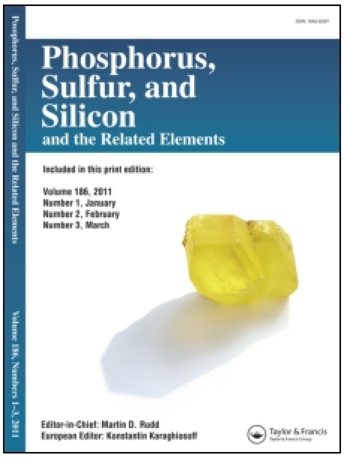

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CONDENSATION REACTION OF 1-OXO-4-CHLOROCARBONYL-1-PHOSPHA-2,6,7-TRIOXABICYCLO[2.2.2]OCTANE WITH *N-t*-BUTYL-*N*-BENZOYLHYDRAZINE

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1-Oxo-4-chlorocarbonyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (**5**) was obtained from phosphorus oxychloride. Benzyl chloroformate was synthesized by the reaction of benzyl alcohol and triphosgene in good yield for the first time. *N-t*-Butyl-*N*-benzoylhydrazine (**11**) was prepared in a new and convenivent procedure with good yield. The reaction of **5** and **11** proceeded smoothly in the presence of sodium carbonate and afforded the desired compound **13** in good yield, while in the presence of triethylamine, the elimination of butyl was observed and afforded the compound **12**.

Keywords: condensation reaction; acylhydrazine; triphosgene[bis(trichloromethyl)carbonate]; caged bicyclic phosphate

INTRODUCTION

Recently, a new class of insect growth regulators, the 1,2-diacyl-1-tert-butylhydrazines, has been found to mimic the action of 20-hydroxyecdysone to activate the ecdysone receptor, leading to lethal premature molting[1–3]. In addition, caged bicyclic phosphates are of considerable chemical and biological importance. Some related compounds of these serve in agrochemistry as antifungal agents, herbicides, and insecticides[4–6]. Considering the wide application of these compounds and their potential to serve as insect growth regulators, we decided to introduce the

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caged bicyclic phosphate group into the structures of acylhydrazines; therefore we designed and synthesized benzoylhydrazines containing the caged bicyclic phosphate group, and studied the condensation reaction of 1-oxo-4-chlorocarbonyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (**5**) with *N*-*t*-butyl-*N*-benzoylhydrazine (**11**).

RESULTS AND DISCUSSION

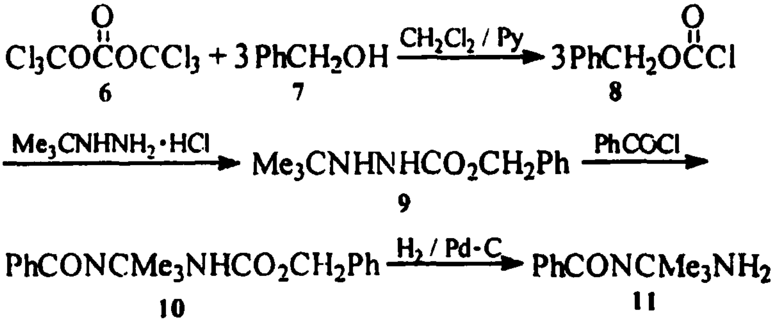
Phosphorus oxychloride (**1**) was condensed with pentaerythritol (**2**) to give 1-oxo-4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (**3**), and subsequent oxidation with concentrated nitric acid and ammonium vanadate provided the corresponding acid (**4**). Further reaction with thionyl chloride using *N*,*N*-dimethylformamide as a catalyst yielded the acyl chloride (**5**) as shown in Scheme 1.

$$\underset{\mathbf{1}}{POCl_3} + \underset{\mathbf{2}}{C(CH_2OH)_4} \longrightarrow \underset{\mathbf{3}}{O{=}P(OCH_2)_3CCH_2OH} \xrightarrow{HNO_3\,/\,NH_4VO_3}$$

$$\underset{\mathbf{4}}{O{=}P(OCH_2)_3CCO_2H} \xrightarrow{SOCl_2\,/\,DMF} \underset{\mathbf{5}}{O{=}P(OCH_2)_3CCOCl}$$

