  Bull. Chem. Soc. Jpn., 58, 3104—3107 (1985) [Vol. 58, No. 11

Versatile Synthesis of Dialkyl Cyclopropylphosphonates *via* Reductive Phosphonation

Toshikazu HIRAO,* Masahiko HAGIHARA, and Toshio AGAWA
Department of Applied Chemistry, Faculty of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565
(Received June 10, 1985)

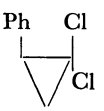
Reductive phosphonation of *gem*-dibromocyclopropanes was accomplished by the reaction with trialkyl phosphites, triethylamine, and water affording dialkyl cyclopropylphosphonates. This unique transformation proceeds by the virtue of trialkyl phosphites and dialkyl phosphonates.

The development of new routes for carbon–phosphorus bond formation is required for the synthetic utility of organophosphorus compounds. From this point of view, we have disclosed the palladium(0)-catalyzed phosphonation[1] as the necessary complement of carbon–phosphorus bond formation because the Arbuzov or Michaelis-Becker reaction is not generally applicable to the synthesis of alkenylphosphonates or arylphosphonates. Cyclopropylphosphonates are known as another class of less readily obtainable compounds due to the difficulty of nucleophilic displacement on a cyclopropane ring. In the course of our investigation[2,3] on reduction with dialkyl phosphonates (commercially named, dialkyl phosphites), we found a novel reductive phosphonation of *gem*-dibromocyclopropanes to give dialkyl cyclopropylphosphonates.[4] The present paper describes details of this methodology.

Results and Discussion

Treatment of the *gem*-dibromocyclopropanes **1** with triethyl phosphite in the presence of triethylamine and water at 90 °C gave mixtures of diethyl *cis*- and *trans*-cyclopropylphosphonates **2**. The

TABLE. PREPARATION OF THE DIALKYL CYCLOPROPYLPHOSPHONATES **2** AND **4**

Run	**1**				$P(OR^4)_3$ R^4, equiv.		Et_3N equiv.	H_2O equiv.	Reaction time/h[a]	Yield/%	
	R^1	R^2	R^3							**2** or **4**	**3**
1	n-C_6H_{13}	H	H	**1a**	Et	1.2	1.2	1.2	55	**2a** 16	27
2	**1a**					2	2	2	55	**2a** 28	32
3	**1a**					4	4	4	55	**2a** 32	48
4	**1a**					4	4	2	55	**2a** 51	17
5	**1a**					4	2	2	55	**2a** 70[b]	24
6	**1a**					4	4	0	55	**2a** 0	trace
7	H	$-(CH_2)_4-$		**1b**	Et	4	4	4	55	**2b** 25	63
8	**1b**					4	4	2	55	**2b** 46	18
9	**1b**					4	2	2	55	**2b** 54[c]	trace
10	**1b**					4	1	1	55	**2b** 52	trace
11	**1b**					4	2	—[d]	55	**2b** 3	trace
12	Ph	H	H	**1c**	Et	4	2	2	35	**2c** 50[e]	7
13	Me_3Si	H	H	**1d**	Et	4	2	2	25	**2d** 37	trace
14	Me_3SiCH_2	H	H	**1e**	Et	4	2	2	60	**2e** 39	trace
15	H	$-(CH_2)_6-$		**1f**	Et	4	2	2	55	**2f** 44	25
16	**1b**				*i*-Pr	4	2	2	45	**4b** 34	9
17	**1c**				*i*-Pr	4	2	2	25	**4c** 52	15
18	**1f**				*i*-Pr	4	2	2	45	**4f** 30	6
19	CN	Me	H	**1g**	Et	4	2	2	10	—	72
20	CO_2Me	Me	H	**1h**	Et	4	2	2	10	—	64
21	 **1i**				Et	4	2	2	60	—[f]	—

a) Reaction temperature, 90 °C. b) *cis*:*trans*=1. c) *endo*:*exo*=1. d) EtOH (2 equiv.) was used instead of water. e) Diethyl *trans*-3-phenyl-2-propenylphosphonate (**5c**, 11%) and *trans*-3-ethoxy-1-phenyl-1-propene (**6c**, <1%) were produced as by-products. f) **1i** was recovered.

