Alkylation of Furans *via cine*-Substitution of α-Nitrofurans with Anions of Nitroalkanes and Subsequent Denitration

Noboro Ono,* Tuo Xian Jun, Aritsune Kaji

Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

cine-Substitution of α-nitrofurans bearing acyl or alkoxycarbonyl groups on the α'-position with the anions of secondary nitroalkanes and subsequent denitration with tributyltin hydride provides a new method for regioselective alkylation of furans.

As electrophilic alkylation of heteroaromatic compounds generally lacks regioselectivity, and hence an alternative method for regioselective alkylation of heteroaromatic compounds is highly desired. In this paper we wish to report a novel method for regioselective alkylation of furans, which consists of cine-substitution of α-nitrofurans with the anions of nitroalkanes and subsequent denitration.

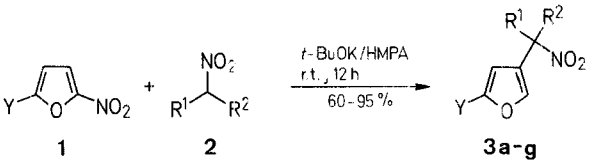
α-Nitrofurans **1** bearing acyl or alkoxycarbonyl groups on the α'-position react with the anions of secondary nitroalkanes **2** to give the *cine*-substitution products **3** regioselectively.[1] This high regioselectivity is only observed when the anions of nitroalkanes are used as nucleophiles.

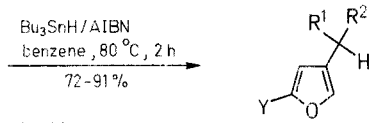
The nitro group of compound **3** is readily replaced by hydrogen by heating a mixture of **3**, tributyltin hydride, and azobisisobutyronitrile in benzene at 80 °C for 2 h to give the alkylated products **4** in good yields[2] (Table 1).

Table 1. Preparation of Compounds **3** and **4**

Y	R^1	R^2	3,	Yield (%)	4,	Yield (%)
CO_2CH_3	CH_3	CH_3	**3a**[a]	88	**4a**	85
CO_2CH_3	CH_3	$(CH_2)_2CO_2CH_3$	**3b**	95	**4b**	80
CO_2CH_3	CH_3	n-C_6H_{13}	**3c**	70	**4c**	90
CO_2CH_3	CH_3	n-C_8H_{17}	**3d**	81	**4d**	91
CO_2CH_3	CH_3	$C_6H_5CH_2$	**3e**	73	**4e**	91
$COCH_3$	CH_3	CH_3	**3f**	60	**4f**	85
$COCH_3$	CH_3	$(CH_2)_2CO_2CH_3$	**3g**	70	**4g**	72

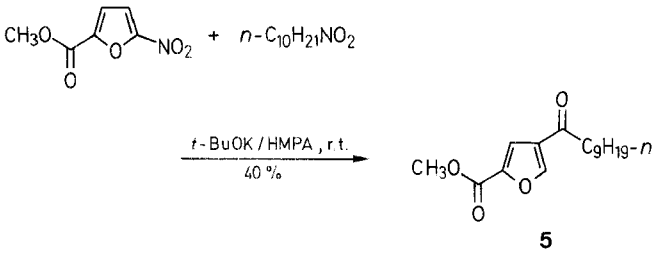
[a] M.p. 52.5°C. Other compounds are all liquids. Isolation by column chromatography gave pure products.





HMPA = hexamethylphosphoric triamide
AIBN = 2,2'-azobisisobutyronitrile

The overall reaction can be regarded as nucleophilic cine-substitution of **1** by alkyl anions. Functionalized nitro compounds can be used as functionalized alkyl anions. The features of the present method are high regioselectivity of the formation of **3** and high functional selectivity in the denitration step. When primary nitro compounds are employed as nucleophiles, acylated compounds **5** are obtained in 40–50% yields. The intermediate such as **3** (R^1 or R^2 = H) is not isolated and the yields are always below 50%.



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As various aromatic nitro compounds undergo nucleophilic substitution reaction with the anions of nitro compounds,[3] the present method using nitroalkanes as alkyl anion equivalents may be useful for the nucleophilic alkylation of aromatic compounds.

Substitution of 1 with the Anions of 2; General Procedure:
To a stirred mixture of the nitro compound **2** (12 mmol) and *t*-BuOK (1.34 g, 12 mmol) in HMPA (10 mL) is added a solution of the α-nitrofuran **1** (10 mmol) in HMPA (5 mL) under argon at room temperature. The resulting mixture is stirred at room temperature for 12 h. The mixture is poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The extract is washed with water (2 × 50 mL) and dried ($MgSO_4$). The solvent is removed under reduced pressure and the residue is subjected to column chromatography on silica gel (hexane/EtOAc, 6:1) to give **3** (Tables 1 and 2).

Denitration of 3; General Procedure:
A mixture of **3** (5 mmol), tributyltin hydride (6 mmol), and AIBN (1 mmol) in benzene (5 mL) is heated at 80°C for 2 h. The resulting mixture is subjected to column chromatography on silica gel (benzene/hexane 1:2) to give **4** (Tables 1 and 2).

