Tetrahedron Letters 56 (2015) 437–440

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Hypervalent iodine(III)-mediated C(sp^3)—H bond arylation, alkylation, and amidation of isothiochroman

Wataru Muramatsu *, Kimihiro Nakano

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki, Nagasaki 852-8521, Japan

ARTICLE INFO

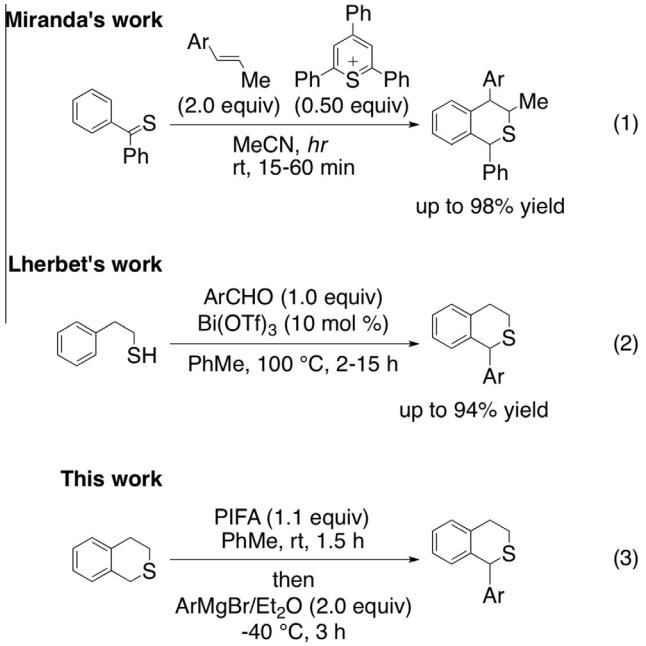
Article history:
Received 13 October 2014
Revised 25 November 2014
Accepted 28 November 2014
Available online 5 December 2014

Keywords:
Isothiochroman
C—H activation
Hypervalent iodine
Arylation
Alkylation
Amidation

ABSTRACT

We have developed a one-step method for introducing aryl, alkyl, and amide groups at the C(1)-position of isothiochromans via an oxidation reaction using hypervalent iodine(III), [bis(trifluoroacetoxy) iodo]benzene (PIFA), followed by an nucleophilic addition reaction using Grignard reagents and an amide.

Methods for the selective functionalization of heterocyclic compounds such as tetrahydroisoquinoline (THIQ) and isochroman have attracted significant attention owing to the various biological activities of heterocyclic compounds.[1] Specifically, a variety of methods used for the activation of inactive C—H bonds, including cross-dehydrogenative-coupling (CDC) reactions,[2] have been investigated during the last few decades. Recently, we reported the organic oxidant-mediated or catalyzed C(sp^3)—H bond arylation, alkylation, and amidation of THIQs and isochromans under mild conditions.[3] Although isothiochroman structurally resembles THIQ and isochroman is expected to serve as a viable candidate for drug development, the direct C(sp^3)—H bond functionalization of isothiochroman has never been reported. In general, functionalized isothiochromans are synthesized via two methods. One method is based on [2+2+2] or [4+2] cycloadditions.[4] For example, Miranda and co-workers reported in 2007 that the photo-induced reaction of thiobenzophenone with arylalkenes in the presence of thiopyrylium salt (50 mol %) afforded isothiochroman derivatives in 32–98% yields (Scheme 1-1).[4c] The thia-Pictet–Spengler reaction is also used to synthesize functionalized isothiochromans. Specifically, Lherbet and co-workers reported in 2008 that a catalytic amount of $Bi(OTf)_3$ accelerated the thia-Pictet–Spengler reaction between phenylethanethiol and arylaldehydes to give the products in 25–94% yields (Scheme 1-2).[5] As a novel route

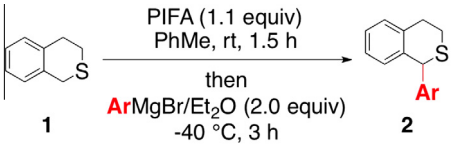


Scheme 1. Strategies for the synthesis of 1-arylisothiochromans.

