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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 2293–2295

A novel and direct synthesis of chroman derivatives using a hypervalent iodine(III) reagent

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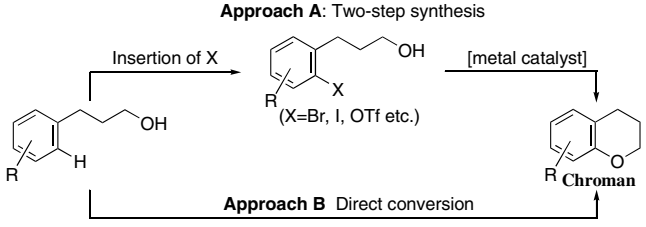
Received 10 January 2004; revised 23 January 2004; accepted 23 January 2004

Abstract—The direct aromatic carbon–oxygen bond-formation reaction was described and the novel and simple synthetic method for chroman derivatives involving aromatic cation radical intermediates was developed using the hypervalent iodine(III) reagent, phenyliodine(III) bis(trifluoroacetate) (PIFA).

The aromatic carbon–oxygen bond-forming reaction is an important strategy for the synthesis of oxygen heterocycles.[1–3] Much attention has been focused on the construction of chroman skeletons,[4] which are common structures in many pharmaceutically and agriculturally important compounds.[5,6] The construction of the aromatic carbon–oxygen bond can be achieved through two approaches: approach A and approach B. Approach A, a two-step synthesis involving a metal-mediated/catalyzed coupling reaction, is the general and predominant approach to date and several methods for this purpose were developed. Although some efficient syntheses have been reported using the palladium-catalyzed reaction,[2] these approaches still require the insertion steps of the functional group. In contrast to approach A, approach B, a direct aromatic carbon–oxygen bond-formation reaction using unfunctionalized aromatics, should be a potentially attractive means to assemble chroman skeletons, however, only a few facile approaches are known[7,8] (Scheme 1).



Scheme 1. Aromatic C–O bond-forming reaction.

Over the past several years, hypervalent iodine(III) reagents have received much attention due to their low toxicity, ready availability, easy handling, and reactivities similar to those of heavy metal reagents.[9] As a continuation of our research on the use of hypervalent iodine(III) reagents in organic synthesis, the direct nucleophilic substitution of electron-rich phenol ethers involving aromatic cation–radical intermediates was originally reported by us[10] and has been extensively applied for the novel synthesis of important aromatic substrates such as biaryls,[11,12] spirodienones,[12] quinone imines,[13] or sulfur-containing heterocycles.[14] In this communication, we focused on the oxygen as a nucleophile and achieved the novel synthesis of chroman derivatives using phenyliodine(III) bis(trifluoroacetate) (PIFA).

Earlier, the intramolecular aromatic carbon–oxygen bond-formation reaction via the aromatic cation radical intermediate was reported using the heavy metal reagent, thallium(III) trifluoroacetate, by McKillop (Table 1, entry 1).[7] However, the yields of the coupling step were low (21–30%). Alternatively, other heavy metal reagent-mediated coupling reaction also did not afford practical routes to chroman derivatives (entries 2 and 3). Moreover, heavy metal reagents are highly toxic and must be handled with great care. In order to develop

Keywords: Chromans; Cyclization; Hypervalent iodine reagents; Heterocycles; Oxidation.
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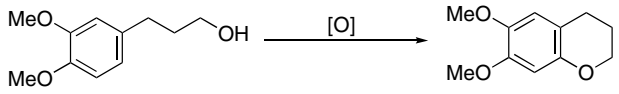
doi:10.1016/j.tetlet.2004.01.104

Table 1. Intramolecular oxidative cyclization of **1a**



1a **2a**

Entry	Conditions	Yield (%)[b]
1[a]	Tl_2O_3, $BF_3{\cdot}Et_2O$, CF_3CO_2H, $(CF_3CO)_2O$, CH_2Cl_2	21
2	RuO_2, $BF_3{\cdot}Et_2O$, CF_3CO_2H, $(CF_3CO)_2O$, CH_2Cl_2	Nr[c]
3	VOF_3, CF_3CO_2H, $(CF_3CO)_2O$, CH_2Cl_2	Nr[c]
4	PIFA, $BF_3{\cdot}Et_2O$, CH_2Cl_2	28
5	PIFA, $H_3[PW_{12}O_{40}]$, CH_3CN	20
6	PIFA, $(CF_3)_2CHOH$	40
7	PIFA, MK-10, $(CF_3)_2CHOH$	55

