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PAPER

Base catalysed synthesis of thiochromans and azo-linked chromenes using allenylphosphonates†

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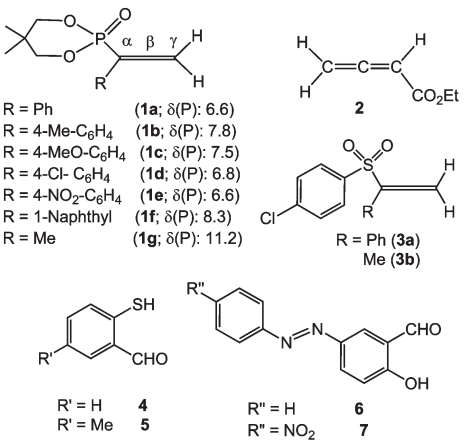
An efficient base catalysed approach to the synthesis of thiochromans/chromenes from allenylphosphonates (and an allenoate) and substrates having SH/OH and CHO groups at appropriate positions has been developed. Several azo-linked chromenes that are bright red pigments are also synthesized. This methodology involves the domino reactions of Michael addition and subsequent cyclisation by intramolecular aldol reaction.

Introduction

Allenes (1,2-dienes) are versatile precursors for diverse synthetically and biologically useful molecules.[1,2] Among these, base/phosphine catalysed domino cyclisation of allenes with substrates possessing OH and CHO groups at *ortho*-positions leading to chromans[3] has attracted great attention in recent years due to diverse biological activities of the products.[4,5] This allene route is one among the more versatile and convenient routes to chromans.[3,6]

During our ongoing work on the synthesis of heterocycles through allenes, we have recently shown that domino cyclisation of allenylphosphonates with salicylaldehydes and 2-formylindole leads to a variety of phosphono-chromenes[7] and phosphono-pyrroloindoles.[8] We were curious to know whether this methodology can be adapted efficiently for thiochromans or *azo*-substituted chromans *via* 2-mercaptobenzaldehydes,[9] or *azo*-substituted salicyclaldehydes.[10] We describe the results in this paper using the allene precursors **1a–g**, **2** and **3a–b**; the other reactants are the 2-mercaptobenzaldehydes **4–5** and *azo*-substituted salicylaldehydes **6–7**. It should be noted that synthetic routes to thiochromans/chromenes are relatively scanty and *azo*-substituted chromenes, that could have interesting photophysical properties, are also rather rare. The main focus of this work is on the utility of allenylphosphonates[11] because this class of precursors are important building blocks in organic synthesis.[12] For comparative purposes, the allenoate **2** is also used.



Results and discussion

First, we treated the allenylphosphonate **1a** with 2-mercaptobenzaldehyde **4** in the presence of K_2CO_3 in ethanol. This reaction led to mainly three types of products (Scheme 1): An ***E*** + ***Z*** isomeric mixture of (β,γ)-cyclised phosphono-thiochroman **8** (***E***-isomer characterised by X-ray crystallography, Fig. 1, top), (β,α)-cyclised phosphono-thiochroman **9** (X-ray structure, Fig. 1, bottom) and the allylphosphonate **10**.

We then wanted to see whether the yield of one of the thiochromans could be maximized or not using different solvents/bases by heating at 90 °C for 4 h (oil bath temperature). The results are summarized in Table 1. Use of PPh_3 or DMAP as the base afforded only low yields of the desired product (Table 1, entries 9, 10). PEG-400 as a solvent also works (Table 1, entry 15), but the yields are only moderate. In some cases, both the regioisomers **8** and **9** (Table 1, entries 1–2, 6–10, 13, 15–16) are obtained. The conditions previously used in the reaction of

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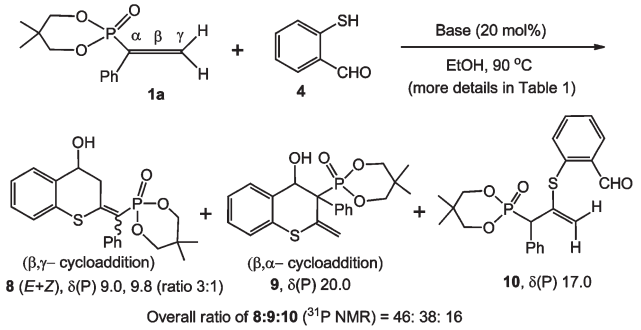