simultaneous reduction took place with phosphonation on a cyclopropane ring (reductive phosphonation). The *gem*-dibromocyclopropanes **1** were recovered almost quantitatively in the reaction without water, indicating that this method differentiates from the Arbuzov phosphonation. The molar ratio of reactants is a dominant factor for the successful results of this reductive phosphonation as shown in Table. The presence of a large quantity of water caused the preferential reduction of the *gem*-dibromocyclopropanes **1** into the corresponding monobromocyclopropanes **3** (runs 3 and 7). The formation of **3** is explained by the reduction of **1** with diethyl phosphonate and triethylamine as reported previously[2] because triethyl phosphite is considered to be hydrolyzed to diethyl phosphonate with water *in situ*. The increase in the amount of triethylamine lowered the yields of **2** (runs 4 and 8). Reductive phosphonation was efficiently performed in case **1**, triethyl phosphite, triethylamine, and water were used in the molar ratio of 1:4:2:2.

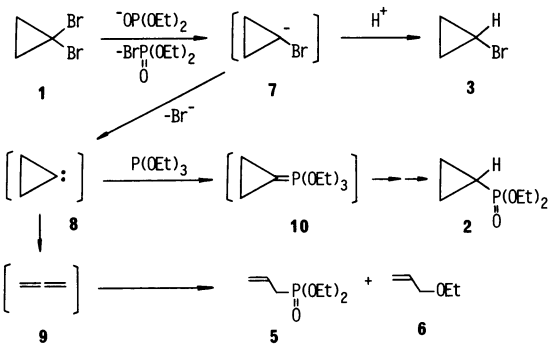
A variety of *gem*-dibromocyclopropanes were converted to **2** (Table). However, starting from *gem*-dibromocyclopropanes with an electron-withdrawing group such as ethoxycarbonyl or cyano group, reduction to the corresponding monobromocyclopropanes occurred exclusively (runs 19 and 20), maybe due to their susceptibility to reduction with diethyl phosphonate and triethylamine even at room temperature.[2] 1,1-Dichloro-2-phenylcyclopropane (**1i**) was not subjected to phosphonation under the conditions employed here (run 21). Use of triisopropyl phosphite yielded the corresponding diisopropyl cyclopropylphosphonate **4**. It should be noted that the formation of by-products (the cinnamylphosphonate and cinnamyl ether derivatives) was extremely depressed as compared to the reaction of **1c** with triethyl phosphite (runs 12 and 17).

The above-mentioned phosphonation seemed curious since diethyl phosphonate present *in situ* can reduce the *gem*-dibromocyclopropanes **1** to the monobromocyclopropanes **3** predominantly. One might consider that **3** intervenes as an intermediate capable of undergoing the Arbuzov phosphonation with triethyl phosphite. The independently prepared 1-bromo-2-phenylcyclopropane (**3c**), however, was not converted to the phosphonate **2c** on treatment with triethyl phosphite (4 equiv.) or with a mixture of triethyl phosphite (4 equiv.), triethylamine (2 equiv.), and water (2 equiv.) at 90 °C for 60 h. On the other hand, the reaction of 7,7-dibromonorcarane (**1b**) with triethyl phosphite, diethyl phosphonate, and triethylamine gave the corresponding cyclopropylphosphonate **2b**. This evidence implies that diethyl phosphonate plays an important role in the phosphonation reaction. Use of ethanol instead of water scarcely caused the present transformation because triethyl phosphite was not hydrolyzed to diethyl phosphonate in the absence of water (run 11).

