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One-pot synthesis of chromenes by Suzuki-Miyaura cross-coupling reactions with benzyl bromides

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An efficient one-pot synthesis of chromenes has been developed from 2-bromocarbaldehydes through tandem benzyl bromide formation followed by Pd(0)-catalyzed Suzuki-Miyaura cross-coupling and substitution reaction.

Keywords: Chromene, tandem reaction, Suzuki-Miyaura cross-coupling, substitution reaction, benzyl bromide.

Introduction

Chromenes are found to be present extensively as core structure in various natural and unnatural organic molecules having diverse biological activities such as affinity to CB_2 receptors, psychoactivity and inspiring antitumor activity (Fig. 1)[1]. The scaffolds are useful as building blocks for the synthesis of variety of biologically active heterocyclic compounds. So, the development of various routes for the synthesis of chromene skeletons has drawn the attention of researchers

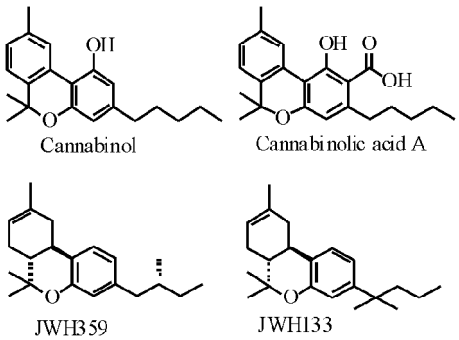


Fig. 1. Few promising biologically active chromene natural products.

over last decades. In literature, palladium-catalyzed various reports are there for the synthesis of chromene derivatives. Among them, Zhou *et al*. reported palladium-catalyzed ring closure of diazonium tetrafluoroborates to produces 6*H*-benzo[*c*]chromenes[2].

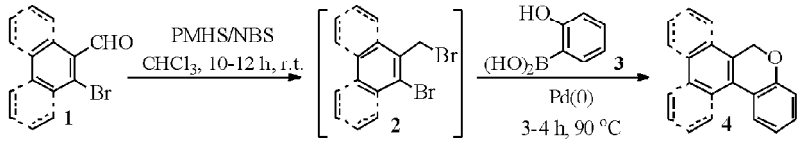
Shen and co-workers developed a synthetic method of chromenes via palladium-catalyzed intramolecular decarboxylative coupling of acids[3]. Recently, we have reported few approaches for the preparation of these scaffolds starting from 2-bromoarylcarbaldehydes[4].

In continuation of our work on palladium-catalyzed development of novel synthetic methodologies, we have observed that aromatic aldehydes can easily undergo cyclization to produce chromene derivatives through a one-pot tandem reaction involving the preparation of benzyl bromides already developed by Das and co-workers[5].

Results and discussion

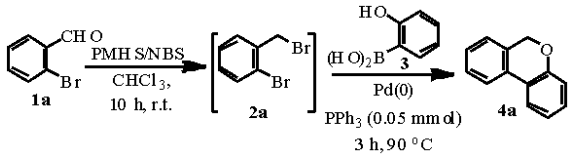
At first, 2-bromocarboxaldehydes (**1**) were converted to the corresponding benzyl bromides (**2**) with polymethylhydrosiloxane (PMHS) in combination with NBS at room temperature for 10–12 h in $CHCl_3$[5]. After completion, the $CHCl_3$ was evaporated under vacuum and the resulting bromides **2** were allowed to undergo Pd(0)-catalyzed tandem reaction with 2-hydroxyphenylboronic acid **3** at 90°C to give chromenes **4** (Scheme 1).

To get the optimal condition, 2-bromobenzaldehyde **1a** was chosen as the standard substance. Initially, it was converted to benzyl bromide **2a** employing standard conditions given by Das *et al*.[5]. Then, after the evaporation of $CHCl_3$ under vacuum, a thorough screening was performed with different combinations of Pd-catalysts, solvents and bases (Table 1).



Scheme 1. Synthesis of chromenes.

Table 1. Optimization of the condition[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	NaOAc	CH_3CN	70
2	$Pd(OAc)_2$	Na_2CO_3	CH_3CN	82
3	$Pd(OAc)_2$	K_2CO_3	CH_3CN	92
4	$Pd(OAc)_2$	K_2CO_3	DMF	80
5	$Pd(OAc)_2$	K_2CO_3	DMSO	78
6	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	84
7	$PdCl_2(PPh_3)_2$	K_2CO_3	CH_3CN	80
8	$PdCl_2$	K_2CO_3	CH_3CN	85

[a]All the reactions were carried out with **1a** (1 mmol), PMHS (1.5 mmol), NBS (1 mmol), **3** (1.1 mmol), Pd-catalyst (5 mol%), base (2.5 mmol) and solvent (5 mL) at 90°C for 3 h. [b]Isolated yields.

We got an optimal condition when substrate **2a** obtained from **1a** (1 mmol) and **3** (1.1 mmol) were heated at 90°C in the presence of $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 mmol), and PPh_3 (0.05 mmol) in dry CH_3CN (Table 1, entry 3).