SCHEME 1

Benzyl alcohol (**7**) was treated with triphosgene (**6**) to obtain benzyl chloroformate (**8**) in good yield for the first time. The new and convenient synthesis of benzyl chloroformate avoids the use of phosgene gas and the necessary and complicated experimental set up associated with it. Then benzyl chloroformate (**8**) was condensed with *t*-butylhydrazine hydrochloride to give *N*-*t*-butyl-*N'*-benzyloxycarbonylhydrazine (**9**), and subsequent acylation with benzoyl chloride yielded *N*-*t*-butyl-*N'*-benzyloxycarbonyl-*N*-benzoylhydrazine (**10**). Further deprotection using 5% Pd-C as a catalyst provided *N*-*t*-butyl-*N*-benzoylhydrazine (**11**) in good yield as shown in Scheme 2. As a consequence of its practical simplicity and high efficiency, this novel method can be applied to the preparation of other *N*-*t*-butyl-*N*-substituted-benzoylhydrazines.



$$\underset{6}{\mathrm{Cl_3CO\overset{O}{\overset{\|}{C}}OCCl_3}} + 3\,\underset{7}{\mathrm{PhCH_2OH}} \xrightarrow{\mathrm{CH_2Cl_2\,/\,Py}} 3\,\underset{8}{\mathrm{PhCH_2O\overset{O}{\overset{\|}{C}}Cl}}$$

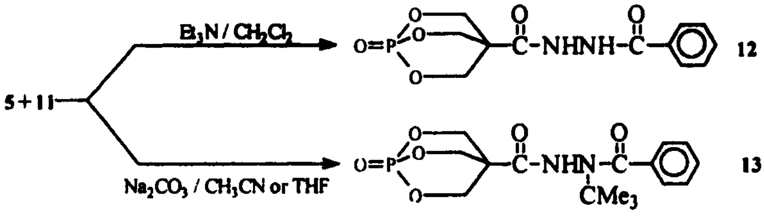
$$\xrightarrow{\mathrm{Me_3CNHNH_2\cdot HCl}} \underset{9}{\mathrm{Me_3CNHNHCO_2CH_2Ph}} \xrightarrow{\mathrm{PhCOCl}}$$

$$\underset{10}{\mathrm{PhCONCMe_3NHCO_2CH_2Ph}} \xrightarrow{\mathrm{H_2\,/\,Pd\text{-}C}} \underset{11}{\mathrm{PhCONCMe_3NH_2}}$$

SCHEME 2

It is interesting to note the great difference in product when 1-oxo-4-chlorocarbonyl-1-phospha-2,6,7-trioxabicyclo[2,2,2]octane (**5**) was condensed with *N*-*t*-butyl-*N*-benzoylhydrazine (**11**) by difference procedures. Thus, when the acyl chloride (**5**) was added to a mixture of *N*-*t*-butyl-*N*-benzoylhydrazine (**11**) and sodium carbonate in anhydrous acetonitrile or furan, a corlorless crystalline solid **13** was obtained in 83.7% yield. However, when the acyl chloride (**5**) was added dropwise to a solution of *N*-*t*-butyl-*N*-benzoylhydrazine (**11**) and triethylamine in methylene dichloride at room temperature or reflux temperature, no reaction could be observed. Conversely, when a solution of *N*-*t*-butyl-*N*-benzoylhydrazine (**11**) and triethylamine in methylene dichloride was added dropwise to a solution of the acyl chloride (**5**) in methylene dichloride, a colorless crystalline solid **12** was obtained in only 37.0% yield, and **11** was recovered in 46.6% yield as shown in Scheme 3. This novel elimination of butyl from a stable benzoylhydrazine was observed for the first time. We believe that this striking difference may be explained by the obvious difference in the acidity of the reaction system and the effect of steric hindrance. In fact, in the process of drop of *N*-*t*-butyl-*N*-benzoylhydrazine (**11**) (formation of **12**), 1-oxo-4-chlorocarbonyl-1-phospha-2,6,7-trioxabicyclo[2,2,2]octane (**5**) as Lewis acid induced **11** to eliminate butyl and give *N*-benzoylhydrazine, which has not the effect of steric hindrance when it is condensed with **5**. Hence, the compound **12** was formed.