Scheme 1

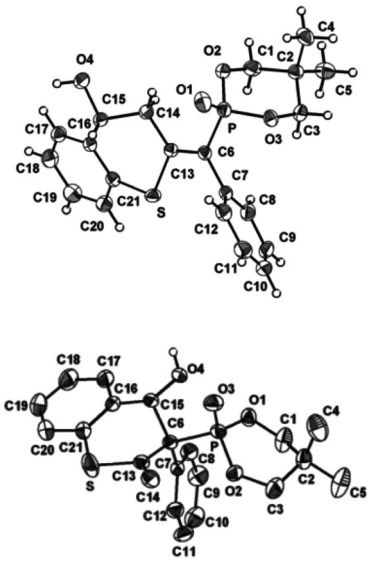


Fig. 1 ORTEP diagrams of compounds (*E*)-**8** (top) and **9** (bottom). Selected bond lengths [Å] with esds in parentheses follow. ***Compound*** (*E*)-**8**: P–C(6) 1.798(3), C(6)–C(13) 1.343(4), C(13)–C(14) 1.509(4), S–C(13) 1.758(3), O(4)–C(15) 1.409(4). [Hydrogen bond parameters (Å, Å, °): O(4)–H(4)···O(1) 0.82 1.93 2.743(4) 175.1°; symmetry code: $2-x, 2-y, 2-z$]. ***Compound*** **9** [hydrogen atoms other than the one attached to oxygen are not shown]: P–C(6) 1.852(2), C(6)–C(7) 1.529(3), C(13)–C(14) 1.319(3), C(6)–C(15) 1.574(3), S–C(13) 1.771(2), O(4)–C(15) 1.406(3) [Hydrogen bond parameters (Å, Å, °): O(4)–H(4)···O(1′) 0.84(3) 1.84(3) 2.673(3) 170.1 °; symmetry code: $-x, -y, -z$].

salicylaldehyde with allenylphosphonates[7] are less effective (Table 1, entry 11) wherein the yield of **8** is reasonable, but not the best. It is found that using K_2CO_3 as the base and dimethyl sulfoxide (DMSO) as the solvent, phosphono-thiochroman **8** could be obtained as the predominant product [95%, $E:Z$ = 5 : 2; ^{31}P NMR evidence, Fig. 2].

To check the scope and limitations of the above reaction, we then conducted the reaction of allenylphosphonates **1a–g** with 2-mercaptobenzaldehydes **4–5** under the optimized conditions [K_2CO_3/DMSO] for the synthesis of (β,γ)-cyclised phosphono-thiochromans **8** and **11–23** (Scheme 2). The yields of the isolated products are good (Table 2). We have separated both *E* and *Z* isomers of **8**, **11–13**, **17–20**. For **14** and **21**, only *E*-isomer was isolated. In the case of **16** and **23**, obtained from α-methyl allenylphosphonate **1g**, only *E*-isomer is formed exclusively. In

Table 1 Effect of reaction conditions on the yield of product **8** from the reaction of allene **1a** with 2-mercaptobenzaldehyde **4**

