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Free radical reactions for heterocycle synthesis. Part 4: A double *ipso* substitution reaction for azacoumarins

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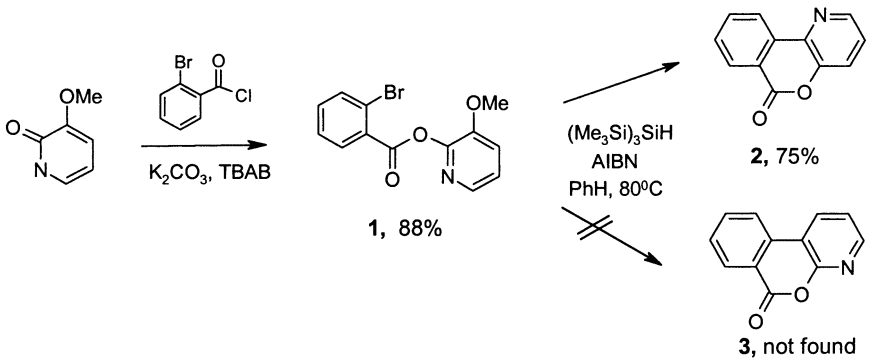
Abstract—A highly efficient route to azacoumarins with an unusual mechanism of double *ipso* substitutions is described.

Intramolecular nucleophilic and electrophilic *ipso* substitution reactions are typical aromatic substitution processes. The radical versions of these reactions, however, have not received much attention until very recent studies on homolytic substitutions of aromatic compounds. Extensive effort in this area has been focused on the development of new synthetic methods and investigation of reaction mechanisms.[1] We recently reported the synthetic utilities of enol benzonate radicals in the construction of isoindolinones, isoquinolinones, and various spiro ring systems.[2] Herein, we describe our new findings on the radical reaction of aryl benzonates in the synthesis of coumarin-based ring systems. Coumarins and their aza-analogs are naturally occurring lactones which possess valuable pharmaceutical properties along with crop protection and analytical utilities.[3]

A radical precursor aryl benzoate **1** is prepared by *O*-acylation of 3-methoxy-2(1*H*)-pyridone with 2-bromobenzoyl chloride in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB). This intermediate is then treated with 1.5 equiv. of tris(trimethylsilyl)silane under a standard radical reaction condition (cat. AIBN, benzene, 80°C) to afford azacoumarin **2** in 75% yield (Scheme 1). We were surprised to find that the structure of the product was 10-oxa-4-azaphenanthren-9-one (**2**) instead of the anticipated direct 1,6-*ipso* substitution product 10-oxa-1-azaphenanthren-9-one (**3**).[4]

Based on the structure of **2**, we proposed a mechanism as shown in Scheme 2 to illustrate this transformation. It is believed that the rearrangement is initiated with a 1,5-*ipso* substitution of radical **4** via intramolecular



Scheme 1.

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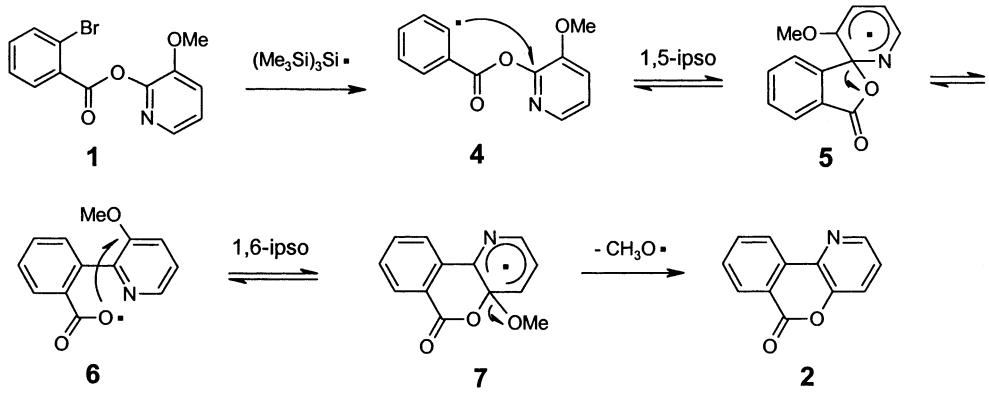
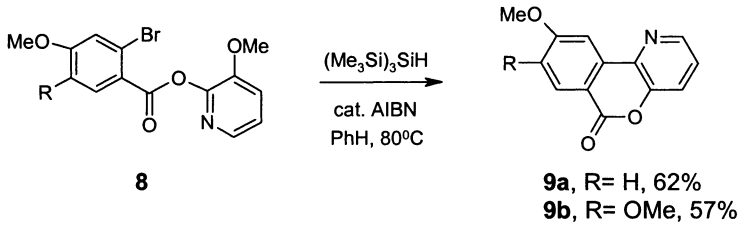


Scheme 2. A double *ipso* substitution mechanism.



