Synthesis and Reactions of the First Examples of the 1,5,2,4-Dioxadiazine Ring System: 2,4-Dialkyl-2*H*-1,5,2,4-dioxadiazine-3,6(4*H*)-diones

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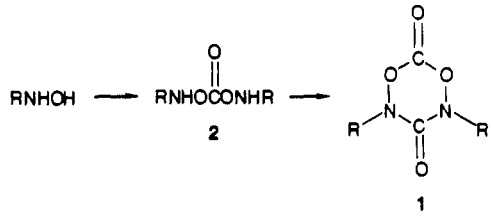
The synthesis and selected reactions of 2,4-di-*tert*-butyl- and 2,4-bis(1,1,3,3-tetramethylbutyl)-2*H*-1,5,2,4-dioxadiazine-3,6(4*H*)-dione are described. Phosgenation of *N*-*tert*-alkylhydroxylamines gives the carbonate compounds **2** which upon further phosgenation afford the dioxadiazines **1**. Acidified silica gel is required for their purification. The dioxadiazines decompose upon heating to give the corresponding nitroso compound and the isocyanate. The ring is rapidly cleaved by nucleophiles such as dimethylamine.

We wish to report the first examples of the title compounds **1a** and **1b**.[1] The previously known dioxadiazines include the 1,2,3,4,[2] 1,2,4,5,[3] 1,4,2,3,[4] and 1,4,2,5[5] isomers but we are not aware of any reports of the 1,5,2,4 system.[6] Furthermore it is rare to find even one carbonyl group as a ring member in any of these isomers.[2]

Structure **1** amounts to a combination of urea and carbonate functionalities and is a diacylated derivative of a hydroxylamine.

Scheme I



a, R = $C(CH_3)_3$
b, R = $C(CH_3)_2CH_2C(CH_3)_3$

Synthesis

Our approach to the synthesis of this system is the phosgenation of *N*-*tert*-alkylhydroxylamines. Earlier workers acylated *N*-*tert*-butylhydroxylamine with acetyl chloride, acetic anhydride, benzoyl chloride, ethyl chloroformate, and other acid chlorides with various bases.[7-9] O-Acylation is the major process, and if pyridine is present diacylation occurs. Aurich and Stork[10] treated *N*-*tert*-butylhydroxyalmine with phosgene in benzene and produced a solution of *N*-(chlorocarbonyl)-*N*-*tert*-butylhydroxylamine which decomposed upon distillation of the solvent. With excess of the hydroxylamine, they obtained *N,N'*-di-*tert*-butyl-*N,N'*-dihydroxyurea in unspecified yield.

When we combined *N*-*tert*-butylhydroxylamine and phosgene with pyridine we obtained a mixture of products including some **1a**. Better yields of **1a** were obtained when the acylation was done in two stages (Scheme I). Treatment of 2 equiv of *N*-*tert*-butylhydroxylamine with 1 equiv of phosgene in benzene at 40 °C using potassium carbonate as base afforded *O,O'*-carbonylbis(*tert*-butylhydroxylamine) (**2a**) in 75% yield. Alternatively, reaction at 0 °C in hexane–ether using excess of the hydroxylamine as base gave *N,N'*-di-*tert*-butyl-*N,N'*-dihydroxyurea (**3**) as the major product (52% yield). Heating **2a** with excess phosgene in hexane in a closed bottle afforded the dioxadiazine **1a** in 75% yield. Similar treatment of *N,N'*-di-*tert*-butyl-*N,N'*-dihydroxyurea required a longer time and gave **1a** in only 45% yield.

A parallel study was undertaken with *N*-(1,1,3,3-tetramethylbutyl)hydroxylamine. In this case only O-acylation occurred in the first stage. With aqueous sodium hydroxide as base, *O,O'*-carbonylbis(1,1,3,3-tetramethylbutyl)hydroxylamine (**2b**) was obtained in 91% yield. Treatment of **2b** with phosgene at 80 °C gave the dioxadiazine **1b** in 54% yield.

A new procedure was developed for the purification of **1a** and **1b**, which may have general value for compounds of high nucleophilic sensitivity. Compounds **1a** and **1b** are too soluble for crystallization even from pentane at −78 °C. Gas chromatography of **1a** gave some pure material, but most of it decomposed. Liquid chromatography on ordinary silica gel led to extensive decomposition even during rapid elution under pressure. Success was found with silica gel that was treated with aqueous HCl and dried. Elution with hexane gave **1a** or **1b** without decomposition and free from a persistent impurity that was probably ClCONROCOCl (IR 1735, 1810 cm^{-1}). The acid treatment, besides protonating nucleophilic sites, lengthens the retention times.

