

An efficient one-pot synthesis and insecticidal activity of 2-amino-4-[aryl or alkyl]-4H-chromene-3-carbonitrile derivatives

Ali Akbari^{a*} and Asghar Hosseini-Nia^b

^aDepartment of Chemistry, Faculty of Science, University of Jiroft, P. O. Box 8767161167, Jiroft, Iran.

^bDepartment of Plant Protection National Research Station of Ornamental Plants, P. O. Box 37815-137, Mahallat, Iran.

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Abstract: Silica supported boron trifluoride (BF₃.SiO₂) is an efficient, readily available and reusable catalyst for synthesis of 2-Amino-4-[aryl or alkyl]-4H-chromene-3-carbonitrile by condensation of malononitrile, cyclic 1,3-dicarbonyl compounds and aldehydes. Insecticidal activity of these compounds against *Spodoptera litura* was observed to be comparable to commercial pyrethroid insecticide, cypermethrin. This reaction under heating offers several advantages including mild reaction condition, high product purity, ease of operation and easy work-up.

Keywords: Insecticidal activity, Aldehyde, 2-Amino-4-[aryl or alkyl]-4H-chromene-3-carbonitrile, 1,3-Dicarbonyl compound, Silica supported boron trifluoride.

Introduction

Chromene (Benzopyran) is one of the privileged scaffolds which appears as an important structural component in various natural products and also possess useful photochemical properties [1]. 4H-chromene and their derivatives with biological properties such as cytotoxic activity [2], antimicrobial activity [3], antioxidant [4], cytotoxic activity against breast cancer [5], selective inhibitors at excitatory amino acid transporters [6], anti-mycobacterial [7], anticancer [8] are currently of great interest.

Silica supported boron trifluoride, unusually shows high Brønsted acidity and which can be controlled by activation temperature. Moreover, it exhibits considerable catalytic activity that enables better accessibility of the reactants to the active sites. The silica supported boron trifluoride is used in several organic transformations, such as synthesis of tetrahydrobenzo[a]xanthenes-11-one [9], 2-amino-4H-pyran-3,4,5-tricarboxylate salt [10], α -amino phosphonates [11], 1,4-dihydropyridines [12], 4(3H)-

quinazolinones [13], 14-aryl or alkyl-14H-dibenzo[a,j]xanthenes [14], 1,2,4,5-tetrasubstituted imidazoles [15], stereoselective Claisen-Schmidt condensation [16], polymerization of styrene [17]. The reported protocol for the syntheses of 2-amino-4-[alkyl or aryl]-4H-chromene-3-carbonitrile is the mixture of aldehydes with malononitrile and dimedone in the presence of a catalyst. This procedure is catalyzed with coordination of IRMOF-3 (Zn₄O(H₂N-TA)₃) [18], rare earth perfluorooctanoate [19], tetrabutylammonium bromide [20], and magnetic nanoparticles Fe₃O₄ [21].

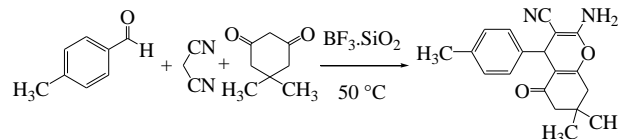
Spodoptera litura is a serious pest causing enormous losses to many economically important cultivated crops such as cotton, soybean, groundnut, tobacco and vegetables [22]. Sometimes it has been found to cause 26–100% yield loss in the field [23]. Its control has depended mostly on application of various insecticides. As a result, many field populations of this pest have developed multiple resistances and field control failure has been observed very frequently [24-28].

Results and discussion

*Corresponding author. Tel: (+98) 348 3260061, Fax: (+98) 348 3260065, E-mail: a.akbari@ujiroft.ac.ir

In our continuing search for insecticidal activity of substances and in connection with our efforts towards the study of synthesis of 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile, we initiated an investigation on the insecticidal activity of these compound adducts against insecticidal. First, we described an efficient synthetic protocol for the preparation of these compounds that were shown to be active against *Spodoptera litura*. In continuation of our efforts on the applications of solid acids in organic synthesis, we investigated the synthesis of 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile in the presence of $\text{BF}_3 \cdot \text{SiO}_2$ under ambient temperature. Herein, we report that $\text{BF}_3 \cdot \text{SiO}_2$ is an efficient and reusable catalyst for the synthesis of 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile derivatives. The reaction of 4-methylbenzaldehyde (1 mmol) with malononitrile (1

mmol), and dimedone (1 mmol) was investigated for optimization of the reaction conditions (Scheme 1).



Scheme 1: Synthesis of 2-amino-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitrile.

