Heteroatom Chemistry
Volume 12, Number 2, 2001

A Convenient Synthesis of *N*-*t*-Butyl-*N*′-Aminocarbonyl-*N*-(Substituted)Benzoylhydrazine Containing α-Aminoalkylphosphonate Groups in a One-Pot Procedure

Qingmin Wang, Zaiguo Li, Runqiu Huang, and Junran Cheng

Research Institute of Elemento-Organic Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

Received 10 October 2000; revised 29 November 2000

ABSTRACT: *A variety of novel N-t-butyl-N'-aminocarbonyl-N-(substituted)benzoylhydrazines containing α-aminoalkylphosphonate groups were synthesized. Treatment of α-aminoalkylphosphonates with triphosgene yielded α-isocyanatoalkylphosphonates, and subsequent addition with N-t-butyl-N-substituted benzoylhydrazines provided the title compounds in a one-pot procedure with good yields. The triphosgene-mediated reaction for the synthesis of α-isocyanatoalkylphosphonates enjoys a number of advantages: the reaction is carried out under mild condition in good yield, triphosgene is relatively safe to handle because of its low vapor pressure and high stability, and the experimental procedure is simple. This method can be applicable to the synthesis of other α-isocyanatoalkylphosphonates and urylenediphosphonates. The structures of all of the products and by-products were confirmed by ^{1}H NMR, ^{31}P NMR, IR and mass spectroscopy, and elemental analysis. We also found that some of the compounds possess potential anti-tobacco mosaic virus (TMV) activities and anticancer activities.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:68–72, 2001

Correspondence to: Runqiu Huang.
Contract Grant Sponsor: National Natural Science Foundation of China
Contract Grant Number: 29832050.

INTRODUCTION

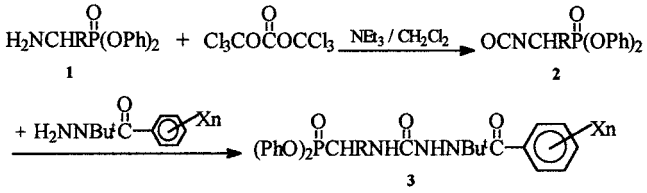
Recently, a new class of insect growth regulators, the 1,2-diacyl-1-*tert*-butylhydrazines, have been found to mimic the action of 20-hydroxyecdysone to activate the ecdysone receptor, leading to lethal premature molting [1–4]. In addition, α-aminophosphonic acid derivatives are of considerable chemical and pharmacological importance as isosteres of aminocarboxylic acids [5,6]. Various related compounds of these types also can serve in agrochemistry as antifungal agents, herbicides, plant regulators, and plant virucides [7,8]. Considering the wide application of these compounds and their potential to serve as insect growth regulators, we decided to introduce the α-aminoalkylphosphonate groups into the structures of acylhydrazines, and therefore, we designed and synthesized a series of the title compounds.

RESULTS AND DISCUSSION

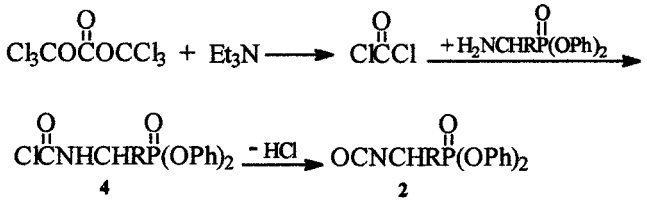
Synthesis of the Products and Reaction Mechanism

We synthesized the title compounds as shown in Scheme 1.

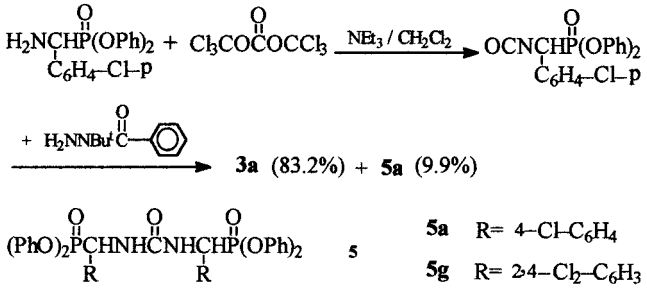
α-Aminoalkylphosphonates **1** were treated with triphosgene to give α-isocyanatoalkylphosphonates **2**, and subsequent addition of *N*-*t*-butyl-*N*-substituted benzoylhydrazines provided the title compounds **3** in a one-pot procedure with good yields.