* Corresponding author. Tel.: +81 95 819 2431.
E-mail address: muramatu@nagasaki-u.ac.jp (W. Muramatsu).

http://dx.doi.org/10.1016/j.tetlet.2014.11.134
0040-4039/

Table 1
PIFA-mediated C(sp^3)—H bond arylation of isothiochroman



"standard" conditions

Entry	Variation from the 'standard' conditions	Yield[a] of **2** (%)
1	None	80 (76)[b]
2	DDQ	42
3	Addition of DDQ (20 mol %)	71
4	No PIFA	0
5	PIDA[c]	68
6	PFPIFA[d]	66
7	C_3F_7(Ph)IOTf	3
8	Ts(Ph)IOH	11
9	PIFA (20 mol %), Oxone® (1.1 equiv)	5
10	PIFA (20 mol %), *m*CPBA (1.1 equiv)	0
11	PIFA (20 mol %), H_2O_2–urea (1.1 equiv)	5
12	PIFA (20 mol %), $K_2S_2O_8$ (1.1 equiv)	11
13	Chloranil	<1
14	*o*-Chloranil	41
15	PhMgCl/Et_2O[e]	33
16	PhMgI/Et_2O	74
17	PhMgBr/THF	61
18	PhZnBr/Et_2O	0
19	PhZnI/Et_2O	0
20	Ph_2Zn	93 (92)[b]
21	PhMgBr/Et_2O (4.0 equiv), $Zn(OMe)_2$ (2.0 equiv)	67
22	PhLi/Bu_2O	17
23	PhCl	77
24	DCE	43[f]
25	CPME	31
26	TBME	47[f]
27	THF	26
28	Et_2O	59
29	MeCN	25
30	DMF	4

[a] The yield was determined by ^{1}H NMR analysis using a calibrated 1,4-bis(trifluoromethyl)benzene as the internal standard.
[b] Isolated yield.
[c] PIDA = [bis(acetoxy)iodo]benzene.
[d] PFPIFA = [bis(trifluoroacetoxy)iodo]pentafluorobenzene.
[e] PhMgCl/Et_2O was provided from the solvent exchange of PhMgCl/THF.
[f] The nucleophilic addition reaction using PhMgBr/Et_2O was carried out at −30 °C.

toward functionalized isothiochromans, herein we report the first direct C(sp^3)—H bond arylation, alkylation, and amidation of isothiochroman under facile conditions (Scheme 1-3).

First, we investigated three previously reported oxidation systems[3] in the C(sp^3)—H bond arylation of isothiochroman **1**[6] in toluene; the results are shown in entries 1–3 of Table 1. When we attempted the oxidation of **1** using [bis(trifluoroacetoxy)iodo]benzene (PIFA, 1.1 equiv) followed by a nucleophilic addition using PhMgBr/Et_2O (2.0 equiv), the Ph-group was introduced in the C(1)-position of **1** to give **2** in the best yield without formation of sulfoxides or sulfones (entry 1, 76% isolated yield). Notably, PIFA is a useful hypervalent iodine(III) reagent, and is often used as an alternative to toxic metallic and organic oxidants.[7] The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) rather than PIFA gave **2** in a lower yield (entry 2, 42% yield). In addition, the yield of **2** slightly decreased when a combination of a catalytic amount of DDQ and PIFA as a co-oxidant was tested (entry 3, 71% yield). On the basis of these results, we evaluated the reaction conditions. In the absence of PIFA, essentially no reaction was observed (entry 4). When several hypervalent iodine(III) reagents were used instead of PIFA, the coupling product **2** was isolated in 3–68% yields (entries 5–8). Several catalytic systems with peroxides as co-oxidants were attempted in place of PIFA (1.1 equiv); unfortunately, the yield of **2** was not improved (entries 9–12).[8]

Using chloranil and *o*-chloranil instead of PIFA gave **2** in <1% and 41% yields, respectively (entries 13 and 14). Under the reaction conditions shown in entries 5–14, unsatisfactory results were obtained. This was because the oxidation of **1** was insufficient under these conditions, and unreacted **1** was recovered.

Next, several organometallic nucleophiles were tested in place of PhMgBr/Et_2O. The use of PhMgCl/Et_2O, PhMgI/Et_2O, and PhLi/Bu_2O led to a decreased yield of **2** (entries 15, 16, and 22, 33%, 74%, and 17% yields, respectively). Interestingly, the Et_2O solution of PhMgBr was more reactive than the THF solution of PhMgBr in the C(sp^3)—H bond arylation (entry 1 vs 17). When PhZnBr/Et_2O and PhZnI/Et_2O were used, contrary to our expectations, neither nucleophile coupled successfully with **1** (entries 18 and 19). On the other hand, the best yield of **2** was afforded with Ph_2Zn (entry 20, 92% isolated yield). However, most of diaryl- and dialkylzinc reagents are not commercially available, and the synthesis and isolation of such reagents in high purities are generally difficult. Moreover, when Ph_2Zn was generated in situ from PhMgBr/Et_2O and $Zn(OMe)_2$,[9] a lower yield was obtained (entry 21, 67% yield) than when the commercially available reagent was utilized (entry 20). Therefore, we chose ArMgBr/Et_2O as the nucleophilic reaction partner for the C(sp^3)—H bond functionalization. PhCl, rather than toluene, resulted in a suitable yield (entry 23, 77% yield). On the other hand, when the reaction was carried out in solvents other than PhCl, only modest yields of **2** were obtained (entries 24–30, 4–59% yields).