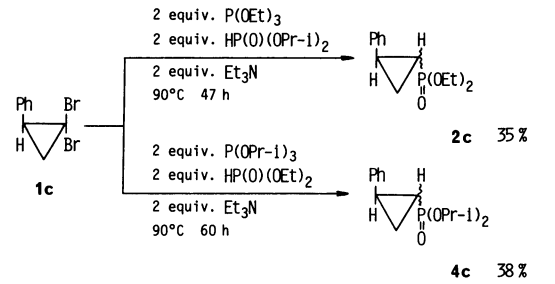
As mentioned above, the cinnamyl derivatives were obtained as by-products (run 12), which are assumed to be resulted from the addition of diethyl phosphonate or ethanol to phenylallene. The allene formation is considered to be derived from 2-phenylcyclopropylidene intermediate. Ring cleavage occurred almost selectively in phosphonation of 1,1-dibromo-2,2-diphenylcyclopropane (**1j**), giving diethyl 3,3-diphenyl-2-propenylphosphonate (**5j**) and 3-ethoxy-1,1-diphenyl-1-propene (**6j**) together with a small amount of the cyclopropylphosphonate **2j**.

The reaction path to the cyclopropylphosphonate **2** might be postulated as depicted in the following scheme. The *gem*-dibromocyclopropane **1** undergoes debromination with the generated anion of diethyl phosphonate giving the carbanion **7**. Diethyl phosphonate is converted to diethyl phosphorobromidate and its degradation accompanies the deposition of $Et_3N \cdot HBr$.[2] Protonation of **7** with diethyl phosphonate or water gives the monobromocyclopropane **3**, which is consistent with reduction with diethyl phosphonate and triethylamine.[2] Elimination of Br^- from **7** results in the generation of the cyclopropylidene **8**. Prior to ring cleavage into the allene **9**, **8** is assumed to interact with triethyl phosphite to afford the ylide **10**. It is conceivable that the degradation of **10** completes the route to the cyclopropylphosphonate **2**.

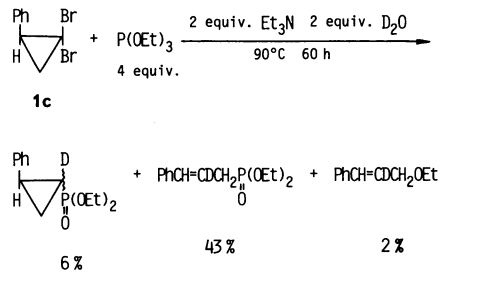
Another possibility is proposed that **8** is subjected to α-addition of diethyl phosphonate, but excluded



by the following observations. Treatment of **1c** with triethyl phosphite, diisopropyl phosphonate, and triethylamine gave the diethyl cyclopropylphosphonate **2c** exclusively. The formation of the diisopropyl cyclopropylphosphonate **4c** was not detected by GLC. The reverse combination of triisopropyl phosphite and diethyl phosphonate led to the exclusive formation of the diisopropyl cyclopropylphosphonate **4c**. These results support that the agent participating in carbon–phosphorus bond formation is trialkyl phosphite.



The α-proton of **2** is essentially derived from water, which was ascertained by the deuterium introduction (>90%) in the reaction of **1b** with deuterium oxide. In the case of **1c**, however, use of deuterium oxide changed the reaction course. Ring-opening phosphonation occurred predominantly producing diethyl 3-phenyl-2-propenyl-2-*d*-phosphonate.



Preparation of cyclopropylphosphonates is not easily accessible because dialkyl diazomethylphosphonates commonly used for their synthesis[5] are potentially carcinogenic and explosive. The present method provides a facile synthesis of dialkyl cyclopropylphosphonates under the mild reaction conditions.

Experimental

IR spectra were taken on a JASCO IRA-1 spectrometer. NMR spectra were obtained on a JEOL JNM FX-90Q spectrometer with tetramethylsilane as an internal standard. Mass spectrometry was performed with Hitachi RMU-6E and JEOL JMS-DX 300 (high resolution) spectrometers.

Materials. *gem*-Dibromocyclopropanes were prepared according to the common method using a phase-transfer catalyst.[6] Trialkyl phosphites and dialkyl phosphonates were purified by distillation.

