Simple, Efficient, and Catalyst-Free Synthesis of (2-Amino-4*H*-1-benzopyran-4-yl)phosphonates in Polyethylene Glycol[1])

by **Biswanath Das***, **Penagaluri Balasubramanyam**, **Gandolla Chinna Reddy**, and **Nayaki Salvanna**

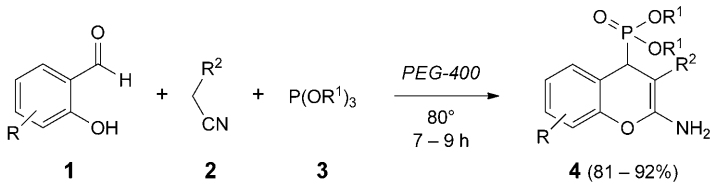
Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India (phone: +91-40-7193434; fax: +91-40-7160512; e-mail: biswanathdas@yahoo.com)

Several (2-amino-4*H*-1-benzopyran-4-yl)phosphonates were efficiently synthesized by employing a multicomponent protocol involving a salicylaldehyde, malononitrile or ethyl cyanoacetate, and a trialkyl phosphite in polyethylene glycol. The latter could be recovered and re-used. No additional solvent or catalyst was required. To the best of our knowledge, this is the first report of the one-pot preparation of (2-amino-4*H*-1-benzopyran-4-yl)phosphonic acid dimethyl esters.

Introduction. – Phosphonates are known to be important enzyme inhibitors, antibiotics, and peptide mimetics [1]. Thus, (2-aminochromen-4-yl)phosphonates (chromene = 2*H*-1-benzopyran) are expected to be valuable pharmacologic as well as pesticidal agents. Recently, two methods have been developed for the multicomponent synthesis of these compounds by using $InCl_3$ [2a] and β-cyclodextrin [2b] as catalysts. However, both methods involve the preparation of phosphonic acid diethyl esters and one of the methods reported only the preparation of (2-amino-3-cyano-4*H*-1-benzopyran-4-yl)phosphonates [2a]. The one-pot synthesis of phosphonic acid dimethyl esters of 2-aminochromenes has not been reported [3].

Results and Discussion. – In continuation of our work [4] on the development of useful synthetic methodologies, we observed that the multicomponent reaction of salicylaldehydes (=2-hydroxybenzaldehydes) **1**, malononitrile or ethyl cyanoacetate **2**, and trialkyl phosphites **3** in polyethylene glycol (PEG) at 80° produced the corresponding (2-amino-4*H*-1-benzopyran-4-yl)phosphonate derivatives **4** (*Scheme*).

Scheme



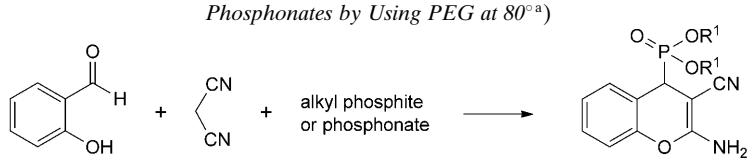
1 **2** **3** **4** (81 – 92%)

Initially the reaction of salicylaldehyde (=2-hydroxybenzaldehyde; **1a**), malononitrile (= propanedinitrile; **2a**; $R^2 = CN$), and different alkyl phosphites or phospho-

[1]) Part 216 in the series, 'Studies on Novel Synthetic Methodologies'.

nates in polyethylene glycol was thoroughly studied (*Table 1*). Considering the different reaction time and the yield of the prepared (2-amino-4*H*-1-benzopyran-4-yl)phosphonates **4** (R^1 = Me or Et), it was realized that the reactivity of the different alkyl phosphites was comparable when the reaction was carried out at 80°. On the other hand, when the reaction was conducted at room temperature, no product at all could be obtained.