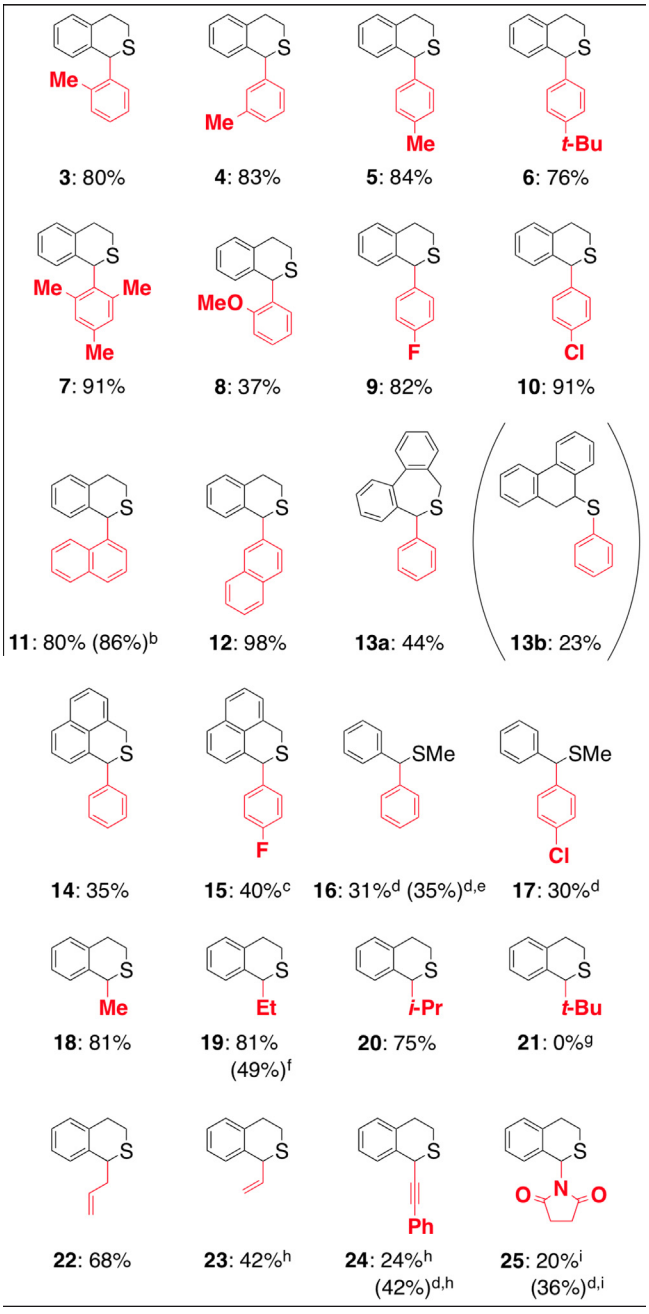
Using the optimized reaction conditions, the C(sp^3)—H bond arylation of isothiochroman with a range of aryl-Grignard reagents furnished the corresponding 1-arylisothiochromans in good yields (Table 2). A variety of aryl-Grignard reagents bearing electron-donating and withdrawing groups in the *ortho*-, *meta*-, and *para*-positions were compatible under the reaction conditions (products **3**–**7** and **9**–**10**, 76–91% yields). Bulky Grignard reagents such as 1-Naph- and 2-Naph-MgBr also coupled with **1** to give the corresponding 1-arylisothiochromans **11** and **12** in 86% and 98% yields, respectively. Unfortunately, 2-methoxyphenyl-MgBr/Et_2O exhibited low reactivity under the reaction conditions, and **8** was only isolated in 37% yield. Next, we applied the reaction conditions to the C(sp^3)—H bond arylation of isothiochroman derivatives.

