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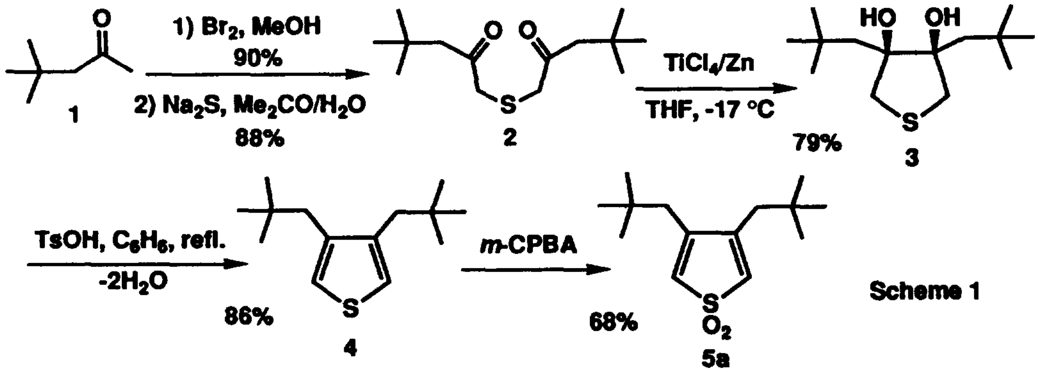
A General Synthesis of Aromatic Compounds Carrying Two Neopentyl Groups on Adjacent Positions

Juzo Nakayama* and Koichi Yoshimura
Department of Chemistry, Faculty of Science, Saitama University,
Urawa, Saitama 338, Japan

Abstract: 3,4-Dineopentylthiophene (4) was synthesized in a good overall yield starting from methyl neopentyl ketone. 3,4-Dineopentylthiophene-1,1-dioxide (5a), easily obtainable by oxidation of 4, undergoes Diels-Alder reactions with a variety of acetylenic dienophiles or their equivalent to furnish aromatic compounds carrying two neopentyl groups on adjacent positions.

The chemistry of aromatic compounds carrying bulky substituents such as *tert*-butyl, neopentyl, and 1-adamantyl groups on adjacent positions has been attracting considerable attention. Interest has focused mostly on their reactivities, strain energies, and structural problems including rotational barrier about the bond between aromatic ring and bulky substituent and also deviation of the aromatic ring from planarity. Thus, much effort has been made for the syntheses of such compounds. As to neopentyl series, however, only a few aromatic compounds carrying two neopentyl groups on adjacent positions are known[1-3] and thus no general synthetic method for this class of compounds is available. We report here a convenient synthesis of a series of aromatic compounds carrying two neopentyl groups on adjacent positions.

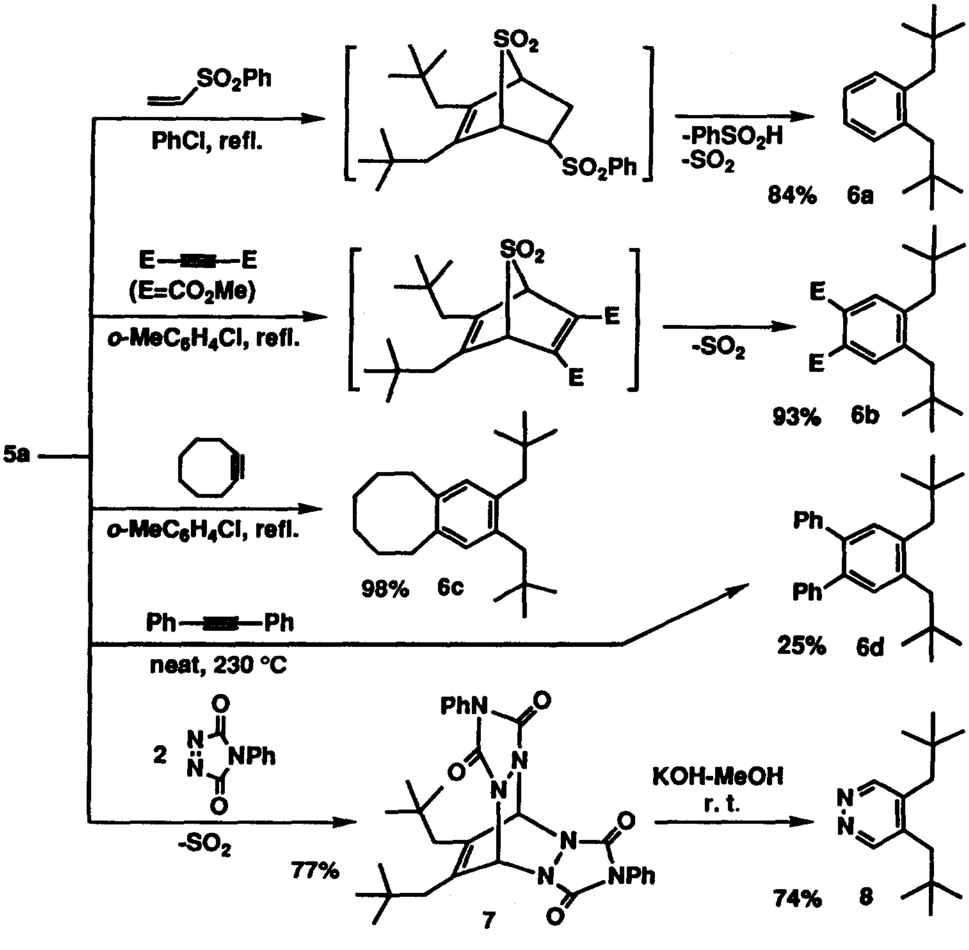
In 1985 we developed a new thiophene synthesis,[4] which is very versatile and enables us to prepare a wide variety of structurally interesting thiophenes including highly congested[5] and strained[6] ones. Application of this method has now allowed the easy synthesis of 3,4-dineopentylthiophene (4) (Scheme 1).