Attempts to prepare the phenyl, 2,6-dimethylphenyl and isopropyl analogues gave little or no ring compound, suggesting that the *tert*-alkyl groups are important in stabilizing the ring compounds.

Characterization

The infrared spectrum of **1a** shows the absence of NH or OH groups and the presence of carbonyl groups at 1810 and 1710 cm^{-1} which are assigned to the carbonate and urea carbonyl groups, respectively. A 60- or 70-cm^{-1} hypsochromic shift occurred upon cyclization of **2a** or **3a** which is greater than the difference between a simple acyclic and a six-membered ring carbonate (20 cm^{-1}) or urea (45 cm^{-1}).

The ^1H NMR spectrum shows only a singlet for the identical *tert*-butyl groups at 1.47 ppm. The ^{13}C NMR shows four signals including two different carbonyl groups

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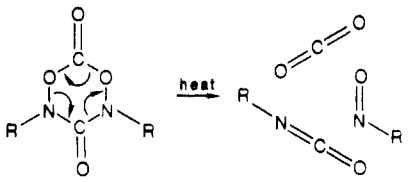
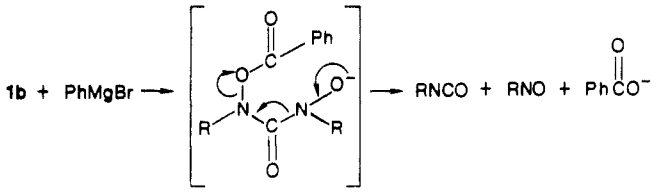
Scheme II



Scheme III



at 152.05 and 160.11 ppm. Finally, X-ray crystallography[11] established the structure.

Compound **1b** showed the same infrared carbonyl absorptions and comparable NMR spectra.

Reactions

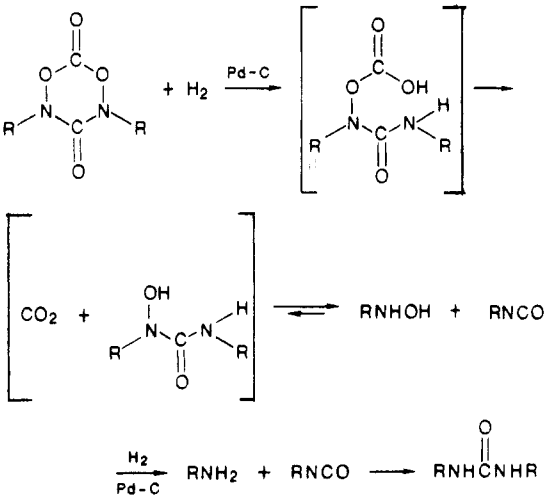
The dioxadiazine **1a** decomposed readily at 90 °C on distillation or in a gas chromatographic column to afford 2-methyl-2-nitrosopropane and *tert*-butyl isocyanate and presumably carbon dioxide. The less volatile **1b** was heated in an evacuated sealed tube for 2 days at 84 °C whereupon 10% of the material decomposed to equimolar amounts of 2,4,4-trimethyl-2-nitrosopentane and 1,1,3,3-tetramethylbutyl isocyanate. We suggest that the ring fragmentation is concerted (Scheme II) although no mechanistic studies have been undertaken.

In solution in methanol **1b** is stable, but addition of a catalytic amount of *p*-toluenesulfonic acid gives cleavage to a mixture of methoxy products. Aqueous solutions, where **1a** and **1b** have low solubility, do not attack appreciably in short times. For example **1a** is stable in contact with water, 4% aqueous HCl, and 4% aqueous sodium hydroxide. The ring is highly susceptible to attack by organic soluble nucleophiles such as dimethylamine. Cold aqueous dimethylamine quickly converted **1b** to the blue nitroso compound plus *N,N*-dimethyl-*N'*-(1,1,3,3-tetramethylbutyl)urea in 53% yield. The carbonate carbonyl is the likely site for initial attack, which may be followed by fragmentation to the unstable dimethylcarbamic acid plus the nitroso compound and the isocyanate. The isocyanate would then combine with dimethylamine to give the observed urea.

