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Facile Construction of Oxa-Aza Spirobicycles *via* a Tandem Carbon-Hydrogen Bond Oxidation

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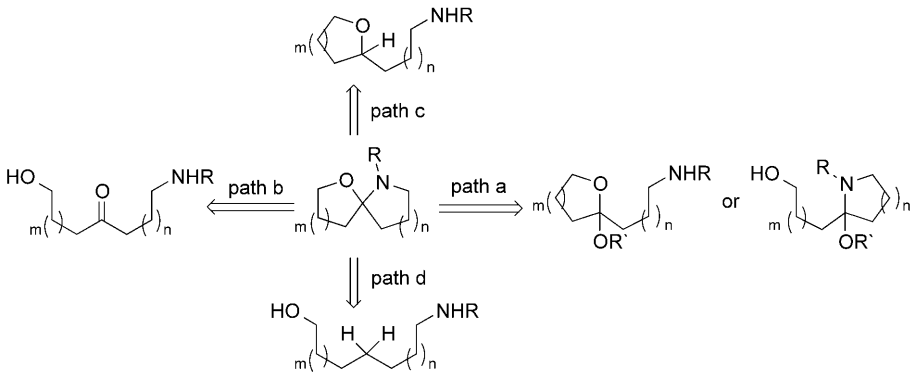
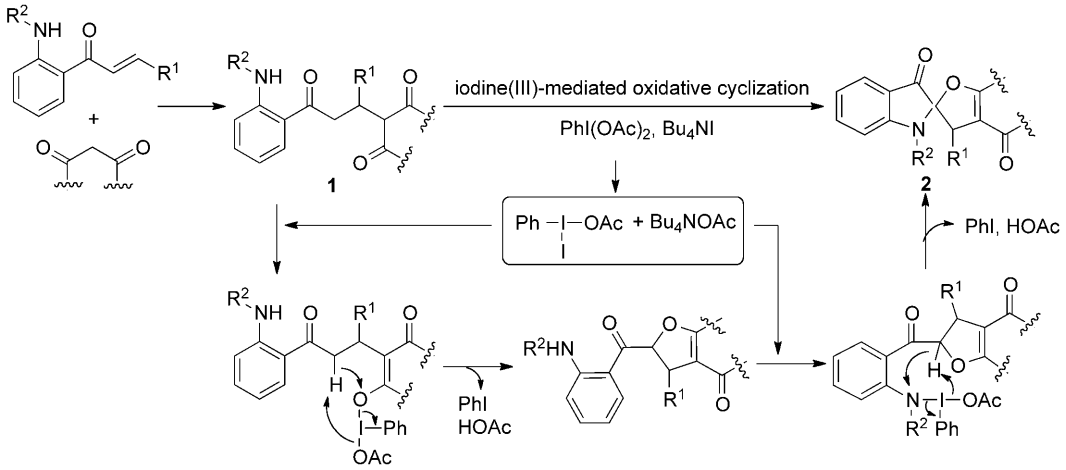
Abstract: An efficient method to construct oxa-aza spirobicycles *via* an iodine(III)-mediated tandem carbon-hydrogen bond oxidation with the combination of iodobenzene diacetate and tetrabutylammonium iodide is reported.

Keywords: C–H activation; cyclization; hypervalent compounds; oxidation; spiro compounds

As important heterocyclic compounds, oxa-aza spirobicycles (spiroaminals or spiroaminoketals) are widely distributed in a number of biologically active compounds. For example, the natural products marineosins A and B,[1] azaspiracid,[2] tomatidine,[3] sanglifehrin A,[4] manzamine X,[5] stemotinine and isostemotinine alkaloids[6] have an oxa-aza spirobicyclic unit as their core structure. These important skeletons have attracted the attention of a number of synthetic research groups, and many synthetic methods have been documented.[7] Cyclization of hemiaminals[8] or hemiketals[9] (path a, Scheme 1) and bicyclization of the functionalized ketone derivatives[10] (path b, Scheme 1) are the classical and commonly used approaches to oxa-aza spirobicyclic systems. Additionally, the Suárez group reported the preparation of oxa-aza spirobicycles in carbohydrate systems *via* an N-radical-mediated intramolecular hydrogen atom transfer (path c, Scheme 1).[11] The Fishwick group found a 1,3-dipolar cycloaddition of azomethine ylides with alkenes to synthesize spiroaminals.[12] Imhof and coworkers described a ruthenium-catalyzed [2+2+1] cycloaddition of ketimines, carbon monoxide and ethylene to access spiro[pyrrolidin-2-one] derivatives.[13] The groups of Bermejo,[14a] Boger,[14b] and Yao[14c] developed oxidative cyclizations of cyclic enamines to provide oxa-aza spirobicyclic compounds. In spite of the considerable amount of effort that has been expended in the preparation of spiroaminals, the direct construction of oxa-aza spirobicyclic skeletons from two carbon-hydrogen bonds is highly desirable (path d, Scheme 1). Recently, we have directed our focus on the hypervalent iodine[15] species-mediated oxidative cyclizations to synthesize various cyclic compounds



Scheme 1. Approaches to oxa-aza spirobicyclic systems.