General Procedure for the Preparation of Dialkyl Cyclopropylphosphonates (2 or 4). To the *gem*-dibromocyclopropane **1** (5.0 mmol) were added trialkyl phosphite (20 mmol), triethylamine (10 mmol), and water (10 mmol) successively. The mixture was stirred at 90 °C for 25—60 h. During the reaction, the white precipitate ($Et_3N \cdot HBr$) separated. After the consumption of **1**, the salt was filtered off and washed with benzene (3×10 mL). The filtrate and washings were evaporated *in vacuo* and the residue was flash column chromatographed to give a mixture of dialkyl *cis*- and *trans*-cyclopropylphosphonates **2** or **4**. Further purification was done by distillation or rechromatography. These results are summarized in Table.

In the preparation of diethyl 2-phenylcyclopropylphosphonate (**2c**), diethyl *trans*-3-phenyl-2-propenylphosphonate (**5c**, 11%) and *trans*-3-ethoxy-1-phenyl-1-propene (**6c**, <1%) were obtained as by-products, which were purified by GLC (conditions: PEG 20 M column, 200 °C) after flash column chromatography.

2a: Bp 98—102 °C/0.07 mmHg† (Kugelrohr); IR (neat) 1240, 1020, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.4—1.8 (m, 23H), 4.06 (quint, 4H, J=7.2 Hz). Found: C, 59.08; H, 10.73; P, 12.13; M^+, 262. Calcd for $C_{13}H_{27}O_3P$: C, 59.52; H, 10.37; P, 11.81; M^+, 262.

2b: Bp 118—120 °C/0.21 mmHg (Kugelrohr); IR (neat) 1240, 1020, 780 cm^{-1}; ^1H NMR ($CDCl_3$) *endo*: δ=0.72 (ddd, 1H, J=9.9, 8.5, 2.9 Hz, CHP), 1.0—2.2 (m, 16H), 4.10 (quint, 4H, J=7.1 Hz); *exo*: δ=0.55 (dt, 1H, J=5.6, 4.7 Hz, CHP), 1.0—2.2 (m, 16H), 4.07 (quint, 4H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$) *endo*: δ=9.49, 14.75, 14.96, 15.88, 16.16, 18.11, 19.08, 19.35, 20.44, 60.37, 60.64; *exo*: δ=11.28, 15.83, 16.05, 16.26, 19.79, 20.44, 22.33, 22.50, 61.02, 61.29. Found: C, 57.13; H, 9.25; P, 13.10; M^+, 232. Calcd for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11; P, 13.34; M^+, 232.

2c: Oil; IR (neat) 1240, 1020, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.10, 1.12 (t, 6H, J=7.1 Hz), 1.4—3.0 (m, 4H), 3.4—4.4 (m, 4H), 6.9—7.2 (m, 5H). Found: C, 61.18; H, 7.55; P, 12.02; M^+, 254. Calcd for $C_{13}H_{18}O_3P$: C, 61.41; H, 7.53; P, 12.18; M^+, 254.

2d: Oil; IR (neat) 1240, 1040, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.00 (s, 9H), 0.2—0.8 (m, 3H), 1.37 (t, 6H, J=7.0 Hz), 4.10 (quint, 4H, J=7.0 Hz). High-resolution MS; Found: 235.0931. Calcd for $C_9H_{20}O_3PSi$ (M^+-CH_3): 235.0918.

2e: Oil; bp 98—100 °C/0.15 mmHg (Kugelrohr); IR

† 1 mmHg=133.322 Pa.

(neat) 1240, 1020, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.22 (s, 9H), 0.4—1.2 (m, 6H), 1.32 (t, 6H, J=7.1 Hz), 4.10 (quint, 4H, J=7.1 Hz). Found: C, 49.65; H, 9.71; P, 11.49; M^+, 264. Calcd for $C_{11}H_{25}O_3PSi$: C, 49.97; H, 9.53; P, 11.72; M^+, 264.

