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Expedient Synthesis of Highly Substituted Fused Heterocoumarins

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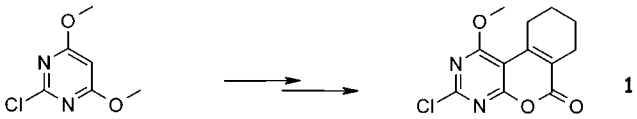
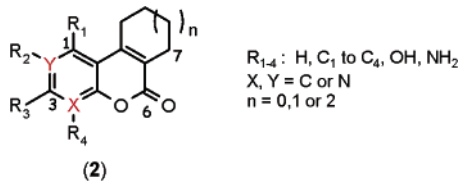
ABSTRACT



Highly substituted fused coumarins can be prepared in two steps starting from the appropriate boronic acids and enol triflates. The synthesis of fused pyrano[2,3-*d*]pyrimidin-7-one (1) is a key example to demonstrate the potential of the method in the elaboration of new coumarin scaffolds.

Over the past decades palladium-mediated cross-coupling reactions have repeatedly proven their efficiency in the synthesis of heterocycles.[1] Recently, Hesse and Kirsch[2] reported the use of the Suzuki cross-coupling reaction for the preparation of fused coumarins. In light of our interest in an efficient preparation of complex coumarins or heterocoumarins under mild conditions, their methodology was particularly interesting for us. The well-known Pechmann condensation[3a] is often used to get direct access to the coumarin scaffold, but the harsh reaction conditions (sulfuric acid, $POCl_3$) are not suitable for the preparation of highly functionalized coumarins.[3b] Although the biological activities shown by coumarins[4] are wide ranging, our interest focused on the preparation of novel tricyclic derivatives of the general formula **2** by virtue of their fungicidal activity seen in our biological screens.[5]

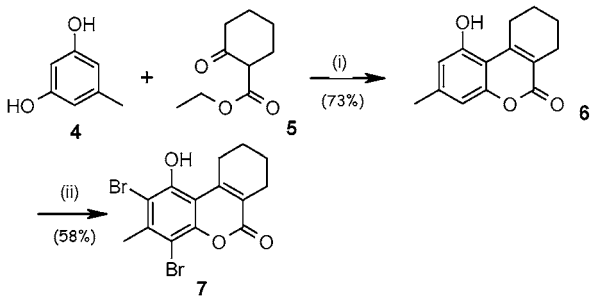
Herein is reported a short and efficient access to highly functionalized fused coumarins, coumarino-pyridines (pyrano-[2,3-*b*]pyridin-2-one; **2** with X = N and Y = C) and coumarino-pyrimidines (pyrano[2,3-*d*]pyrimidin-7-one; **2** with X = Y = N).



(2)

The classical Pechmann condensation (Scheme 1) was employed for the preparation of the coumarin **6** using β-keto

Scheme 1. Pechmann Condensation[a]



[a] Reagents and conditions: (i) $POCl_3$, toluene, 80 °C. (ii) *tert*-Butylammonium tribromide (2.2 equiv), MeOH−CH_2Cl_2, rt.

(1) Undheim, Kjell. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, Ei-ichi, Eds.; John Wiley & Sons: New York, 2002; pp 409−492.
(2) Hesse, S.; Kirsch, G. *Tetrahedron Lett.* **2002**, *43*, 1213−1215.
(3) (a) Horning, E. C. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 281. (b) For recent modifications of the Pechmann condensation under microwave condition allows milder conditions, see: Sugino, T.; Tanaka, K. *Chem. Lett.* **2001**, 110−111.
(4) Murray, R.; Mendez, J.; Brown, S. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley: New York, 1982.
(5) Whittingham, W. G. WO patent 02/28183 A1, 2002.

