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A new domino oxidation—rearrangement of 2,3-dihydrowogonin to negletein

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ABSTRACT

We report an expeditious, iodine-catalysed oxidation of 2,3-dihydrowogonin to negletein which comprises a Wessely–Moser rearrangement (WMR), associated not with an O-demethylation, as usual, but with an oxygen to oxygen methyl shift. In contrast, DDQ in 1,4-dioxane oxidised 2,3-dihydrowogonin to wogonin without rearrangements.

Introduction

Scutellaria baicalensis Georgi is a herb traditionally used in Chinese folk medicine. The root extract was employed to treat hypertension, atherosclerosis, infections and fever, among other ailments.[1,2] One of its major constituents is 5,7-dihydroxy-8-methoxyflavone, a.k.a. wogonin (**1**), which is known to have anti-inflammatory, antioxidant, antiangiogenic[3] and antitumour properties.[4] Despite its simple structure, chemical syntheses are few and far between.[5–7] Huang et al.[6] achieved the best yield with 20% over three steps starting from 3,4,5-trimethoxyphenol and cinnamoyl chloride which were submitted to a Friedel–Crafts acylation affording the corresponding chalcone. While they reported that its partial demethylation and subsequent oxidative cyclisation left a mixture of **1** (24%) and the regioisomeric oroxylin A (**2**; 46%) (Fig. 1), we found a different outcome. Herein, we[8] report a high-yielding synthesis of negletein (**3**) via a domino oxidation–rearrangement of 2,3-dihydrowogonin.

Results and discussion

3,4,5-Trimethoxyphenol was acylated with cinnamoyl chloride according to Huang et al. A careful hydrolytic workup afforded the crystalline BF_2 chelate complex **4** of the known chalcone **5** in over 90% yield (Scheme 1). Figure 2 shows its molecular structure as obtained from a single crystal X-ray diffraction analysis. Basic hydrolysis of complex **4** left chalcone **5**. While Huang et al. had reported to have obtained the corresponding demethylated chalcone **6** upon refluxing of **5** for 2 h in a mixture of 47% HBr and glacial acid, we isolated none of this but a separable mixture of 2,3-dihydrowogonin (**7**) (61%) as colourless fibres and of 2,3-dihydrooroxylin A (**8**) (21%) as a brown solid under identical conditions. Obviously, a twofold demethylation with subsequent ring-closing Michael addition had taken place under the strongly acidic conditions. Recently, Tietze et al. found that heating of 2,3,4-trimethoxy-6-hydroxychalcones in glacial acid alone also led to the formation of flavanones, albeit without demethylation.[9] Next, we tried to oxidise pure 2,3-dihydrowogonin (**7**) to give wogonin (**1**) with catalytic amounts of iodine in DMSO, a protocol also used by the Huang group to cyclise–oxidise chalcones with OH-groups on the A-ring. However, this failed, too. Yet, when carried out under strict exclusion of air[10] this reaction yielded negletein (**3**) as the sole product in over 70% yield. Its NMR data were in line with the literature[11] and its melting point identical to that of an authentic sample.

At first glance the conversion of **7** to **3** resembles the Wessely–Moser rearrangement (WMR) of 5,8-dimethoxy or 5,7,8-trimethoxy flavanones and flavones under demethylating acidic conditions which proceeds by ring opening of the pyrone ring, rotation about the phenyl—C(=O) bond and ring closure to give isomeric flav(an)ones.[12–14] However, in the present case a flavanone is oxidised and the methyl group is retained yet shifted to the oxygen

