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A Wacker–Cook synthesis of isoflavones: formononetine

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ABSTRACT

A total synthesis of the isoflavone formononetine **1** by an oxidative Pd-mediated cyclization of α-methylenedeoxybenzoins **4a–c** is described. Substrates **4a–c** were rapidly assembled using 'protected cyanohydrin' chemistry.

The flavonoids are a group of natural products with interesting medicinal and biological properties, for example, antioxidant, enzymatic, estrogenic, insecticidal, and antimicrobial activities.[1] Recently, the antileukemic activity of genistein, the major isoflavone constituent of soy beans, has been reported and fisetin, a tetrahydroxyflavone present in strawberries and other foods, has been proposed as an oral neurotrophic factor that sustains and enhances memory.[2,3] Therefore, and despite the large number of available methods, the development of new synthetic procedures to efficiently prepare these compounds in the laboratory is an important issue.[4]

During their extensive studies concerning the syntheses of complex indole alkaloids of the macroline/sarpagine type, Cook and coworkers examined the conversion **I**→**II** and found that the involved deprotection–cyclization–oxidation steps can be done in a single operation with a palladium(II) complex (Na_2PdCl_4) and an oxidant (*t*-BuOOH) in a buffered (AcOH–NaOAc) aqueous dioxane or *t*-BuOH media (Scheme 1).[5]

We wish to report that this elegant Wacker–Cook tandem conversion can be extended to the synthesis of isoflavones from α-methylenedeoxybenzoins. Our results are not trivial since α-substituted α,β-unsaturated ketols are known[6] to be inert to the standard Wacker oxidation and, in our case, phenol intermediates can potentially be oxidized under these conditions.

To address this issue, we chose the simple isoflavone formononetine **1** which, in principle, can be prepared by this approach from an appropriately *ortho* substituted α-methylenedeoxybenzoin **4**, and this substrate can, in turn, be obtained by a method reported some time ago from our laboratory[7] as indicated in the retrosynthetic analysis of Scheme 2.

Conjugate addition of the lithium salt of the O-silyl protected cyanohydrin **2**[8] to commercially available (*E*)-4-methoxy-β-nitrostyrene gave a mixture of compounds which without purification was submitted successively to a mild acid treatment (5% aqueous H_2SO_4) to cleave the silyl ether, and a base treatment (Et_3N in acetone) to remove HCN and HNO_2 in the intermediate β-nitro cyanohydrin **3** (R = H). However, to our surprise a 1:1 mixture of the expected α-methylene deoxybenzoin **4a** and nitroenone **5** was obtained in 50% yield, which were separated by column chromatography and fully characterized by spectroscopy (Scheme 3).[9]

Since this ratio remained unchanged regardless if the workup is performed under the rigorous exclusion of air or if oxygen is introduced on purpose, air dehydrogenation of the nitronate adduct can be discarded as an explanation for the formation of **5**. On the other hand, if in the above reaction (*E*)-4-methoxy-β-nitrostyrene is substituted for (*E*)-β-nitrostyrene, after work up and deprotections only the 'normal' product **6** is obtained in 60% yield. The above experiments seem to point out that formation of β-nitroenone **5** involves, after lithium nitronate adduct formation, an intramolecular slow methoxy-assisted benzylic hydride transfer mechanism with the covalent lithium cation as the hydride acceptor, perhaps through a cyclic six-membered intermediate, as depicted in Scheme 4. To explain, the constant 1:1 ratio of **4a** and **5** in the aforementioned experiments, we propose that, as soon as protected nitroenone is formed, replaces lithium cation as hydride acceptor establishing a fast equilibrium with lithium nitronate adduct, which is preserved until quenching.

