

# Preparation of Sterically Crowded *t*-Butylfurans by Direct *t*-Butylation and Cyclisation of *t*-Butyl Substituted 1,4-Diketones. Selective Dehydrodimerisation of Neopentyl Ketones by Lead Dioxide

Hans Wynberg<sup>a</sup> and Ulfert E. Wiersum<sup>\*b</sup>

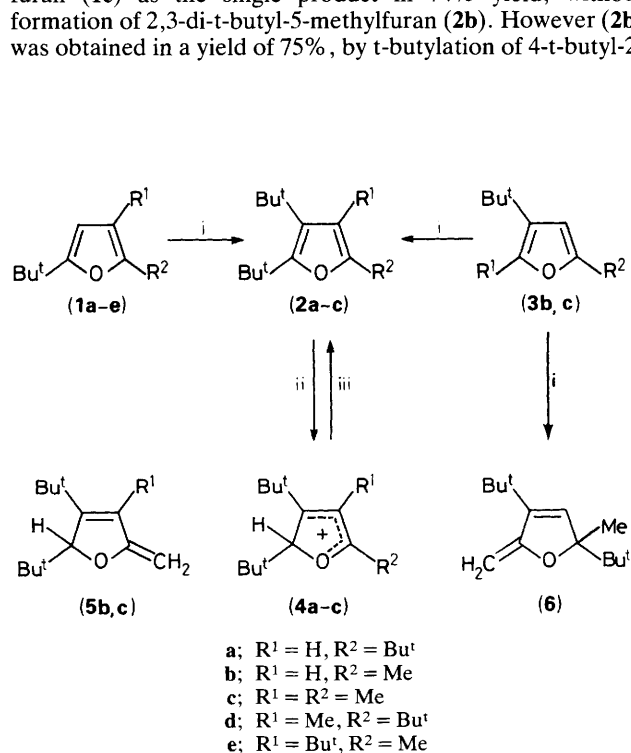
<sup>a</sup> Department of Organic Chemistry, The University, Nyenborgh 16, 9747 AG, Groningen, The Netherlands

<sup>b</sup> Akzo Research Laboratories, Corporate Research Department, Velperweg 76, 6800 SB, Arnhem, The Netherlands

*o*-Di-*t*-butylfurans can be obtained in high yields via Friedel–Crafts alkylation and via cyclisation of 1,4-diketones, but minor differences in the substitution pattern of the starting materials prevent *o*-di-*t*-butylation, or govern escape reactions to relieve the steric strain.

Our preparation, 25 years ago,<sup>1</sup> of 2,3,5-tri-*t*-butylfuran (**2a**), by direct *o*-*t*-butylation of 2,5-di-*t*-butylfuran (**1a**), as part of a programme to study geometric strains and stresses in five-membered ring heteroaromatic compounds,<sup>2</sup> inspired the analogous reaction in the pyrrole series.<sup>3</sup> In contrast, 2,5-di-*t*-butylthiophene, on attempted further Friedel–Crafts *t*-butylation, only rearranges into its 2,4-isomer.<sup>4</sup> This may be guided by the geometry, which is more favourable for direct *o*-di-*t*-butylation in furan and pyrrole than in thiophene and benzene, both in the 2,3- and the 3,4-position. Nevertheless, 3,4-di-*t*-butylthiophene was recently synthesized via non-alkylation pathways<sup>5,6</sup> and was also found to rearrange quantitatively into its 2,4-analogue with aluminium chloride.<sup>6</sup> The preparation of tetra-*t*-butyl-thiophene and -pyrazole, following our strategy for synthesis of *o*-di-*t*-butyl aromatic compounds,<sup>7</sup> was also reported.<sup>8</sup> This led us to further exploration of possible routes to *o*-di-*t*-butylfurans and a study of their furanonium ions.<sup>9</sup>