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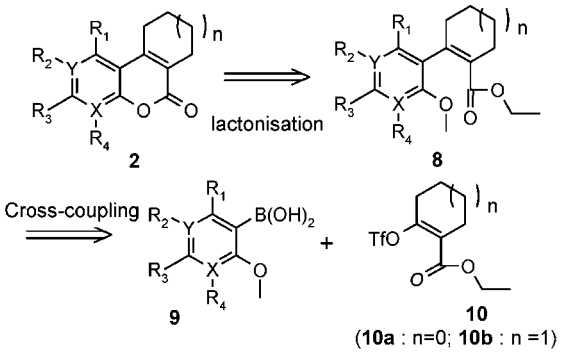
ester **5** and 5-methyl-benzene-1,3-diol **4**. Bromination of **6** with *tert*-butylammonium tribromide afforded **7**, which could be further substituted via cross-coupling reactions. The absence of convergence, as well as the lack of selectivity in the introduction of halogen[6] in the coumarin scaffold, forced us to find a more convenient approach. To render the synthesis more convergent, we retrosynthetically proposed that coumarin **2** could be prepared via deprotection of **8** followed by an in situ lactonization reaction.[7] Preparation of compound **8** could then be envisaged by cross-coupling between boronic acid **9** and the enol triflate **10**[8] (Scheme 2).

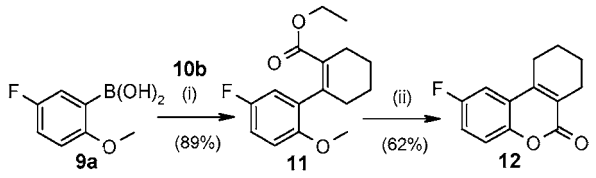
Scheme 2. Retrosynthetic Analysis of Coumarins **1**



The proposed C−C bond disconnection and the appropriate choice of the *o*-methoxyboronic acid[9] **9** provides a very convergent route to coumarin **2** and more generally to substituted coumarin scaffolds in only two steps.

We could first exemplify our approach by the straightforward synthesis of the 2-fluorocoumarin **12** (Scheme 3).

Scheme 3 [a]

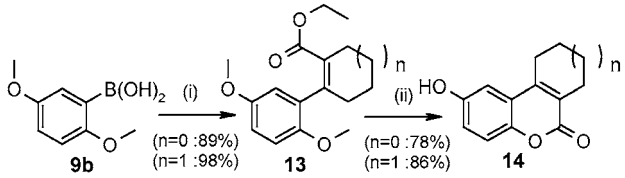


[a] Reagents and conditions: (i) $Pd(TPP)_4$ (5 mol %) in toluene/ethanol/Na_2CO_3 (2 M in water) 3/1/1, reflux 80 min. (ii) BBr_3 (1 M in CH_2Cl_2; 1.4 equiv), CH_2Cl_2, rt. TPP = triphenylphosphine.

The ester **11** was prepared by a Suzuki cross-coupling reaction between the enol triflate **10b**[8] (n = 1) and the commercially available boronic acid **9a**. Deprotection of the methoxy group with a slight excess of BBr_3 furnished the fused coumarin **12** in 62% yield.

2-Hydroxycoumarins **14** (n = 0 or 1) were both obtained in high yields by reacting the corresponding enol triflate of cyclopentanone or cyclohexanone (**10a** or **10b**) and the commercially available boronic acid **9b**. The two-step synthesis was not dependent on the nature of the triflate used for the preparation of our fused coumarins (Scheme 4).

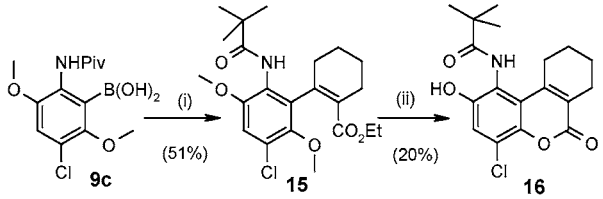
Scheme 4 [a]



[a] Reagents and conditions: (i) **10a** or **10b**; $Pd(TPP)_4$ (5 mol %) in toluene/ethanol/Na_2CO_3 (2 M in water) 3/1/1, reflux 80 min. (ii) BBr_3 (1 M in CH_2Cl_2; 1.4 equiv), CH_2Cl_2, rt.

