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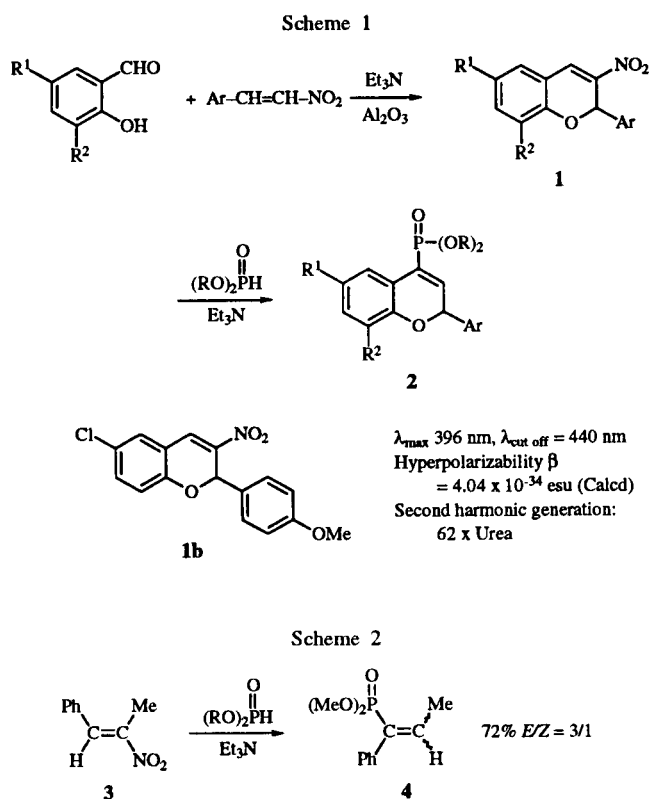
3-Nitrochromenes are readily converted into 4-phosphorylchromenes on treatment with dialkyl phosphite in the presence of triethylamine in 60-70% yield. This method provides a general method for the preparation of alkenyl phosphonates from nitroalkenes and dialkyl phosphite.

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In this paper we wish to report a simple conversion of 3-nitrochromenes **1** into 4-phosphorylchromenes **2**, which might be important precursors for functional materials or biologically active compounds. Chromene ring systems occur widely in plants [1], and they show various biological activities. For example, levcromakalim [2], benzopyran-4-amides [3] and related compounds [4] have been developed for a number of therapeutic targets such as hypertension, angina pectoris, asthma, and urinary incontinence [5]. In addition to the biological activity of chromenes or other benzopyran ring systems, they provide a new framework for non-linear optical devices. Some 3-nitrochromenes **1** exhibit highly effective non-linear optical responses, where an electron donor and acceptor are connected with the chromene ring [6]. This system is different from the classical one-dimensional charge transfer molecules which have been extensively studied for non-linear optical molecules. The charge transfer complex of the one dimensional type absorbs at longer wavelengths and compounds based on such intramolecular charge transfer complex are not suitable for the purpose of second harmonic generation (frequency doubling) due to reabsorption of light. Chromene ring systems may have a good chance for providing colorless non-linear optical materials, for donor and acceptor groups of **1** are perpendicular to one another, thus avoiding a direct conjugation between donor and acceptor groups. Phosphonates are also important compounds, which can exert their biological activity as regulators, mediators, or enzyme inhibitors [7]. In addition, phosphonates have found wide application in general organic synthesis, where the phosphoryl functionality serves as an efficient electron withdrawing group and also a leaving group for substitution or elimination reactions [8]. Furthermore, the phosphoryl group can also serve as an acceptor for non-linear optical materials. Sulfonyl or phosphoryl groups are better than a cyano or nitro group for obtaining colorless non-linear optical materials [9]. So we have an interest in preparing chromenes substituted with a phosphoryl functionality such as 4-phosphorylchromenes **2**, which may show biological and non-linear optical activity. Although many syntheses of benzopyrans [1] and alkenyl phosphonates [8] are to be found in the literature, there have been no effective methods

for the preparation of benzopyran ring systems with a phosphoryl group. Here we report a simple synthesis of **2** starting from **1**. As nitrochromenes **1** are readily prepared from salicylaldehydes and nitroalkenes, the present procedure is attractive for the preparation of **2** with various substituents.