Since **5** is, in principle convertible into **4a**, we first explored some reactions on **5**, but without success.[10] Hence we turned our attention to the modification of reaction conditions to avoid formation of **5** and determined that exchanging the lithium base for more ionic sodium or potassium bases was an attractive, reasonable alternative. From our point of view, sodium or potassium nitronate adducts could not give analogous cyclic intermediates for favorable intramolecular hydride transfers as lithium cation did, and we were pleased to find that with KH as base, the reaction proceeded without incident affording the 'normal' Michael adduct **3** (R = $SiMe_3$, not isolated) as evidenced by the exclusive isolation (65% overall yield) of **4a** under these conditions. Finally, from **4a**, the analogous α-methylene deoxybenzoins **4b** and **4c** were obtained by the standard reactions indicated in Scheme 5.

With substrates **4a–c** in hand, they were subjected to the Cook modification of the Wacker oxidation in separate experiments to give

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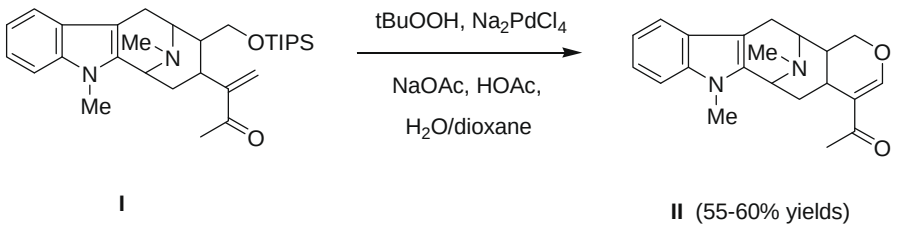
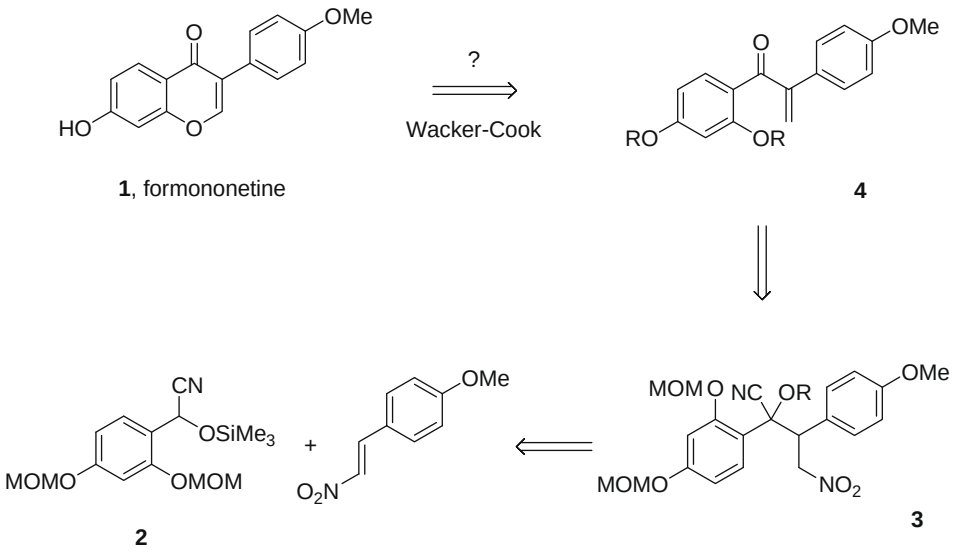
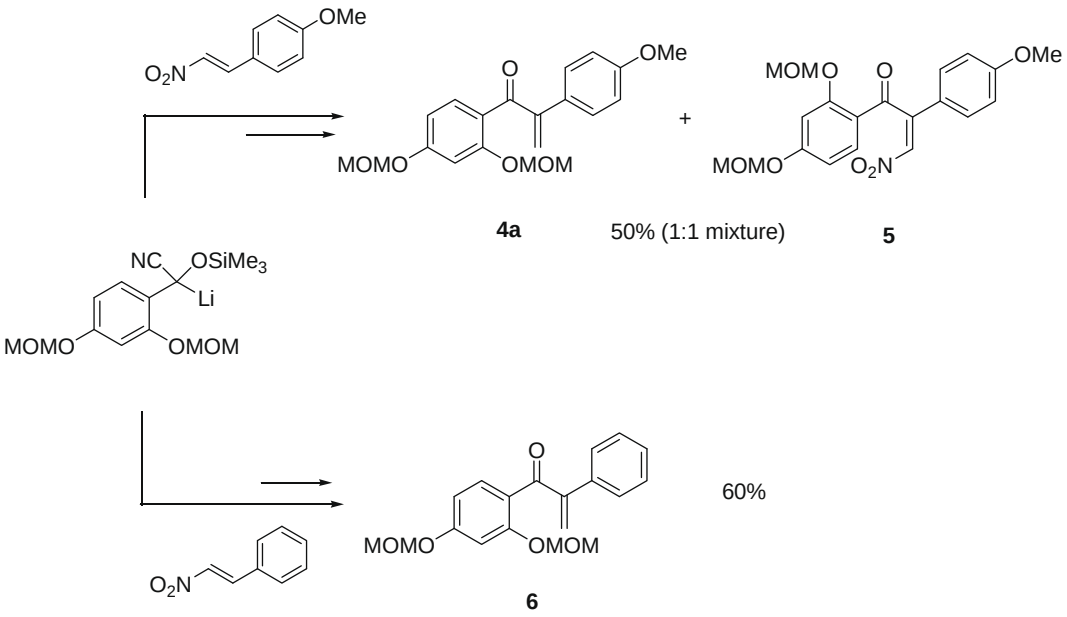


