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Design and synthesis of condensed thienocoumarins by Suzuki–Miyaura reaction/lactonization tandem protocol

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ABSTRACT

A concise and efficient approach to a series of chromen-4-ones with fused thiophene ring has been developed using the Suzuki–Miyaura reaction of bromothiophene-2- and 3-carboxylates with 2-methoxyboronic acids and subsequent cyclization of prepared alkyl (2-methoxy)aryl thiophene-2- and 3-carboxylates under the action of BBr_3/KO*t*Bu. Starting bromothiophenes are easily obtained from corresponding commercially available aminothiophenes by diazotization/bromination reaction.

Heterocyclic systems containing an annulated coumarin moiety are of considerable current interest as scaffolds which have found major applications in medical chemistry. Coumarins (2*H*-1-benzopyran-2-ones) are subunits of many natural products and occur in a range of clinically used pharmaceuticals as well as in natural products that have been isolated from a variety of plant sources[1] and possess diverse bioactivities.[2] On the other hand, the coumarin framework is present in nonpeptidic HIV protease inhibitors,[3] topoisomerase II,[4] and tyrosine kinase[5] inhibitors which are promising drug candidates. At the same time, coumarin derivatives have found a wider application in material sciences, for example, due to their optical properties.[1] Annulated coumarins also show interesting biological activities. For example furocoumarins can be found in many natural products and exhibit antimicrobial and anticancer activities.[6]

The coumestans, 6*H*-benzofuro[3,2-*c*]-[1]benzopyran-6-ones, constitute a class of natural product analogues which have been reported to possess diverse pharmacological properties, such as phytoestrogenic, antibacterial, antifungal, antimyotoxic, and phytoalexine effects.[7] Coumarins annulated to a thiophene ring, thieno[*c*]chromen-4-ones, have only been scarcely reported in the literature so far. They are isosteres of 6*H*-benzo[*c*]chromen-6-ones (coumestans) hence are of high importance for the design of new pharmacologically active compounds.

The subject of the present study is to develop new and efficient methods for the synthesis of thieno[*c*]chromen-4-ones. Based on a retrosynthetic analysis of desired ring systems, we envisaged the synthetic strategy depicted in Figure 1. The synthesis involves four steps. First, the deaminative bromination of commercially available and inexpensive amines **1–3**, second the Suzuki–Miyaura reaction with *ortho*-methoxyphenylboronic acids, and, finally, demethylation and lactonization.

To the best of our knowledge, this strategy has not been previously applied to the synthesis of 4*H*-thieno[3,2-*c*]chromen-4-ones, the main reason for that might be the synthetic accessibility of the starting thiophenes **1–3** and related moieties. Coupled with the Suzuki–Miyaura reaction the 4*H*-thieno[2,3-*c*]chromen-4-one scaffold has been previously synthesized using *ortho*-hydroxyphenylboronic acid; however, this method suffers from the fact that the synthesis of the starting boronic acid is in many cases difficult.[8] Our laboratory had reported the synthesis of thieno[2,3-*c*:5,4-*c*′]dichromene-6,8-dione from dimethyl 3,4-dibromothiophene-2,5-dicarboxylate by the Suzuki–Miyaura reaction without further exploration of this method concerning thienocoumarin synthesis.[9]

An important part of this Letter represents the synthesis of fused benzo[*b*]benzothienocoumarins (6*H*-benzo[4,5]thieno[2,3-*c*]chromen-6-ones). In fact the thiophene ring itself is a known pharmacophore[10] due to its isosterism to the benzene ring.[11] The