Entry	Base/solvent	Yield (%)[a], (*E* : *Z*)
1[e]	K_2CO_3/EtOH	46 (10 : 3)[b,c]
2	Triethanolamine	57 (2 : 1)[b,c]
3	NaOAc/DMSO	82 (5 : 1)[c]
4	CsF/DMSO	69 (10 : 3)[c]
5	K_3PO_4/DMSO	68 (5 : 2)[c]
6	DABCO/DMSO	61 (2 : 1)[b,c]
7	$NaHCO_3$/DMSO	53 (10 : 3)[b,c]
8	Et_3N/DMSO	59 (5 : 1)[b,c]
9	PPh_3/DMSO	37 (10 : 3)[b,c]
10	DMAP/DMSO	37 (2 : 1)[b,c]
11	DBU/DMSO	71 (5 : 1)
12	K_2CO_3/DMF	65 (2 : 1)[c]
13[e]	K_2CO_3/Toluene	58 (10 : 1)[b,c]
14[e]	K_2CO_3/CH_3CN	57 (5 : 1)[c]
15[e]	K_2CO_3/PEG-400	54 (10 : 3)[b,c]
16[f]	K_2CO_3/Dioxane	26 (10 : 11)[b,c]
17	K_2CO_3/DMSO	95 (5 : 2)[d]

[a] Yields are calculated by using ^{1}H/^{31}P NMR spectroscopy. [b] In these cases product **9** (10–38%) is also present. [c] The product **10** (14–53%) is present in these cases. [d] Yield of the isolated product is 80%. [e] 90 °C 6 h^{-1}. [f] 110 °C/6 h (temperature mentioned is of the oil bath used).

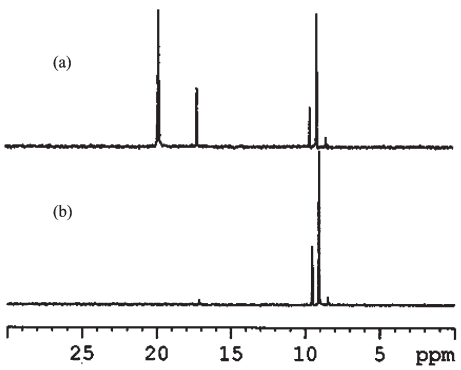
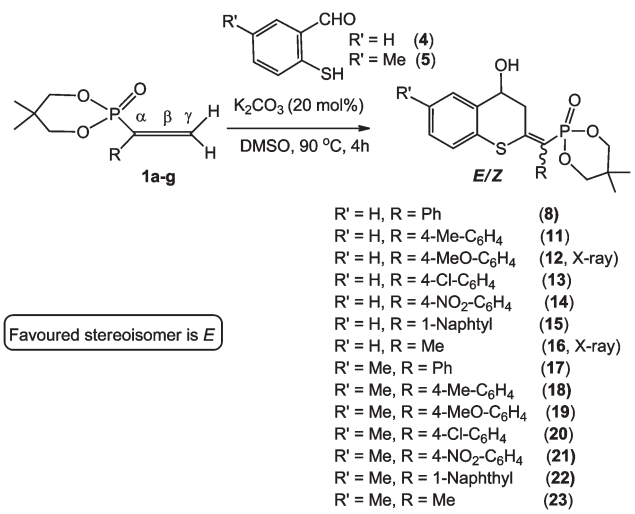


Fig. 2 ^{31}P NMR spectra of the reaction mixture of **1a** with 2-mercapto-benzaldehyde **4** in (a) EtOH at 90 °C/6 h, (b) DMSO at 90 °C/4 h (temperature mentioned is of the oil bath).



Scheme 2 Yields and ^{31}P NMR chemical shifts given in Table 2.

Table 2 ^{31}P NMR data and yields of the compounds **8** and **11–23**[a]

Entry	Compound	δ(P) (*E*)	δ(P) (*Z*)	Yield (%) (*E* : *Z*)[b]
1	**8**	9.0	9.8[b]	80 (5 : 2)
2	**11**	9.2	9.7	78 (10 : 3)
3	**12**	9.4	9.9	79 (5 : 1)
4	**13**	9.2	9.8	80 (10 : 3)
5	**14**	9.2	—	63 (10 : 3)
6	**15**	9.0	9.2	68 (5 : 3)
7	**16**	14.9	—	86
8	**17**	9.2	9.7	79 (10 : 3)
9	**18**	9.4	9.8[c]	76 (10 : 1)
10	**19**	9.4	10.3	78 (5 : 1)
11	**20**	9.4	10.0	81 (5 : 1)
12	**21**	9.4	—	64 (10 : 3)
13	**22**	9.2	9.4	67 (5 : 2)
14	**23**	15.0	—	85

[a] Products **9** and **10** were not detected under these optimized conditions. [b] Yield as given here refers to the combined yield of *E* + *Z* isomers. [c] The isomeric purity is only 95%.