Scheme 1. The Wacker–Cook cyclization–oxidation of alkaloid δ-oxy-α-methylene ketones.



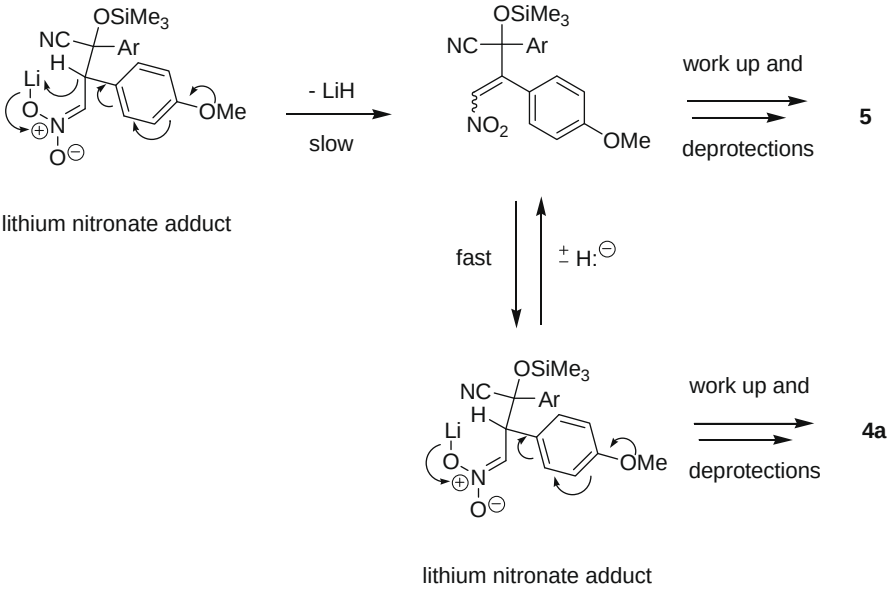
Scheme 2. Retrosynthetic analysis of formononetine based in the Wacker–Cook cyclization as key step.