The procedure of the preparation of **2** is quite simple. A solution of **1**, triethylamine, and dialkyl phosphite in dichloromethane was stirred at room temperature for 24 hours, followed by the usual work-up to give **2** in good yields. The results are summarized in Table 1. The structure of **2** was assigned on the basis of  $^1\text{H}$ -nmr, ms and elementary analyses data. The requisite 3-nitrochromenes **1** are prepared either by the reaction of substituted salicylaldehydes with nitroalkenes under basic conditions [10] or the nitration of chromenes with nitric oxide [11]. Thus, **2** with various substituents can be prepared from readily available materials by simple procedures. The conversion of nitroalkenes into alkenyl phosphonates is not limited to the chromene ring systems, but it may be extended to a general synthesis of alkenyl phosphonates starting from nitroalkenes. For example, the reaction of (*E*)-1-phenyl-2-nitropropene **3** with dimethyl phosphite in the presence of triethylamine gave dimethyl (1-phenyl-1-propenyl)phosphonate **4** with an *E/Z* ratio of 3/1 in 72% yield. Each isomer was separated by column chromatography, and the structural assignments of the *E* and *Z* isomers of **4** were made by analysis of the  $^1\text{H}$  nmr data. It is well established that the coupling constants between olefinic protons and phosphorus in alkenyl phosphonates are in the ranges of  $J_{\text{cis-H,P}} = 10\text{-}30$  Hz and  $J_{\text{trans-H,P}} = 30\text{-}50$  Hz [12]. In the case of *E*-**4** and *Z*-**4**, coupling constants between protons and phosphorus were 23 and 49 Hz, respectively. Other nitroalkenes were also converted into alkenyl phosphonates by this procedure. Such alkenyl phosphonates have been prepared by the Wittig reaction [12], the Arbuzov reaction [13], and palladium catalyzed hydrophosphorylation of alkynes [14]. Now a new method starting from nitroalkenes is added to them. Recent progress on the synthesis of nitroalkenes by the direct nitration of alkenes with nitric oxide [11] makes the present method very attractive. Namely, the present procedure can be used as an indirect phosphorylation of alkenes *via* the nitration of alkenes followed by the reaction with dialkyl phosphite.



preparation of  $\alpha,\beta$ -unsaturated phosphonates by the addition of dialkyl phosphite to nitroalkenes and the subsequent elimination of nitrous acid. The success of the preparation of functionalized alkenes by this process depends on the structure of nitroalkenes and nucleophiles. For example, the reaction of diaryl phosphine oxide to nitroalkenes stops at the stage of the formation of the addition product, from which nitrous acid is not eliminated by treatment of the adduct with bases [16].

The second harmonic generation efficiency of 3-nitrochromene **1a** which was determined by means of the powdered technique was 62 times that of urea [6]. In order to compare second harmonic generation efficiency of **2** with that of **1a**, hyperpolarizabilities of **2** were calculated using the MOPAC PM3 program [17] (Table 1). Compound **2c** showed the large hyperpolarizability value, but it was liquid not to be used for the powdered second harmonic generation test. Although compounds **2e** and **2f** were solid, they were inactive by the powdered second harmonic generation test. The absorption cut off wavelengths of **2** are listed in Table 1. As they have no absorption at 400 nm, they are good candidates for colorless non-linear optical materials. Our search for colorless non-linear optical materials based on phosphorylchromenes is now in progress.

Table 1  
Preparation of Compounds, **2** their Absorption WaveLength ( $\lambda_{\text{cut off}}$ ) and Calculated Hyperpolarizability  $\beta$

Compound	R <sup>1</sup>	R <sup>2</sup>	Ar	R	Yield %	$\lambda_{\text{cutoff}}/\text{nm}$ [a]	$\beta$ ( $\times 10^{-30}$ ) [b]
<b>2a</b>	H	H		Et	78	350	0.43
<b>2b</b>	Cl	H		Et	77	350	0.57
<b>2c</b>	H	MeO		Et	70	360	10.7
<b>2d</b>	H	Cl		Me	60	320	0.57
<b>2e</b>	Cl	H		Me	64	330	0.73
<b>2f</b>	H	MeO		Me	68	330	0.88

Yields refer to pure isolated products. [a] The absorption spectra were measured in methanol. [b] The hyperpolarizability (B) was calculated by MOPAC PM3.