Treatment of **1b** with 1 equiv of phenylmagnesium bromide gave 1,1,3,3-tetramethylbutyl isocyanate (isolated as the dimethylamine derivative in 46% yield), 2,4,4-trimethyl-2-nitrosopentane (25%), and benzoic acid (63%). Attack at the carbonate carbonyl should lead to these products as shown in Scheme III.

Compound **1b** underwent Pd-catalyzed hydrogenation to afford *N,N'*-bis(1,1,3,3-tetramethylbutyl)urea. When the hydrogenation was interrupted before completion, the infrared spectrum showed intense absorption at 2250 cm^{-1}, indicating the presence of the isocyanate. Reductive cleavage of one N–O bond followed by loss of CO_2 would give the hydroxyurea (Scheme IV), which would dissociate[12] to the isocyanate and hydroxylamine. Reduction of the hydroxylamine gives the amine which promptly re-

Scheme IV



combines with the isocyanate to afford the observed final product.

Experimental Section

The proton NMR spectra were obtained at 60 MHz, and the ^{13}C NMR spectra were obtained at 22.5 MHz.

2-Methyl-2-nitrosopropane and 2-methyl-2-nitropropane were prepared by the sodium tungstate catalyzed hydrogen peroxide oxidation of *tert*-butylamine.[13]

***N-tert*-Butylhydroxylamine** was prepared from the nitro or nitroso compound in 65–68% yield using amalgamated aluminum foil.[14]

***O,O'*-Carbonylbis(*N-tert*-butylhydroxylamine) (2a).** *N-tert*-butylhydroxylamine (1.8 g, 0.020 mol) was dissolved in 20 mL of ether, and 5.0 g (0.047 mol) of potassium carbonate was added. To this mixture was added a solution of 1.0 g (0.010 mol) of phosgene in 20 mL of benzene over a period of 15 min with magnetic stirring. The temperature was then raised and maintained at 40 °C for 3 h. The mixture was cooled and filtered and the filtrate evaporated under reduced pressure. The residual solid was recrystallized from hexane, with cooling in a dry ice–acetone bath, to afford 1.5 g (75%) of white crystals: mp 82.5–84.0 °C; IR (neat) 3300, 1750 cm^{-1}; ^1H NMR δ 1.47 (s, 18 H), 6.58 (s, 2 H). Anal. Calcd for $C_9H_{20}N_2O_3$: C, 52.92; H, 9.89; N, 13.71. Found: C, 53.10; H, 9.90; N, 13.78.

***N,N'*-Di-*tert*-butyl-*N,N'*-dihydroxyurea.** A solution of phosgene (6.2 g, 0.063 mol) in 60 mL of hexane was added dropwise, with magnetic stirring, to a solution of 22.0 g (0.25 mol) of *tert*-butylhydroxylamine in 100 mL of ether. The resulting mixture was stirred at room temperature for 3 h and filtered and the filtrate evaporated under reduced pressure. The residual solid was recrystallized from hot cyclohexane to give 6.6 g (51%) of white solid: mp 143–143.5 °C; IR ($CDCl_3$) 3320, 3150, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s). Anal. Calcd for $C_9H_{20}N_2O_3$: C, 52.92; H, 9.89; N, 13.71. Found: C, 53.18; H, 9.81; N, 13.57.

2,4-Di-*tert*-butyl-2*H*-1,5,2,4-dioxadiazine-3,6(4*H*)-dione (1a). A. From 2a. A solution of 1.0 g (0.010 mol) of phosgene in 20 mL of benzene was placed in a pressure bottle. To this was added 0.85 g (0.0040 mol) of crude **2a**, and the bottle was sealed and heated at 80 °C for 2 h. This was cooled and filtered and the benzene solution washed with 4% aqueous HCl and then dried with anhydrous $MgSO_4$. The benzene was evaporated under reduced pressure and the residue chromatographed on a 1 cm × 100 cm column of acidified silica gel eluting with hexane under 5 psi of nitrogen pressure. The product was obtained as an oil (0.70 g, 76%), which eventually crystallized: mp 39.5–40.5 °C; IR (neat) 1810, 1710, 1460, 1340, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s); ^{13}C NMR ($CDCl_3$) δ 160.11, 152.05, 62.08, 26.47; *M*, calcd 230, found cryoscopically in cyclohexane 214 ± 15. The structure

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was confirmed by X-ray crystallography.[11]

The acidified silica gel was prepared as follows: silica gel (60 g, 40–140 mesh was mixed with 200 mL of 3% aqueous hydrochloric acid. This was filtered and dried in an oven at 100 °C for 2 days.