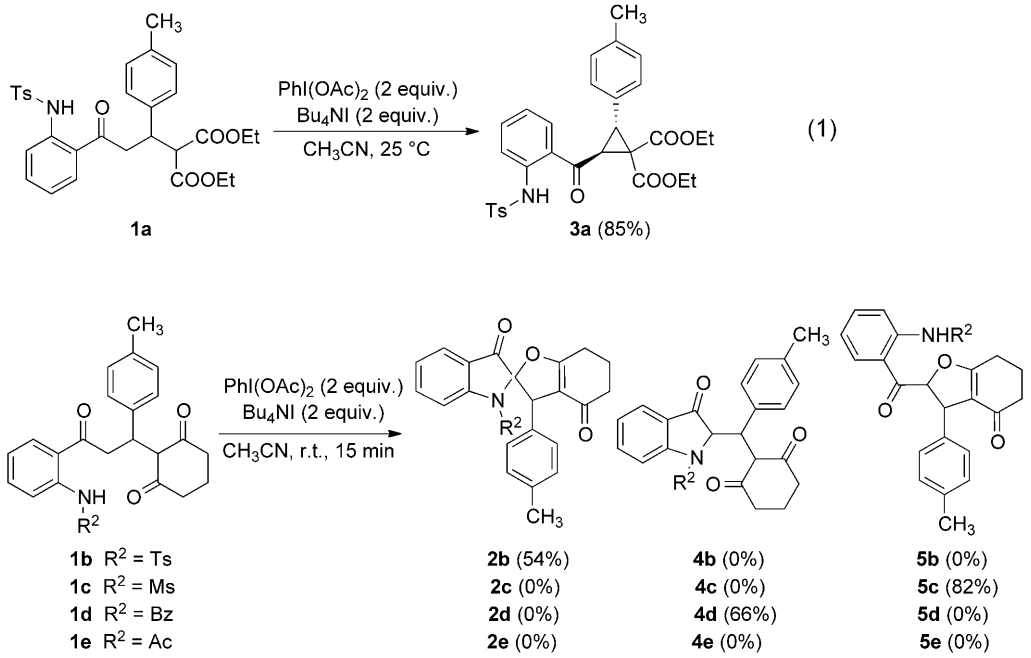


Scheme 2. Proposed reaction pathway for the iodine(III)-mediated construction of oxa-aza spirobicycles.