Reaction at different temperatures and various molar ratios of substrates in the presence of $\text{BF}_3 \cdot \text{SiO}_2$ revealed that the best conditions were solvent-free at 50 °C and a ratio of aldehyde (mmol) : malononitrile (mmol), and dimedone (mmol) : 37% $\text{BF}_3 \cdot \text{SiO}_2$ (g) of 1 : 1 : 1 : 0.5 (Scheme 1 and Table 1).

Table 1: Synthesis of 2-Amino-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitrile via Scheme 1.

Entry	$\text{BF}_3 \cdot \text{SiO}_2$ (g)	Solvent	Conditions	Time (hour)	Yield ^a %
1	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Chloroform	r.t.	3	scarce
2	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Chloroform	Reflux	3	72
3	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Ethanol	r.t.	3	scarce
4	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Ethanol	Reflux	3	75
5	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Water	r.t.	3	scarce
6	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Water	Reflux	3	78
7	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Solvent-free	r.t.	3	scarce
8	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Solvent-free	r.t.	12	77
9	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Solvent-free	35°C	3	57
10	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Solvent-free	50°C	2	72
11	$\text{BF}_3 \cdot \text{SiO}_2$ (0.7)	Solvent-free	50°C	4	95
12	$\text{BF}_3 \cdot \text{SiO}_2$ (0.3)	Solvent-free	50°C	3	94
13	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5)	Solvent-free	50°C	3	95
14	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5) 2 nd run	Solvent-free	50°C	3	93
15	$\text{BF}_3 \cdot \text{SiO}_2$ (0.5) 3 rd run	Solvent-free	50°C	3	93

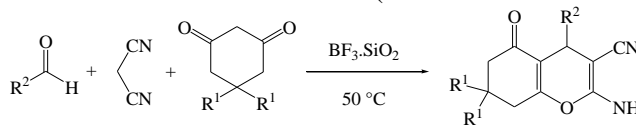
^a Isolated yield

The reusability of the $\text{BF}_3 \cdot \text{SiO}_2$ catalyst was also examined. After each run, the reaction mixture was cooled to room temperature, then CHCl_3 (5 mL) was added to the mixture and stirred for 5 min. The solid was filtered and the catalyst residue was washed with CHCl_3 and reused (Table 1, entries 14 and 15). The catalyst was reusable, although a gradual decline in activity was observed.

The applicability of the present method to a large scale process was examined with 25 mmol of malononitrile, 25 mmol dimedone and 25 mmol of 4-methylbenzaldehyde under thermal conditions which gave 2-amino-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-5,6,7,8-tetrahydro-4*H*-1-benzopyran-3-carbonitrile in 92% yield.

The current method is simple, efficient and less time-consuming for the synthesis of 2-amino-4-[alkyl or

aryl]-4*H*-chromene-3-carbonitrile derivatives. Cyclic 1,3-dicarbonyl compound (1 mmol), malononitrile (1 mmol), and various aldehydes (1 mmol) were used as substrates for the synthesis of 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile derivatives in the presence of (0.5 g) of freshly prepared 37% $\text{BF}_3 \cdot \text{SiO}_2$ under neat conditions at 50 °C (Scheme 2 and Table 2).



Scheme 2: Synthesis of 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile derivatives.

All of the 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile derivatives were also evaluated for insecticidal activity as well as insect growth regulatory

activity against lepidopteran insect pest namely, *Spodoptera litura* (third instar larvae) at 0.1% dose by both contact and feeding method [29]. The results obtained as insecticidal activities against *Spodoptera litura* at 0.1% through both contact and feeding

technique are presented in Figure 1. This Figure was shown to be insecticidal activities of all compounds. Columns represent the percent of inhibition of all compounds against *Spodoptera litura* at 0.1% through both contact and feeding technique.

Table 2: Synthesis of 2-Amino-4-[alkyl or aryl]-4H-chromene-3-carbonitrile derivatives via Scheme 2.^a

Entry	R ¹	R ²	Yield (%)	mp ^o C Found	mp ^o C Reported
1	4-OH-C ₆ H ₄	Me	86	174–175	174-175 ²⁰
2	3-OH-C ₆ H ₄	Me	88	170–171	168-170 ²⁰
3	C ₆ H ₅	Me	88	227–228	231-232 ¹⁸
4	4-Br-C ₆ H ₄	Me	96	205–206	205-207 ²⁰
5	4-MeO-C ₆ H ₄	Me	87	209–210	210-212 ²¹
6	3-Cl-C ₆ H ₄	Me	93	229–231	229-231 ²⁰
7	4-Me-C ₆ H ₄	Me	92	213–214	213-215 ¹⁸
8	4-Cl-C ₆ H ₄	Me	97	217–219	216-219 ¹⁸
9	2-Cl-C ₆ H ₄	Me	93	292–293	191-192 ²¹
10	4-O ₂ N-C ₆ H ₄	Me	92	178–179	176-178 ¹⁸
11	3-O ₂ N-C ₆ H ₄	Me	90	209–210	209-211 ¹⁸
12	2,4-Cl-C ₆ H ₄	Me	83	182–183	182-183 ²⁰
13	2,3-Cl-C ₆ H ₄	Me	85	250–251	249-252 ²⁰
14	C ₆ H ₅	H	91	240–241	173-174 ²¹
15	4-Cl-C ₆ H ₄	H	92	226–227	224-226 ²¹
16	4-MeO-C ₆ H ₄	H	89	191–192	190-192 ²¹
17	4-Me-C ₆ H ₄	H	92	231–232	232-233 ²¹
18	4-O ₂ N-C ₆ H ₄	H	92	235–236	234-236 ²¹