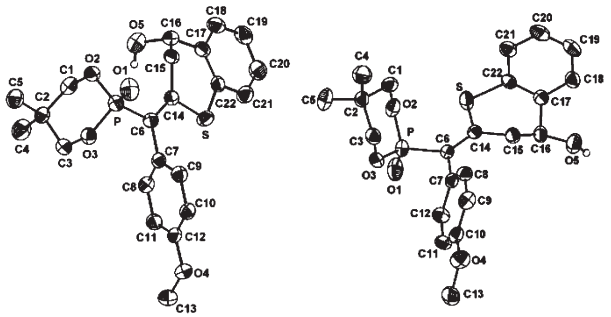
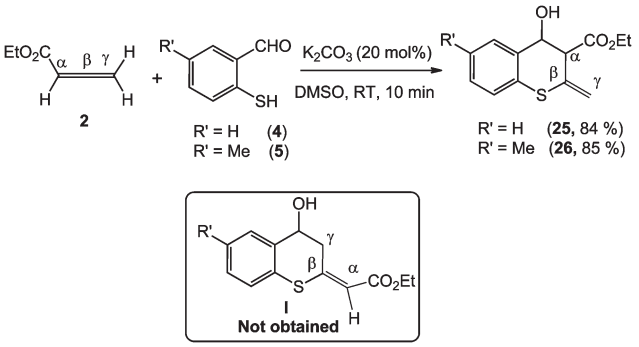


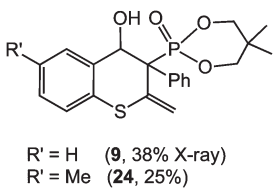
Fig. 3 ORTEP diagrams for the compounds (a) (*E*)-**12** and (b) (*Z*)-**12**. Hydrogen atoms except at the OH group are omitted for clarity. Selected bond lengths [Å] with esds in parentheses: Compound (*E*)-**12**: P–C(6) 1.797(3), C(6)–C(14) 1.346(4), C(14)–C(15) 1.503(4), C(15)–C(16) 1.505(5), S–C(14) 1.754(3), O(5)–C(16) 1.414(3). [Hydrogen bond parameters: O(5)–H(5)···O(1) 0.82 1.90 2.715(4) 171.8°; symmetry code: 1 + *x*, *y*, *z*]. Compound (*Z*)-**12**: P–C(6) 1.803(3), C(6)–C(14) 1.344(4), C(14)–C(15) 1.505(4), C(15)–C(16) 1.520(5), S–C(14) 1.765(3), O(5)–C(16) 1.403(4). [Hydrogen bond parameters: O(5)–H(5)···O(1) 0.82 2.01 2.809(4) 166.3°; symmetry code: 2 − *x*, −*y*, 1 − *z*].

the case of **15** and **22** the R_f values are very close. The structures of both *E* and *Z* isomers of **12** were confirmed by X-ray crystallography (Fig. 3). The *E*-stereochemistry for the phosphono-thiochroman **16** is also confirmed by X-ray structure determination (see ESI† for details). Electron withdrawing groups, rather than electron donating groups on the allene lead to better results. This is possibly because of the presence of electron withdrawing groups, the phenolate anion more readily undergoes addition across allenes and thus can lead to higher yields of the products. All these are (β,γ)-cyclised products.

We have also isolated the (β,α)-cyclised product **24** [which is analogous to product **9** (see Fig. 1)] from the reaction of allene **1a** with 5-methyl-2-mercaptobenzaldehyde **5** *using ethanol as the solvent medium*. This is because the yields of (β,α)-cyclised products **9** and **24** are better using this solvent.