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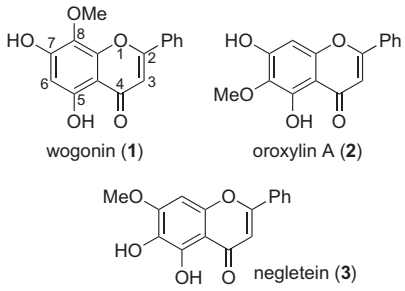
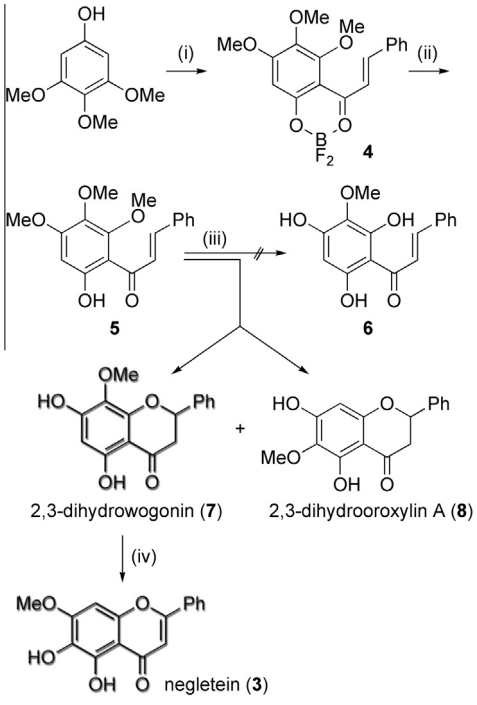


Figure 1. Structures of wogonin (**1**), oroxylin A (**2**), and negletein (**3**).

atom of a neighbouring OH-group. Additional experiments showed that neither wogonin (**1**), nor oroxylin A (**2**) reacted with catalytic amounts of iodine in DMSO under an atmosphere of argon or with solutions containing HI which is likely to develop in the course of the conversion of **7** to **3**. This means that neither wogonin nor oroxylin A is an intermediate en route this reaction. While the stoichiometric iodination of flavanones under basic[15] or strongly acid[16] conditions was reported to afford 3-iodoflavones via the enolate or enol, respectively, we propose a different mechanism for the conversion of **7** to **3** which is only catalytic in iodine (Scheme 2). First, 2,3-dihydrowogonin may get iodinated, i.e., oxidised, in benzylic position to give α-iodoether **9** with concomitant formation of HI. The latter induces a methyl shift from 8-O to 7-O by protonating the most basic 8-O-atom and by abstracting the most acidic H-atom from 7-O. The resulting *para*-hydroquinone **10** is ring-opened by HI-induced cleavage of its α-iodoether to give diiodide **11**α. Its rotamer **11β** can re-cyclise more effectively to afford **12**, a regioisomer of α-iodoether **9**, via displacement of an iodide by the less hindered and more strong nucleophilic OH-group of the *para*-hydroquinone. The final step in the conversion of **7** to **3** is the β-elimination of a second equivalent of HI. The HI gets



Scheme 1. Reagents and conditions: (i) cinnamoyl chloride, $BF_3 \times Et_2O$, 30 min, reflux, 91%; (ii) AcOEt, $NaHCO_3$, 30 min, rt, 83%; (iii) HBr, AcOH, 2 h, reflux, 61% **7**, 21% **8**; (iv) argon atmosphere, iodine, DMSO, 2 h, reflux, 72%.

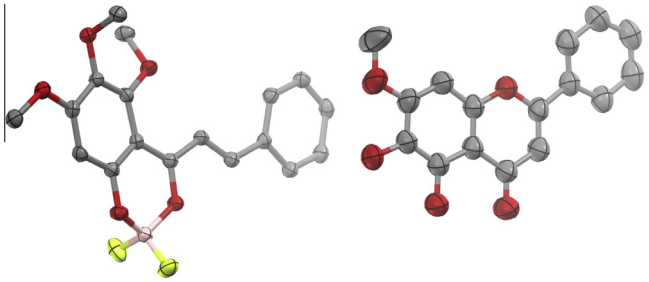
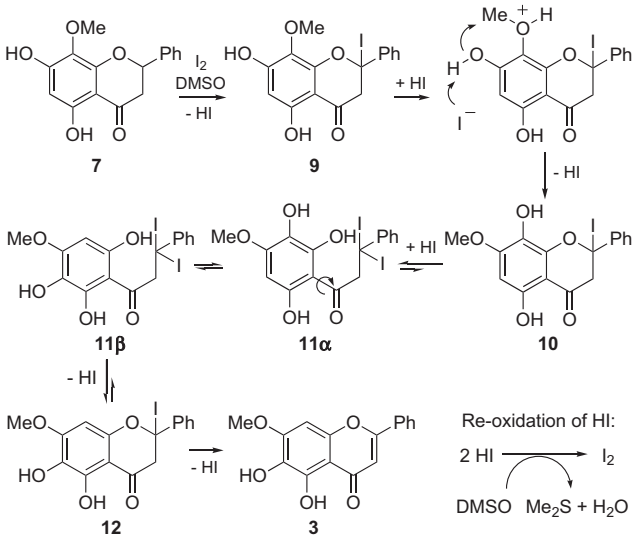