malononitrile (1 mmol), dimedone (1 mmol), aldehydes (1 mmol), and 37% BF₃.SiO₂ (0.5 mmol), solvent-free, 50 °C, 3 hour

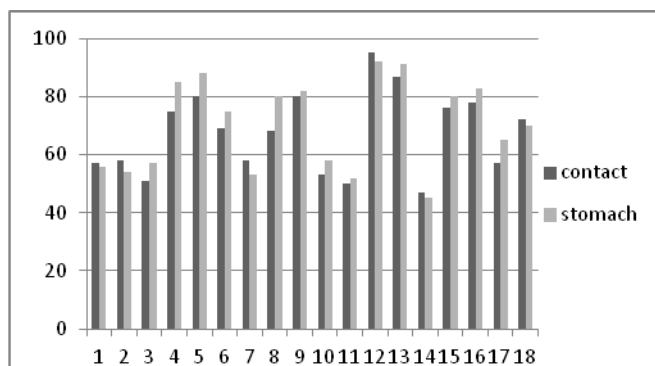


Figure 1: Insecticidal activities of all compounds.

In this work, the increase of the contact and stomach insecticidal activities of compound with methoxy group and halide groups in the molecule is observed, as compounds 4, 5, 6, 8, 9, 12, 13, 15 and 13.

Conclusion

In conclusion, BF₃.SiO₂ is an easily available, non-corrosive, eco-friendly and reusable solid acid. In this article, we have reported a mild, fast and efficient method for the preparation of 2-amino-4-[alkyl or aryl]-4H-chromene-3-carbonitrile derivatives from cyclic 1,3-dicarbonyl, malononitrile, various aldehyde, using catalytic amount of BF₃.SiO₂. These reactions were carried out in good yields and short reaction

times. In contrast to other acids, this reagent does not need special precautions for handling or storage.

These promising results suggest that the evaluation of insecticidal activity should be extended to other structural types of tetrasubstituted pyrroles derivatives.

Experimental

General Procedures: Products were characterized by IR, ¹H-NMR and by comparison of their physical properties with those reported in the literature. IR spectra were run on a Bruker, Eqinox 55 spectrometer. ¹H-NMR spectra were obtained using a Bruker Avans 400 MHz spectrometer (DRX). Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus.

Preparation of BF₃.SiO₂:

3.7 g of BF₃ (7.0 ml of BF₃.Et₂O) was added dropwise to a mixture of 6.3 g of silicagel and 10 ml of chloroform. The mixture was stirred for 1 h at room temperature. The resulted suspension was filtered. The obtained solid was washed with chloroform and dried in a domestic microwave oven for 20 min in power 100 [9].

General procedure for the synthesis of 2-amino-4-[alkyl or aryl]-4H-chromene-3-carbonitrile:

A mixture of Cyclic 1,3-dicarbonyl (1 mmol), various aldehyde (1 mmol), malononitrile (1 mmol), and $\text{BF}_3 \cdot \text{SiO}_2$ (0.5 g) was heated at 50 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated and the crude product was recrystallized from iso-propanol to afford the pure 2-amino-4-[alkyl or aryl]-4*H*-chromene-3-carbonitrile derivatives in 83-97 %.

In vitro insecticidal activity:

The biological assay was conducted against third-instar larvae of *S. litura* (7 ± 1 day old) using the feeding method and topical treatment [29].

Feeding method: The castor leaf was dipped in a 0.1% solution of synthesized compounds for 2 s and then air-dried. Moist filter paper was placed in glass Petri plates (9 cm diameter) on which treated leaf disks were kept. Larvae of *S. litura* preserved for 4 h were released individually into each Petri plates. Thirty replications were kept for each treatment. Solvent was used as control. Mortality was observed after 24 h.

Topical treatment:

The 0.1% stock solution of various compounds was prepared in dichloromethane. 2 mL of each compound was applied on the ventral side of the *S. litura* larvae. Ten treated larvae were released in glass bottles, and fresh tender castor leaves were given as food. Each treatment was kept in triplicate, and solvent was used as control. Mortality was observed after 24 h.