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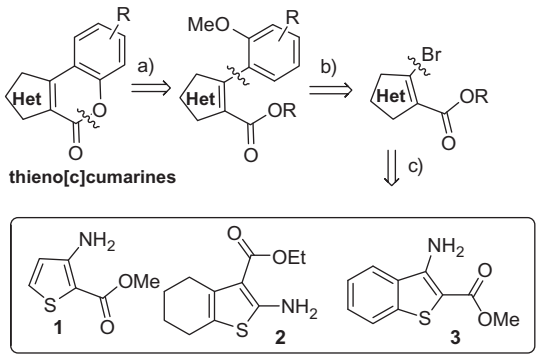
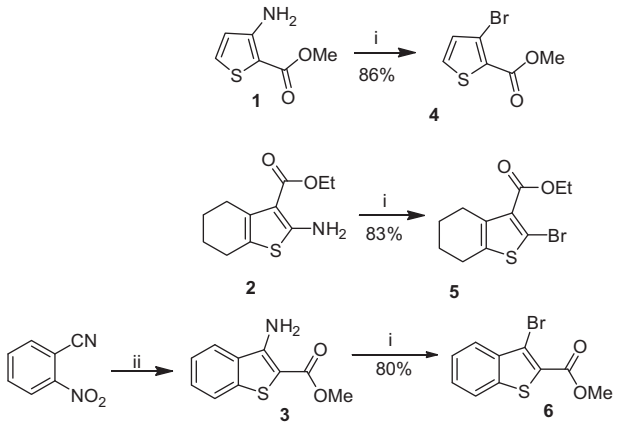
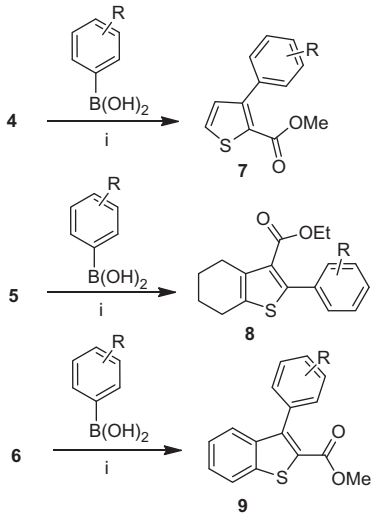


Figure 1. Retrosynthetic analysis: (a) formation of the coumarin ring by lactonization; (b) Suzuki reaction; (c) deaminative bromination.



Scheme 1. Reagents and conditions: (i): *tert*-butyl-nitrite, $CuBr_2$, CH_3CN, 2 h, rt, 10% aq HCl; (ii) $HSCH_2CO_2Me$, KOH, DMF, 0 °C, 1 h.



Scheme 2. Reagents and conditions: (i) $ArB(OH)_2$ (1.2 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.5 equiv), 1,4-dioxane, 90 °C, 4 h.

pharmacological profile of benzothiophenes (selective modulation of estrogen receptor,[12] antifungal activity,[13] HIV protease inhibition,[14] influence on neural protein folding,[15] regulation of bone morphogenetic protein,[16]) and the usefulness of arylated benzothiophenes in the field of electronics[10a,17] inspired us to prepare these compounds.

Table 1
Compounds **7**, **8,** and **9**[a]