Studies on biological activities of the compounds **12** and **13** are now in progress and will be reported ih due course.



SCHEME 3

EXPERIMENTAL

All the melting points were determined with Thomas-Hoover melting point apparatus; the thermometer was not standardized. IR spectra were recorded with a Shimadu-435. ^{1}H NMR spectra were recorded with Bruker AC-P200 using tetramethylsilane as an internal standard. Mass spectra were recorded with HP5988A spectrometer using the El method. Elemental analysis was carried out with a Yanaco CHN Corder MT-3 elemental analyzer.

Triphosgene (**6**) was synthesized by chlorination of dimethylcarbonate [7–8]; it melted at 79°C, IR(KBr, cm^{-1}): 1820, 1178, 925, 810, 675, 517.

1-Oxo-4-hydroxymethyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (**3**) and its corresponding acid (4) were prepared according to previous reports [9–10].

1-Oxo-4-chlorocarbonyl-1-phospha-2,6,7-trioxabicyclo[2.2.2]octane (5)

A mixture of the acid (**4**) (2.55 g, 0.013 mol), thionyl chloride (0.020 mol), chlorobenzene (20 mL) and *N*,*N*-dimethylformamide (3 drops) was stirred at 80°C for 2 h. Then the resulting mixture was cooled to room temperature, and filtered. The product was then washed successively with chlorobenzene and chloroform. Finally, a white powder (2.59 g) was obtained in 93.8% yield.

Benzyl Chloroformate (8)

A solution of distilled benzyl alcohol (7) (10.92 g, 0.101 mol) and distilled pyridine (11.98 g, 0.150 mol) in methylene dichloride (20 mL) was added dropwise to a solution of triphosgene (**6**) (15 g, 0.050 mol) in methylene dichloride (30 mL) at −10°C. Then the resulting mixture was stirred at −10°C for 2 h, followed by 42 additional h of stirring at room temperature. After the solvent was removed under vacuum, the residue was distilled under reduced pressure yielding a colorless liquid (16.89 g) in 98.0% yield. bp: 42–49°C/5–6 mmHg, n_D^{20}: 1.5188. (literature [11], n_D^{20}: 1.5190)

N-t-Butyl-N′-benzyloxycarbonylhydrazine (9)

To a mechanically stirred suspension of *t*-butylhydrazine hydrochloride (11.50 g, 0.092 mol) in toluene (100 mL) was added dropwise a solution of 10% aqueous sodium hydroxide (36.92 g, 0.092 mol) at room temperature. After 15 minutes, the reaction mixture was cooled to −15°C, and solutions of benzyl chloroformate (**8**) (15 g, 0.088 mol) in toluene (30 mL) and 10% aqueous sodium hydroxide (35.16 g, 0.088 mol) were added dropwise and simultaneously from separate addition funnels, while maintaining the temperature below −10°C. Following, the addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The water phase was extracted three times with 100 mL of chloroform. The extraction solvent was combined with the organic phase, and dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was then recrystallized from isopropanol and petroleum ether to obtain a colorless crystalline solid (16.33 g) in 83.6% yield: m.p. 75–77°C. ^{1}H NMR($CDCl_3$, 200 MHz) δ 1.11(s, 9H, Bu^t), 5.16(s, 2H, OCH_2), 5.02(br., 2H, NHNH), 7.38(m. 5H, Ph). IR(KBr): 3264.0, 3240.0 (NHNH); 1713.4 (C=O); 1521.4, 1491.8, 1466.3(Ph); 1406.2, 1381.8(Bu^t); 1260.8(C-O); 828.2, 716.1(Ph).

