# Synthesis of 3-Alkyl-2,5-dimethylfuran Derivatives by Indirect Alkylation of 2,5-Dimethylfuran with Aliphatic Nitrocompounds

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**Abstract:** The preparation of 3-alkyl-2,5-dimethylfuranes via indirect alkylation of 2,5-dimethylfuran is reported. Thus, primary nitroalkanes react with *cis*-3-hexen-2,5-dione giving a tandem Michael addition/elimination of nitrous acid, followed by chemoselective hydrogenation of the C=C double bond of the obtained enones. The Paal–Knorr reaction, performed with *p*-toluenesulfonic acid in diethyl ether, completes the formation of the title compounds. In this context the nitroalkane can be considered as an alkyl cation synthon.

Key words: furan, nitroalkanes, Michael reaction, heterocyclization

By far the most heavily exploited of monocyclic heteroatomic system is the furan ring. Furans and their derivatives are very useful as starting materials in the production of industrially important compounds.<sup>1</sup> It is also well-known that furans are used in acid-catalyzed hydrolysis, auto-oxidation, Diels–Alder reaction, photocyclization, hydrogenation, substitution and so on.<sup>1,2</sup>

In particular, polysubstituted furans play an important role in organic chemistry due to their presence as key structural units in many natural products<sup>3</sup> and in important pharmaceuticals.<sup>4</sup> For this reason, the syntheses of polysubstituted furans, especially the 2,3,5-trisubstituted ones, which are reported to be of particular interest,<sup>5</sup> continue to attract the interest of many synthetic chemists, Herein, we wish to report a new procedure for the preparation of 3-alkyl-2,5-dimethylfuran by the indirect alkylation of 2,5-dimethylfuran.

Nitroalkanes are well known as useful nucleophilic molecules and often they can be employed as alkyl anion synthons.<sup>6</sup> Recently, we have reported a new methodology through which, starting from unsaturated 1,4-diester and nitroalkanes, the nitro group may simultaneously behave both as an electron-withdrawing group and leaving group<sup>7</sup> and this behavior has been applied for the preparation of different targets.<sup>8</sup> Following these results, we planned to prepare the title compounds using 2,5-dimethylfuran and nitroalkanes (Scheme).

It is well known that the oxidative cleavage of furans allows the formation of conjugated 2-en-1,4-diones, thus, cis-3-hexen-2,5-dione (2) can be easily obtained (97%)



Scheme

yield) from 2,5-dimethylfuran (1).<sup>9</sup> The reaction of the dienone 2 with primary nitroalkanes 3, in acetonitrile with DBU as base, proceeded in a tandem process, in which a Michael addition was immediately followed by elimination of nitrous acid, thus giving the corresponding conjugated enone derivatives 4 in good yields. The chemoselective hydrogenation of the C=C double bond of compounds 4 produced 3-alkylhexan-2,5-diones 5, which were then converted to the title compounds 6 (Tables 1– 3).

The acid-catalyzed synthesis of furans from 1,4-diketones has been known for more than a century,<sup>10</sup> however, the heterocyclization of the hexane-2,5-dione required the continuous removal of the produced furan,<sup>11</sup> or harsh reaction conditions.<sup>12</sup> After investigation of the most powerful conditions for conversion of the 3-alkylated hexane-2,5-diones **5** into the furan derivatives **6**, we found that this cyclization can be easily accomplished using half equivalent of *p*-toluenesulfonic acid in refluxing diethyl ether (Scheme).

In conclusion, the present methodology represents an alternative procedure for the title compounds. Moreover, it is important to point out that other functionalities, such as

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 Table 1
 1,4-Dicarbonyl Derivatives 5 and 3-Alkyl-2,5-dimethyl-furans 6 Prepared

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Products <b>5</b> , <b>6</b>	R	Yield (%) <sup>a</sup> of <b>5</b> from <b>2</b>	Yield (%) <sup>a</sup> of 6 (reaction time, h)
a	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub>	88	78 (8)
b	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub>	90	95 (25)
c	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>10</sub>	70	85 (7)
d	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub>	85	94 (10)
e	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>2</sub> CH( <i>t</i> -Bu)CH <sub>2</sub>	80	88 (14)
f	HOCH <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub>	75	77 (8)
g	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>9</sub>	90	86 (12)
h	CH <sub>3</sub> CO(CH <sub>2</sub> ) <sub>2</sub>	80	60 (12)
i	Ph	74	75 (14)
j	PhCH <sub>2</sub>	60	90 (15)

<sup>a</sup> Isolated yield.

ester, keto, hydroxyl and aromatic rings (**6i**,**j**), which are difficult to introduce onto furans by other means,<sup>1,2,5</sup> can be easily introduced by simply choosing the appropriate starting nitroalkane. Additionally, this new exploitation of

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nitroalkanes 3 as an (indirect) alkylating species of an aromatic ring is the first report in which they are used as alkyl cation synthons **a** (Figure).



