Regioselective Nitration of 3-Alkyl-1-benzofurans at the 2-Position

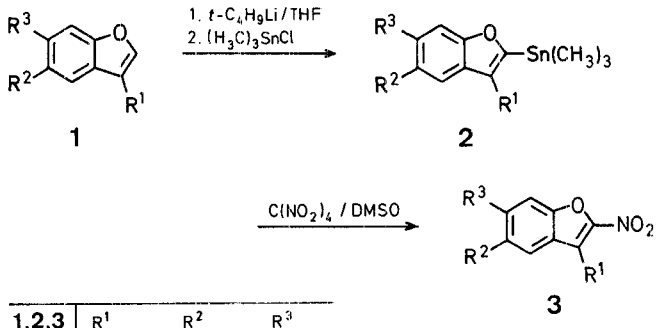
Jacques EINHORN, Pierre DEMERSEMAN, René ROYER*

Service de Chimie de l'Institut Curie, E.R. n° 213 du CNRS, 26 rue d'Ulm, F-75231 Paris Cédex 05, France

It appears that the various biological properties exerted by 2-nitrobenzofurans[1] and the corresponding naphthofurans[2-18] can be modified or enhanced by the presence of an alkyl group in the 3-position[19-21]. However, these effects have not been widely investigated, since the synthesis of 3-alkyl-2-nitrobenzofurans is mostly difficult. Thus, the condensation of bromonitromethane and *ortho*-hydroxylated aromatic aldehydes, which is the main procedure for preparing most of the 3-unsubstituted 2-nitrobenzofurans[1], cannot be applied to *ortho*-hydroxylated aromatic ketones to synthesize 3-alkyl-2-nitrobenzofurans. So far, these latter compounds were only obtained by direct nitration of 3-substituted benzofurans or by replacement of the acyl group in the 2-acyl-3-alkylbenzofurans[1]. These two nitration methods present two major disadvantages:

- they usually lead to low yields;
- unwanted nitration occurs on other activated carbons of the molecules.

We have now found that the 3-alkyl-2-nitro benzofurans **3a–f** can easily be prepared in good yields by treating 3-alkylbenzofurans **1a–f** successively with *t*-butyllithium, then trimethyltin chloride and finally with tetranitromethane in dimethylsulfoxide. The same transformation has also been carried out from 3-phenyl-benzofuran **1g** (Table).



1 2 3

1,2,3	R^1	R^2	R^3
a	CH_3	H	H
b	i-C_3H_7	H	H
c	CH_3	Cl	H
d	CH_3	OCH_3	H
e	CH_3	H	OCH_3
f	CH_3	CH_3	CH_3
g	C_6H_5	H	H

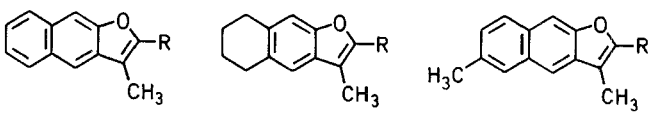
Table. 2-Nitro-1-benzofurans **3** and 2-Nitronaphthofurans **4b**, **5b** and **6b** prepared

Product No.	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ[ppm]
3a	72	98°	$C_9H_7NO_3$ (177.1)	2.7 (s, 3H, CH_3); 7.33–7.67 (m, 3H, 5,6,7-H_{arom}); 7.7 (br. d, 1H, 4-H_{arom}, J_{ortho} = 7.5 Hz)
3b	74	58°	$C_{11}H_{11}NO_3$ (205.2)	1.5 (d, 6H, CH_3); 4.2 (m, 1H, CH); 7.3–7.65 (m, 3H, 5,6,7-H_{arom}); 7.95 (br. d, 4-H_{arom}, J_{ortho} = 7.5 Hz)
3c	84	164°	158°[22]	2.65 (s, 3H, CH_3); 7.55 (br. s, 2H, 6,7-H_{arom}); 7.70 (br. s, 4-H_{arom})
3d	93	133°	$C_{10}H_9NO_4$ (191.2)	2.68 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 7.07 (d, 1H, 4-H_{arom}, $J_{4,6}$ = 2.4 Hz); 7.21 (dd, 1H, 6-H_{arom}, $J_{6,7}$ = 9 Hz); 7.51 (d, 1H, 7-H_{arom})
3e	73	115°	$C_{10}H_9NO_4$ (191.2)	2.7 (s, 3H, CH_3); 3.88 (s, 3H, OCH_3); 6.9–7.1 (m, 2H, 5,7-H_{arom}); 7.55 (d, 1H, 4-H_{arom}, J_{ortho} = 9 Hz)
3f	86	172°	172°[23]	2.35 (s, 3H, 5-CH_3); 2.4 (s, 3H, 6-CH_3); 2.65 (s, 3H, 3-CH_3); 7.3 (s, 1H, 7-H_{arom}); 7.4 (s, 1H, 4-H_{arom})
3g	90	108°	$C_{14}H_9NO_3$ (239.2)	7.3–7.75 (m, H_{arom})
4b	91	222°	222°[19]	2.82 (s, 3H, CH_3); 7.48–7.67 (m, 2H, 6,7-H_{arom}); 7.93–8.06 (m, 3H, 4,5,8-H_{arom}); 8.25 (br. s, 1H, 9-H_{arom})
5b	77	148–149°	148–149°[24]	1.83 (m, 4H, 6,6,7,7-H_4); 2.65 (s, 3H, CH_3); 2.91 (m, 4H, 5,5,8,8-H_4); 7.2 (s, 1H, 4-H_{arom}); 7.5 (s, 1H, 9-H_{arom})
6b	92	248°	248°[19]	3.11 (s, 3H, CH_3); 3.96 (s, 3H, OCH_3); 7.34 (br. s, 1H, 6-H_{arom}); 7.36 (dd, 1H, 8-H_{arom}, $J_{8,9}$ = 9 Hz, $J_{8,6}$ = 2.5 Hz); 7.62 (d, 1H, 4-H_{arom}, $J_{4,5}$ = 9 Hz); 7.9 (d, 1H, 5-H_{arom}, $J_{5,4}$ = 9 Hz); 8.34 (d, 1H, 9-H_{arom}, $J_{9,8}$ = 9 Hz)