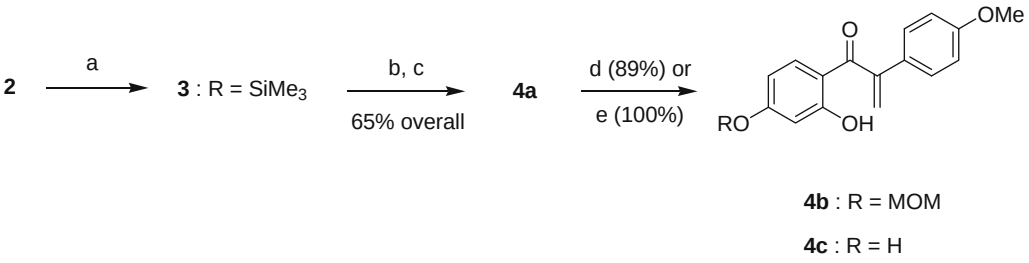
Scheme 3. Nitroenone byproduct **5** is formed when the lithium salt of protected cyanohydrin **2** is used.

the isoflavone formononetine **1** in 52–58% yields (Scheme 6). In our preliminary experiments, we successfully used dioxane as solvent, but the acid catalyzed removal of the protecting groups (for substrates **4a** and **4b**) was extremely slow. On the other hand, with *t*-BuOH as solvent, both the cyclization and acid hydrolysis proceeded at reasonable rates and was the solvent of choice in these particular cases.[13]

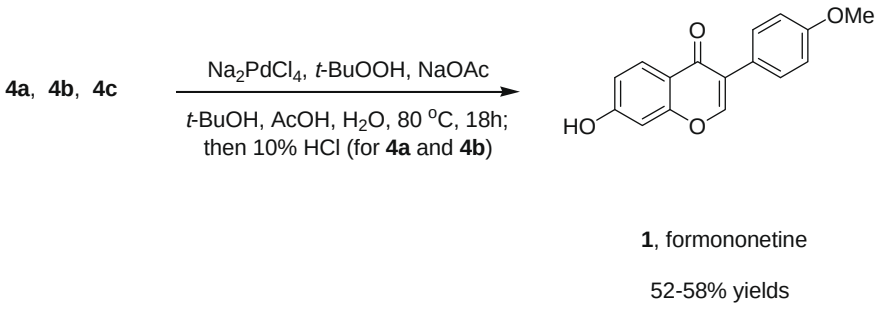
The remarkable stability of free phenol groups under these oxidation conditions is noteworthy and allows its use in unprotected form in this reaction. This is very important since hydroxylated isoflavones are common as natural products and also because free phenol groups usually interfere in the base catalyzed cyclization methods used in isoflavone or isoflavanone



Scheme 4. Mechanism proposal for the formation of nitroenone **5**. Ar = 2,4-bis-(MOM)phenyl group.



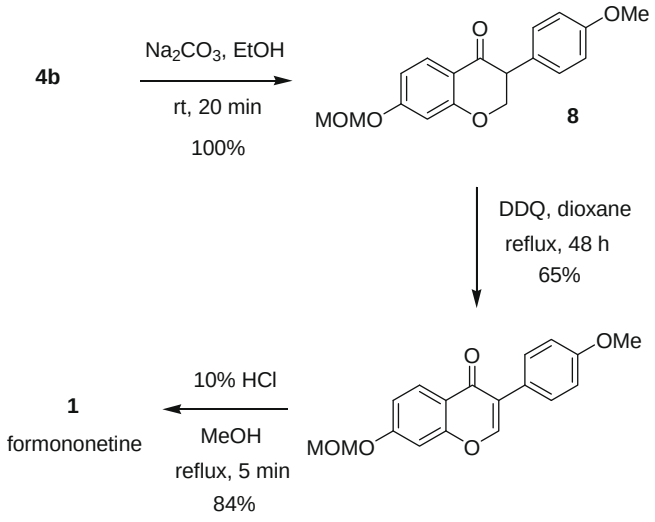
Scheme 5. Syntheses of enones **4a**–**c**. Reagents and conditions: (a) KH, DME, rt, then (*E*)-4-methoxy-β-nitrostyrene, then Na_2HPO_4 buffer in H_2O; (b) 5% H_2SO_4 in H_2O, THF, 50 °C, 14 h; (c) Et_3N, Me_2CO, rt; (d) BCl_3, CH_2Cl_2, rt; (e) 20% H_2SO_4 in H_2O, THF, 55 °C, 3 h.