SCHEME 1



SCHEME 2



SCHEME 3

Medved and Kabachnik have reported the synthesis of diethyl α-isocyanatoalkylphosphonates by use of diethyl α-aminoalkylphosphonates and phosgene, but only in 36% yield [9]. This method has not achieved much synthetic utility, in part due to the high toxicity of phosgene gas and the necessary and complicated experimental setup associated with use of it.

We found that triphosgene can be used to convert diphenyl α-aminoalkylphosphonates **1** to diphenyl α-isocyanatoalkylphosphonates **2** under mild conditions in the presence of triethylamine through the steps shown in Scheme 2. At first, the nucleophilic attack of triethylamine on triphosgene forms phosgene, which is condensed with **1** to give α-chlorocarbonylaminophosphonates **4**. Then α-isocyanatoalkylphosphonates **2** are obtained from **4** by elimination of one molecule of hydrogen chloride.

The intermediate **2** shows a very strong IR band at approximately 2240 cm^{-1}, indicating the presence of the cumulative double bond of N=C=O. The intermediates **2** are highly moisture sensitive. No isocyanates **2** were obtained by regular column chromatography probably because of reactions with water and other nucleophilic species present in silica gel. Reactions of **2** with nucleophiles were best carried out in one pot without isolating the isocyanate intermediate **2**. The triphosgene-mediated reaction for the synthesis of α-isocyanatoalkyl-phosphonates outlined here enjoys a number of advantages over the previous method [9] in that the reaction is carried out under mild condition in good yield, and triphosgene is safer to use than phosgene due to its lower vapor pressure and higher stability. Also the experimental procedure is very simple. Furthermore, this highly efficient method is expected to have wide synthetic utility for other α-isocyanatoalkylphosphonates.

In some cases, small amounts of urylenediphosphonates **5** were isolated as by-products, as shown in Scheme 3. They can be formed by the reaction of α-aminoalkylphosphonates **1** with the intermediates **2**. The formation of **5** can be retarded by use of a lower temperature and a slower rate of addition of **1**. For example, a solution of α-amino-4-chlorobenzylphosphonate (2.68 mmol) and triethylamine in 10 mL of methylene dichloride was added dropwise to a solution of triphosgene in 5 mL of methylene dichloride during 50 minutes at −10°C. Finally, the title compound **3a** was obtained in 83.2% yield. At the same time, the by-product **5a** was obtained in 9.9% yield. If the rate of addition of **1** was carried out during 2 hours at −15°C, the title compound **3a** was obtained in higher yield, and the by-product **5a** was not detected.

It has been reported that urylenediphosphonates **5** can be prepared from urea, phosphite esters, and aldehydes [10]. However, this method requires rigid experimental conditions and provides low yields (limited to 60% or less). We found that treatment of triphosgene with 2 equivalents of α-aminoalkylphosphonates in the presence of triethylamine afforded urylenediphosphonates in high yield (>80%). As a consequence of its practical simplicity and high efficiency, this new method for synthesis of urylenediphosphonates is expected to have wide synthetic utility for the preparation of symmetrical ureas of type **5**.

The Structures of the Products and By-Products

All the products and by-products were colorless crystalline solids, and their structures were confirmed by ^{1}H NMR, ^{31}P NMR, IR and mass spectroscopy, and elemental analysis. The data are summarized in Tables 1–3.

