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Unexpected Truce–Smiles type rearrangement of 2-(2′-pyridyloxy)phenylacetic esters: synthesis of 3-pyridyl-2-benzofuranones†

W. Randal Erickson* and Marc J. McKennon

Dow AgroSciences, 9330 Zionsville Rd, Indianapolis, IN 46268, USA

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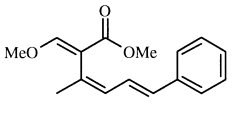
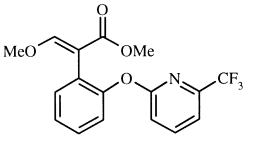
Abstract

Enolization of 2-(2′-pyridyloxy)phenylacetic acid esters with either potassium or sodium hydride induced a Truce–Smiles rearrangement, producing pyridine substituted 2-benzofuranones. Rearrangement of a 2-(4-nitrophenoxy)phenylacetate and a 2-(2′-pyrimidyloxy)phenylacetate produced similar results.

As a part of our fungal crop disease management program, we have targeted many structures belonging to the strobilurin class of compounds for use as oömycete control in vines. One of them, β-methoxyacrylate **1**, is structurally related to the natural product Strobilurin A. Both **1** and Strobilurin A share the β-methoxyacrylate subunit, believed to be the toxiphore responsible for the observed potent fungicidal activity of this compound class.[1]



Strobilurin A



1

Many procedures exist for the synthesis of this moiety.[2] The most straightforward involves formylation of the corresponding ester enolate, followed by *O*-methylation of the resultant aldehyde.[3] However, no formylation adducts were produced when compounds **2** were submitted to these literature conditions (Scheme 1). Rather, enolate attack on the pyridine ring was observed.

* Corresponding author. E-mail: wrerickson@dowagro.com

† Dedicated to the memory of Professor Arthur G. Schultz.

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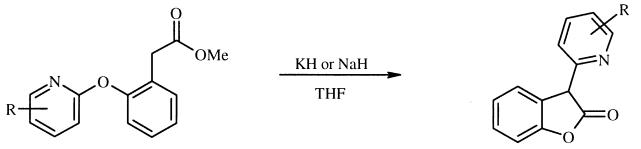
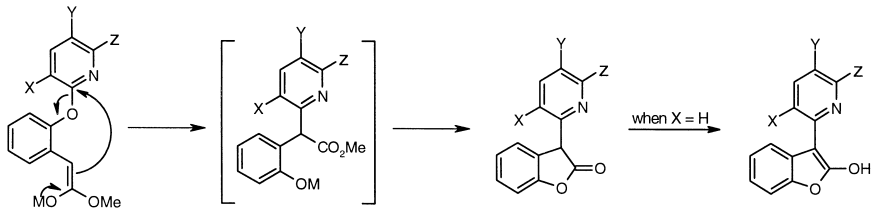
We now wish to report this Truce–Smiles type rearrangement of 2-(2-pyridyloxy)phenylacetic acid esters **2** as a method for preparation of 3-pyridyl-2-benzofuranones **3**.



2 **3**

Scheme 1.

The requisite esters **2** were prepared by treating the disodium salt of 2-hydroxyphenylacetic acid with the corresponding halopyridine in DMSO, followed by esterification with MeI/K_2CO_3 (Scheme 2). The formylation of **2a** was attempted by enolization with KH/THF at –20°C followed by treatment with methyl formate. The following empirical observations were noted. (1) No reaction between the ester enolate and methyl formate was observed at –20°C. (2) When the reaction was warmed to 0°C, a deep green color appeared. (3) Aqueous quench of the reaction produced a bright orange solid after extraction. (4) ^{1}H NMR showed no resonances upfield of 5.2 ppm, indicating loss of the ester methyl group and α-methylene. (5) Also absent was the diagnostic signal at ~7.4 ppm indicative of the vinyl proton present in the enol form of a formyl ester. (6) Mass spectral analysis indicated loss of 32 amu with respect to **2a**, indicating a loss of methanol during the course of the reaction. (7) Exposure of the orange product to weak base (K_2CO_3) regenerated the green color seen during the formylation attempt. (8) Similar treatment of **2b** (NaH/THF at 0°C) gave nearly identical spectral results, but surprisingly without any appreciable color changes during reaction, followed by isolation of a colorless product.