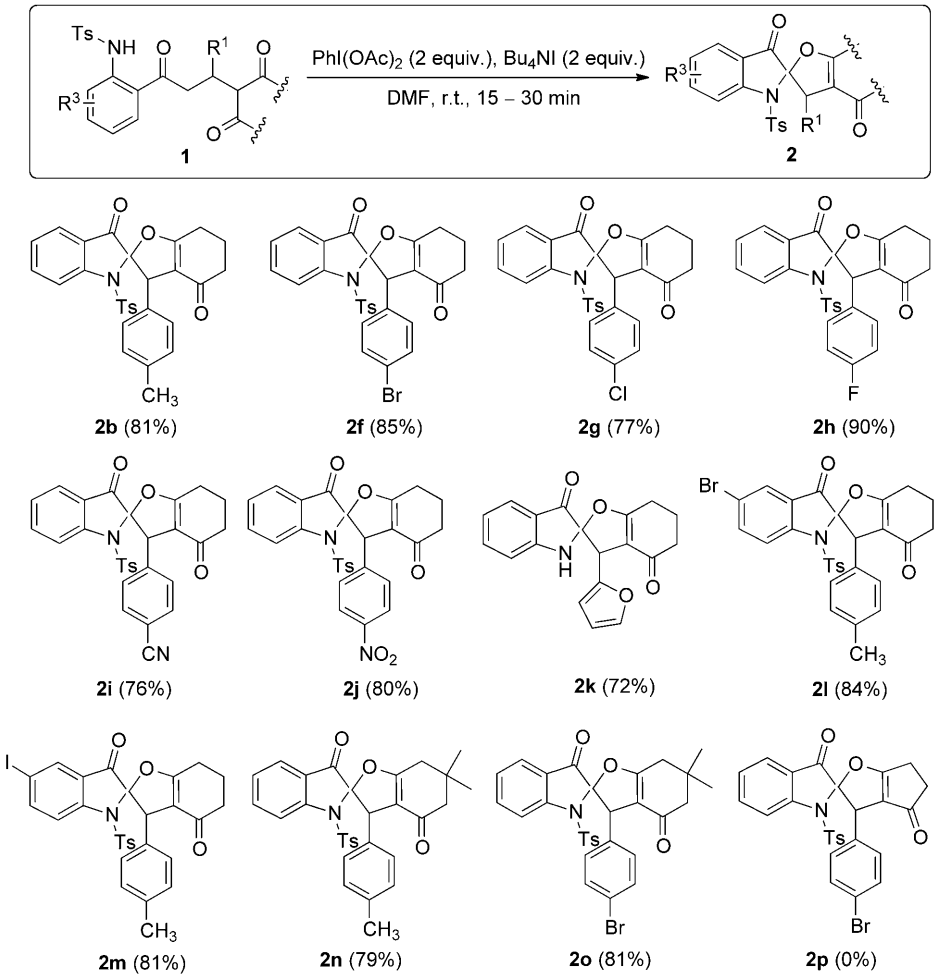
such as aziridines,[16a] cyclopropanes,[16b] oxetanes,[16c] azetidines,[16d] and dihydrofurans.[16e] In order to further extend the utility of this approach, we investigated the possibility of constructing oxa-aza spirobicycles *via* an iodine(III)-mediated tandem carbon-hydrogen bond oxidation with the combination of iodobenzene diacetate and tetrabutylammonium iodide (Scheme 2). The acyclic precursor **1** could be prepared from the corresponding Michael addition of β-dicarbonyl compounds with 1-(2-aminophenyl)-prop-2-en-1-one derivatives.[17]

First, we examined the oxidative cyclization of compound **1a** derived from diethyl malonate and *N*-Ts-1-(2-aminophenyl)-3-*p*-tolylprop-2-en-1-one under the previously optimized conditions [$PhI(OAc)_2$ (2.0 equiv.), Bu_4NI (2.0 equiv.), CH_3CN, 25 °C] [Scheme 3, Eq. (1)]. The reaction proceeded smoothly and afforded one major product after 10 min. However, the ^1H NMR spectrum of the isolated compound indicated that it was not the expected oxa-aza spirobicyclic compound **2a**, but a cyclopropanation product **3a**.

To inhibit the cyclopropanation, the malonate group in **1a** was replaced by a cyclohexane-1,3-dione group.[16e] To our delight, the desired oxa-aza spirobicyclic product **2b** was isolated in 54% yield from the



Scheme 3. Examination of the nitrogen protecting groups.



Scheme 4. Construction of oxa-aza spirobicycles under the optimized conditions.

reaction of **1b** (Scheme 3). Further investigation indicated that *N*-Ts protection in substrate **1** was essential for the formation of oxa-aza spirobicyclic product. When a Ms group was used instead of the Ts group, only one oxygen-cyclization product **5c** was generated. When the protecting group was changed to the benzoyl group, a nitrogen-cyclization product **4d** was obtained. When *N*-acetyl protected substrate **1e** was employed, no reaction was observed under the same conditions.

The screening of solvents revealed that the reaction could be conducted in various organic solvents, and DMF was the best choice, in which product **2b** was formed in 81% yield. Increasing or decreasing the amounts of $PhI(OAc)_2$ and Bu_4NI did not improve the yield. A sluggish reaction was observed when the reaction was conducted at 0 °C. While optimizing the reaction conditions, we found that the reaction was not sensitive to moisture and air. Even when the reaction was carried out in an air-open system with water as the solvent, the reaction gave rise to the oxa-aza spirobicyclic product **2b** in 51% yield. As the control experiments, when $PhI(OAc)_2$ was replaced by PhIO, or when Bu_4NI was replaced by Bu_4NBr, no oxa-aza spirobicyclic product was formed.