The highly functionalized coumarin **16** was obtained under the same conditions in moderate yield by coupling the boronic acid **9c**[10a] with enol triflate **10b** (Scheme 5). The

Scheme 5 [a]



[a] Reagents and conditions: (i) **10b**, $Pd(TPP)_4$ (5 mol %) in toluene/ethanol/Na_2CO_3 (2 M in water) 3/1/1, reflux 3 h. (ii) BBr_3 (1 M in CH_2Cl_2; 2.1 equiv), CH_2Cl_2, rt.

Suzuki cross-coupling reaction afforded the coumarin precursor **15** in 51% yield, as well as 46% of unreacted **9c**. Treatment with BBr_3 finally provided coumarin **16** with the protected nitrogen and the free phenol group.

We rationalized the moderate yield of the lactonization step by comparing the previous synthesis of coumarins **12** and **14**. In the case of **16**, the presence of the *o*-pivaloyl amide is certainly responsible for the lower yield (50% of recovered material is bis demethylated but not cyclized). The bulky pivaloyl group can generate steric interactions with the cyclohexane moiety disturbing the intermediate required

(6) The coumarin **7** can be prepared with an excess of *tert*-butylammonium tribromide, but the use of only 1 equiv of the brominating agent provides mixture of regioisomers in positions 2 and 4.

(7) Dubuffet, T.; Loutz, A.; Lavielle, G. *Synth. Commun.* **1999**, *29*, 929−936.

(8) Synthesis and chemical stability of cyclic enol triflate described by Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972−6975.

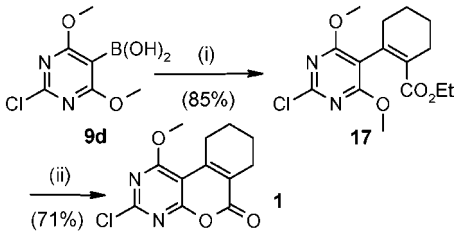
(9) Based on SciFinder, around 200 *o*-methoxy boronic acids are registered and more than 20 commercially available.

(10) (a) The pivaloyl-protected 4-chloro-2,5-dimethoxy-phenylamine is treated with *n*-BuLi in THF followed by addidtion of $B(OMe)_3$. After aqueous workup and chromatography, the boronic acid **9c** is obtained in 50% yield. (b) The 2-chloro-4,6-dimethoxy-pyrimidine was treated in the same condition as in (a) (^{n}BuLi, $B(OMe)_3$) and afforded **9d** in 75% yield (see Supporting Information) (c) The 2-fluoro-pyridine was treated in the same condition as in (a) (^{n}BuLi, $B(OMe)_3$) and afforded **9e** in 80% yield.

for the cyclization. Nevertheless, with sufficient quantity of **16** in our hands, synthesis of new libraries of fused coumarins was undertaken.

The functional group tolerance of our approach was further exemplified by the preparation of fused aza-coumarins such as pyrano[2,3-*d*]pyrimidin-7-one[11a] (**1**). Related pyrimidine derivatives can be prepared from barbituric acid[11a,b] but usually are limited by the choice of substituents. The preparation of the coumarino-pyrimidine **1** is shown in Scheme 6. The boronic acid **9d** is readily accessible from the commercially available pyrimidine.[10b]

Scheme 6 [a]



[a] Reagents and conditions: (i) **10b**, $Pd(TPP)_4$ (5 mol %) in toluene/ethanol/Na_2CO_3 (2 M in water) 3/1/1, reflux 2 h. (ii) BBr_3 (1 M in CH_2Cl_2; 5 equiv), CH_2Cl_2, reflux.

Following the Suzuki cross-coupling reaction between **9d** and **10b**, the lactonization of **17** failed using the conditions that were successful for the synthesis of **12** and **14**.[12] However, refluxing **17** overnight in the presence of 5 equiv of BBr_3, gave methoxy-diazacoumarin **1**. Unexpectedly, even by forcing the conditions (BBr_3 10 equiv, refluxing 48 h in CH_2Cl_2) the second methoxy group was not cleaved.