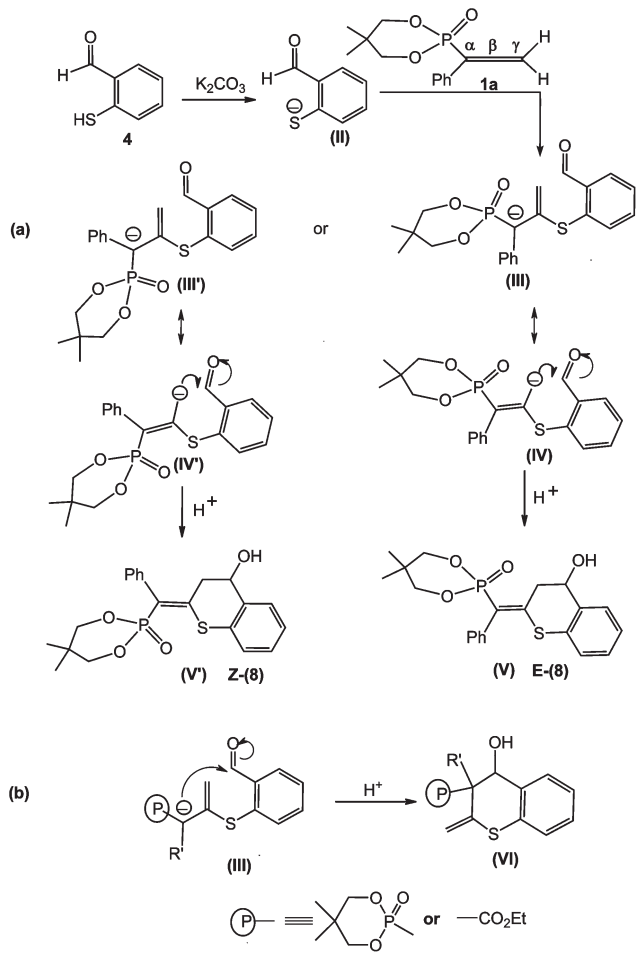
Scheme 3



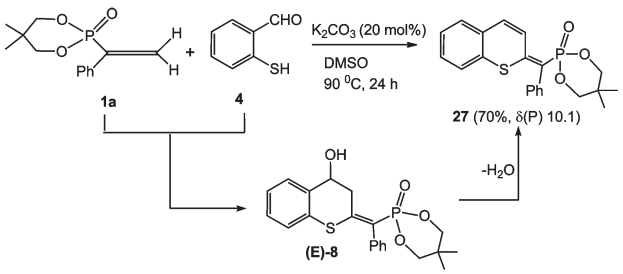
We then performed the reaction of allenoate **2** with 2-mercaptobenzaldehydes **4–5**. The reaction was complete in 10 min and led to thiochromans **25–26** as exclusive products (Scheme 3). Longer reaction times led to a mixture of products. Compounds **25** and **26** are (β,α)-cyclisation products; it may be noted that in the alternative (β,γ)-product **I**, only one olefinic proton [and an up-field C*H*$_2$ multiplet] should have been observed. This reaction is similar to that reported earlier with normal salicylaldehydes.[3a] Since the analogous allenylphosphonate (OCH$_2$CMe$_2$CH$_2$O)P(O)CH=C=CH$_2$ underwent isomerisation to the alkyne (OCH$_2$CMe$_2$CH$_2$O)P(O)C≡CMe under these conditions,[12a] an exact comparison between the two systems could not be made.

A plausible mechanism for the reaction which proceeds most likely through a domino oxo-Michael addition followed by aldol condensation[3c,7] is shown in Scheme 4. Here two possibilities exist: (β,α)-attack and (β,γ)-attack. The first one leads to the kinetically controlled product (**VI**) and the second one leads to thermodynamically controlled product (**V**). First, the base (K$_2$CO$_3$) abstracts proton from 2-mercaptobenzaldehyde and generates thiolate intermediate **II** which reacts with allenylphosphonate **1a** at β-position to give **III/III′**. Species **IV/IV′** are resonance forms of **III/III′**.[3c] Intermediates **IV** and **IV′** undergo intramolecular aldol reaction followed by protonation to afford the final products **V** and **V′**. Formation of **VI** occurs *via* **III** without the rearrangement of carbanion, as shown by the last equation in Scheme 4. In both allenylphosphonates and allenylsulfones, the α-position is sterically hindered with phosphorus ring/sulfonyl moiety and a substituent. Because of this, (β,α)-cyclisation is less favoured (minor product) when compared to (β,γ)-cyclisation product (major product). Cyclisation in the case of allenoate **2** occurs at the (β,α)-position as the α-position is not hindered.