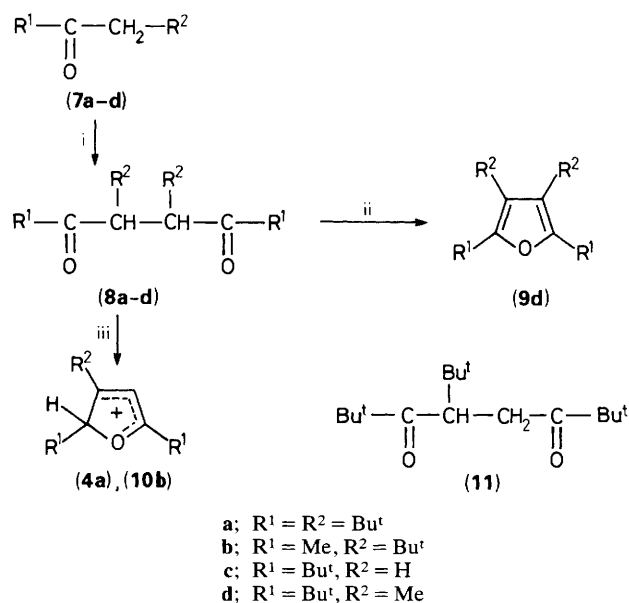
The *t*-butylations (Scheme 1) were performed as described previously, with a 1 : 1 : 1 ratio of the furan, *t*-butyl chloride, and aluminium chloride, in boiling carbon disulphide.<sup>1,4</sup> 2-*t*-Butyl-5-methylfuran (**1b**) yielded 2,4-di-*t*-butyl-5-methylfuran (**1e**) as the single product in 74% yield, without formation of 2,3-di-*t*-butyl-5-methylfuran (**2b**). However (**2b**) was obtained in a yield of 75%, by *t*-butylation of 4-*t*-butyl-2-



**Scheme 1.** Reagents and conditions: i, Bu<sup>t</sup>Cl, AlCl<sub>3</sub>, CS<sub>2</sub>; ii, 96% H<sub>2</sub>SO<sub>4</sub>; iii, NaHCO<sub>3</sub>, H<sub>2</sub>O.

methylfuran (**3b**).<sup>†</sup> Unexpectedly (**2b**) was reversibly recovered from its stable furanonium ion (**4b**), formed by dissolving it in 96% sulphuric acid, without formation of the isomeric exo-methylene-2,5-dihydrofuran (**5b**). This reaction was seen<sup>9</sup> during *t*-butylation of (**1c**), leading to the furanonium ion (**4c**), which is deprotonated to give 2,3-di-*t*-butyl-4-methyl-5-methylene-2,5-dihydrofuran (**5c**), instead of (**2c**), thus minimising the steric strain at the expense of the aromaticity of the furan ring. Rigorous *t*-butylation of (**1d**), (**1e**), (**2a**), and (**2b**) left these furans unchanged and failed as a route to other *o*-di-*t*-butylfurans. 3,4-Di-*t*-butylation, attempted with 2,5-dimethyl-3-*t*-butylfuran (**3c**), gave rise to an anomalous substitution in the 5-position, at the expense of the aromaticity of the furan ring, with formation of the dihydrofuran (**6**).<sup>9</sup>

In an alternative approach, the preparation of *o*-di-*t*-butylfurans was studied by ring-closure experiments with 1,4-diketones<sup>11</sup> (Scheme 2). On treatment with phosphorus pentoxide<sup>4</sup> at 180 °C, or by refluxing it in benzene with a trace of toluene-*p*-sulphonic acid, the octanedione (**11**) cyclised smoothly to give (**2a**), but the tetra-*t*-butyl analogue (**8a**) and



**Scheme 2.** Reagents and conditions: i, PbO<sub>2</sub>; ii, P<sub>2</sub>O<sub>5</sub>; iii, 96% H<sub>2</sub>SO<sub>4</sub>.

<sup>†</sup> Satisfactory analytical data were obtained for all new compounds reported. The furans (**1a–d**) and (**3c**) were obtained from the corresponding 1,4-diketones by ring closure with phosphorus pentoxide.<sup>4,9</sup> Compound (**3b**) was prepared via its 5-acetyl derivative,<sup>10</sup> after oxidation and decarboxylation.

the di-*t*-butylhexanedione (**8b**) resisted ring closure under these conditions. With phosphorus pentoxide, above 200 °C, a multitude of cracking products emerged from (**8a**) and (**8b**). The diketone (**11**) dissolved in 7 h in concentrated sulphuric acid, to form the furanium ion (**4a**).<sup>9</sup> The diketones (**8a**) and (**8b**) needed about 30 h for dissolution in concentrated sulphuric acid, but cyclisation had occurred with di-*t*-butylation, to give the furanium ions (**4a**) and (**10b**), respectively, which we had noted earlier were formed with sulphuric acid solutions of the furans (**2a**) and (**3c**).<sup>9‡</sup>