Figure

We believe that this procedure represents a progressive evolution of the practical utilization of functionalized nitroalkanes as strategic tools in organic synthesis, not only as a synthetic equivalent of carbanions<sup>6</sup> but, now, also as a synthetic equivalent of carbocations.

<sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> at 200 MHz on a Varian Gemini instrument; *J* values are given in Hz. IR spectra were recorded with a Perkin Elmer 257 spectrophotometer. Mass spectra were determined on a capillary GC/MS operating in the split mode with He carrier gas and fitted with a mass-selective detector (MDS). The reactions were monitored by TLC, or GC performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran Glass, stationary phase OV1. Microanalyses were performed using a Fisons model EA 1108. The products were purified by flash chromatography on Merck silica gel with EtOAc–petroleum ether as eluent.

Table 2 Spectroscopic Data for 1,4-Dicarbonyl Derivatives 5a-j

Product	IR (film) (cm <sup>-1</sup> )	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) $\delta$ (ppm), $J$ (Hz)	MS: <i>m/z</i> (%)
5a	1712	0.88 (t, 3 H, <i>J</i> = 7.0), 1.20–1.30 (m, 6 H), 1.50–1.60 (m, 2 H), 2.14 (s, 3 H), 2.24 (s, 3 H), 2.43 (d, 1 H, <i>J</i> = 14.5), 2.90 (d, 1 H, <i>J</i> = 10.0), 3.00–3.10 (m, 1 H)	141, 127, 114, 100, 85, 71, 59, 55, 43 (100)
5b	1710 1705	1.50–1.60 (m, 4 H), 2.15 (s, 3 H), 2.25 (s, 3 H), 2.32 (t, 2 H, $J$ = 6.7), 2.45 (d, 1 H, $J$ = 14.3), 2.92 (d, 1 H, $J$ = 9.8), 3.00–3.10 (m, 1 H), 3.67 (s, 3 H)	214 (M <sup>+</sup> ), 196, 181, 172, 157, 137, 114, 97 (100), 71, 43
5c	1712 1706	1.20–1.30 (m, 20 H), 2.14 (s, 3 H), 2.23 (s, 3 H), 2.30 (t, 2 H, $J$ = 7.4), 2.42 (d, 1 H, $J$ = 14.4), 2.90 (d, 1 H, $J$ = 9.9), 3.00–3.10 (m, 1 H), 3.68 (s,3H)	326 (M <sup>+</sup> ), 308, 269, 114, 97, 71, 43 (100)
5d	1712	0.88 (t, 3 H, <i>J</i> = 6.5), 1.20–1.40 (m, 18 H), 2.14 (s, 3 H), 2.24 (s, 3 H), 2.42 (d, 1 H, <i>J</i> = 14.4), 2.90 (d, 1 H, <i>J</i> = 10.0), 3.00–3.10 (m, 1 H)	254 (M <sup>+</sup> ), 239, 221, 211, 197, 169, 141, 128, 114, 85, 71, 43 (100)
5e <sup>a</sup>	1712 1708	0.85 (s, 9 H), 1.20–1.70 (m, 7 H), 2.15 (s, 3 H), 2.25 (s, 3 H), 2.40 (t, 2 H, <i>J</i> = 13.8), 2.46 (d, 1 H, <i>J</i> = 14.2), 2.91 (d, 1 H, <i>J</i> = 9.4), 3.00–3.10 (m, 1 H), 3.67 (s, 3H)	298 (M <sup>+</sup> ), 280, 241, 114, 97, 71, 57, 43 (100)
5f	3410 1708	1.20–1.60 (m, 10 H), 2.13 (s, 3 H), 2.22 (s, 3 H), 2.41 (d, 1 H, <i>J</i> = 14.0), 2.89 (d, 1 H, <i>J</i> = 10.0), 2.90–3.00 (m, 1 H), 3.64 (t, 2 H, <i>J</i> = 6.5)	214 (M <sup>+</sup> ), 196, 171, 157, 139, 128, 114, 71, 43 (100)
5g	1712	0.88 (t, 3 H, $J = 6.5$ ), 1.20–1.30 (m, 20 H), 2.14 (s, 3 H), 2.24 (s, 3 H), 2.42 (d, 1 H, $J = 14.4$ ), 2.90 (d, 1 H, $J = 9.6$ ), 3.00–3.10 (m, 1 H)	268 (M <sup>+</sup> ), 250, 225, 211, 183, 141, 128, 114 (100), 85, 71, 43
5h	1715	1.40–1.60 (m, 4 H), 2.13 (s, 3 H), 2.14 (s, 3 H), 2.24 (s, 3 H), 2.42 (t, 2 H, <i>J</i> = 4.7), 2.48 (d, 1 H, <i>J</i> = 14.0), 2.90 (d, 1 H, <i>J</i> = 9.9), 2.90–3.10 (m, 1 H)	180, 155, 141, 128, 123, 114, 95, 85, 71 (100), 43
5i	1708	2.08 (s, 3 H), 2.13 (s, 3 H), 2.30–2.60 (m, 2 H), 2.80–3.30 (m, 2 H), 3.20–3.40 (m, 1 H), 7.10–7.70 (m, 5 H)	204, 186, 171, 161, 147 (100), 91, 71, 43
5j	1710	1.60–1.80 (m, 1 H), 1.80–2.00 (m, 1 H), 2.15 (s, 3 H), 2.24 (s, 3 H), 2.40–2.60 (m, 3 H), 2.90–3.20 (m, 2 H), 7.10–7.40 (m, 5 H)	200, 185, 175, 129, 114 (100), 91, 77, 71, 43

