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A concise approach to chiral chromenes based on levoglucosenone

Alexander V. Samet [a,*], Dmitriy N. Lutov [a], Sergei I. Firgang [a], Konstantine A. Lyssenko [b], Victor V. Semenov [a]

[a] N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Pr., 119991 Moscow, Russia
[b] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilov St., 119991 Moscow, Russia

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ABSTRACT

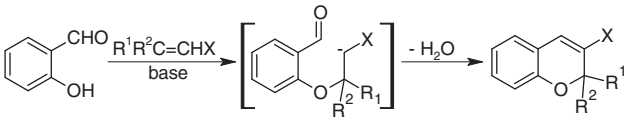
Levoglucosenone, a chiral α,β-unsaturated ketone derived from cellulose, undergoes a stereoselective domino oxa-Michael–aldol reaction with 2-hydroxybenzaldehydes affording optically active pyrano[3,4-*b*]chromenes. The latter are further converted into 2*H*-chromenes via a Beckmann fragmentation reaction.

A number of biologically active natural compounds contain the 2*H*-chromene structural motif, and interest in the synthesis of these compounds is growing rapidly.[1] Reaction of 2-hydroxybenzaldehydes with α,β-unsaturated carbonyl compounds, or other activated alkenes represents a possible synthetic approach to 2*H*-chromenes[1,2] (Scheme 1).

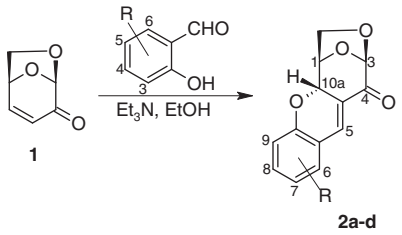
In particular, such reactions with cyclic α,β-unsaturated carbonyl compounds (i.e., cyclohexenones[3] or pyranones[4]) afford fused chromenes. The use of a chiral catalyst in these transformations can result in the formation of optically active chromene derivatives,[5] though ee values are not always high. Another possible approach to the latter compounds requires the use of suitable chiral substrates. Thus, levoglucosenone (**1**) [(1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]oct-2-ene-4-one], an unsaturated ketone prepared by acid-catalyzed pyrolysis of cellulose,[6] is known to undergo stereoselective addition reactions on the C=C bond on the side opposite to the anhydro bridge,[7,8] resulting in its application for the synthesis of optically active compounds.[9]

With 2-hydroxybenzaldehydes, levoglucosenone **1** undergoes a stereoselective domino oxa-Michael–aldol reaction[3a,10] (the phenolate-anion attacks from the side opposite to the anhydro bridge[11]) (Scheme 2).

In most cases, these reactions proceed smoothly and in high yields[12] (Table 1), however, with 5-nitrosalicylaldehyde the reaction was much slower and the yield was lower (cf. Ref. 3a). This is probably due to the poor nucleophilicity of the nitrophenolate-anion.



Scheme 1. Domino oxa-Michael–aldol reaction.



Scheme 2.

The reaction of pyranochromene **2a** with nucleophiles (Nu = OMe^-, SPh^-) in MeOH or EtOH failed to yield the anticipated adducts **A** (cf. Ref. 3a), but instead produced a mixture of epimer **2a′**[11] and products of an unusual recyclization **3** (Scheme 3).

Most probably, the mechanism involves $S_N'2$ substitution with concomitant chromene ring-opening to yield intermediate **B**. The latter could undergo either intramolecular nucleophilic $S_N'2$ attack by the phenolate-anion with ring-closure, resulting in epimer **2a′** [pathway (a)] or $S_N'2$ attack by the external nucleophile affording the recyclization products **3a,b** via intermediate **C** [pathway (b)] (Scheme 4).

* Corresponding author.
E-mail addresses: sametav@server.ioc.ac.ru, sametav@yahoo.com (A.V. Samet).