TABLE 1 Physical Constants of Products **3** and By-Products **5**

					Elemental Analysis(%)		*Found (Calcd)*
No.	*Xn*	*R*	*m.p. (°C)*	*Yield (%)*	*C*	*H*	*N*
3a	H	4–Cl–C_6H_4	199–201	83.2	62.97(62.89)	5.12(5.28)	7.10(7.10)
3b	H	Ph	174–175	86.1	66.56(66.78)	5.56(5.78)	7.55(7.54)
3c	3,5-Me_2	4–Cl–C_6H_4	140–142	81.4	63.59(63.92)	5.51(5.69)	6.74(6.78)
3d	2-F	Ph	200–201	81.6	64.62(64.69)	5.19(5.43)	7.41(7.30)
3e	2-F	4–Cl–C_6H_4	214–215	72.1	60.75(61.04)	4.79(4.96)	6.85(6.89)
3f	H	2–Cl–C_6H_4	205–206	85.7	62.77(62.89)	5.01(5.28)	7.26(7.10)
3g	3,5-Me_2	2,4–Cl_2–C_6H_3	100–102	79.6	61.09(61.04)	4.86(4.96)	6.58(6.89)
3h	H	3–NO_2–C_6H_4	188–189	85.0	61.71(61.79)	4.81(5.19)	9.10(9.30)
3i	3,5-Me_2	3–NO_2–C_6H_4	115–117	90.8	62.70(62.85)	5.37(5.59)	8.80(8.88)
3j	3,5-Me_2	4–NO_2–C_6H_4	216–217	73.8	62.77(62.85)	5.52(5.59)	8.80(8.88)
3k	3,5-Me_2	4–Me–C_6H_4	164–166	88.2	67.84(68.10)	6.42(6.38)	6.65(7.00)
31	3,5-Me_2	H	150–152	67.9	63.61(63.64)	6.37(6.32)	7.99(8.24)
5a	/	4–Cl–C_6H_4	174–175	/	60.55(60.56)	3.93(4.17)	3.59(3.62)
5g	/	2,4–Cl_2–C_6H_3	150–151	/	55.18(55.60)	3.77(3.59)	3.68(3.33)

TABLE 2 ^{1}HNMR Data of Products **3** and By-Products **5**

Compound	δ
3a	1.20(s), 1.28(s)(9H, Bu^t); 5.50(dq, 1H, CHPO, $^2J_{PH}$ = 22.9 Hz, $^3J_{HH}$ = 10.4 Hz, J = 6.3 Hz); 6.57–7.40(m, 19H, Ph)
3b	1.20(s), 1.27(s)(9H, Bu^t); 5.43–5.46(m, 1H, CHPO); 6.44(s), 6.47(s)(2H, NH); 6.60–7.30(m, 20H, Ph)
3c	1.27(s, 9H, Bu^t); 1.80(s), 2.02(s)(6H, Me); 5.51(dd, 1H, CHPO, $^2J_{PH}$ = 22.9 Hz, $^3J_{HH}$ = 10.4 Hz); 6.50–7.30(m, 17H, Ph)
3d	1.32(s), 1.39(s)(9H, Bu^t); 5.20–5.61(m, 1H, CHPO); 6.69–7.40(m, 19H, Ph); 8.58(s), 8.66(s)(2H, NH)
3e)	1.15(s), 1.24(s)(9H, Bu^t); 5.45(dd, 1H, CHPO, $^2J_{PH}$ = 22.9 Hz, $^3J_{HH}$ = 10.4 Hz); 6.66–7.28(m, 18H, Ph); 7.79(br., 1H, NH)
3f	1.30(s), 1.34(s)(9H, Bu^t); 6.12–6.32(m, 1H, CHPO); 6.52–7.40(m, 19H, Ph); 7.80(br., 1H, NH)
3g	1.27(s, 9H, Bu^t); 1.85(s), 2.02(s)(6H, Me); 6.11(dd, 1H, CHPO, $^2J_{PH}$ = 22.9Hz, $^3J_{HH}$ = 9.4Hz); 6.55–7.30(m, 16H, Ph); 7.64(br, 1H, NH)
3H	1.27(s, 9H, Bu^t); 5.59(dd, 1H, CHPO, $^2J_{PH}$ = 22.9Hz, $^3J_{HH}$ = 9.4Hz); 6.65–8.21(m, 19H, Ph); 7.91(br, 1H, NH)
3i	1.32(s), 1.39(s)(9H, Bu^t); 1.93(s), 2.12(s)(6H, Me); 5.73(dd, 1H, CHPO, $^2J_{PH}$ = 23.2Hz, $^3J_{HH}$ = 10.0Hz); 6.56–8.36(m, 17H, Ph); 8.54(s, 1H, NH)
3i (100°C)	1.42 (s, 9H, Bu^t); 1.98(s), 2.15(s)(6H, Me); 5.68(dd, 1H, CHPO, $^2J_{PH}$ = 19.8 Hz, $^3J_{HH}$ = 9.9 Hz); 6.64–8.36(m, 17H, Ph); 8.54(br., 1H, NH)
3j	1.29 (s, 9H, Bu^t); 1.61(s), 1.81(s)(6H, Me); 5.66(dd, 1H, CHPO, $^2J_{PH}$ = 22.9 Hz, $^3J_{HH}$ = 9.4 Hz); 6.60–8.07(m, 17H, Ph)
3k	1.27 (s, 9H, Bu^t); 1.78(s), 2.00(s)(6H, C_6H_3-Me_2); 2.35(s, 3H, C_6H_4-Me); 5.53(dd, 1H, CHPO, $^2J_{PH}$ = 22.4Hz, $^3J_{HH}$ = 9.9 Hz); 6.53–7.40(m, 17H, Ph)
3l	1.37 (s, 9H, Bu^t); 2.12(s, 6H, Me); 3.76(dd, 2H, CH_2PO, $^2J_{PH}$ = 9.4 Hz, $^3J_{HH}$ = 5.2Hz); 6.80–7.36(m, 18H, Ph); 7.6(br., 1H, NH)
5a	5.78(dd, 1H, CHPO, $^2J_{PH}$ = 22.9 Hz, $^3J_{HH}$ = 10.4 Hz); 6.80–7.30(m, 28H, Ph)
5g	5.88–6.04(m, 1H, CHPO); 6.80–7.60(m, 26H, Ph)