To examine the scope of this approach, several 2-bromocarboxaldehydes **1a-g** were tested under the above optimized reaction conditions; the results of which are summarized in Table 2. 2-Bromocarboxaldehydes **1a-g** both electron-donating and electron-withdrawing groups underwent the conversion smoothly. However, aliphatic 2-bromoaldehydes were not tested as Das and co-workers[5] already reported that these aldehydes were failed to deliver benzyl bromides. The reaction was tolerant to alkyl, halogen, nitro and ether groups. Due to the lack of availability of $Me_2S^+BrBr^-$ in our laboratory, the combination of PMHS and NBS was chosen for the conversion.

Experimental

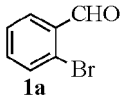
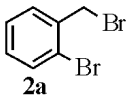
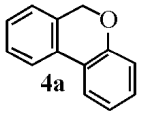
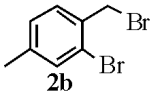
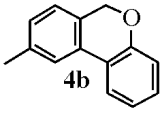
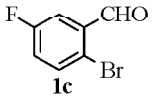
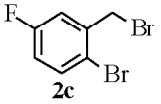
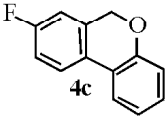
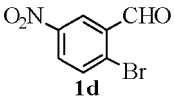
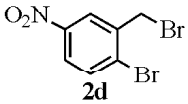
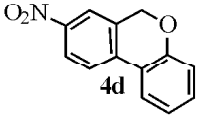
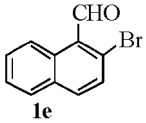
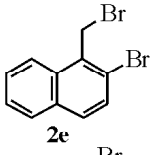
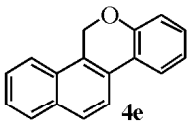
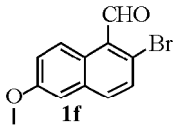
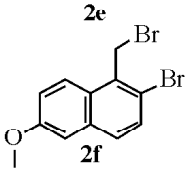
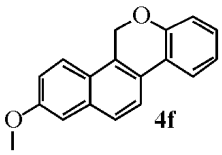
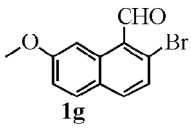
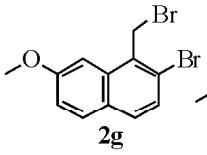
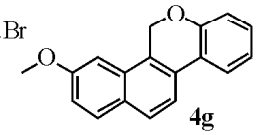
All yields were determined after column chromatography purification using silica gel (60–120 mesh) purchased from Rankem, India. Bruker-200 (200 MHz) or Bruker-400 (400 MHz) and Bruker-200 (50 MHz) were used to record ^1H NMR and ^{13}C NMR spectra respectively using $CDCl_3$. ^1H NMR data of compounds are reported by using the following abbreviations: chemical shifts, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, q = quartet), coupling constant (Hz) and for ^{13}C δ is in ppm. Open capillaries were used to determine melting points and are uncorrected.

General procedure for the synthesis of chromenes:

2-Bromocarboxaldehyde (1 mmol), PMHS (1.5 mmol) and NBS (1 mmol) were added to $CHCl_3$ (5 mL) and the mixture was stirred at room temperature for 10–12 h. The progress of the reaction was monitored by TLC. After completion, the $CHCl_3$ was evaporated under vacuum. Then, 2-hydroxyphenylboronic acid (1.1 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 mmol) and PPh_3 (0.05 mmol) were added in dry CH_3CN (5 mL) under Ar and the mixture was stirred at 90°C for 3–4 h. The progress of the reaction was followed by TLC. After completion, the mixture was cooled to room temperature and water (10 mL) was added. The mixture was extracted with EtOAc (3×10 mL) and the extract was dried and concentrated. The crude product was subjected to purify through column chromatography (silica gel, hexane-EtOAc) to afford the pure chromenes.

6H-Benzo[c]chromene (**4a**): Colorless oil, R_f = 0.4 (pet. ether:EtOAc = 100:1); ^1H NMR (200 MHz in $CDCl_3$) δ: 4.98

Table 2. One-pot synthesis of chromenes through benzyl bromide preparation and Suzuki-Miyaura cross-coupling with 2-hydroxyphenylboronic acid **3**[a]

Entry	Substrate	Time	Bromide	Product	Time	Yield[b]
1	 **1a**	10	 **2a**	 **4a**	3	92
2	 **1b**	10	 **2b**	 **4b**	3	90
3	 **1c**	12	 **2c**	 **4c**	3	90
4	 **1d**	12	 **2d**	 **4d**	3	82
5	 **1e**	11	 **2e**	 **4e**	4	80
6	 **1f**	11	 **2f**	 **4f**	4	82
7	 **1g**	11	 **2g**	 **4g**	4	80

[a]Reagents and conditions: **1a** (1 mmol), PMHS (1.5 mmol), NBS (1 mmol), 3 (1.1 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 mmol). [b]Isolated yields.

(s, 2H), 6.86–7.02 (m, 3H), 7.07–7.24 (m, 3H), 7.54–7.62 (m, 2H); ^{13}C NMR (50 MHz in $CDCl_3$) δ: 68.6, 117.6, 122.2, 122.3, 123.1, 123.5, 124.8, 127.8, 128.6, 129.6, 130.3, 131.6, 155.0.

Conclusions

We have developed a straight-forward and efficient method for the synthesis of various chromenes through a one-pot tandem benzyl bromide preparation/Suzuki-Miyaura cross-coupling followed by substitution reaction directly from easily available starting materials. Hopefully, this approach can equally be employed for the preparation of chromene-based natural products with potential pharmacological importances.

Acknowledgement

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