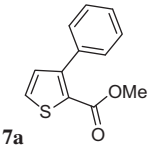
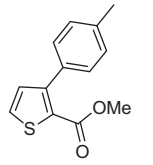
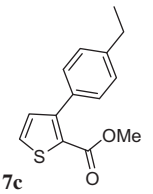
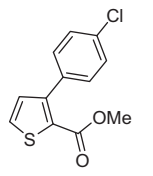
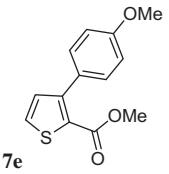
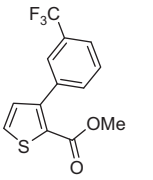
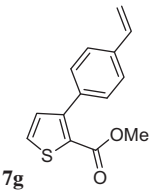
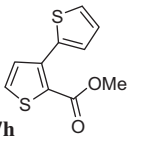
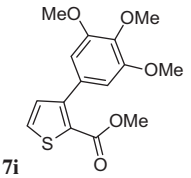
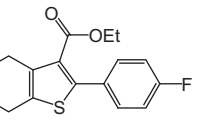
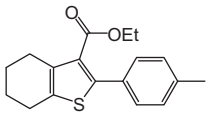
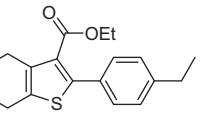
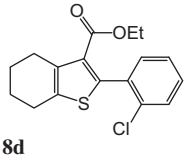
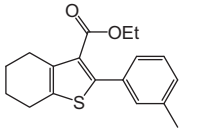
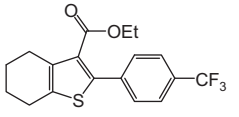
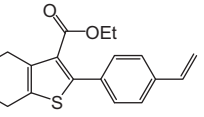
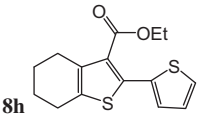
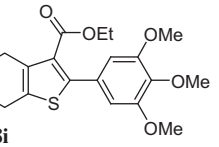
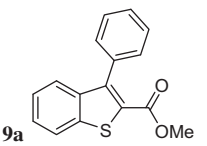
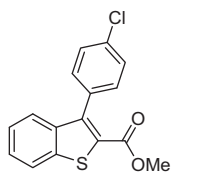
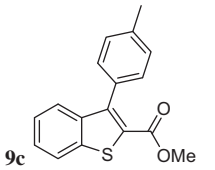
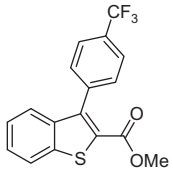
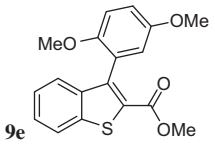
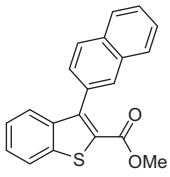
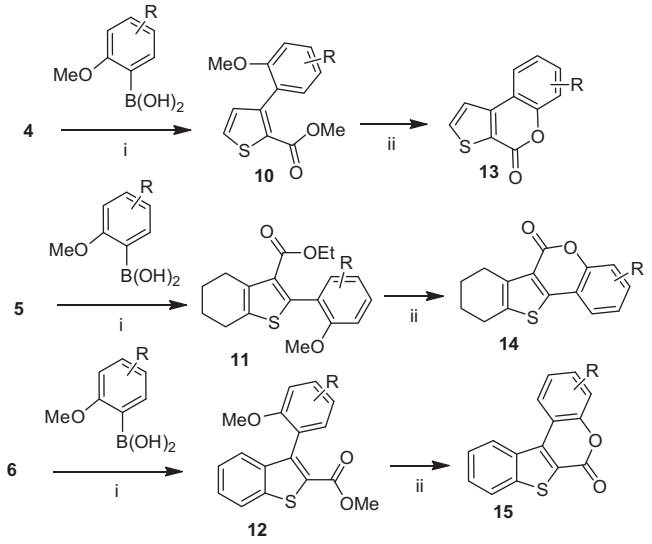
Structure	%	Structure	%
 **7a**	78	 **7b**	78
 **7c**	79	 **7d**	80
 **7e**	77	 **7f**	85
 **7g**	82	 **7h**	65
 **7i**	74	 **8a**	83
 **8b**	80	 **8c**	79
 **8d**	82	 **8e**	70
 **8f**	85	 **8g**	75
 **8h**	60	 **8i**	79
 **9a**	88	 **9b**	71

Table 1 (*continued*)

Structure	%	Structure	%
 **9c**	79	 **9d**	88
 **9e**	74	 **9f**	84

[a] Yields of isolated products.



Scheme 3. Reagents and conditions: (i): $ArB(OH)_2$ (1.2 equiv), $Pd(PPh_3)_4$ (5 mol %), K_3PO_4 (1.5 equiv), 1,4-dioxane, 90 °C, 4h; (ii): (a) BBr_3, CH_2Cl_2, (b) KO*t*Bu, H_2O.