The present conversion of nitroalkenes into alkenyl phosphonates proceeds *via* the addition of dialkyl phosphite to nitroalkenes followed by elimination of nitrous acid. Such addition-elimination sequences using a nitro group as the activating and the leaving group provide a useful method for the preparation of functionalized alkenes such as  $\alpha,\beta$ -unsaturated nitriles or esters [15]. To the best of our knowledge, this is the first example of the

## EXPERIMENTAL

The <sup>1</sup>H nmr spectra were recorded on JEOL JNM-400, chemical shifts (in deuteriochloroform) being reported in the data scale (ppm) relative to tetramethylsilane. The ir spectra were recorded on a Hitachi 270-30 spectrometer. Mass spectra were measured on a Hitachi M-80B instrument operating at 20 eV. Microanalyses were performed at the Advanced Instrumentation Center for Chemical Analysis, Ehime University.

### General Procedure for Synthesis of 4-Dialkoxyphosphinylchromenes 2a-f.

To a stirred solution of 3-nitrochromene **1** (2 mmoles) and dialkyl phosphite (2 mmoles) in dichloromethane (50 ml) was added triethylamine (1 ml) at room temperature. The resulting solution was stirred at room temperature for 24 hours, poured into water, and extracted with ethyl acetate. The organic layer was dried with anhydrous sodium carbonate, concentrated *in vacuo*, and the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate = 10/1) to give pure **2**.

#### 4-Diethoxyphosphinyl-2-phenylchromene (2a).

This compound was obtained as a colorless oil; ir:  $\nu$  3400, 2960, 1535, 1487, 1325, 1235, 1200, 970, 800, 720  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.71 (m, 9H), 6.81 (dd, 1H,  $J = 3.9$ ,  $J_{\text{P-H}} = 20$  Hz), 5.58 (q, 1H,  $J = 3.8$  Hz), 4.19 (m, 4H), 1.39 (m, 6H); ms:  $m/z$  344 ( $\text{M}^+$ , 48) 315(19), 207.

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{21}\text{O}_4\text{P}$ : C, 66.28; H, 6.10. Found: C, 66.38; H, 6.13.

#### 2-p-Anisyl-6-chloro-4-diethoxyphosphinylchromene (2b).

This compound was obtained as a colorless oil; ir:  $\nu$  2960, 1538, 1510, 1480, 1235, 11785, 1200, 970, 800, 710  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.64-7.15 (m, 7H), 6.86 (dd, 1H,  $J = 3.7$ ,  $J_{\text{P-H}} = 20$  Hz), 5.45 (q, 1H,  $J = 3.8$  Hz), 4.18 (m, 4H), 3.83 (s, 3H), 1.39 (m, 6H). ms:  $m/z$  408 ( $\text{M}^+$ , 39), 379 (41), 273 (100).

*Anal.* Calcd. for  $\text{C}_{20}\text{H}_{22}\text{O}_5\text{P}\text{Cl}$ : C, 58.75; H, 5.38. Found: C, 58.68; H, 5.37.

#### 2-p-Anisyl-8-methoxy-4-diethoxyphosphinylchromene (2c).

This compound was obtained as a colorless oil; ir:  $\nu$  2960, 2930, 1543, 1535, 1510, 1460, 1240, 1020, 970, 720  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.70-7.20 (m, 7H), 6.96 (dd, 1H,  $J = 3.8$ ,  $J_{\text{P-H}} = 20$  Hz), 5.92 (q, 1H,  $J = 4.0$  Hz), 4.23 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 1.38 (m, 5H). ms:  $m/z$  404 ( $\text{M}^+$ , 40), 375 (49), 267 (100).

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{25}\text{O}_6\text{P}$ : C, 62.37; H, 6.19. Found: C, 62.28; H, 6.24.