Table 1. *Reaction of Salicylaldehyde* (**1a**) *and Malononitrile* (**2a**) *with Various Phosphites and Phosphonates by Using PEG at 80°* [a])



1a **2a** **4**

Alkyl phosphite or phosphonate	R^1	Time [h]	Yield [%] [b])
$(MeO)_3P$	Me	7	92
$(EtO)_3P$	Et	7	91
$Me_3SiOP(OMe)_2$	Me	7	91
$HP(O)(OMe)_2$	Me	8	86
$HP(O)(OEt)_2$	Et	8	84
$(MeO)_3P$ [c])	Me	24	n.r. [d])

[a]) Reaction conditions: salicylaldehyde (**1a**; 1.0 mmol), malononitrile (**2a**; 1.1 mmol), alkyl phosphite or phosphonate (1.1 mmol), *PEG-400* (2 g). [b]) Yield of isolated phosphonate **4a** (R^1 = Et) or **4i** (R^1 = Me). [c]) Reaction carried out at r.t. [d]) No reaction.

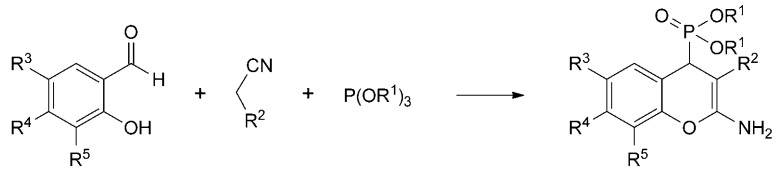
Finally, both the phosphites $(MeO)_3P$ and $(EtO)_3P$ were used in polyethylene glycol at 80° to prepare efficiently a series of (2-amino-4*H*-1-benzopyran-4-yl)phosphonate derivatives **4** from various salicylaldehydes **1** (*Table 2*).

The 3-hydroxynaphthalene-2-carboxaldehyde also underwent the conversion smoothly (*Table 2*, *Entry 10*). Both malononitrile (**2a**; R^2 = CN) and ethyl cyanoacetate (**2b**; R = COOEt) were applied to prepare the products. The conversion was complete within 7–9 h, and the products **4** were formed in high yields (81–92%). No additional solvent or catalyst was required. The structures of the products were established from their spectral (^{1}H- and ^{13}C-NMR and MS) and analytical data.

Polyethylene glycol (*PEG-400*) is an eco-friendly, biologically acceptable, and H_2O-soluble compound. It is inexpensive, thermally stable, recyclable, and nontoxic. Its applications as a reaction medium have not yet been fully explored [5]. In the present conversion, it was successfully utilized for the preparation of (2-amino-4*H*-1-benzopyran-4-yl)phosphonate derivatives. Possibly, the role of PEG is to activate the C=O group of the salicylaldehydes by H-bonding and thus to facilitate the nucleophilic attack by the malononitrile or ethyl cyanoacetate to form the products [2a]. The PEG was recovered from the reaction mixture and was recycled three times without loss of activity.

In conclusion, we developed a convenient and facile method for the synthesis of (2-amino-4*H*-1-benzopyran-4-yl)phosphonates from salicylaldehydes, malononitrile or

Table 2. *Synthesis of (2-Amino-4*H*-1-benzopyran-4-yl)phosphonates in PEG at 80°* [a])



1 **2** **4**

Entry	R^1	R^2	R^3	R^4	R^5	Product	Time [h]	Yield [%] [b])
1	Et	CN	H	H	H	**4a**	7	91
2	Et	CN	Cl	H	Cl	**4b**	8	89
3	Et	COOEt	Cl	H	Cl	**4c**	8	90
4	Et	CN	Br	H	Br	**4d**	8	87
5	Et	COOEt	Br	H	Br	**4e**	8	89
6	Et	CN	Me	H	H	**4f**	8	85
7	Et	CN	H	H	MeO	**4g**	9	82
8	Et	COOEt	H	H	MeO	**4h**	9	81
9	Me	CN	H	H	H	**4i**	7	92
10	Me	CN	–CH=CH–CH=CH–		H	**4j**	8	91
11	Me	CN	H	Et_2N	H	**4k**	9	85
12	Me	COOEt	H	H	MeO	**4l**	9	83
13	Me	COOEt	Cl	H	H	**4m**	9	90