Compound **1** was submitted to cross-coupling reactions to replace the chlorine atom successfully with CN, aromatics, and acetylene derivatives. This family of compounds showed weak but interesting broad spectrum in vivo fungicidal activities in our screens.[13]

In addition, fused coumarino-pyridines[14] or pyrano-[2,3-*b*]pyridin-2-one were prepared following a slightly different process starting from the boronic acid **9e**.[15a,10c]

Nucleophilic displacement of a fluorine ortho to the nitrogen in the pyridine ring is precedented in the literature.[15b] Hence, δ-lactonization resulting from the nucleophilic attack of the carboxylate at the pyridine C2 position was expected to be straightforward (Figure 1).

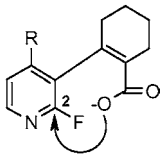
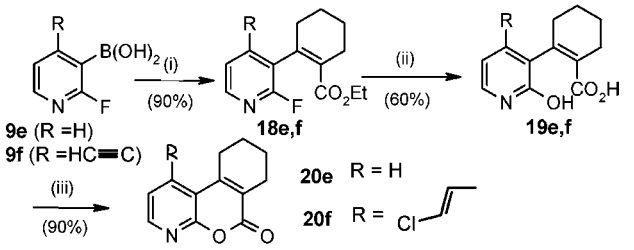


Figure 1. Lactonization by fluorine displacement at C2.

The cross-coupling reaction of boronic acid **9e** followed by saponification of the ester **18e** provided the seco-acid **19e** and not the expected aza coumarin **20e**. During the saponification, the fluorine atom is readily displaced by water. This limitation was overcome by treating **19e** with oxalyl chloride in dichloromethane, which afforded the coumarin **20e** (R = H) in 90% yield. Attempts to realize the one-step cyclization from the carboxylate failed by other methods such as saponification with potassium trimethylsilanolate.[16] Interestingly, the alkyne-substituted compound **19f** was readily transformed into the chlorovinyl derivative **20f** under the same conditions, providing a very useful scaffold for further coupling reactions. In summary, we report a short and

Scheme 7 [a]



[a] Reagents and conditions: (i) **10b**, $Pd(TPP)_4$ (5 mol %) in toluene/ethanol/Na_2CO_3 (2 M in water) 3/1/1, reflux 2 h. (ii) LiOH, THF/H_2O, rt. (iii) $(COCl)_2$ in CH_2Cl_2, 0 °C to rt.

efficient synthetic access to highly functionnalized coumarins combining two reliable methodologies. This method has been successfully applied for the two-step preparation of various substituted novel aromatic or heteroaromatic coumarins.

Acknowledgment. We are grateful to the Analytic Service of Syngenta and especially Dr. T. Winkler for useful structure elucidation.

Supporting Information Available: Experimental procedures and analytical data for the preparation of **1** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0362461

(11) (a) Habib, N. S.; Kappe, T. *Monatsh. Chem.* **1984**, *115*, 1459−1466. (b) Harris, R. L. N.; Huppatz, J. L.; Teitei, T. *Aus. J. Chem.* **1979**, *32*, 669−679 (coumarino-pyridine described only as unwanted compound).

(12) After 24 h at room temperature, only 5% of the corresponding coumarin could be detected by NMR ^1H.

(13) Compound **1** was submitted to Sonogashira coupling reaction (2 mmol of 1 in 8 mL of dimethylformamide was treated with 4 mmol of ethynyltrimethylsilane in the presence of 5% $Pd(TPP)_2Cl_2$ and 10% CuI at room temperature for 1 h. The crude compound was deprotected with *tert*-butylammonium fluoride in THF to afford 1 mmol of ethynyl analogue of **1** (2-ethynyl-4-methoxy-5,6,7,8-tetrahydro-10-oxa-1,3-diaza-phenanthren-9-one). Leaf spots and rust such as *Septoria*, *Pyricularia oryzae*, *Pyrenophora teres*, and *Puccina recondita* were 90% controlled in vivo by this compound at 200 ppm.

(14) Trecourt, F.; Marsais, F.; Gungor, T.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, *9*, 2409−2415.

(15) (a) Sutherland, A.; Gallagher, T. *J. Org. Chem.* **2003**, *68*, 3352−3355 for the preparation of the boronic acid. (b) Cherng, Y. *Tetrahedron* **2002**, *58*, 4931−4935.

(16) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.