Table 2. Spectral Data of Compounds **3** and **4**

Compound	Molecular Formula[a]	IR (Film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
3a	$C_9H_{11}NO_5$ (213.2)	1540, 1740	1.92 (s, 6H); 3.88 (s, 3H); 7.32 (s, 1H); 7.74 (s, 1H)
3b	$C_{12}H_{15}NO_7$ (285.3)	1540, 1720, 1740	1.92 (s, 3H); 2.2–2.5 (m, 2H); 2.5–2.8 (m, 2H); 3.76 (s, 3H); 3.96 (s, 3H); 7.36 (s, 1H); 7.76 (s, 1H)
3c	$C_{14}H_{21}NO_5$ (283.3)	1540, 1740	0.76–1.08 (m, 3H); 1.08–1.60 (m, 8H); 1.88 (s, 3H); 2.0–2.3 (m, 2H); 3.91 (s, 3H); 7.24 (s, 1H); 7.60 (s, 1H)
3d	$C_{16}H_{25}NO_5$ (331.4)	1540, 1740	0.7–1.0 (m, 3H); 1.0–1.5 (m, 12H); 1.88 (s, 3H); 2.0–2.3 (m, 2H); 3.96 (s, 3H); 7.28 (s, 1H); 7.62 (s, 1H)
3e	$C_{15}H_{15}NO_5$ (289.3)	1540, 1740	1.80 (s, 3H); 3.40 (d, 1H, J = 12); 3.80 (d, 1H, J = 12); 3.96 (s, 3H); 7.0–7.4 (m, 5H); 7.38 (s, 1H); 7.60 (s, 1H)
3f	$C_9H_{11}NO_4$ (197.2)	1540, 1680	1.98 (s, 6H); 2.52 (s, 3H); 7.36 (s, 1H); 7.78 (s, 1H)
3g	$C_{12}H_{15}NO_2$ (269.3)	1540, 1680, 1740	2.94 (s, 3H); 2.20–2.80 (m, 4H); 2.54 (s, 3H); 3.80 (s, 3H); 7.36 (s, 1H); 7.84 (s, 1H)
4a	$C_9H_{12}O_3$ (168.1)	1740	1.21 (d, 6H, J = 7); 2.66–2.98 (m, 1H); 3.94 (s, 3H); 7.16 (s, 1H); 7.42 (s, 1H)
4b	$C_{12}H_{16}O_3$ (240.1)	1740, 1720	1.24 (d, 3H, J = 7); 1.72–2.14 (m, 2H); 2.16–2.28 (m, 2H); 2.60–2.96 (m, 1H); 3.74 (s, 3H); 3.96 (s, 3H); 7.20 (s, 1H); 7.47 (s, 1H)
4c	$C_{14}H_{22}O_3$ (238.2)	1740	0.85–1.02 (m, 3H); 1.02–1.80 (m, 13H); 2.50–2.80 (m, 1H); 3.94 (s, 3H); 7.10 (s, 1H); 7.35 (s, 1H)
4d	$C_{16}H_{26}O_5$ (266.2)	1740	0.96–1.04 (m, 3H); 1.04–1.80 (m, 17H); 2.40–2.76 (m, 1H); 3.90 (s, 3H); 7.16 (s, 1H); 7.32 (s, 1H)
4e	$C_{15}H_{16}O_3$ (244.1)	1740	1.28 (d, 3H, J = 7); 2.64–3.16 (m, 3H); 3.80 (s, 3H); 7.04–7.48 (m, 7H)
4f	$C_9H_{12}O_2$ (152.1)	1680	1.18 (d, 6H, J = 7); 2.24 (s, 3H); 2.54–2.95 (m, 1H); 7.08 (s, 1H); 7.32 (s, 1H)
4g	$C_{12}H_{16}O_4$ (224.1)	1680, 1720	1.24 (d, 3H, J = 7); 1.68–2.04 (m, 2H); (s, 3H); 7.08 (s, 1H); 7.38 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.31, H ±0.22, H ±0.15.

[b] Record at 100 MHz on a Jeol PS-100 spectrometer.

Reaction of 1 with Primary Nitroalkanes:

The reaction is carried out in the same way as in the case of the preparation of **3**. To a stirred mixture of 1-nitrodecane (2.24 g, 12 mmol), *t*-BuOK (1.34 g, 12 mmol) in HMPA (10 mL) is added a solution of methyl 5-nitrofuran-2-carboxylate (1.71 g, 10 mmol) in HMPA (5 mL). After the same work up as described in the preparation of **3**, the residue is subjected to column chromatography on silica gel (hexane/EtOAc, 6:1) to give *methyl 4-(1-oxodecyl)furan-2-carboxylate* **(5)**; yield: 1.12 g (40%); m.p. 70–71°C.

MS: $m/e = 280$ (M^+, 9%); 220 ($M-CH_3COOH$, 7%); 168 ($M-C_7H_{14}$, 100%).

HRMS: m/e = calc. for $C_{16}H_{24}O_4$: 280.1678, found: 280.1678.

IR (KBr): $\nu = 1670$, 1740 cm^{-1}.

^1H-NMR ($CDCl_3$/TMS): $\delta = 0.88$ (t, 3H, $J = 8$ Hz); 1.2–1.8 (m, 14H); 2.76 (t, 2H, $J = 8$ Hz); 3.96 (s, 3H); 7.60 (s, 1H); 8.18 (s, 1H).

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(1) Barnes, B.J., Newcombe, P.J., Norris, R.K., Wilson, K. *J. Chem. Soc. Chem. Commun.* **1985**, 1408.
(2) Review: Ono, N., Kaji, A. *Synthesis* **1986**, 693.
(3) Review: Beck, J.R. *Tetrahedron* **1978**, *34*, 2057.
Gorvin, J.H., Whalley, D.P. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1364.
Goldman, P., Wuest, J.D. *J. Am. Chem. Soc.* **1981**, *103*, 6224.
Kornblum, N., Cheng, L., Kerber, R.C., Kestner, M.M., Newton, B.N., Pinnick, H.W., Smith, R.G., Wade, P.A. *J. Org. Chem.* **1976**, *41*, 1560.