[a]) Reaction conditions: salicylaldehyde (1.0 mmol), malononitrile (**2a**; $R^2 = CN$) or ethyl cyanoacetate (**2b**; $R^2 = COOEt$) (1.1 mmol), triethyl phosphite (**3a**; $R^1 = Et$) or trimethyl phosphite (**3b**; ($R^1 = Me$) (1.1 mmol), *PEG-400* (2 g). [b]) Yield of isolated phosphonate.

ethyl cyanoacetate, and alkyl phosphites in polyethylene glycol. The application of an eco-benign reaction medium under catalyst-free conditions, the recyclization of the medium, the high yield and the general applicability are the notable advantages of the method. To the best of our knowledge, this is the first report of the one-pot synthesis of (2-amino-4*H*-1-benzopyran-4-yl)phosphonic acid dimethyl esters.

The author thanks *CSIR* and *UGC*, New Delhi, for financial assistance.

Experimental Part

*(2-Amino-4*H*-1-benzopyran-4-yl)phosphonate Derivatives: General Procedure.* To a mixture of salicylaldehyde **1** (1.0 mmol), malononitrile or ethyl cyanoacetate **2** (1.1 mmol), and alkyl phosphite **3** (1.1 mmol), *PEG-400* (2 g) was added. The mixture was heated at 80°. After completion of the reaction (TLC monitoring), the mixture was poured onto cold H_2O (10 ml) and extracted with AcOEt (3 × 10 ml). The extract was concentrated and the residue subjected to CC (SiO_2, hexane/AcOEt): pure phosphonate.

The aq. portion was filtered, and the filtrate was lyophilized to recover the *PEG-400* which was subsequently recycled three times for the same reaction without affecting the yields of the products.

P-*(2-Amino-3-cyano-4*H*-naphtho[2,3-*b*]pyran-4-yl)phosphoric Acid Dimethyl Ester* (**4j**): ^{1}H-NMR (200 MHz, $CDCl_3$): 8.05 (*d*, *J* = 8.0, 1 H); 7.82 (*t*, *J* = 8.0, 1 H); 7.79 (*d*, *J* = 8.0, 1 H); 7.61 (*t*, *J* = 8.0, 1 H); 7.50 (*t*, *J* = 8.0, 1 H); 7.21 (*d*, *J* = 8.0, 1 H); 5.14 (br. *s*, 2 H); 4.58 (*d*, *J* = 18.0, 1 H); 3.71 (*d*, *J* = 10.0, 3 H); 3.55 (*d*, *J* = 10.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 162.9; 133.0; 130.6; 129.2; 128.4;

126.4; 124.0; 118.9; 117.8; 54.0 (*d*, *J* = 6.5); 53.8 (*d*, *J* = 6.5); 48.9; 32.8 (*d*, *J* = 145.0). ESI-MS: 331 ($[M+H]^+$). Anal. calc. for $C_{16}H_{15}N_2O_4P$: C 58.18, H 4.55, N 8.49; found: C 58.26, H 4.63, N 8.41.

P-*(2-Amino-3-cyano-7-(diethylamino)-4*H*-1-benzopyran-4-yl)phosphoric Acid Dimethyl Ester* (**4k**): ^{1}H-NMR (200 MHz, $CDCl_3$): 7.01 (*d*, *J* = 8.0, 1 H); 6.39 (*dd*, *J* = 8.0, 1.5, 1 H); 6.30 (*d*, *J* = 1.5, 1 H); 5.87 (br. *s*, 2 H); 4.51 (*d*, *J* = 20.0, 1 H); 3.59 (*d*, *J* = 10.0, 6 H); 3.41–3.28 (*m*, 4 H); 1.13 (*t*, *J* = 7.0, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 160.9; 152.3; 148.8; 130.3; 116.2; 108.5; 99.8; 54.4 (*d*, *J* = 6.0); 53.3 (*d*, *J* = 6.0); 49.8; 44.9; 34.6 (*d*, *J* = 144.0); 12.9. ESI-MS: 352 ($[M+H]^+$). Anal. calc. for $C_{16}H_{22}N_3O_4P$: C 54.70, H 6.27, N 11.97; found: C 54.62, H 6.33, N 11.91.