After establishing the above reaction, we wanted to synthesize phosphono-thiochromenes, by dehydrating the hydroxyl substituted thiochromans prepared by us. This could be readily accomplished in the reaction using allenylphosphonate **1a** with



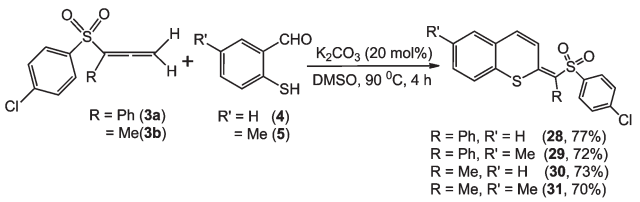
Scheme 4



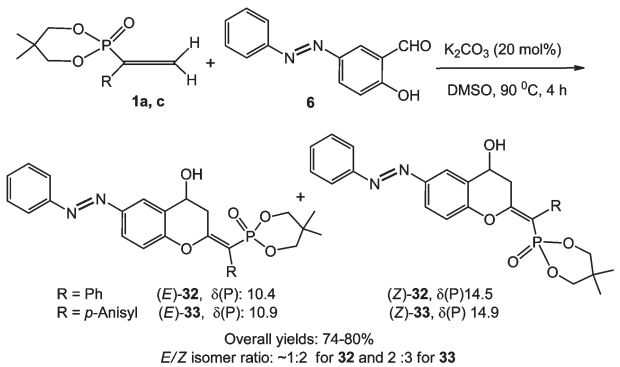
Scheme 5

2-mercaptobenzaldehyde **4** by simply prolonging the reaction time from 4 h to 24 h. Thus we could obtain phosphono-thiochromene **27** (Scheme 5) in good yield. In this compound, appearance of two olefinic protons signals and disappearance of the signals due to thiochroman ring CH_2 protons (present in **8**) in ^{1}H NMR establishes the structure as depicted. Since the isomer of **8** with (*E*)-configuration was the major product prior to dehydration an analogous (*E*) configuration is assigned to **27**.

In an effort to extend this methodology, we have chosen allenylsulfones (**3a**–**b**) in place of allenylphosphonates. Compared to allenylphosphonates, allenylsulfones reacted much faster with



Scheme 6



Scheme 7

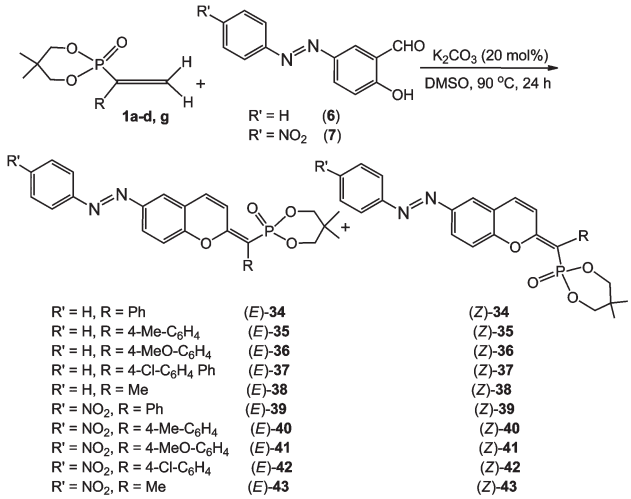
mercaptobenzaldehydes (**4**–**5**) to furnish thiochromenes (**28**–**31**) in decent yield (Scheme 6).