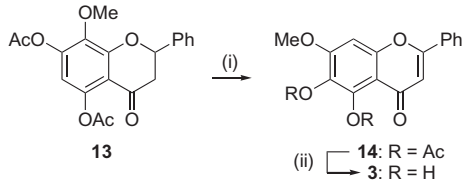
Figure 2. Molecular structures of chalcone BF_2 complex **4** (left; CCDC 1429261) and of negletein (**3**; right; CCDC 1429260), obtained via the route outlined in Scheme 3, both as thermal ellipsoid representations at 50% probability level (H-atoms omitted).



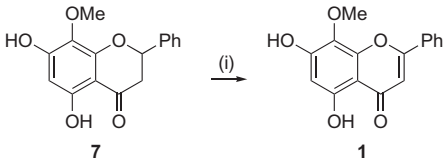
Scheme 2. Tentative mechanistic proposal for the oxidation of 2,3-dihydrowogonin (**7**) to negletein (**3**) by catalytic iodine/DMSO.

re-oxidised to iodine by the solvent DMSO for which there is literature precedent.[17]

Mixtures of azobisisobutyronitrile (AIBN) and *N*-bromo-succinimide (NBS) in CCl_4[18] also oxidised 2,3-dihydrowogonin to negletein. Even the bisacetylated 2,3-dihydrowogonin **13**[19] furnished bisacetylated negletein **14**[20] when oxidised with NBS/AIBN in CCl_4 (Scheme 3). The formal retention of the acetyl groups during this rearrangement was surprising yet may be rationalised by their known migratory propensity[21] and by assuming a mechanism similar to the one shown in Scheme 2. HBr rather than HI would initiate the methyl shift by cleavage of the neighbouring acetate, followed by acetyl migrations and the WMR. Deprotection of **14** required refluxing with 3 N hydrochloric acid in acetone for 16 h since the more common basic protocols led to decomposition. An X-ray diffraction analysis of suitable crystals of the product negletein confirmed its identity (Fig. 2).



Scheme 3. Reagents and conditions: (i) CCl_4, NBS, AIBN, 2 h, reflux, 49%; (ii) acetone, 3 N HCl, 16 h, reflux, 100%.



Scheme 4. Reagents and conditions: (i) DDQ, 1,4-dioxane, 16 h, reflux, 36%.

Finally, we found that our initial intention, the oxidation of 2,3-dihydrowogonin (**7**) to wogonin (**1**), was possible in a moderate 36% yield by means of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 1,4-dioxane according to a general protocol by Kim et al.[22] (Scheme 4). Unlike oxidations with I_2/DMSO or NBS, such with DDQ do not imply free hydrohalic acids which are apparently required for the induction of the observed methyl shifts and WMR.

Conclusion

Contrary to previous reports, we found that 2,3-dihydro-wogonin cannot be oxidised to wogonin by halo oxidants such as I_2/DMSO or NBS. Instead, negletein was formed as the sole product of a domino sequence comprised of a methyl shift, a Wessely–Moser rearrangement, and the formation of a 2-alkene. Flavones such as wogonin and oroxylin A did not react under these conditions. In principle, other flavanones with aptly positioned hydroxy and methoxy groups should also be amenable to this reaction. Work is in progress to clarify this point.

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Supplementary data

Supplementary data (experimental procedures, compound characterisation, and copies of ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.093.

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