B. From *N,N'*-Di-*tert*-butyl-*N,N'*-dihydroxyurea. A solution of 4.0 g (0.040 mol) of phosgene and 2.09 g (0.0100 mol) of *N,N'*-di-*tert*-butyl-*N,N'*-dihydroxyurea in 50 mL of hexane was heated at 80 °C in a sealed pressure bottle for 16 h. After the mixture cooled, two layers appeared. The upper layer was separated, washed with 30 mL of 4% aqueous HCl, and dried over anhydrous $MgSO_4$. Evaporation under reduced pressure afforded 1.2 g (52%) of crude **2a**, which was purified on acidified silica gel as above to afford 1.0 g (45%).

***N*-(1,1,3,3-Tetramethylbutyl)hydroxylamine.** Forrester's procedure was adapted to this case.[14] A solution of 23.1 g (0.145 mol) of 2,4,4-trimethyl-2-nitropentane[13] in 500 mL of ether was prepared in a 1-L flask equipped with a mechanical stirrer and reflux condenser. Rolls of amalgamated aluminum foil were prepared according to Forrester and added to the flask at such a rate as to maintain a controllable reflux. The mixture was stirred an additional hour and filtered and the residue washed with two 100-mL portions of ether. The combined filtrate and washings were dried over anhydrous $MgSO_4$ and evaporated to leave a pale blue liquid residue. Distillation gave 12.1 g (64%) of pure product which solidified at room temperature: bp 63 °C (0.6 mm) [lit. bp 50–53 °C (0.02 mm)]; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.17 (s, 6 H), 1.48 (s, 2 H), 5.52 (s, 1 H).

Beginning instead with 2,4,4-trimethyl-2-nitrosopentane and half as much aluminum, this procedure gave the hydroxylamine in 68% yield.

***O,O'*-Carbonylbis(1,1,3,3-tetramethylbutylhydroxylamine) (2b).** A solution of phosgene (1.2 g, 0.012 mol) in 15 mL of hexane was added dropwise with stirring to a mixture of 1,1,3,3-tetramethylbutylhydroxylamine (2.9 g, 0.020 mol), sodium hydroxide (1.0 g, 0.025 mol), water (15 mL), and hexane (20 mL). The mixture was stirred an additional 10 min, and the upper layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure to give a pale blue residue. Recrstallization from hexane with dry ice–acetone cooling gave 2.9 g (85%) of white solid product: IR (neat) 3220, 1740, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (s, 9 H), 1.53 (s, 6 H), 1.83 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.31, 60.16, 51.57, 31.54, 31.28, 26.21. Anal. Calcd for $C_{12}H_{36}N_2O_3$: C, 64.52; H, 11.47; N, 8.85. Found: C, 64.70; H, 11.50; N, 8.78.

2,4-Bis(1,1,3,3-tetramethylbutyl)-2*H*-1,5,2,4-dioxadiazine-3,6(4*H*)-dione (1b). In a glass Parr pressure bottle were placed **2b** (3.8 g, 0.012 mol) and a solution of phosgene (3.0 g, 0.030 mol) in 40 mL of hexane. The bottle was stoppered, clamped, and heated at 80 °C for 2 h. Two layers appeared. The upper blue layer was separated and evaporated under reduced pressure to give 2.4 g of crude **1b**. Chromatography on a 8 mm × 1 m column of acidified silica gel eluting with hexane under 5 psi of nitrogen pressure gave 2.2 g (54%) of colorless oil (**1b**): IR (neat) 1810, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 2 H), 1.52 (s, 6 H), 1.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 159.33, 152.66, 65.98, 50.60, 31.45, 31.25, 27.25. Anal. Calcd for $C_{18}H_{34}N_2O_4$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.42; H, 9.96; N, 8.19.

Thermal Decomposition of 1b. A sample of **1b** was sealed in a glass tube under vacuum and heated at 84 °C for 2 days. ^1H NMR of the now blue material showed that 90% remained unchanged, and 10% of it had decomposed to afford equivalent amounts of 2,4,4-trimethyl-2-nitrosopentane[13] and 1,1,3,3-tetramethylbutyl isocyanate. The infrared spectrum confirmed the presence of the isocyanate (2250 cm^{-1}).

