Tetrahedron Vol. 36, pp. 1877 to 1878
© Pergamon Press Ltd., 1980. Printed in Great Britain
0040-4020/80/0615-1877/$02.00/0

A USEFUL PREPARATION OF 5-NITRO-2-FURAN DERIVATIVES

M. D'AURIA, G. PIANCATELLI* and A. SCETTRI
Centro di Studio per la Chimica delle Sostanze Organiche Naturali del CNR,
c/o Istituto di Chimica Organica dell'Università di Roma, Italia

(*Received UK 24 September 1979*)

Abstract—Alkyl-(5-bromo-2-furyl) carbinols **1** are converted with good yields into the corresponding 5-nitro derivatives **2** by reaction with silver nitrite. Furthermore, the singular reactivity of pyridinium chlorochromate towards products **2** results in high yields of (5-nitro-2-furyl) alkyl ketones **3** with a long side chain.

Simple furan compounds with no electron-withdrawing groups can be nitrated only by mixtures of acetic anhydride and nitric acid giving only moderate yields.[1] Other nitrating agents, e.g. NO_2^+ BF_4^-, particularly effective with aromatic substrates, give very poor results with furan derivatives.[2]

We now describe a single-step procedure, that allows the direct conversion of alkyl-(5-bromo-2-furyl)-carbinols **1** into the corresponding nitro-derivatives **2** under mild and simple conditions. Furthermore, we show that pyridinium chlorochromate (PCC), instead of the usual attack upon the furan ring,[3] oxidises the products **2** to the corresponding (5-nitro-2-furyl) alkyl ketones **3** with excellent yields (Scheme 1).

Nitrofurans are important antibacterial drugs[4] and have widespread commercial use.

The starting materials **1** were easily obtained by condensation of the readily available[5] 5-bromo-2-formyl-furan with alkylmagnesium bromides which were converted into the corresponding (5-nitro-2-furyl)-carbinols **2** in good yield.

Although the mechanism of the conversion **1**→**2** was not investigated, the presence of water and a sufficiency of Ag^+ ions are known to be important. Anhydrous conditions or the use of $NaNO_2$ as reagent† lead to much lower reaction rates and yields.

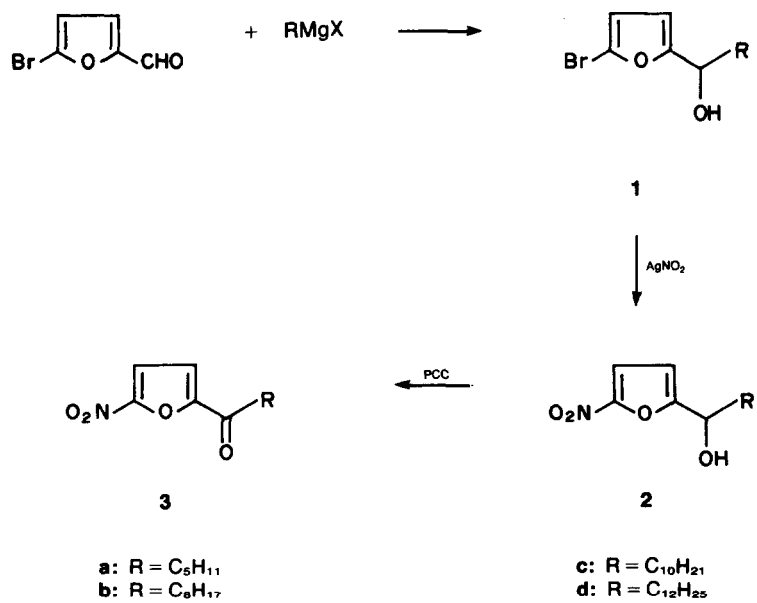
Furthermore a mechanism of aromatic nucleophilic substitution seems unlikely since, under the same conditions as **1**, 5-bromo-2-formyl-furan was recovered completely unchanged.

Our previous investigation[3] of the reaction of PCC upon furan derivatives (2-furylcarbinols and 5-bromo-2-furylcarbinols) had shown its regiospecific behaviour and that it acts as oxidant and dienophile towards the furan ring, leaving the alcoholic function untouched. The type of product depended strictly on the nature of substituents in 2 and 5 positions of the starting materials.

But, on account of the deactivation of the heteroaromatic nucleus by the $-NO_2$ group in compounds **2**, PCC preferentially oxidises the alcoholic function, leading to (5-nitro-2-furyl) alkyl ketones **3**. The mild conditions and the high yields obtained make this procedure more useful for preparative purposes than the routes at present employed.‡

†With or without the presence of catalytic amounts of Ag^+.

‡Only 5-nitro-2-acetyl-furan can be prepared satisfactorily through the known procedure[6] involving acylation and nitration of the furan ring.