We have earlier reported the synthesis of biaryl lactones by a combination of the Suzuki–Miyaura reaction of various alkyl 2-trifluoromethylsulfonyloxy-salicylates with *ortho*-methoxyphenylboronic acids and subsequent BBr_3-mediated demethylation and lactonization.[18] Snieckus et al. reported the combination of the directed ortho metalation with the Suzuki–Miyaura reaction and subsequent lactonization.[19]

With our concept in hand, we have started the investigation of the synthesis of thieno[*c*]coumarins. The synthesis of compounds **4–6** was achieved starting from **1 to 3** by a deamination/bromination reaction (Scheme 1). This transformation swiftly took place in acetonitrile using *tert*-butyl nitrite as the diazotization agent and copper bromide as the source of halogen.

As a next step, we have tested the Suzuki–Miyaura C–C coupling of obtained compounds with the set of commercially available aromatic and heteroaromatic boronic acids. The reaction of **4–6**, carried out in 1,4-dioxane under reflux and using $Pd(PPh_3)_4$ as the catalyst and potassium phosphate as the base, afforded products **7–9** in excellent yields (Scheme 2, Table 1).

Inspired by these successful results next we have switched on the development of the preparative synthetic methods toward condensed thienocoumarins following the proposed retrosynthetic analysis (Fig. 1). The reaction of **4–6** with *ortho*-methoxyphenylbo-

Table 2
Synthesis of compounds **10–15**[a]

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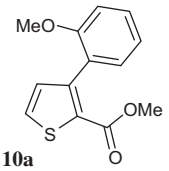
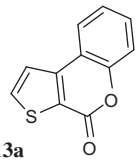
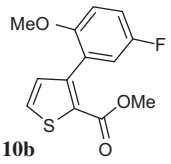
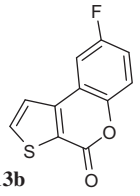
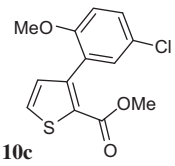
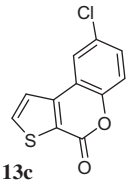
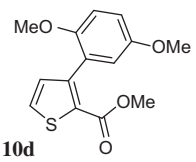
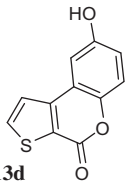
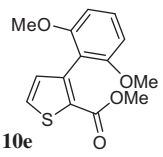
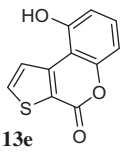
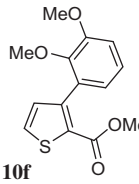
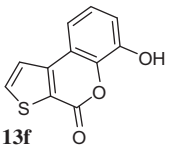
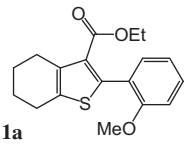
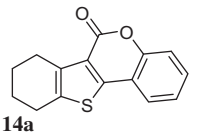
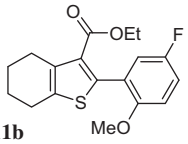
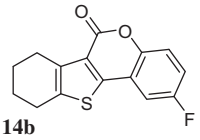
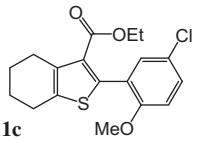
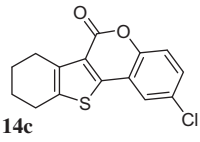
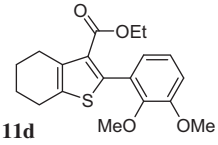
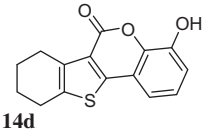
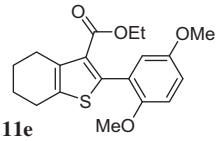
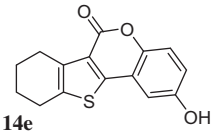
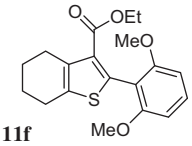
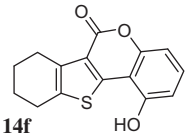
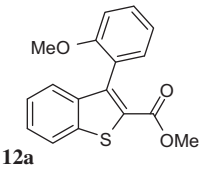
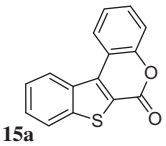
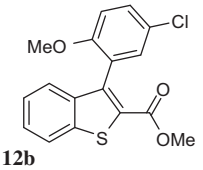
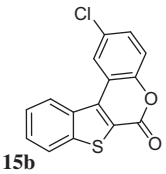
 **10a**	78	 **13a**	86
 **10b**	80	 **13b**	79
 **10c**	85	 **13c**	75
 **10d**	78	 **13d**	76
 **10e**	75	 **13e**	80
 **10f**	77	 **13f**	81
 **11a**	79	 **14a**	83
 **11b**	77	 **14b**	85
 **11c**	80	 **14c**	82
 **11d**	71	 **14d**	75

