (1924).

[3] P. Lakshminarayana, P. Shanmugam, K. K. Balasubramaniam, *Tetrahedron Lett.* **1970**, 4947.

[4] F. Boberg, G. R. Schulze, *Chem. Ber.* **90**, 1215 (1957).

[5] G. R. Schulze, F. Boberg, *German Patent* 965408; *C. A.* **53**, 16150 (1959).

[6] M. Koremura, H. Oku, T. Shono, T. Nakanishi, *Takamine Kenkyusho Nempo* **13**, 212 (1961); *C. A.* **57**, 16451 (1962).

[7] J. Mason-Harley, *J. Chem. Soc.* **1953**, 200.