With the optimized reaction conditions established, various substrates were examined, and representative results are shown in Scheme 4. The reaction was found to tolerate a range of different groups with different electronic demands on the aromatic rings. Substrates containing a cyclohexane-1,3-dione group were successfully converted to the oxa-aza spirobicyclic products in yields ranging from 72% to 90%. When the cyclohexane-1,3-dione group was replaced by the 5,5-dimethylcyclohexane-1,3-dione group, the corresponding products **2n** and **2o** were also formed in good yields. When substrate **1p** derived from cyclopentane-1,3-dione was employed, a complicated reaction was observed, and no desired oxa-aza spirobicyclic product was isolated. The oxa-aza spirobicyclic structure of the obtained products was further confirmed by the single-crystal diffraction analysis of product **2o** (Figure 1).[18]

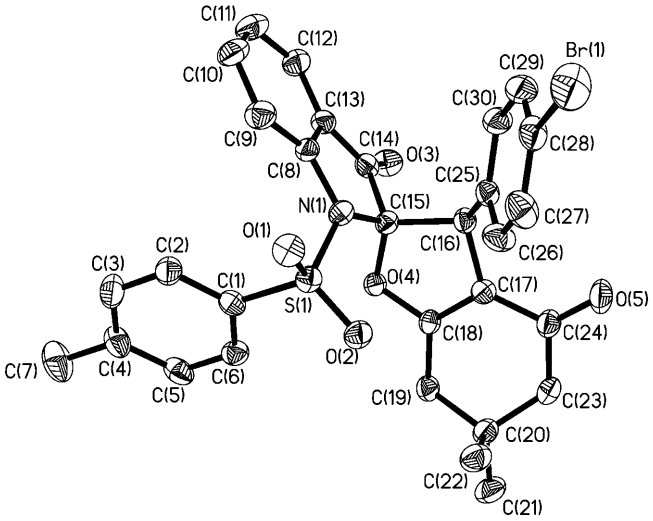


Figure 1. X-ray diffraction structure of **2o**.

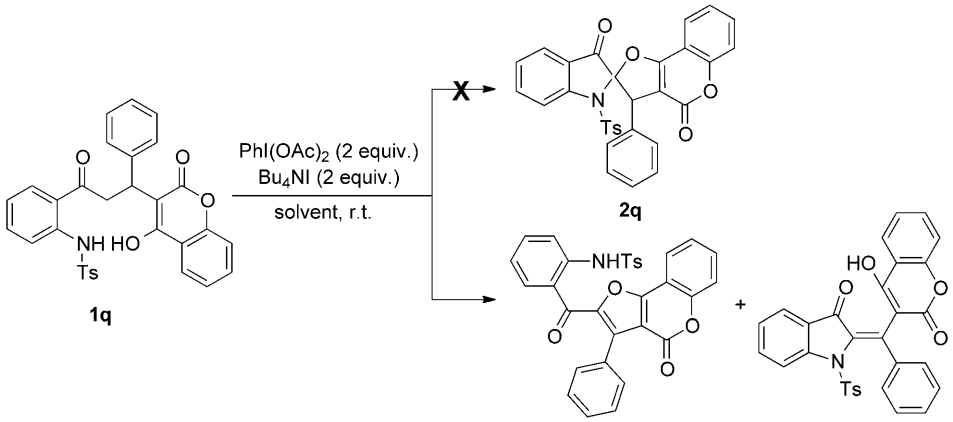
Interestingly, the reaction of substrate **1q**, which was prepared from the Michael addition of *N*-Ts 1-(2-aminophenyl)-3-phenylprop-2-en-1-one with 4-hydroxy-2*H*-chromen-2-one, did not afford oxa-aza spirobicyclic product **2q**, but gave rise to a furan derivative **6** and a 2-methyleneindolin-3-one derivative **7** in 71% and 14% yields, respectively. Moreover, further studies revealed that the ratio of product **6** to product **7** was solvent dependent. When the reaction was conducted in acetonitrile, 2-methyleneindolin-3-one derivative **7** was generated as the major product in 67% yield (Scheme 5). When the amounts of $PhI(OAc)_2$ and Bu_4NI were decreased to 1 equivalent each, both of the reactions in DMF and in CH_3CN gave rise to the same product **8** in similar yields. However, the further treatment of **8** with $PhI(OAc)_2$ and Bu_4NI in DMF and in CH_3CN provided compound **6** and compound **7** as the major product, respectively. According to the above results, products **6** and **7** are presumed to be formed from oxa-aza spirobicyclic product **2q** *via* a selective cleavage of a carbon-nitrogen or a carbon-oxygen bond, and this bond cleavage is solvent dependent (Scheme 6).

In conclusion, we have developed an efficient method to construct oxa-aza spirobicycles *via* an iodine(III)-mediated tandem carbon-hydrogen bond oxidation with the combination of iodobenzene diacetate and tetrabutylammonium iodide. Currently work is in progress to extend its scope, to explore its reaction mechanism and possible synthetic applications.