Reaction of 1b with Dimethylamine. A solution of **1b** (2.0 g, 0.0058 mol) in 10 mL of hexane was chilled in an ice bath. To this was added 10 mL of aqueous dimethylamine (0.056 mol). The mixture became deep blue within 5 min. After the mixture was stirred 30 min the upper layer was separated, dried ($MgSO_4$), and evaporated, leaving a blue oil. Upon addition of cold hexane, a white precipitate of *N,N*-dimethyl-*N'*-(1,1,3,3-tetramethylbutyl)urea appeared (0.62 g, 53%): mp 82.5–83.3 °C; IR ($CDCl_3$) 3450, 1600, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9 H), 1.90 (s, 6 H), 1.69 (s, 2 H), 2.82 (s, 6 H), 4.22 (s, 1 H). Anal. Calcd for $C_{11}H_{23}N_2O$: C, 65.95; H, 12.07; N, 13.98. Found: C, 65.83; H, 11.95; N, 13.96.

Reaction of 1b with Phenylmagnesium Bromide. A solution of phenylmagnesium bromide was prepared from bromobenzene (1.1 g, 0.0070 mol) and magnesium turnings (0.2 g, 0.0070 mol) in 30 mL of ether and added dropwise with a syringe over a 3-min period to a stirred solution of **1b** (2.5 g, 0.0070 mol) chilled in an ice bath. A greenish brown color appeared. After being stirred at room temperature for 30 min the mixture was quenched with 30 mL of 5% aqueous HCl. The organic layer was separated and washed with two 20-mL portions of saturated aqueous $NaHCO_3$. The infrared spectrum of the organic layer showed the presence of isocyanate (2250 cm^{-1}). Aqueous dimethylamine (5 mL, 0.007 mol) was added to the organic layer and stirred for 30 min. The organic layer was separated and dried over $MgSO_4$. The solvent was removed, leaving a viscous liquid which, upon addition of cold hexane, gave a white precipitate of *N,N*-dimethyl-*N'*-(1,1,3,3-tetramethylbutyl)urea, which was filtered and recrystallized from hot hexane to yield 0.65 g (46%); spectra and melting point were as above. The hexane filtrate was evaporated under reduced pressure, and the residual liquid was passed through a 8 mm × 1 m silica gel column with hexane as eluant. The blue band was separated and identified spectrally as 2,4,4-trimethyl-2-nitrosopentane (0.25 g, 25%).[13] The combined $NaHCO_3$ wash was acidified and extracted with three 15-mL portions of ether. The combined extract was dried and evaporated to afford benzoic acid (0.54 g, 63%).

Hydrogenation of 1b. A hydrogenation bottle was charged with a solution of **1b** (0.40 g, 0.0012 mol) in 50 mL of hexane and 0.020 g of 5% Pd–C. This was shaken under 30 psi of hydrogen for 3 days. After 2 equiv of hydrogen were absorbed the solution was filtered, dried with $MgSO_4$ and evaporated to afford white solid *N,N'*-bis(1,1,3,3-tetramethylbutyl)urea. Recrystallization from 10 mL of hot hexane gave 0.20 g (60%), mp 149–150 °C (lit.[15] mp 150–151 °C); IR ($CDCl_3$) 3420, 3360, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.33 (s, 6 H), 1.65 (s, 2 H), 4.00 (s, 1 H).

Registry No. **1a**, 103258-84-0; **1b**, 103258-86-2; **2a**, 103258-83-9; **2b**, 103258-85-1; *tert*-butylamine, 75-64-9; 2-methyl-2-nitrosopropane, 917-95-3; 2-methyl-2-nitropropane, 594-70-7; *N*-*tert*-butylhydroxylamine, 16649-50-6; *N,N'*-di-*tert*-butyl-*N,N'*-dihydroxyurea, 56796-54-4; 2,4,4-trimethyl-2-nitropentane, 5342-78-9; *N*-(1,1,3,3-tetramethylbutyl)hydroxylamine, 98544-91-3; 2,4,4-trimethyl-2-nitrosopentane, 31044-98-1; 1,1,3,3-tetramethylbutylisocyanate, 1611-57-0; *N,N*-dimethyl-*N'*-(1,1,3,3-tetramethylbutyl)urea, 90228-48-1; *N,N'*-bis(1,1,3,3-tetramethylbutyl)urea, 2092-58-2.

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