Scheme 6. Use of the Wacker–Cook method in the synthesis of isoflavones from α-methylene deoxybenzoins.

syntheses. As an example from our laboratory, α-methylenedeoxybenzoin **4c** is recovered unchanged when treated with base reagents (alkaline carbonates, tertiary amines), but **4b** cyclizes quantitatively to isoflavanone **8** in 20 min at rt with Na_2CO_3 in EtOH (Scheme 7). For the purpose of comparison, an authentic sample of formononetine was secured from **8** by DDQ dehydrogenation and acid catalyzed removal of the phenol protecting group.

We hope that the method reported herein will find ample use in the synthesis of more complex hydroxylated isoflavones. We are currently pursuing work along these lines to contribute to this issue.



Scheme 7. Alternative synthesis of formononetine.

Acknowledgments

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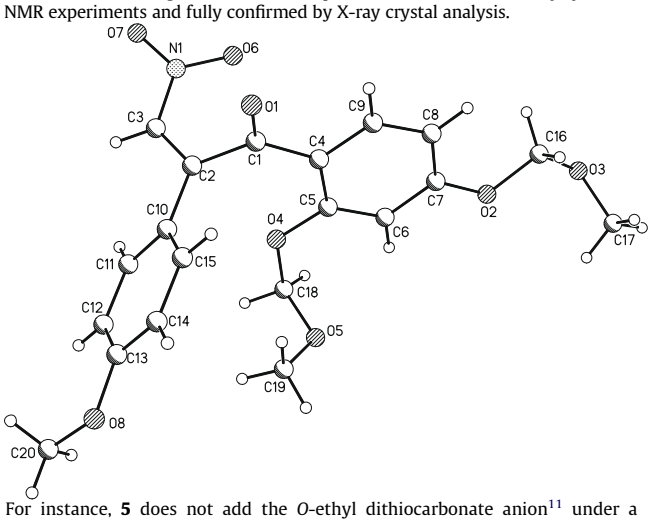
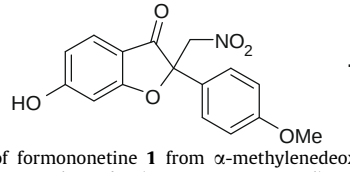
6. Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91–94.
7. Ferriño, S. A.; Maldonado, L. A. *Synth. Commun.* **1980**, *10*, 717–723.
8. Protected cyanohydrin **2** was obtained in 83% overall yield from commercial 2,4-dihydroxybenzaldehyde by bis methoxymethylation ($ClCH_2OMe$, NaH, THF) and cyano O-silylation (Me_3SiCN, catalytic KCN and 18-crown-6, C_6H_6). See: Greenlee, W. J.; Hangauer, D. G. *Tetrahedron Lett.* **1983**, *24*, 4559–4562. for the cyano O-silylation reaction.
9. Nitroenone **5**: Yellow crystalline solid; mp 158–160 °C (EtOH–hexanes). IR (KBr): 1645, 1597, 1505, 1333, 1256, 1158, 1132, 1004 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 9 Hz, 2H), 7.36 (s, 1H), 6.89 (d, J = 9 Hz, 2H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 5.19 (s, 2H), 5.0 (s, 2H), 3.81 (s, 3H), 3.46 (s, 3H), 3.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.13, 163.43, 162.40, 158.87, 153.83, 132.81, 130.61, 129.49, 122.85, 119.17, 114.79, 109.59, 102.30, 94.13, 94.02, 56.40, 56.17, 55.44. MS (EI, 70 eV): m/z (%) 403 (M^+, 1), 312 (42), 225 (56), 45 (100). HRMS (FAB): $[M+1]^+$ calcd for $C_{20}H_{22}NO_8$, 404.1345, found: 404.1342.The *Z* configuration of this compound was first established by cycleNOE NMR experiments and fully confirmed by X-ray crystal analysis.