[a] Yield of pure isolated product; purity checked by T.L.C. on silica gel (chloroform as developer) and ^{1}H-N.M.R. spectrometry.
[b] The microanalyses were in good agreement with the calculated values: C ± 0.25; H ± 0.3; N ± 0.25.
[c] The spectra were recorded at 90 MHz, except for compound **4b** (100 MHz, FT) and **6b** (250 MHz, FT).

This method enabled us to synthesize several hitherto unknown 2-nitrobenzofurans **3a**, **3b**, **3d**, **3e**, **3g** and to afford sufficient amounts of 5-chloro-3-methyl-2-nitrobenzofuran **3c** and 2-nitro-3,5,6-trimethylbenzofuran **3f**, which are respectively known[1] to be potent oxyuricides or amoebicides and show[21] only weak genotoxicity.

Naphthofurans **4a**, **5a**, and **6a** can be similarly transformed into nitro derivatives **4b**, **5b**, and **6b** (Table). In this connection, it is noteworthy that the compound **6b**, which is normally difficult to obtain[19], has been found to be more mutagenic than 7-methoxy-2-nitronaphtho[2,1-*b*]furan (R 7000)[3,4,7,8,15–17].



4 **5** **6**

4,5,6	R
a	H
b	NO_2

The 1-benzofurans **1a**[25], **1b**[22], **1c**[26], **1d**[27], **1e**[28], **1f**[29], **1g**[30] and the naphthofurans **4a**[19], **5a**[24], **6a**[19] were prepared according to published procedures.

Regioselective Nitration of 1-Benzofurans 1 and Naphthofurans 4a, 5a, 6a; General Procedure:

A 1.5 molar pentane solution of *t*-butyllithium (6.1 ml, 8.7 mmol) is slowly added with a syringe to a well-stirred and cooled (−60 °C) solution of the appropriate benzo- or naphthofuran derivative **1**, **4a**, **5a** or **6a** (7.9 mmol) in dry tetrahydrofuran (15 ml) under nitrogen. Stirring is continued at −60 °C for 1 h (2 h for **1b** and **1g**, which react more slowly due to steric hindrance). Trimethyltin chloride (1.8 g, 8.7 mmol) in dry tetrahydrofuran (7 ml) is then quickly added and the mixture is allowed to come to room temperature. The stirring is continued for 2 h more (4 h in the eases of compounds **1b** and **1g**). The solution is then cooled to −50 °C and quenched with water (5 ml), added in one portion. The mixture is allowed to warm to room temperature, diluted with water (200 ml), and extracted with ether (3 × 80 ml). The ether solution is washed with water (3 × 100 ml), dried with sodium sulfate, and the solvent is evaporated at 40 °C at atmospheric pressure, then under reduced pressure (15 torr).