Although the reaction of simple salicylaldehydes with allenylphosphonates had been studied prior to this work,[7] it was thought useful to extend this to those salicylaldehydes with pendant chromophores such that the products may be useful as pigments in a later work. With this idea in mind, under the conditions employed for 2-mercaptobenzaldehydes, we first treated the *azo*-substituted salicylaldehyde **6** with the allenylphosphonates **1a** and **1c** and obtained the phosphono-chromans **32**–**33** as (*Z*) and (*E*) isomeric mixtures (Scheme 7). Both the *azo*-substituted salicylaldehyde **6** and the corresponding phosphono-chromans **32**–**33** are red in colour. Both the (*Z*) and (*E*) isomers of **32** and **33** have been isolated by using column chromatography.

Under the above conditions, the reaction of allene **1b** with the *azo*-substituted salicylaldehyde **6** led to a mixture of chromans and chromenes (like Scheme 5) because one isomer of chroman underwent faster dehydration. Hence we continued the reaction for 24 h to obtain the chromene exclusively. Under these conditions, the reaction of *azo*-substituted salicylaldehydes **6**–**7** with allenylphosphonates **1a**–**d**, **g** afforded phosphono-*azo*-chromenes **34**–**43** (Scheme 8). We have also separated individual isomers in all the cases. The overall (combined) isolated yields of the two isomers are moderate to good (Table 3). Compound (*E*)-**35** is characterised by X-ray crystallography (Fig. 4).

Conclusions

An efficient allene based route to thiochromans was developed. Under base catalysed reactions, the reactivity of allenylphosphonates with 2-mercaptobenzaldehyde leading to thiochromans is different from that of allenyl sulfones and allenoate (EtO_2C)-CH═C═CH_2 (**2**) under the same conditions. The reaction using



Scheme 8

Table 3 ^{31}P NMR data and isolated yields of the (*E*) and (*Z*) isomers of **34–43**

Entry	Compound	δ(P) (*E*)	δ(P) (*Z*)	Yield (%)(*E* : *Z*)[a]
1	**34**	14.9	11.7	76 (10.9)
2	**35**	15.2	11.9	72 (4 : 5)
3	**36**	15.3	12.0	73 (7 : 10)
4	**37**	15.0	11.4	74 (1 : 1)
5	**38**	20.9	17.0	80 (5 : 3)
6	**39**	14.5	11.2	80 (1 : 1)
7	**40**	14.7	11.5	76 (5 : 3)
8	**41**	14.9	11.6	76 (1 : 1)
9	**42**	14.6	11.0	78 (1 : 1)
10	**43**	20.5	16.6[b]	74 (5 : 2)

[a] Yields of the isolated pure compounds = combined yield of *E* + *Z* isomers. [b] The isomeric purity is only 90%.

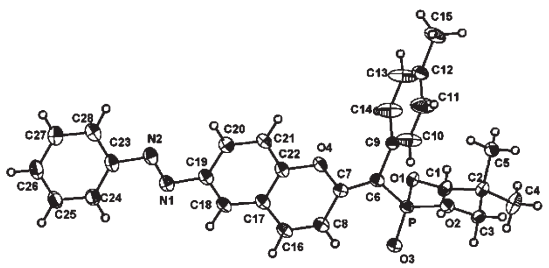


Fig. 4 An ORTEP diagram of compound (*E*)-**35**. Selected bond lengths [Å] with esds in parentheses: P–C(6) 1.766(2), C(6)–C(7) 1.358(3), C(7)–C(8) 1.442(3), C(8)–C(16) 1.337(3), O(4)–C(7) 1.381(2).

2 is much faster than that using **1a–g**. In the case of α-substituted allenylphosphonates (**1a–g**), (β,γ)-attack is favoured whereas in the case of allenoate **2**, (β,α)-attack is favoured. It appears that subtle electronic/steric factors contribute to these differences. The reactions of allenes with azo-linked salicylaldehydes afforded bright red coloured pigments that could have interesting photochemical properties (under investigation).

