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Tetrahedron Letters 49 (2008) 1578–1581
Tetrahedron Letters

Synthesis of 2-substituted 2*H*-chromenes using potassium vinyltrifluoroborates

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Received 6 December 2007; revised 28 December 2007; accepted 3 January 2008
Available online 8 January 2008

Abstract

2*H*-Chromenes were synthesized from salicylaldehyde using potassium vinylic borates in the presence of secondary amines. We synthesized these 2*H*-chromene derivatives as a part of an ongoing project to develop inhibitors for TGF-β receptors. Potassium vinyl trifluoroborates react with salicylaldehydes at 80 °C in the presence of a secondary amine and produced 2-substituted 2*H*-chromene derivatives with a 70–90% yield.

Keywords: Chromenes; Potassium organic trifluoroborate; TGF-β inhibitors; Signal transduction

We have a long-term goal to develop novel chemical screens capable of analyzing important biological systems by interfacing libraries of small molecules, in the context of developing zebrafish embryos. Toward this end, we were interested in developing potential new inhibitors of TGF-β signaling using 2-substituted 2*H*-chromene derivatives.

2*H*-Chromenes are an important class of oxygenated heterocyclic compounds.[1] Many biologically active natural products contain a chromene ring system.[2] In recent years, there has been increased interest in the synthesis of 2*H*-chromenes due to the number of compounds that possess this group, and that show a variety of activities including as antidepresssant, antihypertensive, anti-tubulin, antiviral, antioxidative, activator of potassium channels and inhibition of phosphodiesterase IV or dihydrofolate reductase.[3] Based on the importance of these compounds, a number of research groups have developed methodologies to synthesize these compounds. The approaches used include intramolecular cyclization of Wittig intermediates,[4] microwave-assisted reaction of salicylaldehyde with enamines,[5] catalytic Petasis reaction of salicylaldehydes,[6] ring-closing olefin metathesis,[7] Baylis–Hillman reaction of 2-hydroxybenzaldehydes with methyl vinyl ketones,[8] Claisen rearrangement of propargyl phenol ethers,[9] Pd-catalyzed ring closure of 2-isoprenyl phenols,[10] electrocyclic ring closure of vinylquinone derivatives,[11] and the Ylide annulation reaction.[12] Despite the availability of these existing methods for the synthesis of chromene derivatives, there remains a demand for general strategies that can more efficiently provide variously substituted chromene systems.

In the context of our goal to generate small molecule probes to study the biology of key signal transduction pathways, including transforming growth factor beta (TGF-β) pathways, we were interested in developing improved methods for the synthesis of a 2*H*-chromene library.

In this Letter, we report a practical and highly efficient procedure for preparing diverse chromene derivatives using potassium vinyltrifluoroborate as a substrate for the Petasis reaction in the presence of catalytic amounts of dibenzylamine as a secondary base at 80 °C in dimethyl

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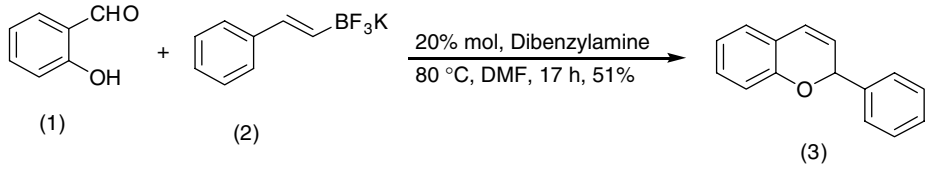
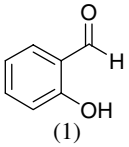
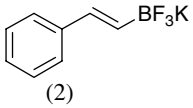
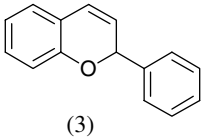
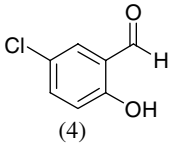
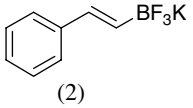
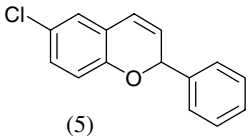
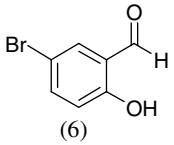
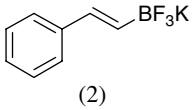
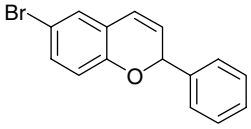
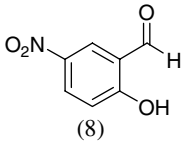
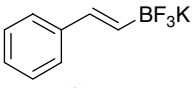
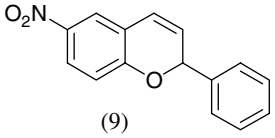
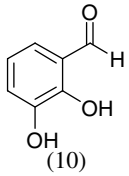
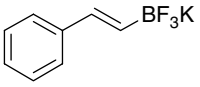
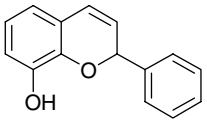
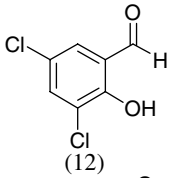
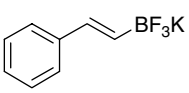
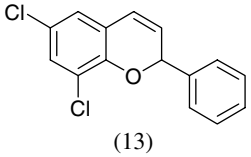
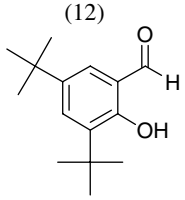
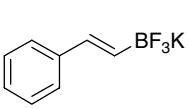
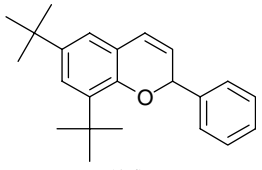
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.008



Scheme 1.

formide. This procedure is complementary to that of Finn and Kabalka, which in both cases uses boronic acid. The utility of organoboronic acids in organic synthesis has flourished in recent years, particularly through developments in Miyaura–Suzuki coupling,[13] allyl-boration,[14,15] copper catalyzed arylboronic acid–hetero atom coupling[16] and Petasis reaction.[17,18] However, these organoboron derivatives have many limitations:[19] (i) quantitative analysis and stoichiometric reactions using boronic acids are often difficult because of the rapid equilibrium between the boronic acids and the corresponding cyclic, trimeric anhydrides (boroxines), (ii) the diols utilized to generate

Table 1
Synthesis of 2-substituted 2*H*-chromenes from salicylaldehydes in the presence of 20% mol dibenzylamine in DMF at 80 °C

Entry	Aldehydes	Potassium vinylboronic	Product[a]	Yield[b] (%)
1	 (1)	 (2)	 (3)	51
2	 (4)	 (2)	 (5)	89
3	 (6)	 (2)	 (7)	71
4	 (8)	 (2)	 (9)	90
5	 (10)	 (2)	 (11)	54
6	 (12)	 (2)	 (13)	83
7	 (14)	 (2)	 (15)	78

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