*2-Amino-4-(dimethoxyphosphinyl)-8-methoxy-4*H*-1-benzopyran-3-carboxylic Acid Ethyl Ester* (**4l**): ^{1}H-NMR (200 MHz, $CDCl_3$): 7.08 (*t*, *J* = 8.0, 1 H); 6.95 (*dd*, *J* = 8.0, 1.5, 1 H); 6.83 (*dd*, *J* = 8.0, 1.5, 1 H); 4.41 (*d*, *J* = 18.0, 1 H); 4.22 (*q*, *J* = 7.0, 2 H); 3.90 (*s*, 3 H); 3.71 (*d*, *J* = 10.0, 3 H); 3.53 (*d*, *J* = 10.0, 3 H); 1.31 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 168.7; 162.0; 154.3; 147.9; 124.6; 121.9; 121.1; 111.0; 77.3; 60.0; 56.1; 53.3 (*d*, *J* = 6.5); 35.0 (*d*, *J* = 144.0); 14.8. ESI-MS: 358 ($[M+H]^+$). Anal. calc. for $C_{15}H_{20}NO_7P$: C 50.42, H 5.60, N 3.92; found: C 50.38, H 5.67, N 3.99.

*2-Amino-6-chloro-4-(dimethoxyphosphinyl)-4*H*-1-benzopyran-3-carboxylic Acid Ethyl Ester* (**4m**): ^{1}H-NMR (200 MHz, $CDCl_3$): 7.16–7.08 (*m*, 2 H); 6.94 (*d*, *J* = 8.0, 1 H); 4.79 (*d*, *J* = 18.0, 1 H); 4.10 (*q*, *J* = 7.0, 2 H); 3.68 (*d*, *J* = 10.0, 3 H); 3.62 (*d*, *J* = 10.0, 3 H); 1.09 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 168.2; 162.1; 153.6; 129.8; 129.0; 128.2; 125.6; 119.1; 77.0; 62.1; 54.2 (*d*, *J* = 6.5); 34.8 (*d*, *J* = 145.0); 14.6. ESI-MS: 362, 364. Anal. calc. for $C_{14}H_{17}ClNO_6P$: C 46.47, H 4.70, N 3.87; found: C 46.58, H 4.63, N 3.82.

REFERENCES

[1] F. R. Atherton, C. H. Hassal, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29; M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.* **1989**, *32*, 1652; P. Kafarski, B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193; B. Stowasser, K.-H. Budt, J.-Q. Li, A. Peyman, D. Ruppert, *Tetrahedron Lett*. **1992**, *33*, 6625.

[2] a) P. Jayashree, G. Shanthi, P. T. Perumal, *Synlett* **2009**, 917; b) S. N. Murthy, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, *Tetrahedron Lett*. **2010**, *51*, 3649.

[3] L. B. Gaied, H. Zantour, *Phosphorus, Sulfur Silicon Relat. Elem*. **2000**, *165*, 17.

[4] B. Das, P. Balasubramanyam, M. Krishnaiah, B. Veerajaneyulu, G. C. Reddy, *J. Org. Chem.* **2009**, *74*, 4393; B. Das, P. Balasubramanyam, B. Veerajaneyulu, G. C. Reddy, *J. Org. Chem.* **2009**, *74*, 9505; B. Das, P. Balasubramanyam, M. Krishnaiah, B. Veerajaneyulu, G. C. Reddy, *Synthesis* **2009**, 3467.

[5] T. J. Dickerson, N. N. Reed, K. D. Janda, *Chem. Rev.* **2002**, *102*, 3325; S. Chandrasekhar, C. Narasihmulu, S. S. Sultana, N. R. Reddy, *Chem. Commun*. **2003**, 1716.

Received December 20, 2010