Scheme 3.

attack at the 2-position of the pyridine ring to generate a carbonyloxy radical **6**. Since the decarboxylation rate of aromatic carbonyloxy radicals ($k=10^4$–10^5 s^{-1})[5] is significantly slower than alkyl carbonyloxy radicals ($k=10^8$–10^{10} s^{-1}), it gives radical **6** a chance to undergo a second 1,6-*ipso* substitution to displace the methoxy group. Further support for *ipso* substitution of aromatic carbonyloxy radicals comes from a study by Togo and Yokoyama in oxidative cyclization of *o*-arylaromatic acids.[6] The first *ipso* displacement process described in Scheme 2 may be reversible. However, extrusion of the methoxy radical is essentially irreversible, which drives the reaction to completion. The methoxy group seems to be critical to promote the whole rearrangement process. To test this hypothesis, we carried out a control reaction using a radical precursor similar to aryl benzoate **1** with the exception that it has no methoxy group at the 3-position of the pyridine. In this case, cyclized product **2** is obtained in less than 10% yield, while the major component (85%) is the direct reduction product.

Two other methoxy-substituted azacoumarins are prepared (Scheme 3). The structure of **9b**[7] is confirmed by an X-ray diffraction study (Fig. 1). This reaction has been applied to the synthesis of coumarins, but yields are relatively low compared to the azacoumarins. Since benzene is a less activated ring system than pyridine, the competition between the cyclization and the direct reduction of the initial radicals yields a mixture of the cyclized product **11** and the direct reduction product **12** (Scheme 4).

In brief, we have discovered a mechanistically interesting reaction that is synthetically useful for the synthesis of azacoumarins.

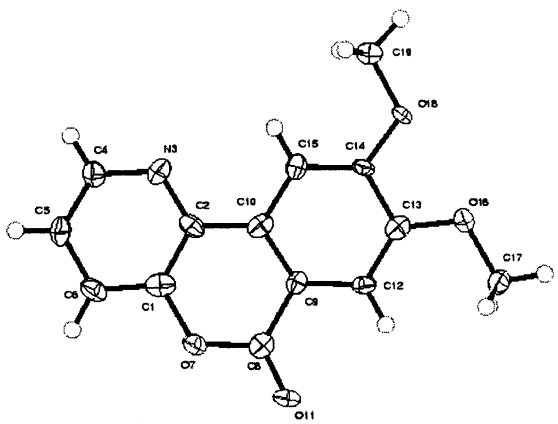
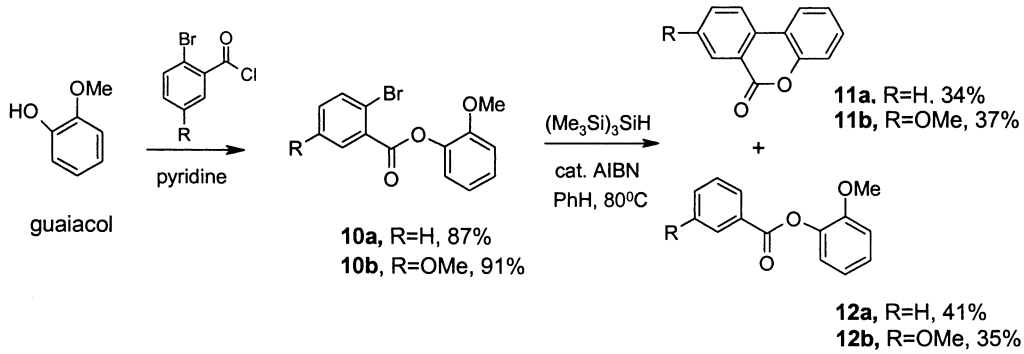


Figure 1. X-Ray structure of **9b**.

Acknowledgements

The authors thank William Marshall for the X-ray structural analysis of **9b**.



Scheme 4.

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7. Analytical data for **9b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, CH_3), 4.14 (s, CH_3), 7.25 (m, 1H), 7.66 (d, 1H), 7.75 (s, 1H), 8.09 (s, 1H), 8.59 (d, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.8 (q), 55.0 (q), 102.4 (d), 108.4 (d), 114.1 (s), 122.4 (d), 123.0 (d), 129.1 (s), 135.1 (s), 144.0 (d), 145.7 (s), 149.8 (s), 153.8 (s), 158.3 (s); IR (neat) 1719 (s, C=O) cm^{-1}; MS *m*/*e* (rel. int.) 258 (M^++1, 100).