2 **3** **4**

a X = H, Y = H, Z = CF_3 **c** X = H, Y = H, Z = H

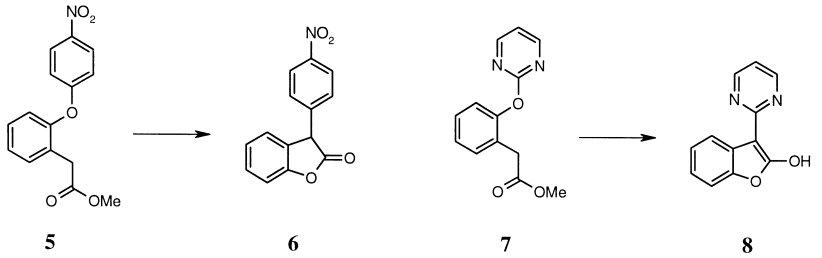
b X = CF_3, Y = Cl, Z = H **d** X = Cl, Y = H, Z = H

Scheme 2.

All of these seemingly anomalous observations were consistent with the production of a 3-substituted 2-benzofuranone **3** as the product of a Truce–Smiles type rearrangement of **2**. For example, treatment of **2a** with either NaH or KH[4] produced a colorless ester enolate that was stable in solution at temperatures below 0°C. Warming above this temperature induced the rearrangement, producing an intermediate phenoxide which spontaneously lactonized to the benzofuranone **3a**.

The observed color changes could arise from overlap of the various π-systems during the course of the reaction; i.e. the benzofuranones **3a** and **3c** underwent tautomerism to the orange colored 2-hydroxybenzofurans **4a** and **4c**, which are green when deprotonated.[5] These tautomers appear to be stabilized further by intramolecular hydrogen bonding to the pyridine nitrogen. In the case of **3b** and **3d**, steric interactions between the 3-substituent of the pyridine moiety and H-5 of the benzofuranone ring prevent co-planarity of the two rings, precluding formation of the 2-hydroxybenzofurans **4b** and **4d**. Spectral data support this supposition: **3b** and **3d** exhibit a carbonyl stretch at 1820–1815 cm^{-1} whereas **4a** and **4c** show a strong IR band at 1680–1675 cm^{-1}.

We wished to briefly examine the generality of this rearrangement with other activated aromatic ring systems. Treatment of **5** (prepared from 1-fluoro-4-nitrobenzene) with NaH in THF at 0°C resulted in a deep violet solution (Scheme 3). Extractive work-up with ethyl acetate and dilute HCl followed by chromatography gave the nitrophenol adduct **6**, isolated as a pale straw colored solid. The presence of the keto form is supported by a singlet at 5.3 ppm in the proton NMR spectrum and an IR resonance at 1792 cm^{-1}.



5 **6** **7** **8**

Scheme 3.

Finally, as anticipated, the rearrangement of **7** (prepared from 2-chloropyrimidine) was facile, giving the hydroxybenzofuran **8**, isolated as a bright orange red solid. Curiously, organic solutions of **8** did not change color within a pH range of 3 to 10, suggesting an extremely tight intramolecular hydrogen bond between the enolic hydrogen and a pyrimidine nitrogen. Examination of the proton NMR spectrum of compound **8** provided further evidence.[6] In THF-d_8 at ambient temperature, the benzene protons appear normal, but the pyrimidine protons H-4′ and H-6′ (adjacent to the nitrogens) appear as broad singlets (8.8 and 8.2 ppm) while the H-5′ proton appears as a triplet (6.7 ppm). This supports the hypothesis of hydrogen bonding locking the rings in a planar configuration (or nearly so), but the pyrimidine ring 'snaps' back and forth between its two nitrogens rapidly on the NMR time scale. Cooling to minus 10°C slows this rotation, allowing the non-equivalent H-4′ and H-6′ resonances to be observed as sharp multiplets. A rotational barrier of 17 kcal/mol was calculated,[7] and the observed spectrum agrees with the predicted model.

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3. (a) Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1987**, *52*, 4303. (b) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *2*, 5397. (c) Nakata, T.; Kuwabara, T.; Tani, Y.; Oishi, T. *Tetrahedron Lett.* **1982**, *23*, 1015.
4. Lithium salts of **2** do not appear to undergo this rearrangement.
5. For similar observations in 3-phenyl-2-benzofuranones, see: (a) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Org. Chem.* **1987**, *52*, 5425. (b) Black, T. H.; Arrivo, S. M.; Schumm, J. S.; Knobeloch, J. M. *J. Chem. Soc., Chem. Commun.* **1986**, 1524.
6. The authors wish to thank Dr. Scott Thornburgh for his assistance in acquisition and interpretation of these spectra.
7. Spectra were calculated with the program DNMRSIM Version 1.0 (1994, Heinrich-Heine-University, Dusseldorf Germany), a PC version of the Binsch program DNMR3. Input parameters were as follows: $\omega_A = 2634$ Hz (8.78 ppm), $\omega_B = 2463$ Hz (8.21 ppm), $\omega_C = 2001$ Hz (6.67 ppm), $J_{AB} = 2.39$ Hz, $J_{AC} = 4.29$ Hz, $J_{BC} = 6.35$ Hz.