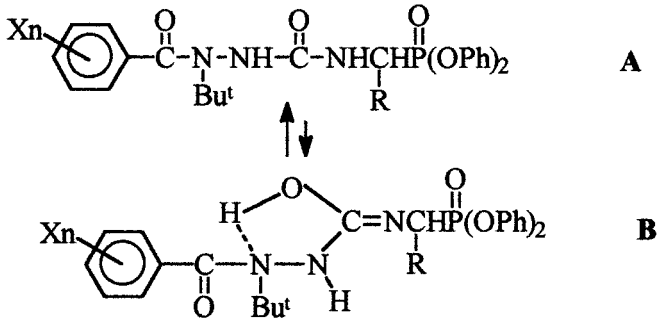
The products may undergo enolization as shown in Scheme 4.

The hydrazine **A** may be converted into the enol form **B** at room temperature. The *t*-butyl groups in **A** and **B** are magnetically nonequivalent, and therefore, the H atoms of the *t*-butyl groups of the products show two single peaks. Owing to the unstability of the enol form **B**, it can be converted into the hydrazine **A** at higher temperature (100°C) and the H atoms of the *t*-butyl groups of the products obtained at 100°C exhibit a single peak (for example, **3i** in Table 2). These results are in full agreement with expected data of novel *N*-*t*-butyl-*N*′-alkoxyl-*N*-(substituted)-benzoylhydrazines [11]. The H atom at the α-C sometimes exhibits a dd peak due to the coupling of the P atom and the (N-)H atom but sometimes exhibits this interaction as a multiplet.

The δ_p of the product **3a** is 15.57, whereas the δ_p

TABLE 3 IR Data of Some Products

Compound	*IR (cm^{-1}) (KBr)*
3a	3343.0, 3062.5, 3043.0, 2915.5, 1707.1, 1682.5, 1588.0, 1533.7, 1486.4, 1360.5, 1241.7, 1197.6, 1155.1, 955.8, 759.8, 721.7, 685.5, 655.2
3i	3360.0, 3103.0, 2951.0, 1707.6, 1660.8, 1624.7, 1589.4, 1527.6, 1486.1, 1382.0, 1348.6, 1236.4, 1200.1, 948.5, 760.2, 731.4, 684.0
5a	3341.0, 3053.0, 1691.0, 1588.0, 1540.2, 1487.2, 1263.3, 1242.4, 1198.8, 1184.0, 1156.7, 1087.0, 1066.9, 1021.0, 937.7, 763.9, 721.7, 685.9



SCHEME 4

of the corresponding intermediate diphenyl α-amino-4-chlorobenzylphosphonate is 17.05. Owing to the effect of steric hindrance, the P chemical shift of the product **3a** is found at a higher field.

The IR data of **3a, 3i**, and **5a** are listed in Table 3. We can see from Table 3 that all absorption bands appear as expected. For **3a**, 3343.0 cm^{-1} (s) corresponds to an N–H stretching absorption band, 1707.1 cm^{-1} (s) and 1682.5 cm^{-1} (s) to C=O stretching absorption bands, 1588.0 cm^{-1} (s) and 1486.4 cm^{-1} (s) to phenyl ring stretching absorption bands in the group OPh, 1241.7 cm^{-1} (s) to the P=O stretching absorption bands, 1197.6 cm^{-1} (s) and 1155.1 cm^{-1} (s) to the C–O stretching absorption bands in the Ph–O–P, and 955.8 cm^{-1} (s) due to the P–O stretching absorption band in the P–O–Ph group.