The symmetrical 1,4-diketones (**8a–d**) were prepared by oxidative radical dehydrodimerisation,<sup>13</sup> simply by boiling the neat ketones (**7a–d**) for 1–7 days with lead dioxide.<sup>14</sup> A more elaborate coupling with lead tetra-acetate, *via* trimethylsilyl enolates, was also reported.<sup>15</sup>§ We found the dimerisation unselective, producing low yields of 1,4-diketones in admixture with other condensation products, in the case of pinacolone (**7c**) and *t*-butyl ethyl ketone (**7d**). This is not surprising since the carbonyl group engages in radical addition reactions.<sup>17</sup> In contrast, the neopentyl ketones (**7a**) and (**7b**) gave selective dimerisations in 60–70% yields, although more slowly and at higher temperatures, to form (**8a**), m.p. 89–90.5 °C, and (**8b**), m.p. 119.5–120.5 °C, respectively.

---

‡ The diketone (**11**),  $n_D^{20}$  1.4335, was prepared from (**2a**) by ring opening with bromine in methanol<sup>12</sup> to the corresponding octenedione, m.p. 47–48 °C, which was reduced to (**11**) with zinc and sodium hydroxide. 2,2,4,5,7,7-Hexamethyloctane-3,6-dione (**8d**) gave 2,5-di-*t*-butyl-3,4-dimethylfuran (**9d**) with phosphorus pentoxide. Diketones (**8c**) and (**8d**) dissolved in 2–4 h in concentrated sulphuric acid, yielding the furans (**1a**) and (**9d**) upon hydrolysis.

§ Note added in proof: A similar coupling, very recently reported with ketone (**7d**), was found to be ineffective with ketone (**7a**) for preparation of (**8a**).<sup>16</sup>

The kinetic stabilisation against secondary reactions of the intermediate acylneopentyl radicals as well as of the furanium ions, is an exclusive feature of *t*-butyl substituents, also seen in other highly reactive classes.<sup>18</sup>

Received, 31st October 1989; Com. 9/04677A

## References

- 1 H. Wynberg and U. E. Wiersum, *Chem. Commun.*, 1965, 1.
- 2 H. Wynberg, *Acc. Chem. Res.*, 1971, **4**, 65.
- 3 R. Rammasseul and A. Rassat, *Chem. Commun.*, 1965, 453.
- 4 H. Wynberg and U. E. Wiersum, *J. Org. Chem.*, 1965, **30**, 1058.
- 5 L. Brandsma, J. Meyer, H. D. Verkruisje, A. J. M. Duisenberg, and J. Kroon, *J. Chem. Soc., Chem. Commun.*, 1980, 922.
- 6 J. Nakayama, S. Yamaoka, and M. Hoshino, *Tetrahedron Lett.*, 1988, **29**, 1161.
- 7 Ae. de Groot and H. Wynberg, *J. Org. Chem.*, 1966, **31**, 3954.
- 8 A. Krebs, E. Franken, and M. Müller, Abstracts of the 11th International Congress of Heterocyclic Chemistry, Heidelberg, B.R.D., August 16–21, 1987, p. 166; see also: A. Krebs, B. Kaletta, W. Ulrich-Nickel, W. Rüger, and L. Tikwe, *Tetrahedron*, 1986, **42**, 1693.
- 9 H. Wynberg and U. E. Wiersum, *Tetrahedron Lett.*, 1967, 2951; 1975, 3619.
- 10 A. T. Balaban and C. D. Nenitzesco, *Chem. Ber.*, 1960, **93**, 599.
- 11 L. T. Scott and J. O. Naples, *Synthesis*, 1973, 209.
- 12 J. Levisalles, *Bull. Soc. Chim. Fr.*, 1957, 995.
- 13 P. Gouverneur, *Ind. Chim. Belg.*, 1974, **39**, 329; 467.
- 14 R. Brettell, *Chem. Commun.*, 1970, 342.
- 15 Y. Kobayashi, T. Taguchi, and E. Tokuno, *Tetrahedron Lett.*, 1977, 3741.
- 16 N. Kuhn and K. Jendral, *Chemiker Zeitung*, 1989, **113**, 289.
- 17 G. E. Hawkins and R. Large, *J. Chem. Soc., Perkin Trans. 1*, 1977, 280; G. Brunton, H. C. McBay, and K. U. Ingold, *J. Am. Chem. Soc.*, 1977, **99**, 4447.
- 18 G. Maier, *Angew. Chem.*, 1988, **100**, 317; *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 309; M. Regitz and P. Binger, *ibid.*, 1988, **100**, 1541; *ibid.*, 1988, **27**, 1484.