Scheme 1

Thus, commercially available methyl neopentyl ketone (**1**) was brominated in methanol to afford bromomethyl neopentyl ketone regioselectively in 90% yield.[7] Treatment of the bromo ketone with $Na_2S\cdot 9H_2O$ in acetone-water produced the diketo sulfide (**2**) in 88% yield. Intramolecular reductive coupling of **2** with a low-valent titanium reagent, prepared from titanium(IV) chloride and zinc powder in THF,[8] gave the thiolanediol **3** in 79% yield. *p*-Toluenesulfonic aicd-catalyzed dehydration of **3** in refluxing benzene cleanly afforded the expected 3,4-dineopentylthiophene (**4**) in 86% yield, thus allowing the first synthesis of this congested thiophene.[9]

Oxidation of **4** with *m*-chloroperbenzoic acid (*m*-CPBA) provided the corresponding thiophene-1,1-dioxide **5a** in 68% yield. The dioxide **5a** behaves as a typical diene, undergoing Diels-Alder reactions with a variety of dienophiles to give the corresponding adducts in excellent yields (Scheme 2). Thus, heating **5a** with phenyl vinyl sulfone in refluxing chlorobenzene for 15 h gave *o*-dineopentylbenzene (**6a**) directly in 84% yield; the initial adduct extrudes sulfur dioxide and benzenesulfinic acid to produce **6a** under the applied conditions.[5c,d] Compound **6a** was first synthesized in 1974 starting from *o*-xylene in two ways in very low overall yields (1.8 and 1.7%);[2] 3,4,5,6-tetramethyl-1,2-dineopentylbenzene, the first compound of



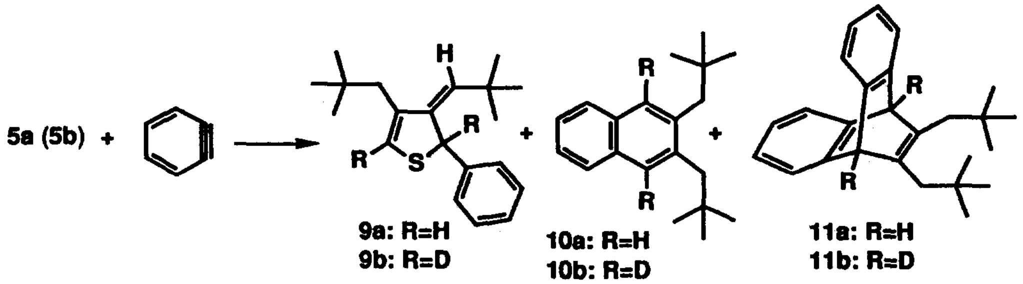
Scheme 2

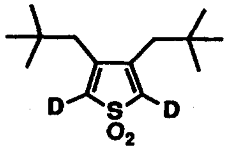
this class, was synthesized in 1964.[1] The reaction of **5a** with dimethyl acetylenedicarboxylate (DMAD) in refluxing *o*-chlorotoluene afforded dimethyl 4,5-dineopentylphthalate (**6b**) in 93% yield with elimination of sulfur dioxide from the initial adduct. The reaction of **5a** with a strained cycloalkyne, cyclooctyne, in refluxing *o*-chlorotoluene for 2 h afforded the *o*-dineopentylbenzene derivative **6c** with a fused eight-membered ring in 98% yield. Even diphenylacetylene reacted with **5a** under forcing conditions (230 °C, neat, 1 h) to give compound **6d** though in modest yield (25%).