#### 4-Dimethoxyphosphinyl-2-phenylchromene (2d).

This compound was obtained as a colorless oil; ir:  $\nu$  2952, 1490, 1456, 1328, 1306, 1286, 1238, 1052, 1030, 1006, 820, 762, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.73-7.25 (m, 9H), 7.09 (dd, 1H,  $J = 5.5$ ,  $J_{\text{P-H}} = 20$  Hz), 5.58 (q, 1H,  $J = 9.1$  Hz), 3.75 (d, 3H,  $J = 10.3$  Hz), 3.62 (d, 3H,  $J = 10.3$  Hz). ms:  $m/z$  316 ( $\text{M}^+$ , 6), 237 (14), 207 (100).

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{17}\text{O}_4\text{P}$ : C, 64.56; H, 5.38. Found: C, 64.71; H, 5.44.

#### 2-p-Anisyl-6-chloro-4-dimethoxyphosphinylchromene (2e).

This compound was obtained as colorless crystals, mp 157-158 $^\circ$ ; ir:  $\nu$  2956, 1660, 1610, 1514, 1482, 1284, 1248, 1176, 1118, 1026, 852, 840, 822, 794, 700  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.64-7.05 (m, 7H), 6.93 (dd, 2H,  $J = 5.6$ ,  $J_{\text{P-H}} = 20$  Hz), 5.46 (q, 1H,  $J = 3.9$  Hz), 3.84 (s, 3H), 3.78 (d, 3H,  $J = 10.3$  Hz), 3.71 (d, 3H,  $J = 10.3$  Hz); ms:  $m/z$  380 ( $\text{M}^+$ , 15), 273 (100), 271 (99), 165 (36).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{18}\text{O}_5\text{P}\text{Cl}$ : C, 56.76; H, 4.73. Found: C, 56.48; H, 4.64.

#### 4-Dimethoxyphosphinyl-8-methoxy-2-phenylchromene (2f).

This compound was obtained as colorless crystals, mp 113-114 $^\circ$ ; ir:  $\nu$  2940, 1584, 1488, 1212, 1102, 1050, 1026, 834,

822, 764, 738, 696, 544  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr:  $\delta$  7.737.05 (m, 8H), 6.93 (dd, 1H,  $J = 5.2$ ,  $J_{\text{P-H}} = 20$  Hz), 5.61 (q, 1H,  $J = 3.9$  Hz), 4.20 (q, 1H,  $J = 5.2$  Hz), 3.78 (d, 3H,  $J = 10.3$  Hz), 3.76 (s, 3H), 3.66 (d, 3H,  $J = 10.3$  Hz); ms:  $m/z$  345 ( $\text{M}^+$ , 17), 267 (32), 237 (100).

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{19}\text{O}_5\text{P}$ : C, 62.42; H, 5.49. Found: C, 62.20; H, 5.67.

#### Dimethyl (1-Phenyl-1-propenyl)phosphonate (4).

The same procedures as in the preparation of **2** were employed to give **4** as a colorless liquid in 73% yield; ir:  $\nu$  3476, 2952, 2848, 1494, 1444, 1252, 1184, 1056, 1028, 826;  $^1\text{H}$  nmr:  $\delta$  for *E*-isomer (major) 7.38 (m, 5H), 7.05, 6.99 (q, 1H,  $J = 6-8$  Hz,  $J_{\text{P-H}} = 23$  Hz), 3.70 (d, 6H,  $J = 10.1$  Hz), 1.75, 1.74 (d, 3H,  $J = 6.8$  Hz);  $\delta$  for the *Z*-isomer 7.30 (m, 5H), 6.66, 6.53 (q, 1H,  $J = 7.3$  Hz,  $J_{\text{P-H}} = 49$  Hz), 3.69 (d, 6H,  $J = 11.2$  Hz), 2.26, 2.25 (d, 3H,  $J = 7.2$  Hz). ms:  $m/z$  226 ( $\text{M}^+$ , 100), 115 (67).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{15}\text{O}_3\text{P}$ : C, 58.41; H, 6.64. Found: C, 58.12; H, 6.58.