Experimental Section

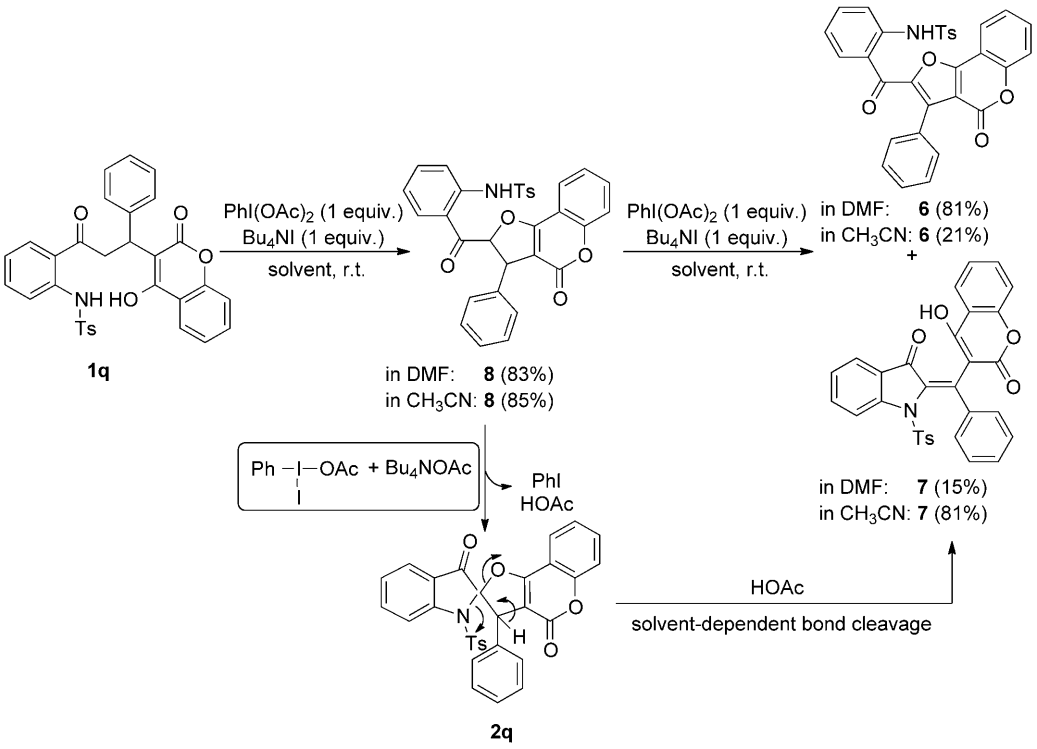
Typical Experimental Procedure

$PhI(OAc)_2$ (161 mg, 0.5 mmol) was added into the mixture of substrate **1b** (126 mg, 0.25 mmol) and Bu_4NI (185 mg, 0.5 mmol) in DMF (2 mL) at 25 °C. Upon completion by TLC after 15 min, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (25 mL), and extracted by ethyl acetate (25 mL × 3). The organic layer was dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to give product **2b** as a colorless solid; yield: 101 mg (81%); mp 188–190 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 7.3$ Hz, 1H), 7.63 (d, $J = 8.3$ Hz, 2H), 7.48 (t, $J = 7.8$ Hz, 1H), 7.24–7.27 (m, 1H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.13 (t, $J = 7.3$ Hz, 1H), 6.99 (d, $J = 8.3$ Hz, 2H), 6.83 (d, $J =$



Solvent	**6** (%)	**7** (%)
DMF	71	14
dioxane	62	20
$ClCH_2CH_2Cl$	56	28
toluene	31	52
EtOAc	26	48
CH_3CN	18	67

Scheme 5.



Scheme 6.

7.8 Hz, 2H), 4.83 (s, 1H), 2.71–2.88 (m, 2H), 2.45–2.66 (m, 2H), 2.33 (s, 3H), 2.27 (s, 3H), 2.10–2.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 194.9$, 194.1, 176.6, 152.0, 144.6, 138.7, 137.4, 136.0, 130.2, 129.7, 129.1, 128.6, 127.8, 125.3, 124.4, 120.7, 115.0, 114.8, 102.4, 55.0, 37.3, 24.2, 21.7, 21.6, 21.3; HR-MS: $m/z = 522.1320$, calcd. for $C_{29}H_{25}NNaO_5S$ $[M+Na]^+$: 522.1351.

Acknowledgements

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[18] CCDC 817211 contains the supplementary crystallographic data of compound **2o** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44)-1223-336033.

