



On the bromination of methyl 2-methyl-3-furoate[†]

Haripada Khatuya*

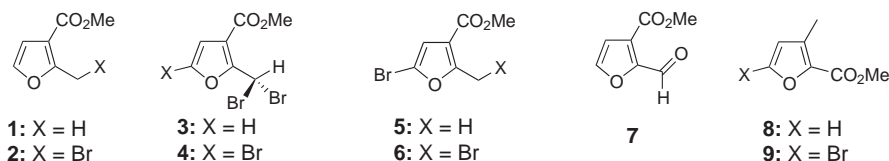
Department of Chemistry (0506), University of California-San Diego, La Jolla, CA 92093, USA

Received 2 June 1999; accepted 30 January 2001

Abstract—Methyl 2-methyl-3-furoate was subjected to bromination with *N*-bromosuccinimide (NBS), a milder brominating reagent, under different reaction conditions to obtain a variety of selective brominated products. © 2001 Elsevier Science Ltd. All rights reserved.

In connection with the synthesis of some terpenes it was necessary to prepare compound **2**. Hence compound **1**¹ was subjected to bromination with NBS (1.05 equiv.), using a radical initiator (benzoyl peroxide), and led to the expected compound **2**² in 93% yield, along with minor amounts (ca. 5%) of the 5-bromo derivative **5**. It was reasoned that the use of more than 1.05 equiv. of NBS would increase the percentage of **5**. Hence the present study was undertaken.³

When the above reaction was repeated without the radical initiator, the **2/5** ratio remained nearly the same. The use of excess NBS (2.2 equiv.) under the radical conditions led to isolation of *gem*-dibromo compound **3** in 63% yield (vide Table 1) along with a trace amount of 5-bromo derivative **6**. Thus, the use of excess NBS further substituted the side chain, in lieu of the ring. Those two sets of experiments indicated ring substitution might be possible. The use of 2.8

**Table 1.** Bromination of **1** with NBS

Entry	Conditions, yield (%)	Product	¹ H NMR δ (ppm)	¹³ C NMR δ (ppm)
1	NBS (1.05), Bz ₂ O ₂ (cat.), CCl ₄ , reflux, 14 h, 93%	2	See Ref. 2	21.0, 51.6, 111.2, 115.6, 142.6, 155.2, 162.9
2	NBS (2.2), Bz ₂ O ₂ (cat.), CCl ₄ , reflux, 24 h, 63%	3	3.89 (s, 3H), 6.69 (d, 1H), 7.39 (s, 1H), 7.51 (d, 1H)	25.0, 52.1, 110.8, 112.4, 143.7, 154.9, 162.5
3	NBS (2.8), Bz ₂ O ₂ (cat.), CCl ₄ , reflux, 20 h, 46%	4	3.87 (s, 3H), 6.62 (s, 1H), 7.32 (s, 1H)	23.6, 52.4, 110.8, 112.4, 125.0, 143.7, 161.5
4	NBS (1.2), DMF, 0°C; 40°C, 4 h, 82%	5	2.56 (s, 3H), 3.82 (s, 3H), 6.54 (s, 1H)	13.6, 51.4, 111.9, 115.7, 119.8, 160.5, 163.1
5	NBS (2.3), DMF, 0°C; rt, 3 h, 41%	6	3.88 (s, 3H), 4.76 (s, 2H), 6.34 (s, 1H)	20.3, 52.0, 112.8, 118.0, 123.2, 156.7, 161.9

Keywords: furans; halogenation; halocompounds; radicals and radical reactions.

* Present address: The R. W. Johnson P. R. I., 3210 Merryfield Row, San Diego, CA 92121, USA. Fax: (858) 784-3116; e-mail: hkhatuya@prius.jnj.com

[†] The author wishes to thank Professor E. Wenkert for his encouragement and support.

equiv. of NBS afforded the ring brominated product **4** (46%).

The structure of *gem*-dibromo compound **3** was established from the chemical shift of the methine proton (vide Table 1) and by a chemical transformation. Thus, when compound **3** was warmed at 50°C in wet DMF, solvolysis occurred and a new compound was obtained, whose ¹H NMR spectrum [δ (ppm): 3.89 (s, 3H), 6.90 (d, 1H, $J=1.5$ Hz), 7.65 (br.s, 1H) and 10.24 (s, 1H)] supported the aldehyde **7**.

In search of a selective ring bromination, a non-protic polar solvent (viz. DMF) was considered. When furan **1** was reacted with NBS (1.2 equiv.), a clean 5-brominated product (**5**) was obtained in 82% yield. On the other hand, with 2.3 equiv. of NBS, the side chain as well as ring brominated product (**6**) was obtained.

Encouraged by these results, the bromination of furan **8** was carried out employing NBS, invariably a mixture of furans **8** and **9**⁴ was isolated. The conversion was found to be most effective when Br₂ (1.8 equiv.) was added at 40–45°C and the solution then heated at 50°C.^{4a} As the ester group at the 2-position deactivates both the double bonds in furan **8**, a stronger brominating agent was required. A 3-carboethoxy group (i.e. **1**) deactivates predominantly its conjugated double bond, permitting a milder brominating agent to be effective.

Experimental:

Compound 4: A mixture of furan **1** (1.70 g, 12.1 mmol), NBS (6.10 g, 33.9 mmol) and (PhCO)₂O₂ (0.030 g) was refluxed in CCl₄ (25 mL) for 20 h. After the usual work-up, the ¹H NMR spectrum of the crude material

revealed the expected product **4** to be contaminated with minor amounts of **5** and **6** [**4**:(**5**+**6**)=90:10]. SiO₂ chromatography (1% EtOAc in light petroleum ether) afforded compound **4** (2.11 g, 46%).

Compound 6: NBS (33.4 g, 0.30 mol) was added in portions to a solution of furan **1** (15.0 g, 0.11 mol) in anhyd. DMF (20 mL) at 0°C. After an additional 1 h the reaction mixture was allowed to warm to rt and stirred for 3 h more. Water (100 mL) was added and extracted with ether. The combined extracts were washed with water, brine, and then dried. Distillation of the crude material under reduced pressure (110°C/0.2 mmHg) gave 12.97 g (41%) of **6**.

References

1. (a) Adapted from the literature procedure: Winberg, H. E.; Fawcett, F. W.; Mochel, W. E.; Theobald, C. W. *J. Am. Chem. Soc.* **1960**, *82*, 1428; (b) For NMR data, see: Padwa, A.; Zhi, L.; Fryxell, G. E. *J. Org. Chem.* **1991**, *56*, 1077.
2. (a) Khatuya, H., Taken from Ph.D. Dissertation, University of California-San Diego, 1995; (b) After completion of this work there appeared a paper on the preparation and use of **2**: Salimbeni, A.; Canevotti, R.; Paleari, F.; Poma, D.; Caliarì, S.; Fici, F.; Cirillo, R.; Renzetti, A. R.; Subissi, A.; Belvisi, L.; Bravi, G.; Scolastico, C.; Giachetti, A. *J. Med. Chem.* **1995**, *38*, 4806.
3. For a study on 3-methylindoles, see: Zhang, P.; Liu, R.; Cook, J. M. *Tetrahedron Lett.* **1995**, *36*, 3103.
4. (a) Wenkert, E.; Khatuya, H.; Klein, P. S. *Tetrahedron Lett.* **1999**, *40*, 5171; (b) Grigg, R.; Knight, J. A.; Sargent, M. V. *J. Chem. Soc. (C)* **1966**, 976.