Scheme 1.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. NMR spectra were recorded with a Jeol 60 HL spectrometer and a Perkin–Elmer R 32 spectrometer in CCl_4 solns using TMS as an internal standard. IR spectra were determined with a Perkin–Elmer 257 spectrometer in 1% CCl_4 solns. Mass spectra were obtained with an AEI MS–12 instrument.

Compounds **1**

General procedure. 3.5 g (20 mmoles) of 5 - bromo - 2 - formyl - furan, diluted with 12 ml anhyd Et_2O, were added at 0° to a Grignard reagent prepared from 1.07 g Mg and 40 mmoles alkyl bromide in 25 ml anhyd Et_2O. After 1 hr, 100 ml of a cold soln, satd with NH_4Cl, were added and the mixture was stirred for 2 hr. Then the usual work-up yielded the crude product that was purified through chromatography on SiO_2. The elution with C_6H_6–Et_2O 9:1 gave **1**, as oily matters.

1-(5-*Bromo*-2-*furyl*)-*hexane*-1-*ol* **1a**, yield 72%, oil. NMR (CCl_4, δ): 6.15 (dd, 2H, J = 3 Hz), 4.53 (t, 1 H), 1.93 (s, 1 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3610, 1125. MS, *m/e*: 246 (M^+), 248 (M^+ + 2). (Found: C, 48.60; H, 6.10;-Br, 32.42. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.58; H, 6.07; Br, 32.39.

1-(5-*Bromo*-2-*furyl*)-*nonane*-1-*ol* **1b**, yield 70%, oil. NMR (CCl_4, δ): 6.20 (m, 2 H), 4.54 (t, 1 H), 2.14 (s, 1 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3610, 1125. MS, *m/e*: 288 (M^+), 290 (M^+ + 2). (Found: C, 54.01; H, 7.36; Br, 27.83. Calcd. for $C_{13}H_{21}BrO_2$: C, 53.98; H, 7.26; Br, 27.68%).

1-(5-*Bromo*-2-*furyl*)-*hendecane*-1-*ol* **1c**, yield 74%, oil. NMR (CCl_4, δ): 6.17 (dd, 2 H, J = 3 Hz), 4.53 (t, 1 H), 1.90 (s, 1 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3610, 1125, MS, *m/e*: 316 (M^+), 318 (M^+ + 2). Found: C, 56.87; H, 7.73; Br, 2504. Calcd. for $C_{15}H_{25}BrO_2$: C, 56.78; H, 7.89; Br, 25.24%).

1-(5-*Bromo*-2-*furyl*)-*tridecane*-1-*ol* **1d** yield 75%, oil. NMR (CCl_4, δ): 6.15 (dd, 2 H, J = 3 Hz), 4.53 (t, 1 H), 1.94 (s, 1 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3610, 1125. MS, *m/e*: 344 (M^+), 346 (M^+ + 2). Found: C, 59.01; H, 8.63; Br, 2350. Calcd. for $C_{17}H_{29}BrO_2$: C, 59.13; H, 8.40; Br, 23.19%).

Compounds **2**

General procedure. 6 mmoles of $AgNO_2$ were added to a soln of 1 mmole of **1** in 20 ml of a mixture acetone–water 4:1 and stirred in the dark for 48 hr at 60°. The residue was filtered off and washed with Et_2O. The organic phase was washed with water until disappearance of Ag^+ ions and then dried over Na_2SO_4. After the removal of the solvent under reduced pressure, the crude oily product was purified through column chromatography on SiO_2. The elution with 9:1 C_6H_6–Et_2O yielded **2**, as oily matter.

1-(5-*Nitro*-2-*furyl*)-*hexane*-1-*ol* **2a**, yield 55%, oil. NMR (CCl_4, δ): 7.13 (d, 1 H, J = 4 Hz), 6.41 (d, 1 H, J = 4 Hz), 4.68 (t, 1 H), 2.50 (broad s, 1 H), 1.78 (m, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3600, 3140, 1586, 1498, 1352, 1240, 1018. MS, *m/e*: 213 (M^+). (Found: C, 56.15; H, 7.20; N, 6.40. Calcd. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 7.09%).

1-(5-*Nitro*-2-*furyl*)-*nonane*-1-*ol* **2b**, yield 50%, oil. NMR (CCl_4, δ): 7.16 (d, 1 H, J = 4 Hz), 6.42 (d, 1 H, J = 4 Hz), 4.57 (t, 1 H), 2.95 (broad s, 1 H), 1.75 (m, 2 H). IR(1% CCl_4, ν_{max} cm^{-1}): 3600, 3140, 1590, 1501, 1354, 1238, 1016. MS, *m/e*: 255 (M^+). (Found: C, 61.30; H, 8.25; N, 5.35. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49%).