(*continued on next page*)

Table 2 (*continued*)

Structure	%	Structure	%
 **11e**	74	 **14e**	75
 **11f**	82	 **14f**	79
 **12a**	86	 **15a**	74
 **12b**	70	 **15b**	80

[a] Yields of isolated products.

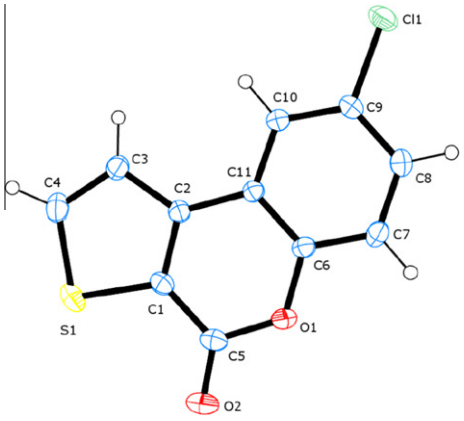


Figure 2. Molecular structure of compound **13c**.

ronic acids gave products **10–12** which were treated with BBr_3 and subsequently with potassium *tert*-butoxide to give thienocoumarins **13–15** (Scheme 3, Table 2). The products **10–12** could be isolated, as we report here, however BBr_3/KO*t*Bu-induced cyclization proceeds even with crude compounds, hence this protocol can be regarded either as tandem or as a sequential one. We suppose the BBr_3 performs demethylation of aryl-methoxy groups leaving the ester group intact.[20] Thereafter KO*t*Bu forms the phenolate ion which undergoes transacylation forming the desired lactone. Base-induced cyclization indirectly supports our assumption that the ester group is not affected by BBr_3 since *o*-coumaric acids are known to form the coumarin ring under the action of acids rather than bases.[21]

The constitution of the synthesized heterocyclic scaffolds was established by the NMR method and the structures of compounds **13c** and **15a** were unambiguously confirmed by the X-ray crystal structure analysis (Figs. 2 and 3).[22]

In conclusion, we have described a facile and efficient method for the preparation of thieno[*c*]chromen-4-ones by a four step

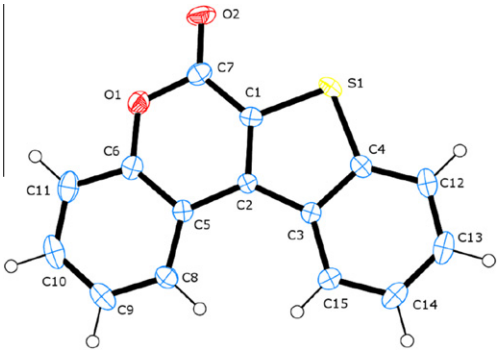


Figure 3. Molecular structure of compound **15a**.

synthetic strategy starting from readily available amino-thiophenes via diazotization–bromination/Suzuki–Miyaura reaction/KO*t*Bu induced lactonization. The scope and limitation of the method were extensively studied and the structures of two products were unambiguously confirmed by a single crystal X-ray diffraction.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.096.

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22. Crystallographic data (excluding structure factors) for the structures **13c** and **15a** reported in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 866896 and no. 866897 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.