Experimental section

General information

Chemicals were purified when required according to standard procedures. All reactions, unless stated otherwise, were performed in a dry nitrogen atmosphere. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using a 400 MHz spectrometer in $CDCl_3$ (unless stated otherwise) with shifts referenced to $SiMe_4$ ($\delta = 0$) or 85% H_3PO_4 ($\delta = 0$). Infrared spectra were recorded neat or by using KBr pellets on an FT-IR spectrometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Microanalyses were performed using a CHNS analyzer. For TLC, glass microslides were coated with silica-gel-GF_{254} (mesh size 75 μ) and spots were identified using iodine or UV chamber as appropriate. For column chromatography, silica gel of 100–200 mesh size was used. LC-MS and HRMS (ESI-TOF) equipment was used to record mass spectra for isolated compounds where appropriate. LC-MS data were obtained using electrospray ionization on a C-18 column at a flow rate 0.2 mL min^{-1} using MeOH–water (90 : 10) as eluent. Characterization data for all the new compounds reported here are provided in the ESI.†

(i) Typical procedure for the synthesis of 9–10 (compound 8 was present but not isolated in this case). To a 25 mL round-bottomed flask containing allene **1a** (0.200 g, 0.76 mmol), 2-mercaptobenzaldehyde **4** (0.136 g, 0.98 mmol) and K_2CO_3 (0.021 g, 0.15 mmol), was added EtOH (4 mL). The contents were heated at 90 °C (temperature mentioned is of the oil bath) for 6 h. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The whole organic layer was washed with water (3 × 25 mL), dried (Na_2SO_4), filtered, concentrated and the products [**8–10**, R_f values were in the order: **10** > **9** > (*Z*)-**8** > (*E*)-**8**] were isolated by column chromatography (hexane–EtOAc; 1 : 1) on silica gel. Compounds (*Z*)-**8** and (*E*)-**8** were not isolated in this case.

(ii) General procedure for the synthesis of thiochromans 8, 11–31. To a 25 mL round-bottomed flask containing allene (one of **1a–g**) (0.76 mmol), 2-mercaptobenzaldehyde **4** or **5** (0.98 mmol) and K_2CO_3 (0.021 g, 0.15 mmol), was added DMSO (4 mL) under N_2 atmosphere. The contents were heated at 90 °C for 4 h under N_2 atmosphere. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The whole organic layer was washed with water (3 × 25 mL), dried (Na_2SO_4), filtered, concentrated and the products were isolated by column chromatography (hexane–EtOAc; 1 : 1) on silica gel. Both *Z* and *E* isomers are formed in most cases. Details on the combined yield of *Z* and *E* isomers are given in Table 2. Isolated yield of individual isomer as applicable in each case is given here.

(iii) General procedure for the synthesis of *azo*-substituted phosphono-chromans 32–33 and azo substituted phosphono-chromenes 34–43. To the allenylphosphonate **1a** or **1c** (0.76 mmol), *azo*-substituted salicylaldehyde **6** (0.221 g, 0.98 mmol) and K_2CO_3 (0.021 g, 0.15 mmol) in a 25 mL RBF, was added DMSO (4 mL) and the contents heated at 90 °C for 4 h. The reaction mixture was quenched with water (5 mL) and

extracted with CH_2Cl_2 (3 × 25 mL). The whole organic layer was washed with water (3 × 25 mL), dried (Na_2SO_4), filtered, concentrated and the products were isolated by column chromatography (hexane–EtOAc; 2 : 3) on silica gel. Here, the *E*-isomer eluted before the *Z*-isomer in each case. [*i.e.* (R_f (*E*-isomer) > R_f (*Z*-isomer)]. Phosphono-chromenes **34–43** were synthesised using same molar quantities, procedure and the work up as that for **32** except that the reaction time was 24 h (instead of 4 h). The products were isolated by column chromatography (hexane–EtOAc; 1 : 1) on silica gel. Here, the *E*-isomer eluted before the *Z*-isomer in each case. [*i.e.* (R_f (*E*-isomer) > R_f (*Z*-isomer)].

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