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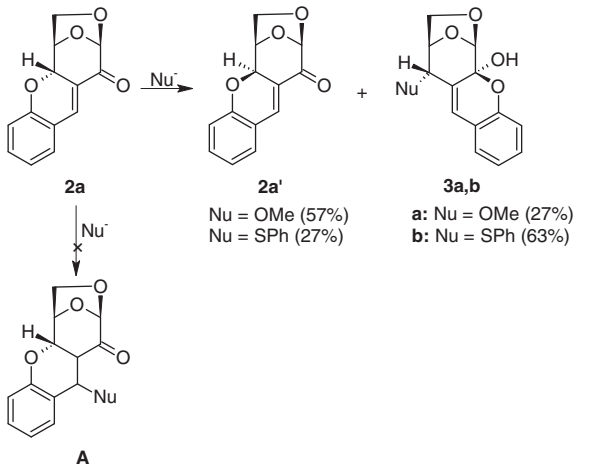


Scheme 3. Reaction of **2a** with nucleophiles.

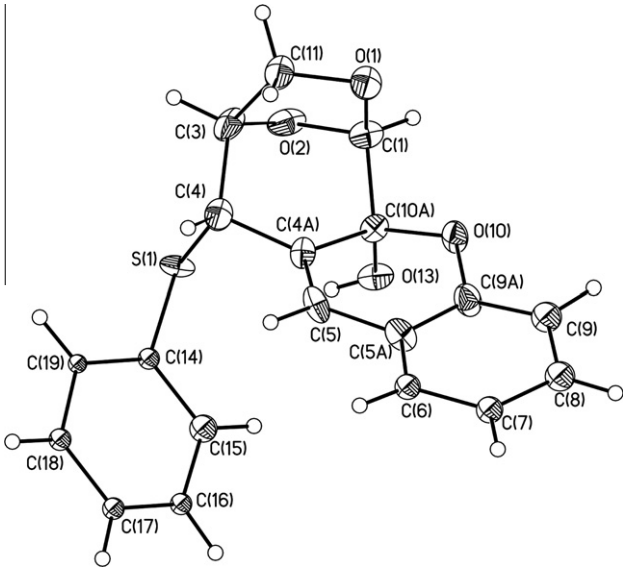


Figure 1. X-ray structure of product **3b** (ORTEP presentation).

Table 1
Yields of products **2** and **4**

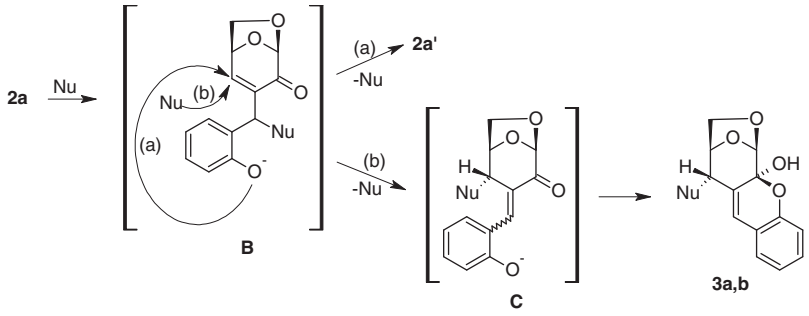
R	Yield of **2**[a] (%)	Yield of **4** (%)
H (**a**)	84	69
5-Br (**b**)[b]	86	67
3-MeO (**c**)[b]	91	59
5-NO_2 (**d**)[b]	36[c](52[d])	

[a] Performed at rt for 5 h.
[b] Position of substituents on the 2-hydroxybenzaldehydes is indicated.
[c] Reaction run for 72 h.
[d] Reaction run for 10 days.

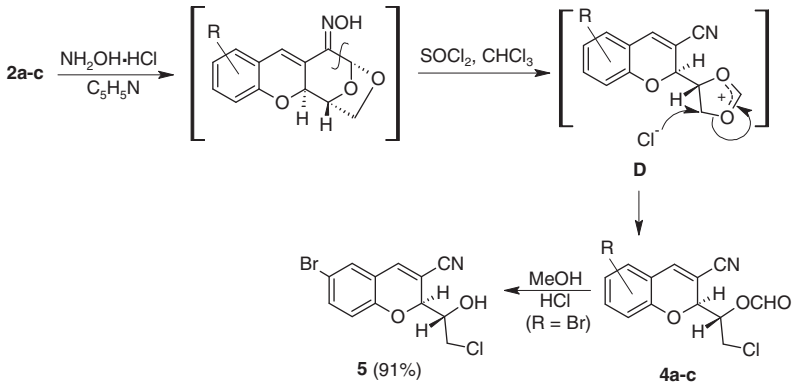
The structure of product **3b** was confirmed by X-ray diffraction[13] (Fig. 1).