10. For instance, **5** does not add the *O*-ethyl dithiocarbonate anion[11] under a variety of conditions and is remarkably stable to $NaBH_4$ even in boiling MeOH. However, the acid hydrolysis of **5** proceeds with cyclization to coumaranone **7** in 90% yield, but this compound was also useless because it was recovered unchanged toward base treatments.[12]
11. Ouvry, G.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2907–2909.
12. Coumaranone **7**: Pale yellow crystalline solid; mp 177–178 °C (EtOH–hexanes). IR (KBr): 3178, 1675, 1611, 1557, 1306, 1255, 1169, 1029 cm^{-1}. ^1H NMR (300 MHz, C_3D_6O): δ 9.98 (broad signal, OH, exchanges with D_2O), 7.53 (d, J = 9 Hz, 2H), 7.52 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 9 Hz, 2H), 6.70 (dd, J = 9, 1.8 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 5.37 (AB system, J_{AB} = 14.4 Hz, 2H), 3.77 (s, 3H). ^{13}C NMR (75 MHz, C_3D_6O): δ 194.81, 174.10, 167.91, 161.23, 127.19, 127.09, 126.44, 115.10, 113.37, 112.98, 99.41, 88.48, 79.29, 55.62. MS (EI, 70 eV): m/z (%) 315 (M^+, 30), 269 (100), 137 (80), 133 (97). HRMS (FAB): $[M+1]^+$ calcd for $C_{16}H_{14}NO_6$, 316.0821, found 316.0829



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13. The synthesis of formononetine **1** from α-methylenedeoxybenzoin **4b** is a representative example. **4b** (80 mg, 0.254 mmol), Na_2PdCl_4 (89 mg, 0.305 mmol), and NaOAc (21 mg, 0.254 mmol) are dissolved in a mixture of *t*-BuOH (5.4 mL), AcOH (1.8 mL), and water (5.4 mL) in a 25 mL round bottomed flask; a 70% *t*-BuOOH solution in water (0.05 mL, 0.36 mmol) is added. The reaction mixture is heated in an oil bath at 80 °C for 18 h, cooled at rt, diluted with a water-ice mixture (3 mL), and acidified with 10% aqueous HCl (5 mL). After refluxing for 6 h it was cooled at rt, neutralized with solid $NaHCO_3$, and the organic solvent removed at reduced pressure (rotary evaporator). The suspension was diluted with brine and extracted with AcOEt (3 × 10 mL), the organic layers dried over Na_2SO_4 and the solvent removed at reduced pressure (rotary evaporator). The dark brown semisolid was purified by silica gel flash chromatography using a 4:1 mixture of hexanes/AcOEt as eluent to give 32 mg (53% yield) of formononetine as colorless needles, mp 254–256 °C (EtOH); lit. mp 257 °C: Mahal, H. S.; Rai, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1769–1771. Using this procedure, **4a** and **4c** gave formononetine in 58 and 52% yields, respectively, but it should be noted that, in the latter case, the HCl treatment is not required.Formononetine **1**. IR (KBr): 1622, 1583, 1446, 1266, 1246, 1177, 1024 cm^{-1}. ^1H NMR (300 MHz, CD_3OD + DMSO-d_6): δ 8.07 (s, 1H), 7.93 (d, J = 9 Hz, 1H), 7.38 (d, J = 9 Hz, 2H), 6.88 (d, J = 9 Hz, 2H), 6.84 (dd, J = 9, 2 Hz, 1H), 6.76 (d, J = 2 Hz, 1H), 3.71 (s, 3H) ^{13}C NMR (75 MHz, CD_3OD + DMSO-d_6): δ 176.96, 164.00, 160.61, 159.19, 154.29, 131.16, 128.29, 125.37, 125.05, 117.95, 116.13, 114.58, 103.05, 55.60. MS (EI, 70 eV): m/z (%) 269 (M^{+1}, 100), 268 (M^+, 72), 132 (62).