### REFERENCES AND NOTES

- [1] E. E. Schweizer and D. Meeder-Nycz, in *Chromenes, Chromanones, and Chromones*, G. P. Ellis, ed, The Chemistry of Heterocyclic Compounds, John Wiley and Sons, New York, 1977, p 29.
- [2] V. A. Ashwood, R. E. Buckingham, F. Cassidy, J. M. Evans, E. A. Faruk, T. C. Hamilton, D. J. Nash, G. Stemp, and K. Willcocks, *J. Med. Chem.*, 29, 2194 (1986).
- [3] H. Koga, H. Sato, T. Ishizawa, N. Taka, and T. Takahashi, *Tetrahedron Letters*, 36, 87 (1995).
- [4a] D. R. Buckle, D. S. Eggleston, I. L. Pinto, D. G. Smith, and J. M. Tedder, *Biomed. Chem. Letters*, 2, 1161 (1992); [b] R. Bergmann and R. Gericke, *J. Med. Chem.*, 33, 492 (1990).
- [5] D. M. Robertson and M. I. Steinberg, *J. Med. Chem.*, 33, 1529 (1990).
- [6] N. Ono, K. Sugi, T. Ogawa, and S. Aramaki, *J. Chem. Soc. Chem. Commun.*, 1781 (1993).
- [7a] R. Engel, *Chem. Rev.*, 77, 349 (1977); [b] M. R. Harnden, A. Parkin, M. J. Parratt, and R. M. Perkins, *J. Med. Chem.*, 36, 1345 (1993).
- [8] For recent review, see, T. Minami and J. Motoyoshiya, *Synthesis*, 333 (1992).
- [9] The nitro and cyano groups have been mostly used as an electron acceptor for non-linear optical devices, see; [a] P. N. Prasad and D. J. Williams, *Introduction to Nonlinear Optical Effective Molecules and Properties*, John Wiley and Sons, New York, 1991. The functional groups consisted of the third row elements such as sulfonyl or phosphonyl groups may be better for the colorless materials than the nitro or cyano group, see: [b] S. Nijhuis, G. L. Rikken, E. E. Havinga, W. T. Hoeve, H. Wynberg, E. W. Meijer, *J. Chem. Soc., Chem. Commun.*, 1093 (1990); [c] C. Dehu, F. Meyers, J. L. Bredas, *J. Am. Chem. Soc.*, 115, 6198 (1993); [d] The second harmonic generation efficiency of  $\beta$ -phosphonyl *p*-dimethylaminostyrene is 13 times that of urea, whose efficiency is better than the corresponding nitro compounds; see T. Ogawa, N. Usuki, and N. Ono, Abstract of the 68th National Meeting of the Chemical Society of Japan, Nagoya, 1A406 (1994).
- [10] S. V. Rajender, K. Mirayam, and W. K. Geroge, *Synthesis*, 486 (1982).
- [11] E. Hata, T. Yamada, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 68, 3629 (1995).
- [12] Y. Xu, M. T. Flavin, and Ze-Qi Xu, *J. Org. Chem.*, 61, 7697 (1996) and references therein.
- [13] A. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, 81, 415 (1981).
- [14] Li-Ban Han and M. Tanaka, *J. Am. Chem. Soc.*, 118, 1571 (1996).
- [15a] For a review on this topic, see: N. Ono, in *Nitro Compounds*:

Recent Advances in Synthesis and Chemistry, H. Feuer and T. N. Nielsen, eds, VCH Publishers; New York, 1990; Chapter 1, for recent papers, see: [b] C. D. Weis and G. R. Newkome, *J. Org. Chem.*, **55**, 5801 (1990); [c] R. Ballini, and G. Bosica, *Tetrahedron*, **51**, 4213 (1995); [d]

R. Ballini and P. Astolfi, *Liebigs Ann.*, 1879 (1996).

[16] M. Yamada and M. Yamashita, *Synthesis*, 1026 (1982).

[17] H. A. Kurtz, J. J. P. Stewart, and K. M. Dieter, *J. Comput. Chem.*, **11**, 82 (1990).