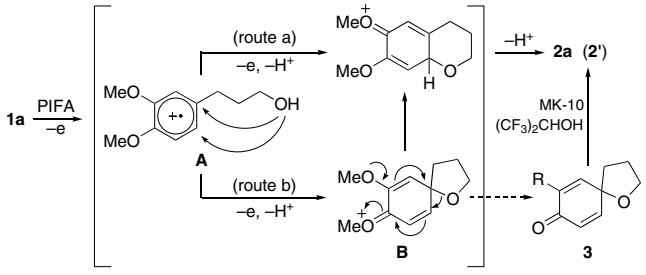
[a] Ref. 9.
[b] Isolated yield.
[c] Nr: not recorded.

a versatile route to the chroman derivatives via the aromatic cation radical pathway, the reactivity of the PIFA-mediated cyclization of 3-(3,4-dimethoxyphenyl)propanol (**1a**) was studied under various reaction conditions. When the reaction was carried out in the presence of acid additives, low yields were observed (entries 4–5). On the other hand, a notable extension of the reaction yield was exerted in poorly nucleophilic polar solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol ($(CF_3)_2CHOH$) (entry 6) and the further addition of solid acid additives such as MK-10 caused improvement in the yield (entry 7).

Similarly, reactions of other open precursors (**1**) with PIFA were investigated in $(CF_3)_2CHOH$ with added MK-10 and the results are shown in Table 2. The chroman derivatives (**2**) were produced in moderate yields (entries 1–8), while the approach for the cumaran derivative was unsuccessful and some dimer type products were obtained (entry 9). The reactivity of the methyl ether derivative was similar to that of the hydroxy ones (entry 2). However, other protecting derivatives (e.g., *O*-silyl, *O*-acetyl, *O*-alkyl) were given the chromans in low yield.

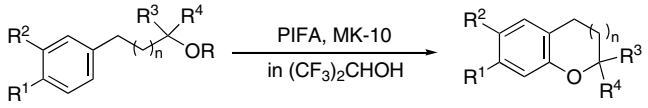
A plausible reaction mechanism leading to **2a** is envisaged as shown in Scheme 2. The radical cation **A** is initially formed by the reaction of the electron-rich aromatic ring with PIFA as mentioned in our previous study.[10] Two plausible routes are then assumed: direct coupling (route a) or coupling to intermediate **B** followed by rearrangement (route b). The spirodienone-type compounds (**3**) were also detected as a side product (29–32%) when the reaction was carried out using PIFA/$H_3[PW_{12}O_{40}]$.[15] Moreover, compound **3** was converted into the corresponding chroman derivatives (**2′**) under $(CF_3)_2CHOH$ including MK-10, while deterioration of the conversion was observed in the absence of MK-10. Although a direct coupling pathway (route a) cannot be rejected, the isolation of **3** and the formation of **2e–g** in Table 2 indicated the coupling reaction predominantly proceeds via route b.

A typical experimental procedure is as follows: To a stirred solution of the open-chain precursor (**1**) in $(CF_3)_2CHOH$ was added MK-10 (500 mg/mmol) and PIFA (1.05 equiv) at 0 °C. Stirring was continued for 0.5–4 h at 0 °C to rt. The solution was then filtered and



Scheme 2. Possible reaction forming mechanism for **2a**.

Table 2. PIFA-mediated synthesis of chroman derivatives



1 **2**

Entry	Substrate	R^1	R^2	R^3	R^4	R	*n*	Product	Yield (%)[a]
1	**1a**	OMe	OMe	H	H	H	1	**2a**	55
2	**1b**	OMe	OMe	H	H	Me	1	**2a**	57
3	**1c**	OMe	OMe	Me	H	H	1	**2c**	49
4	**1d**	OMe	OMe	Me	Me	H	1	**2d**	52
5	**1e**	OMe	H	H	H	H	1	**2e**	43
6	**1f**	OMe	H	Me	H	H	1	**2f**	45
7	**1g**	OMe	H	Me	Me	H	1	**2g**	46
8	**1h**	OCH_2O		H	H	H	1	**2h**	57
9	**1i**	OMe	OMe	H	H	H	0	**2i**	(Trace)

[a] Yield of isolated products.

concentrated in vacuo. Purification of the residue by column chromatography on silica gel gave the corresponding chroman derivatives (**2**).[7]

In conclusion, we have developed a novel and direct synthetic method for chroman derivatives via the cation radical pathway using hypervalent iodine reagent. The simplicity of the reaction protocol[15] employing unfunctionalized aromatics in mild reaction systems may find many advantages for its application to the synthesis of various types of chroman derivatives. Detailed studies along these lines are now in progress.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (S) (No 7690) from the Ministry of Education, Science, Sports, and Culture, Japan.

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15. Heteropoly acids contain water of hydration, which would assist in the formation of spirodienone-type compounds.[12]