The C(sp^3)—H bond arylation of a 7-membered isothiochroman derivative[10] with PhMgBr gave the coupling product **13a** and side product **13b** in 44% and 23% yields, respectively.[11] The C(sp^3)—H bond arylation furnished the corresponding coupled products **14**–**17**[12] in unsatisfactory yields (30–40% yields) despite the fact that a 6-membered isothiochroman derivative[13] and acyclic benzylsulfide were consumed completely under the optimized reaction conditions.

Finally, we demonstrated the coupling reaction of isothiochroman **1** with alkyl-Grignard reagent, amide, malonate, and amine under the optimized reaction conditions. When a variety of Grignard reagents including alkyl-, alkenyl-, and alkynyl-MgBr were used as the nucleophilic reaction partners, moderate to excellent yields of the corresponding coupled products **18**–**20** and **22**–**24** were obtained.[14] With *t*-BuMgCl, the *t*-Bu-group was not introduced at the C(1)-position of **1** at all. This was because *t*-BuMgCl might not have been able to approach the C(1)-position of **1** owing to steric hindrance. The coupling reaction between **1** and succinimide proceeded and coupling product **25** was isolated in 20% yield.[14] Unfortunately, the coupling reaction with amines such as aniline and dimethylamine did not proceed to afford the corresponding products. Further, the reaction with diethyl malonate gave not the desired coupling compound[15] but undesired byproducts.[16]

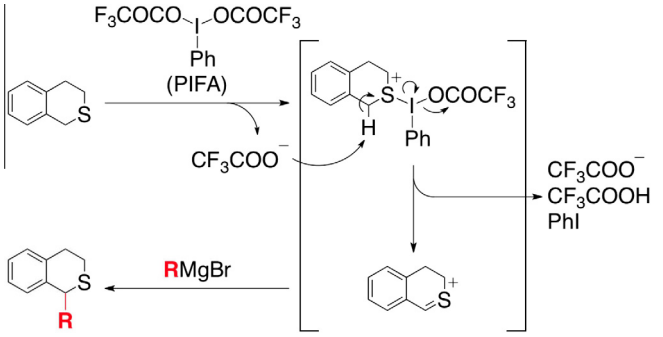
The proposed reaction mechanism is shown in Scheme 2. The nucleophilic substitution reaction of isothiochroman with PIFA,

Table 2
PIFA-mediated C(sp^3)—H bond arylation, alkylation, and amidation of isothiochroman and its derivatives[a]



[a] Standard reaction conditions: PIFA (1.1 equiv) in toluene at room temperature for 1.5 h, then RMgBr/Et_2O at −40 °C for 3 h.
[b] The nucleophilic addition with 1-Naph-MgBr/Et_2O was carried out at 0 °C.
[c] In toluene (0.20 M).
[d] The yields were determined by ^1H NMR analysis using a calibrated 1,4-bis (trifluoromethyl)benzene as the internal standard.
[e] The reaction was carried out in PhCl.
[f] Et_2Zn/toluene was used instead of the EtMgBr/Et_2O.
[g] *t*-BuMgCl/Et_2O was used.
[h] THF solution of Grignard reagents was used in place of Et_2O solution.
[i] The reaction using succinimide was carried out at room temperature.

followed by the deprotonation of the sulfonium cation intermediate with the trifluoroacetate ion (CF_3COO^-) gives the thionium cation intermediate. Then, the nucleophilic addition reaction of aryl- or alkyl-Grignard reagents to the intermediate gives the desired coupling products.



Scheme 2. Proposed mechanism for the C(sp^3)—H bond functionalizations of isothiochroman.

In conclusion, the PIFA-mediated C(sp^3)—H bond arylation of isothiochroman and its derivatives was achieved. The coupling reaction can proceed with a wide range of aryl-Grignard reagents under facile conditions. In addition, the reaction conditions can be applied in the C(sp^3)—H bond alkylation and amidation of isothiochroman. The reaction mechanism and a method for catalytic and stereoselective C(sp^3)—H bond functionalizations, including the arylation, alkylation, and amidation of isothiochroman and its derivatives, are currently under investigation.

Acknowledgments

This research was funded by Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.134.