The crude organotin derivative **2** so obtained is dissolved in the minimum amount of anhydrous dimethyl sulfoxide (7–30 ml) and tetranitromethane (0.96 ml, 8.7 mmol) is added with stirring. The mixture is stirred for 1 h (during which the nitro compound sometimes begins to separate as crystals) and water (300 ml) is added. In most cases, the solid nitro compound is separated by suction, washed with water, then with a small amount of cold pentane. After drying in vacuum, the product is purified, if necessary, by recrystallization (cyclohexane or methanol), or by passing through a short column of silica gel (eluent: dichloromethane). After addition of water to the reaction mixture, the crude nitro compounds **3b**, **3d**, and **3e** separated as a viscous oil. In these cases, the product is extracted with chloroform (3 × 50 ml), washed with water (3 × 50 ml), the organic layer is dried with sodium sulfate, and chromatographed on a short silica gel column (20 g, eluent: chloroform). Removal of the solvent affords pure nitro compound as a solid.

Received: April 2, 1984

* Address for correspondence.

[1] R. Royer, *Ann. Pharm. Fr.* **41**, 299 (1983).
[2] R. Cavier, J.-P. Buisson, J. Lemoine, R. Royer, *Eur. J. Med. Chem.* **16**, 73 (1981).
[3] N. Weill-Thevenet, J.-P. Buisson, R. Royer, M. Hofnung, *Mutation Research* **88**, 355 (1981).
[4] S. Nocentini, J. Coppey, J.-P. Buisson, R. Royer, *Mutation Research* **90**, 125 (1981).
[5] J. Gruest, L. Montagnier, J.-P. Buisson, R. Royer, *Bull. Cancer* **68**, 328 (1981).

[6] R. Cavier, J.-P. Buisson, R. Royer, *Eur. J. Med. Chem.* **17**, 91 (1982).
[7] N. Weill-Thevenet, J.-P. Buisson, R. Royer, M. Hofnung, *Mutation Research* **104**, 1 (1982).
[8] D. Averbeck, M. Moradi, J.-P. Buisson, R. Royer, *C.R. Acad. Sci. Ser. C* **295**, 181 (1982).
[9] J.-P. Buisson, G. Lamotte, P. Demerseman, R. Royer, R. Cavier, *Eur. J. Med. Chem.* **18**, 169 (1983).
[10] A. Goldé, D. Rouillard, J.-P. Buisson, R. Royer, *Antimicrobial Agents and Chemotherapy* **23**, 328 (1983).
[11] A. Amgar, R. Cavier, J.-P. Buisson, R. Royer, *Ann. Pharm. Fr.* **41**, 283 (1983).
[12] J. Einhorn, G. Lamotte, J.-P. Buisson, P. Demerseman, R. Royer, R. Cavier, *Eur. J. Med. Chem.* **19**, 143 (1984).
[13] J.-P. Buisson, R. Royer, P. Gayral, *Eur. J. Med. Chem.* **19**, 249 (1984).
[14] M. Venegas, M. Sala, J.-P. Buisson, R. Royer, I. Chouroulinkov, *Cancer Research*, **44**, 1969 (1984).
[15] Z.Z. Su, J.J. Cornelis, J. Rommelaere, *Carcinogenesis* **2**, 1039 (1981).
[16] P. Quillardet, O. Huisman, R. d'Ari, M. Hofnung, *Biochimie* **64**, 797 (1982).
[17] P. Quillardet, O. Huisman, R. d'Ari, M. Hofnung, *Proc. Natl. Acad. Sci. USA*, **79**, 5971 (1982).
[18] D. Le François-Chabas, L. Montagnier, *C.R. Acad. Sci. Ser. C* **296**, 283 (1983).
[19] J. Einhorn, P. Demerseman, R. Royer, R. Cavier, *Eur. J. Med. Chem.* **18**, 175 (1983).
[20] J. Einhorn, P. Demerseman, R. Royer, R. Cavier, *Eur. J. Med. Chem.* **18**, 233 (1983).
[21] J. Einhorn, P. Demerseman, R. Royer, R. Cavier, P. Gayral, *Eur. J. Med. Chem.*, in press.
[22] R. Royer, L. René, P. Demerseman, R. Cavier, J. Cenac, *Chim. Thér.* **6**, 79 (1971).
[23] R. Royer, L. René, P. Demerseman, *Chim. Thér.* **8**, 139 (1973).
[24] J. Einhorn, P. Demerseman, L. René, R. Royer, R. Cavier, *Eur. J. Med. Chem.* **18**, 79 (1983).
[25] A. Hantzch, *Ber. Dtsch. Chem. Ges.* **19**, 1294 (1886).
[26] D.S. Deorha, P. Gupta, *Indian J. Chem.* **2**, 459 (1964).
[27] A.V. Graffenried, St. v. Kostanecki, *Ber. Dtsch. Chem. Ges.* **43**, 2155 (1910).
[28] Y. Tahara, *Ber. Dtsch. Chem. Ges.* **24**, 2460 (1891).
[29] R. Royer, L. René, *Bull. Soc. Chim. Fr.* **1970**, 1029.
[30] W. Davies, S. Middleton, *J. Chem. Soc.* **1958**, 822.