The EI-MS (15 ev) of the product **3i** gives the molecular ion peaks (630.40, M) and those of the main fragments.

BIOLOGICAL ACTIVITY

The preliminary biological tests showed that insecticidal activities of the products are low. However, we found that some of the compounds possess potential anti-TMV activities. For example, at 500 ppm, the inhibitory rate of compound **3b** to TMV is 20%, and we found that some of the compounds possess potential anticancer activities. For example, at 10^{-4} M, the inhibition rate of compound **3d** to A-549 attains 74.0%, and the inhibition rate of compound **3e** to BEL-7402 attains 66.7%.

EXPERIMENTAL

All the melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded with a Shimadu-435 spectrometer. ^{1}H NMR and ^{31}P NMR spectra were recorded with a Bruker AC-P200 instrument, tetramethylsilane and 85% H_3PO_4 being used as internal and external standards, respectively. Elemental analyses were carried out with a Yanaco CHN Corder MT-3 elemental analyzer. Mass spectra were recorded with an HP5988A spectrometer using the EI method.

Synthesis of Intermediates

α-Aminoalkylphosphonates **1** were prepared according to reported procedures [4,12]. Triphosgene was synthesized by chlorination of dimethyl carbonate [13]. *N*-*t*-butyl-*N*-substituted benzoylhydrazines were obtained by a convenient procedure [14].

Synthesis of the Products **3:** *General Procedure*

A solution of α-aminoalkylphosphonate **1** (2.68 mmol) and triethylamine (8.04 mmol) in 10 mL of methylene dichloride was added dropwise to a solution of triphosgene (1.34 mmol) in 10 mL of methylene dichloride during 2 hours under magnetic stirring at −15°C, and then the resulting mixture was stirred at room temperature for 1 hour. A solution of *N*-*t*-butyl-*N*-substitutedbenzoylhydrazine (2.41 mmol) in 10 mL of methylene dichloride was added to the mixture with stirring at room temperature. After the addition, the reaction mixture was stirred at room temperature for 8 hours. After the solvent had been removed under vacuum, the residue was dissolved in 20 mL of ethyl acetate and filtered. The

filtrate was evaporated and the residue was purified by vacuum column chromatography on silica gel using a mixture of petroleum ether (60–90°C) and ethyl acetate as the eluent. Finally, colorless crystalline **3** was obtained.

REFERENCES

[1] Wing, K. D. Science 1988, 241(4864), 467–469.
[2] Wing, K. D.; Slawecki, R. A.; Carlson, G. R. Science 1988, 241(4864), 470–472.
[3] Hsu, A. C. T. ACS Symposium Series 443 (Synthesis and Chemistry of Agrochemical II), American Chemical Society, Washington 1991, 478–490.
[4] Wing, K. D. U.S. Patent 5,424,333, 1995, Chem Abstr 123(1995)313108e.
[5] Borloo, M.; Jiao, X. Y.; Wojtowicz, H.; Rajan, R.; Verbruggen, C.; Augustyns, K.; Haemers, A. Synthesis 1995, 1074.
[6] Wang, Q. M.; Chen, Z.; Zeng, Q.; Huang, R. Q. Heteroat Chem 1999, 10(3), 209.
[7] Gruszeeha, G.; Soroka, M. Pol J Chem 1979, 53, 2327.
[8] Dai, Q.; Chen, R. Y. Heteroat Chem 1997, 8(3), 203.
[9] Medved, T. Y.; Kabachnik, M. I. Izvest Akad Nauk SSSR Otdel Khim Nauk 1956, 684.
[10] Birum, G. H. J Org Chem 1974, 39(2), 209.
[11] Wang, Q. M.; Li, Z. G.; Huang, R. Q. CCS Symposium Series 2000, China Chemical Society, Beijing, 2000, 318.
[12] Wang, Q. M.; Zeng, Q. Symposium Of Agrochemicals IX Chinese Chemical Society, China Chemical Society, Shanghai, 1998, 238.
[13] Eckert, H.; Forstor, B. Angew Chem Int Ed Engl 1987, 26(9), 894.
[14] Wang, Q. M.; Huang, R. Q. Phosphorus Sulfur Silicon 2000, 161, 173.