THE FIRST SYNTHESIS OF 4,5-DI-t-BUTYLPYRIDAZINE

Juzo Nakayama* and Atsushi Hirashima

Department of Chemistry, Faculty of Science, Saitama University,

Urawa, Saitama 338, Japan

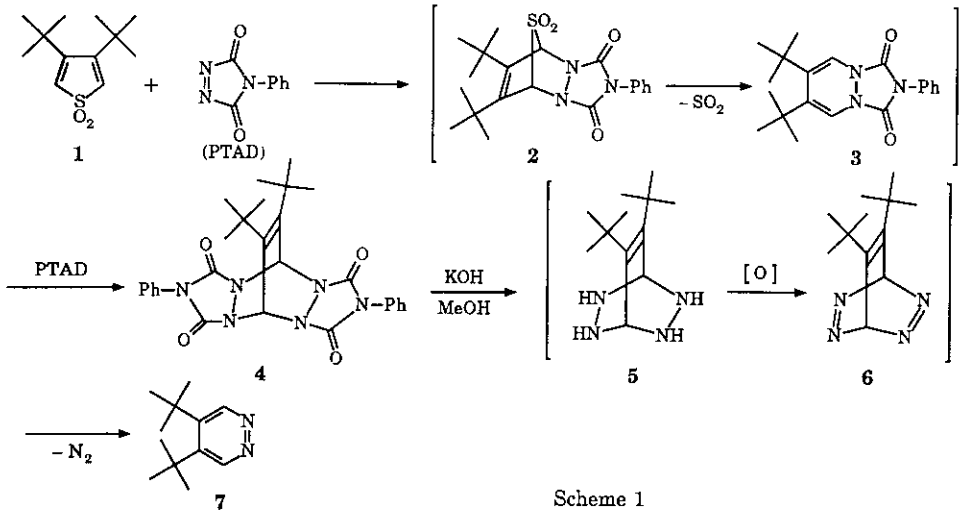
Abstract —— 3,4-Di-t-butylthiophene 1,1-dioxide (1) reacts with 2 equiv. of 4-phenyl-1,2,4-triazoline-3,5-dione in refluxing toluene to give the bis-adduct 4 in 87% yield. KOH-Induced methanolysis of 4, followed by spontaneous air-oxidation and nitrogen extrusion of the resulting hydrazo compound 5, affords 4,5-di-t-butylpyridazine (7) directly in one-pot in 80% yield.

The chemistry of o-di-t-butylbenzene and its related compounds continues to attract much attention because of interest in the influence of steric repulsion between bulky t-butyl groups on the reactivities and molecular structures.[1] We recently reported a facile synthesis of 3,4-di-t-butylthiophene and its conversion into 3,4-di-t-butylthiophene 1,1-dioxide (1) in high yield.[2] We have also shown that 1 reacts with a series of acetylenes and their synthetic equivalents to give o-di-t-butylbenzene and its derivatives in good yields.[3] We report here the first synthesis of 4,5-di-t-butylpyridazine (7) starting from 1 (Scheme 1). Although the synthesis of a 3,4,5-tri-t-butylpyridazine derivative was reported,[4] no successful synthesis of the parent 7 has appeared. To our knowledge, 2,3-di-t-butylquinoxaline[5] and 2,3,5-tri-t-butylpyrazine[6] are the only other diazines that have been successfully synthesized and possess two t-butyl groups at the vicinal position.

Heating 1 with 2 equiv. of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in refluxing toluene for 3 h gave the bis-adduct 4[7] in 87% yield. The initial adduct 2 extrudes sulfur dioxide to afford the cyclic diene 3, which further reacts with PTAD to give 4 as the final product. Even the use of 1 equiv. of PTAD afforded 4 as the sole product because 3 acts as a better diene on PTAD than 1 does. The end point of the present reaction can be easily monitered by disappearance of the red color due to PTAD.

KOH-Induced methanolysis of 4 smoothly proceeded; a suspension of 4 in methanol containing potassium hydroxide was stirred at room temperature until the mixture became transparent and the usual work-up of the mixture gave 4,5-di-t-butylpyridazine (7) directly in 80% yield.[8] Expected hydrazo compound 5 could not be isolated even when the reaction was conducted under nitrogen probably because 5 is extremely easily air-oxidized to the azo-compound 6, which loses nitrogen to give 7.

7: Mp 108.5-109 °C (from hexane); ir (KBr) 3112, 3030, 2960, 1505, 1492, 1369, 1219, 709 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.58 (18H, s, Me), 9.19 (2H, s, pyridazine ring); ^{13}C nmr ($CDCl_3$) δ 33.07 (q, methyls of t-butyl), 36.10 (s, quaternary carbon of t-butyl), 146.45 (s, $C_{4,5}$ of pyridazine ring), 150.57 (d, $C_{3,6}$ of pyridazine ring); ms m/z 192 (M^+). Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57. Found: C, 74.73; H, 10.35; N, 14.54.



Scheme 1

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7. 4: Colorless crystals from benzene, mp 220 °C (dec.); ir (KBr) 1779, 1745 cm^{-1} (C=O); ^1H nmr ($CDCl_3$) δ 1.46 (18H, s, Me), 6.84 (2H, s, methine), 7.35-7.63 (10H, m, Ph); ^{13}C nmr ($CDCl_3$) δ 31.98 (q), 34.85 (s), 66.27 (d), 125.43 (d), 128.90 (d), 129.28 (d), 130.69 (s), 141.58 (s), 154.14 (s); ms (FAB) m/z 515 (M^++1). Anal. Calcd for $C_{28}H_{30}N_6O_4$: C, 65.39; H, 5.88; N, 16.33. Found: C, 65.40; H, 5.90; N, 16.23.
8. To a stirred and ice-cooled suspension of 730 mg (1.4 mmol) of 4 in 20 ml of methanol was added 630 mg (11.2 mmol) of potassium hydroxide dissolved in 6 ml of methanol. The mixture was slowly warmed to room temperature and stirred until the mixture turned transparent (3 h). The mixture was diluted with 200 ml of ether, stirred for 2 h, washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was passed through a short column of silica gel with dichloromethane as the eluent to give 215 mg (80%) of 7 as colorless needles (a small amount of methyl phenylcarbamate was first eluted from the column).

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