1-(5-*nitro*-2-*furyl*)-*hendecane*-1-*ol* **2c**, yield 52%, oil. NMR (CCl_4, δ): 7.15 (d, 1 H, J = 4 Hz), 6.41 (d, 1 H, J = 4 Hz), 4.70 (t, 1 H), 2.45 (broad s, 1 H), 1.80 (m, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3600, 3140, 1585, 1500, 1352, 1011. M, *m/e*: 283 (M^+). (Found: C, 63.70; H, 9.01; N, 4.81. Calcd. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94%).

1-(5-*Nitro*-2-*furyl*)-*tridecane*-1-*ol* **2d**, yield 62% oil NMR (CCl_4, δ): 7.10 (d, 1 H, J = 4 Hz), 6.36 (d, 1 H, J = 4 Hz), 4.62 (t, 1 H), 3.40 (broad s, 1 H), 1.75 (m, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3600, 3138, 1590, 1500, 1352, 1237, 1013. MS, *m/e*: 311 (M^+). (Found: C, 65.40; H, 9.50; N, 4.63. Calcd. for $C_{17}H_{27}NO_4$: C, 65.57; H, 9.39; N, 4.50%).

Compounds **3**

General procedure. 1 mmole of **2**, dissolved in 10 ml anhyd CH_2Cl_2, was added to a suspension of 2 mmoles of PCC in 10 ml anhyd CH_2Cl_2 and the mixture was stirred at 45° for 24 hr. Then, after the usual isolation procedure,[7] the crude product was chromatographed on SiO_2. The elution with 4:1 C_6H_6–n–hexane yielded **3**.

1-(5-*Nitro*-2-*furyl*)-*hexane*-1-*one* **3a**, yield 77%, plates from MeOH–H_2O, mp = 52–53°. NMR (CCl_4, δ): 7.28 (d, 1 H, J = 3 Hz), 7.14 (d, 1 H, J = 3 Hz), 2.88 (t, 2 H), 1.80 (m, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3170, 3150, 1690, 1380, 1342, 1170, 1010. MS, *m/e*: 211 (M^+). (Found: C, 57.01; H, 6.03; N, 6.78. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63%).

1-(5-*Nitro*-2-*furyl*)-*nonane*-1-*one* **3b**, yield 75%, plates from MeOH, mp = 70–71°. NMR (CCl_4, δ): 7.30 (d, 1 H, J = 3 Hz), 7.15 (d, 1 H, J = 3 Hz), 2.90 (t, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3150, 3130, 1692, 1375, 1350, 1175, 1013. MS, *m/e*: 253 (M^+). (Found: C, 61.49; H, 7.67; N, 5.66. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53%).

1-(5-*Nitro*-2-*furyl*)-*hendecane*-1-*one* **3c**, yield 72%, plates from MeOH, mp = 80–81°. NMR (CCl_4, δ): 7.28 (d, 1 H, J = 3 Hz), 7.17 (d, 1 H, J = 3 Hz), 2.88 (t, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3170, 3148, 1690, 1382, 1348, 1170, 1011. MS, *m/e*: 281 (M^+). (Found: C, 64.21; H, 8.38; N, 5.07. Calcd. for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98%).

1-(5-*Nitro*-2-*furyl*)-*tridecane*-1-*one* **3d**, yield 85%, plates from MeOH, mp = 85–86°. NMR (CCl_4, δ): 7.32 (d, 1 H, J = 3 Hz), 7.22 (d, 1 H, J = 3 Hz), 2.93 (t, 2 H). IR (1% CCl_4, ν_{max} cm^{-1}): 3170, 3149, 1692, 1384, 1350, 1175, 1013. MS, *m/e*: 309 (M^+). Anal. (Found: C, 66.14; H, 8.71; N, 4.70. Calcd. for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53%).

REFERENCES

[1]For a review of furans nitration and nitrating agents, see: P. Krkokska, A. Juràsek and J. Kovàc, *Chem. Listy* **62**, 182 (1968).

[2]G. Olàh, S. Kuhn and A. Mlinkò, *J. Chem. Soc.* 4257 (1956).

[3a]G. Piancatelli, A. Scettri and M. D'Auria, *Tetrahedron Letters* 2199 (1977); [b]G. Piancatelli, A. Scettri, and M. D'Auria, *Ibid.* 1507 (1979).

[4]K. Miura, *Progr. Med. Chem.* **5**, 320 (1967).

[5]Z. N. Nazarova, *Zh. Obshchei Khim.* **24**, 575 (1954); *Chem. Absts*, **49**, 6214 (1955).

[6]A. P. Dunlop and F. N. Peters, *The Furans*, pp. 153–156. Reinhold, New York (1953).

[7]E. J. Corey and J. W. Suggs, *Tetrahedron Letters* 2647 (1975).