Acknowledgments

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References

- [1] Thomas, N.; Zachariah, S. M. *Asian J. Pharm. Clin. Res.* **2013**, *6*, 11.
- [2] Zonouzi, A.; Mirzazadeh, R.; Safavi, M.; Ardestani, S. K.; Emami, S.; Foroumadi, A. *Iran. J. Pharm. Res.* **2013**, *12*, 679.
- [3] Sangani, C. B.; Shah, N. M.; Patel, M. P.; Patel, R. G. *Med. Chem. Res.* **2013**, *22*, 3831.
- [4] Abdelgawad, M. A.; Elshemy, H. A. H.; Abdellatif, K. R. A.; Omar, H. A. *J. Chem. Pharm. Res.* **2013**, *5*, 387.
- [5] Kandeel, M. M.; Kamal, A. M.; Abdelall, E. K. A.; Elshemy, H. A. H. *Der Pharma. Chemica.* **2012**, *4*, 1653.
- [6] Huynh, T. H. V.; Abrahamsen, B.; Madsen, K. K.; Gonzalez-Franquesa, A.; Jensen, A. A.; Bunch, L. *Bioorg. Med. Chem.* **2012**, *20*, 6831.
- [7] Kamdar, N. R.; Haveliwala, D. D.; Mistry, P. T.; Patel, S. K. *Anti-Infective Agents* **2012**, *11*, 41.
- [8] Patil, S. A.; Wang, J.; Li, X. S.; Chen, J.; Jones, T. S.; Hosni-Ahmed, A.; Patil, R.; Seibel, W. L.; Li, W.; Miller, D. D. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4458.
- [9] Akbari, A.; Hosseini-Nia, A. *J. Saudi Chem. Soc.* **2013**. In press.
- [10] Akbari, A.; Azami-Sardooui, Z.; Hosseini-Nia, A. *J. Korean Chem. Soc.* **2013**, *57*, 455.
- [11] Rajasekhar, D.; Rao, D. S.; Srinivasulu, D.; Raju, C. N.; Balaji, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2013**, *188*, 1017.
- [12] Sadeghi, B.; Namakkoubi, A.; Hassanabadi, A. *J. Chem. Res.* **2013**, *37*, 11.
- [13] Wu, L.; Ma, W.; Yang, L.; Yan, F. *Asian J. Chem.* **2010**, *22*, 6053.
- [14] Mirjalili, B. B. F.; Bamoniri, A.; Akbari, A. *Tetrahedron Lett.* **2008**, *49*, 6454.
- [15] Sadeghi, B.; Mirjalili, B. B. F.; Hashemi, M. M. *Tetrahedron Lett.* **2008**, *49*, 2575.
- [16] Sadeghi, B.; Mirjalili, B. F.; Hashemi, M. M. *J. Iranian Chem. Soc.* **2008**, *5*, 694.
- [17] Boodhoo, K. V. K.; Dunk, W. A. E.; Vicevic, M.; Jachuck, R. J.; Sage, V.; Macquarrie, D. J.; Clark, J. H. *Journal of Applied Polymer Science* **2006**, *101*, 8.
- [18] Rostamnia, S.; Morsali, A. *Inorganica Chimica Acta* **2014**, *411*, 113.
- [19] Wang, L. M.; Shao, J. H.; Tian, H.; Wang, Y. H.; Liu, B. *Journal of Fluorine Chemistry* **2006**, *127*, 97.
- [20] Mobinikhaledi A.; Bodaghi Fard M. A. *Acta Chim. Slov.* **2010**, *57*, 931.
- [21] Rostami, A.; Atashkar, B.; Gholami, H. *Catal. Commun.* **2013**, *37*, 69.
- [22] Demchuk, O. M.; Kielar, K.; Pietrusiewicz, K. M. *Pure Appl. Chem.* **2011**, *83*, 633.
- [23] Canter, N. *Tribol. Lubr. Technol.* **2011**, *67*, 14.
- [24] Yamanoi, T.; Inoue, R.; Oda, Y.; Hamasaki, K. *MolBank* **2010**, *2010*, 1.
- [25] Aliyan, H.; Fazaeli, R.; Massah, A. R.; Momeni, A. R.; Naghash, H. J.; Moeinifard, B. *Asian J. Chem.* **2010**, *22*, 873.
- [26] Buzin, P.; Lahcini, M.; Schellenberg, J.; Schwarz, G.; Kricheldorf, H. R. *Macromolecules* **2010**, *43*, 6511.
- [27] Socha, A. M.; Sello, J. K. *Org. Biomol. Chem.* **2010**, *8*, 4753.
- [28] Pastore, A.; Adinolfi, M.; Iadonisi, A.; Valerio, S. *Carbohydr. Res.* **2010**, *345*, 1316.
- [29] Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *Eur. J. Org. Chem.* **2010**, 3945.