The dioxide **5a** reacted with two molecules of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in refluxing benzene to give the bis-adduct **7** in 77% yield with loss of sulfur dioxide. Treatment of **7** with KOH/MeOH furnished 4,5-dineopentylpyridazine (**8**) in one-pot in 74% yield.[5b,c,10]

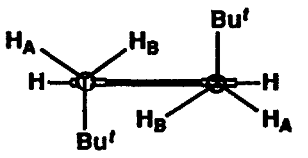
The reaction of **5a** with benzyne, generated by thermal decomposition of 2-carboxybenzenediazonium chloride (4 equiv) in refluxing 1,2-dichloroethane in the presence of propylene oxide,[12] is of interest. Thus, the reaction gave the ene reaction product **9a** as the major product in 68% yield. The expected 2,3-dineopentylnaphthalene (**10a**)[3b] was the minor product (20%) along with the barrelene derivative **11a** (7.5%), which arose from the further cycloaddition of **10a** with benzyne. The geometry of the exocyclic double bond part of **9a** was determined by NOE experiments.[11] To make more sure the structure of compounds **9a-11a**, the dideuterated dioxide **5b** was prepared by dilithiation of **5a** with butyllithium followed by treatment with D_2O and allowed to react with benzyne to afford the sulfone **9b** as the major product along with **10b** and **11b** in low yields. The most stable conformation of **5a** would be the one given below (see **12**)[3b] and therefore the less hindered hydrogen H_A (but not hindered H_B) would participate in the ene reaction to give **9a** in which *tert*-butyl and neopentyl groups are placed in the opposite direction. To our knowledge, this is the first instance that thiophene-1,1-dioxide participated in the ene reaction.[13] The formation of **11a** reveals that the cycloadditon of **10a** with benzyne occurred on the more congested benzene ring but not the unsubstituted and hence less hindered one.

It is thus now possible to obtain a variety of aromatic compounds carrying two neopentyl groups on adjacent positions, if we once prepare 3,4-dineopentylthiophene-1,1-dioxide (**5a**).