N-t-Butyl-N′-benzyloxycarbonyl-N-benzoythydrazine (10)

A solution of benzoyl chloride (7.59 g, 0.054 mol) in methylene dichloride (15 mL) was added dropwise to a solution of **9** (12 g, 0.054 mol) and triethylamine (6.58 g, 0.065 mol) in methylene dichloride (40 mL) under magnetic stirring at 0°C, then the resulting mixture was stirred at room temperature for 2 h. Then the solid was filtered off and the filtrate was washed successively with 2% aqueous hydrochloric acid and 10% aqueous sodium bicarbonate, and dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The soid was then recrystallized from ethanol to obtain a colorless crystalline solid (15.79 g) in 89.6% yield: m.p. 150–152°C. Analysis: calcd. for $C_{19}H_{22}N_2O_3$, C 69.92, H 6.79, N 8.58; found C 69.82, H 6.85, N 8.78. ^1H NMR(DMSO, 200 MHz) δ 1.40(d, 9H, Bu^t), 4.80–5.05(m, 2H, OCH_2), 6.84–7.37(m, 10H, Ph), 9.83(s, NH). IR(KBr): 3219.5 (NH); 1742.5, 1622.0 (C=O); 1578.4, 1531.5, 1498.1 (Ph); 1403.3, 1382.3 (Bu^t); 738.6, 712.9 (Ph).

N-t-Butyl-N-benzoylhydrazine (11)

To a solution of **10** (13.50 g, 41.40 mmol) in methanol (100 mL) was added 5% Pd-C. Hydrogen gas was then admitted to the solution. The reaction was monitored by TLC and stopped after complete consumption of **10**. The solid was filtered off and the filtrate was concentrated under vacuum to obtain a white powder (7.67 g) in 96.4% yield: m.p. 127–129°C. ^1H NMR($CDCl_3$, 200 MHz) δ 1.48(s, 9H, Bu^t), 3.90(s, 2H, NH_2), 7.28–7.56(m, 5H, Ph). IR(KBr): 3276.0 (NH_2); 1620.5 (C=O); 1573.1, 1529.5, 1508.8 (Ph); 1375.6, 1350.0 (Bu^t); 719.6, 696.7 (Ph).

Compound 12

A solution of **11** (0.3 g, 1.5 mmol) and distilled triethylamine (0.18 g, 1.8 mmol) in methylene dichloride (10 mL) was added dropwise to the stirred and cooled (-10°C) mixture of 5 (0.32 g, 1.5 mmol) and methylene dichloride (25 mL), then the resulting mixture was stirred at room temperature for 4 h. The solid was filtered off and the filtrate was concentrated and chromatographed on a silica gel column using a mixture of petroleum ether (60–90°C) and ethyl acetate as the eluent. Finally, a colorless crystalline solid **12** (0.17 g) was obtained in 37.0% and **11** was recovered in 46.6% yield. **12**: m.p. 239–241°C. Analysis: calcd. for $C_{12}H_{13}N_2O_6P$, C 46.16, H 4.20, N 8.97; found C 46.02, H 4.05, N 8.98. ^1H NMR($CDCl_3$, 200 MHz) δ 5.02(d, 6H, OCH_2, $^3J_{PH}$=6.6Hz), 7.52–8.01(m, 5H, Ph).

Compound 13

A solution of **5** (0.54 g, 2.82 mmol) in anhydrous furan (10 mL) was added dropwise to the stirred and cooled (0°C) mixture of **11** (0.60 g, 2.82 mmol), sodium carbonate (0.30 g, 2.82 mmol) and anhydrous furan (20 mL). Then the resulting mixture was stirred at room temperature for

12 h. The solid was filtered off, and the filtrate was washed successively with 2% aqueous hydrochloric acid and 10% aqueous sodium bicarbonate, and then dried with anhydrous magnesium sulfate and filtered. The solvent was removed by distillation to give a white solid. The solid was purified by column chromatography on a silica gel using a mixture of petroleum ether (60–90°C) and ethyl acetate as the eluent. Finally, a colorless crystalline **13** (0.87 g) was obtained in 83.7% yield: m.p. 225–227°C. Analysis: calcd. for $C_{16}H_{21}N_2O_6P$, C 52.17, H 5.75, N 7.61; found C 52.13, H 5.68, N 7.38. ^1H NMR($CDCl_3$, 200 MHz) δ 1.41(s, 9H, Bu^t), 4.26–4.40(m, 6H, OCH_2), 7.24–7.60(m, 5H, Ph), 9.65(s, 1H, NH). IR(KBr), 3247.0 (NH), 1700.0, 1668.6 (C=O), 1299.3 (O=P), 1007.9 (O-C), 953.6 (P-O), 864.5, 829.6 ($P(OCH_2)_3$). MS(EI), 368.33(M, 15%).

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