References and notes

1. (a) Taylor, E. C.; Weissberger, A.; Eds. The Chemistry of Heterocyclic Compounds; John Wiley & Sons: New York, 1981, 1990, 1995, Vol. 38, Parts 1–3.; (b) Dalterio, S.; Bartke, A.; Burstein, S. *Science* **1977**, *196*, 1472; (c) Charifson, P. S. *Drugs Fut.* **1989**, *14*, 1179; (d) Hoffman, B.; Cho, S. J.; Zheng, W.; Wyrick, S.; Nichols, D. E.; Mailman, R. B.; Tropsha, A. *J. Med. Chem.* **1999**, *42*, 3217; (e) Ohtaka, A.; Ukai, M.; Hatanaka, T.; Kobayashi, S.; Ikeda, K.; Sato, S.; Miyata, K.; Sasamata, M. *Eur. J. Pharmacol.* **2004**, *492*, 243; (f) Cardozo, L.; Lisec, M.; Millard, R.; Trip, O. V.; Kuzmin, I.; Drogendijk, T. E.; Huang, M.; Ridder, A. M. *Urology* **1919**, *2004*, 172.
2. (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335; (b) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686; (c) Tsang, A. S.-K.; Jensen, P.; Hook, J. M.; Hashmi, A. S. K.; Todd, M. H. *Pure Appl. Chem.* **2011**, *83*, 655.
3. (a) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Lett.* **2013**, *15*, 3650; (b) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Biomol. Chem.* **2014**, *12*, 2189; (c) Muramatsu, W.; Nakano, K. *Org. Lett.* **2014**, *16*, 2042.
4. (a) Kamphuis, J.; Grootenhuis, P. D. J.; Bos, H. J. T. *Tetrahedron Lett.* **1983**, *24*, 1101; (b) Okuma, K.; Shiki, K.; Sonoda, S.; Koga, Y.; Shioji, K.; Kitamura, T.; Fujiwara, Y.; Yokomori, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 155; (c) Argüello, J. E.; Pérez-Ruiz, R.; Miranda, M. A. *Org. Lett.* **2007**, *9*, 3587; (d) Argüello, J. E.; Pérez-Ruiz, R.; Miranda, M. A. *Org. Lett.* **1884**, *2010*, 12.
5. Lherbet, C.; Soupaya, D.; Baudoin-Dehoux, C.; André, C.; Blonski, C.; Hoffmann, P. *Tetrahedron Lett.* **2008**, *49*, 5449.
6. Isothiochroman **1** was provided from phenylethyl mercaptan and paraformaldehyde in trifluoroacetic acid. See: Isobe, K.; Takeda, N.; Mohri, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1989**, *37*, 3390.
7. For examples, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299; (b) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052; (c) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185; (d) Duschek, A.; Kirsch, S. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1524; (e) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517; (f) Kita, Y.; Dohi, T.; Morimoto, K. J. *Synth. Org. Chem. Jpn.* **2011**, *69*, 1241; (g) González, D. F.; Benfatti, F.; Waser, J. *ChemCatChem* **2012**, *4*, 955; (h) Yusubov, M. S.; Zhdankin, V. V. *Curr. Org. Synth.* **2012**, *9*, 247.

8. (a) Hossain, M. D.; Kitamura, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 142; (b) Page, T. K.; Wirth, T. *Synthesis* **2006**, 3153; (c) Zagulyaeva, A. A.; Yusubov, M. S.; Zhdankin, V. V. *J. Org. Chem.* **2010**, *75*, 2119.
9. Choi, J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 9102.
10. The 7-membered isothiochroman derivative was provided from 2,2′-bis(bromomethyl)biphenyl and sodium sulfide. See: Foubelo, F.; Moreno, B.; Soler, T.; Yus, M. *Tetrahedron* **2005**, *61*, 9082.
11. The yields were calculated by ^{1}H NMR analysis after a mixture of **13a** and **13b** was isolated because we could not separate **13a** and **13b** completely by SiO_2 column chromatography. Fortunately, we could isolate a small amount of **13a** with high purity to analyze the conformation.
12. Isolation of **16** and **17** was difficult because plural side products were produced under the reaction conditions. Fortunately, we could isolate a small amount of **16** and **17** with high purity to analyze both conformations.
13. The 6-membered isothiochroman derivative was provided from 1,8-bis(hydroxymethyl)naphthalene in two steps. See: (a) Ref. 10.; (b) Sundaresan, A. K.; Ramamurthy, A. *J. Org. Chem.* **2007**, *9*, 3575.
14. The coupling products **24** and **25** slowly decomposed on SiO_2.
15. Pellicciari, R.; Curini, M.; Ceccherelli, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, *10*, 1155.
16. Lewis acid such as $InCl_3$ was not added in the coupling reaction with diethyl malonate. See Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *118*, 1983.