<sup>a</sup> Diastereomeric mixture.

Product	IR (film) (cm <sup>-1</sup> )	<sup>1</sup> H NMR (CDCl <sub>3</sub> ) δ ppm, <i>J</i> (Hz)	<sup>13</sup> C NMR (CDCl <sub>3</sub> ) δ ppm	MS: <i>m/z</i> (%)
6a	_	0.89 (t, 3 H, J = 7.8), 1.20–1.40 (m, 6 H), 2.15 (s, 3 H), 2.22 (s, 3 H), 2.24 (t, 2 H, J = 8.8), 5.78 (s, 1 H)	149.44, 145.12, 119.71, 107.95, 31.35, 29.01, 25.25, 22.45, 14.02, 11.92, 11.70	166 (M <sup>+</sup> ), 151, 137, 123, 109 (100), 95, 43
6b	1708	1.80 (m, 2 H, <i>J</i> = 14.0), 2.15 (s, 3 H), 2.21 (s, 3 H), 2.20–2.30 (m, 4 H), 3.65 (s, 3 H), 5.75 (s, 1 H)	174.56, 149.71, 145.94, 118.87, 107.68, 51.95, 33.77, 25.77, 24.48, 13.92, 11.77	196 (M <sup>+</sup> ), 181, 165, 147, 135, 122, 109 (100), 103, 95, 43
6с	1708	1.20–1.40 (m, 18 H), 2.15 (s, 3 H), 2.21 (s, 3 H), 2.20–2.40 (m, 4 H), 3.67 (s, 3 H), 5.77 (s, 1 H)	174.84, 149.37, 145.41, 120.22, 107.88, 51.92, 34.60, 34.05, 30.18, 29.96, 29.91, 29.77, 29.72, 29.54, 25.44, 25.30, 25.19, 13.94, 11.81	308 (M <sup>+</sup> ), 293, 277, 249, 235, 221, 207, 193, 179, 165, 151, 123, 110 (100), 95, 59
6d	-	0.88 (t, 3 H, <i>J</i> = 6.5), 1.20–1.30 (m, 16 H), 2.16 (s, 3 H), 2.21 (s, 3 H), 2.24 (t, 2 H, <i>J</i> = 7.4), 5.77 (s, 1 H)	149.37, 145.40, 120.24, 107.88, 32.39, 30.94, 30.12, 29.98, 29.80, 25.31, 23.17, 14.59, 13.94, 11.81	236 (M <sup>+</sup> ), 221, 207, 193, 179, 165, 151, 137, 123, 110 (100), 95, 43
6e	1708	0.88 (s, 9 H), 1.20–1.40 (m, 5 H), 2.16 (s, 3 H), 2.22 (s, 3 H), 2.30–2.40 (m, 4 H), 3.67 (s, 3 H), 5.78 (s, 1 H)	175.10, 149.59, 145.34, 120.20, 107.73, 51.97, 34.57, 33.56, 32.47, 28.31, 28.15, 27.05, 25.80, 13.93, 11.88	280 (M <sup>+</sup> ), 265, 249, 223, 123, 109 (100), 95, 57, 43
6f	3368	1.30–1.40 (m, 8 H), 2.15 (s, 3 H), 2.21 (s, 3 H), 2.25 (t, 2 H, <i>J</i> = 7.0), 3.64 (t, 2 H, <i>J</i> = 6.5), 5.77 (s, 1 H)	149.45, 145.45, 120.05, 107.83, 63.50, 33.23, 30.88, 29.52, 26.08, 25.23, 13.96, 11.83	196 (M <sup>+</sup> ), 181, 165, 123, 109 (100), 95, 85, 71, 43
6g	_	0.88 (t, 3 H, <i>J</i> = 6.3), 1.20–1.40 (m, 18 H), 2.15 (s, 3 H), 2.22 (s, 3 H), 2.25 (t, 2 H, <i>J</i> = 7.2), 5.75 (s, 1 H)	149.37, 145.39, 120.24, 107.89, 32.41, 30.96, 30.14, 30.00, 29.84, 29.79, 25.32, 23.19, 14.61, 13.94, 11.81	250 (M <sup>+</sup> ), 235, 221, 207, 193, 179, 165, 151, 123, 110 (100), 95, 43