2f: Oil; IR (neat) 1240, 1020, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.7—2.2 (m, 15H), 1.33 (t, 6H, J=7.1 Hz), 4.06 (quint, 4H, J=7.1 Hz). High-resolution MS; Found: 260.1514. Calcd for $C_{13}H_{25}O_3P$ (M^+): 260.1540.

4b: Oil; IR (neat) 1250, 1010, 790, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.4—2.2 (m, 23H), 4.4—4.9 (m, 2H). High-resolution MS; Found: 260.1522. Calcd for $C_{13}H_{25}O_3P$ (M^+): 260.1540.

4c: Oil; IR (neat) 1240, 1010, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.0—1.5 (m, 15H), 2.1—2.7 (m, 1H), 4.1—4.9 (m, 2H), 7.1—7.5 (m, 5H). High-resolution MS; Found: 282.1389. Calcd for $C_{15}H_{23}O_3P$ (M^+): 282.1384.

4f: Oil; IR (neat) 1240, 1000, 780, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.6—2.2 (m, 15H), 1.30 (d, 12H, J=6.7 Hz), 4.3—4.9 (m, 2H). High-resolution MS; Found: 288.1852. Calcd for $C_{15}H_{29}O_3P$ (M^+): 288.1852.

Phosphonation with Trialkyl Phosphite and Dialkyl Phosphonate. To the *gem*-dibromocyclopropane **1** (5.0 mmol) were added trialkyl phosphite (10 mmol), dialkyl phosphonate (10 mmol), and triethylamine (10 mmol). The mixture was stirred at 90 °C for 47—60 h. Workup was carried out as mentioned above to give **2** or **4**. Yields were shown in the equation or scheme. The selectivity was checked by GLC (conditions: PEG 20 M column, 200 °C).

Phosphonation in the Presence of D_2O. To the *gem*-dibromocyclopropane **1** (5.0 mmol) were added triethyl phosphite (20 mmol), triethylamine (10 mmol), and D_2O (10 mmol). The mixture was stirred at 90 °C for 60 h. Workup and isolation of products were done as mentioned above. Starting from **1b**, the corresponding α-deuteriocyclopropylphosphonate was obtained in 27% yield. Diethyl 2-phenylcyclopropyl-1-*d*-phosphonate (6%), diethyl 3-phenyl-2-propenyl-2-*d*-phosphonate (43%), and 3-ethoxy-1-phenyl-2-*d*-1-propene (2%) were obtained in the phosphonation reaction of **1c**. The olefinic geometry was not determined. In every case, the deuterium content was more than 90%.

This work was partially supported by the Grant-in-Aid for Developmental Scientific Research from the Ministry of Education, Science, and Culture.

References

1) T. Hirao, T. Masunaga, Y. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, **21**, 3595 (1980); *Synthesis*, **1981**, 56; T. Hirao, T. Masunaga, N. Yamada, Y. Ohshiro, and T. Agawa, *Bull. Chem. Soc. Jpn.*, **55**, 999 (1982).

2) T. Hirao, T. Masunaga, Y. Ohshiro, and T. Agawa, *J. Org. Chem.*, **46**, 3745 (1981).

3) T. Hirao, S. Kohno, Y. Ohshiro, and T. Agawa, *Bull. Chem. Soc. Jpn.*, **56**, 1881 (1983); T. Hirao, T. Masunaga, K. -i. Hayashi, Y. Ohshiro, and T. Agawa, *Tetrahedron Lett.*, **24**, 399 (1983).

4) T. Hirao, M. Hagihara, Y. Ohshiro, and T. Agawa, *Synthesis*, **1984**, 60.

5) D. Seyferth, R. S. Marmor, and P. Hilbert, *J. Org. Chem.*, **36**, 1379 (1971); J. R. Reid and R. S. Marmor, *ibid.*, **43**, 999 (1978).

6) W. E. Keller, "Compendium of Phase-Transfer Reactions and Related Synthetic Methods," Fluka AG, 1979.