The structure of **3a** was assigned based on similarities in the NMR spectra with those of **3b**. In particular, the chemical shifts of C(10a) in the ^{13}C NMR spectra were very close: δ 92.60 for **3a** and δ 92.32 for **3b**.

On reaction with $SOCl_2$, the oximes of pyranochromenes **2** (prepared from **2** and $NH_2OH{\cdot}HCl$) were converted into 3-cyano-2*H*-chromenes **4** in good yields[14] (Table 1). The reaction proceeds via the Beckmann fragmentation[15] with cleavage of the intermediate



Scheme 4. Plausible reaction mechanisms.



Scheme 5. Beckmann fragmentation of the oximes of pyranochromenes **2**.

1,3-dioxolan-2-ylium cation **D** by attack of Cl^- at the least sterically hindered position[16,17] (Scheme 5). Acidic hydrolysis of the formate **4b** affords chlorohydrin **5**. The structure of **4b** was confirmed by X-ray crystallographic analysis, the details of which will be published elsewhere.

In conclusion, the carbohydrate ketone, levoglucosenone (**1**) proved to be a suitable template for the stereoselective synthesis of optically active functionalized 2*H*-chromenes via a domino oxa-Michael–aldol reaction followed by transformation of the carbohydrate fragment under Beckmann fragmentation conditions.

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Supplementary data

Supplementary data (experimental procedures for compounds **2a**′, **3a**,**b** and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.004.

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11. The ^{1}H NMR spectra of compounds **2a** and **2a**′ (epimers at C-10a) differ mainly in the coupling constant values $J_{1,10a} \approx 0$ Hz for **2a** and $J_{1,10a} = 5.2$ Hz for **2a**′ (cf. Refs. 7b and 8b).
12. *Preparation of pyrano[3,4-b]chromen-4(3H)-ones **2a–d** (general procedure).* To a solution of levoglucosenone (**1**) (0.63 g, 5 mmol) and the corresponding 2-hydroxybenzaldehyde (5 mmol) in EtOH (3 ml), was added Et_3N (0.10 g, 1 mmol) at rt. After 5 h (72 h for **2d**) the resulting suspension was diluted with H_2O (3 ml) and the precipitate filtered and dried.
13. *Crystallographic data for **3b***: $C_{19}H_{16}O_4S$, Mr = 340.38, monoclinic, space group $P2_12_12_1$, $a = 6.667(2)$, $b = 7.903(3)$, $c = 30.055(9)$ Å, $V = 1583.5(9)$ Å^3, $Z = 4$, $d_{calcd} = 1.428$ gm^{-3}, $\mu = 2.225$ mm^{-1}, $F(0\,0\,0) = 712$. Intensities of 8099 reflections were measured with a Bruker SMART APEX CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, $\theta/2\theta < 56°$] and 3784 independent reflections [$R_{int} = 0.0348$] were used for further refinement. The absorption correction was performed empirically using APEX2 (Bruker, 2005). Analysis of Fourier density synthesis revealed that the SPh substituent is disordered by two positions with equal occupancies. The refinement converged to w$R2 = 0.0531$ and GOF = 1.000 for all independent reflections ($R1 = 0.0749$ was calculated against F for 3104 observed reflections with $I > 2\sigma(I)$). The refinement of absolute structure led to a Flack parameter (Flack, H.D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881) equal to 0.00(17). All calculations were performed using SHELXTL PLUS 5.0 (Sheldrick, G.M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122). CCDC 799240 contains the supplementary crystallographic data for **3b**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: (+44) 1223 336033; or deposit@ccdc.cam.ac.uk.
14. *Preparation of chromenes **4a–c** (general procedure).* A solution of ketone **2a–c** (2 mmol) and $NH_2OH{\cdot}HCl$ (2.5 mmol) in pyridine (4 ml) was stirred for 24 h at rt, the solvent removed in vacuo and the residue triturated with H_2O (10 ml). The resulting oxime precipitate was filtered, dried in vacuo and used in the next step without further purification. To a solution of the above oxime in dry $CHCl_3$ (3 ml), a solution of $SOCl_2$ (1.5 ml) in dry $CHCl_3$ (1 ml) was added dropwise at 0 °C with stirring. The resulting mixture was kept at 0 °C for 40 min and then evaporated to dryness. The residue was chromatographed on silica gel (eluent: hexane/EtOAc, 5:1) to afford nitriles **4a–c**.
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