6h	1718	1.76 (m, 2 H), 2.12 (s, 3 H), 2.15 (s, 3 H), 2.21 (s, 3 H), 2.28 (t, 2 H, <i>J</i> = 7.3), 2.41 (t, 2 H, <i>J</i> = 13.0), 5.75 (s, 1 H)	209.43, 149.72, 145.85, 119.09, 107.67, 43.31, 30.39, 24.77, 24.50, 13.92, 11.78	180 (M <sup>+</sup> ), 162, 147, 137, 122 (100), 109, 95, 71, 57, 43
6i	_	2.20 (s, 3 H), 2.22 (s, 3 H), 3.64 (s, 2 H), 5.71 (s, 1 H), 7.10–7.30 (m, 5 H)	149.35, 149.32, 145.65, 141.15, 128.37, 128.35, 128.33, 125.89, 118.30, 107.80, 31.21, 29.72, 13.48	186 ( M <sup>+</sup> 100), 171, 153, 143, 128, 109, 95, 91, 77, 57, 43
6j	_	2.05 (s, 3 H), 2.25 (s, 3 H), 2.50–2.70 (m, 2 H), 2.70–2.90 (m, 2 H), 5.81 (s, 1 H), 7.20–7.40 (m, 5 H)	149.57, 145.91, 142.51, 128.99, 128.77, 126.35, 119.28, 118.87, 107.78, 37.36, 27.59, 14.00, 11.67	200 (M <sup>+</sup> ), 109 (100), 91, 77, 43

#### Table 3 Spectroscopic Data for 3-Alkyl-2,5-dimethylfuranes 6a-j

#### Saturated 1,4-Dicarbonyl Derivatives (5); General Procedure

To a solution of nitroalkane **3** (15 mmol) and *cis*-3-hexen-2,5-dione (**2**, 1.68 g, 15 mmol), in CH<sub>3</sub>CN (100 mL), DBU (2.28 g, 15 mmol) was added at r.t. The solution was then stirred for 6 h and evaporated. The crude residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with 2 N HCl ( $2 \times 20$  mL), dried (Na<sub>2</sub>SO<sub>4</sub>), passed through a bed of Celite and evaporated. To the obtained product **4**, EtOAc (150 mL) and 10% Pd/C (0.3 g) were added and the suspension was hydrogenated (40 psi) at r.t. for 6 h. The catalyst was removed by filtration through a Celite pad and washed with EtOAc ( $3 \times 20$  mL). After evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc–petroleum ether) giving the pure product **5**.

## 3-Alkyl-2,5-dimethylfuran Derivatives (6); General Procedure

*p*-Toluensulfonic acid (0.43 g, 2.5 mmol) was added to a solution of 3-alkylatedhexane-2,5-dione **5** (5 mmol) in Et<sub>2</sub>O (40 mL). The solution was refluxed for the appropriate time (see Table 1), then washed with H<sub>2</sub>O ( $2 \times 10$  mL), dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated and purified by flash chromatography.

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