5b



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7. Although bromination of **1** has been investigated under a variety of conditions, the reported yields of BrCH$_2$COCH$_2$C(CH$_3$)$_3$ are not good generally. For example, see Overberger, C. G.; Berenbaum, M. B. *J. Am. Chem. Soc.* **1952**, *74*, 3293: Sarel, S.; Newman, M. S. *J. Am. Chem. Soc.* **1956**, *78*, 5416: Thorpe, J. W.; Warkentin, J. *Can. J. Chem.* **1973**, *51*, 927: Ho, K. W.; Guthmann, J. E. *J. Poym. Sci. Part A; Polym. Chem.* **1989**, *27*, 2435. We have found that addition of bromine in a single stream to an ice-cooled methanol solution of **1** affords BrCH$_2$COCH$_2$C(CH$_3$)$_3$ selectively in high yield.
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9. All new compounds gave satisfactory elemental analysis results (high resolution mass spectra in some cases) and supporting spectral data. NMR data (CDCl$_3$ as the solvent) are given below. **2**: ^{1}H NMR δ 1.02 (s, 18H), 2.45 (s, 4H), 3.27 (s, 4H); ^{13}C NMR δ 29.55 (q), 31.06 (s), 42.51 (t), 53.20 (t), 204.33 (s). **3**: ^{1}H NMR δ 1.07 (s, 18H), 1.42 [d, *J*=14.6 Hz, 2H, CH$_2$Bu(*t*)], 1.52 [d, *J*=14.6 Hz, 2H, CH$_2$Bu(*t*)], 2.37 (s, 2H, OH), 2.90 (d, *J*=11.2 Hz, 2H, CH$_2$), 2.97 (d, *J*=11.2 Hz, 2H, CH$_2$); ^{13}C NMR δ 31.40(s), 31.52 (q), 36.72 (t), 44.24 (t), 85.67 (s). **4**: ^{1}H NMR δ 0.90 (s, 18H), 2.50 (s, 4H), 6.88 (s, 2H); ^{13}C NMR δ 29.61 (q), 32.35 (s), 42.00 (t), 121.39 (d), 140.05 (s). **5a**: ^{1}H NMR δ 0.98 (s, 18H), 2.29 (s, 4H), 6.26 (s, 2H); ^{13}C NMR δ 29.58 (q), 32.47 (s), 40.62 (t), 126.93 (d), 144.76 (s). **6a**: ^{1}H NMR δ 0.89 (s, 18H), 2.63 (s, 4H), 7.10 (s, 4H); ^{13}C NMR δ 29.82 (q), 32.96 (s), 45.80 (t), 124.94 (d), 131.49 (d), 138.58 (s). **6b**: ^{1}H NMR δ 0.90 (s, 18H), 2.68 (s, 4H), 3.89 (s, 6H), 7.48 (s, 2H); ^{13}C NMR δ 29.63 (q), 33.11 (s), 45.60 (t), 52.43 (q), 128.52 (s), 131.82 (d), 142.40 (s), 168.40 (s). **6c**: ^{1}H NMR δ 0.87 (s, 18H), 1.32 (m, 4H), 1.63 (m, 4H), 2.56 (s, 4H), 2.69 (m, 4H), 6.80 (s, 2H); ^{13}C NMR δ 25.97 (t), 29.84 (q), 31.85 (t), 32.51 (t), 32.84 (s), 45.50 (t), 132.00 (d), 136.17 (s), 137.54 (s). **6d**: ^{1}H NMR δ 0.98 (s, 18H), 2.69 (s, 4H), 7.16 (m, 12H); ^{13}C NMR δ 29.92 (q), 33.08 (s), 45.61 (t), 126.09 (d), 127.74 (d), 129.92 (d), 133.72 (d), 136.90 (s), 137.82 (s), 141.79 (s). **7**: ^{1}H NMR δ 1.09 (s, 18H), 2.38 (s, 4H), 6.54 (s, 2H), 7.43 (m, 10H); ^{13}C NMR d 30.30 (q), 33.17 (s), 43.19 (t), 67.00 (d), 125.40 (d), 128.93 (d), 129.30 (d), 130.59 (s), 134.54 (s), 154.00 (s). **8**: ^{1}H NMR δ 0.93 (s, 18H), 2.63 (s, 4H), 8.87 (s, 2H); ^{13}C NMR d 29.48 (q), 33.20 (s), 42.63 (t), 137.85 (s), 153.79 (d). **9a**: ^{1}H NMR δ 0.95 [s, 9H, =CH$\underline{\text{Bu}}$(*t*)], 1.07 [s, 9H, CH$_2\underline{\text{Bu}}$(*t*)], 2.42 [d, one of $\underline{\text{CH}_2}$Bu(*t*)], 2.53 [d, one of $\underline{\text{CH}_2}$Bu(*t*)], 5.23 (s, 1H, methine), 6.13 (s, 1H, exocyclic vinylene H), 6.28 (s, 1H, enodcyclic vinylene H), 7.19 (m, 2H), 7.36 (m, 3H); ^{13}C NMR d 29.63 (q), 30.38 (q), 32.04 (s), 34.61 (s), 40.78 (t), 66.60 (d), 125.69 (d), 128.70 (d), 128.87 (d), 128.92 (d), 131.34 (s), 134.41 (s), 143.98 (d), 151.76 (s). **10a**: ^{1}H NMR δ 0.92 (s, 18H), 2.81 (s, 4H), 7.37 (m, 2H), 7.57 (s, 2H), 7.74 (m, 2H); ^{13}C NMR d 29.77 (q), 33.17 (s), 45.97 (t), 124.92 (d), 127.09 (d), 129.46 (d), 131.77 (s), 137.57 (s). **11a**: ^{1}H NMR δ 0.86 (s, 18H), 2.18 (s, 4H), 4.89 (s, 2H), 6.90 (m, 4H), 7.21 (m, 4H); ^{13}C NMR δ 30.38 (q), 33.23 (s), 44.55 (t), 57.11 (d), 122.63 (d), 123.97 (d), 144.43 (s), 146.43 (s).
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