

# Communications

## New Synthetic Route to 2-Pyridones and Its Application toward the Synthesis of (±)-Ipalbidine†

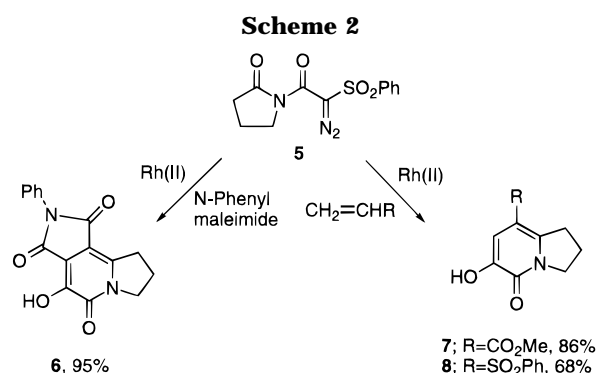
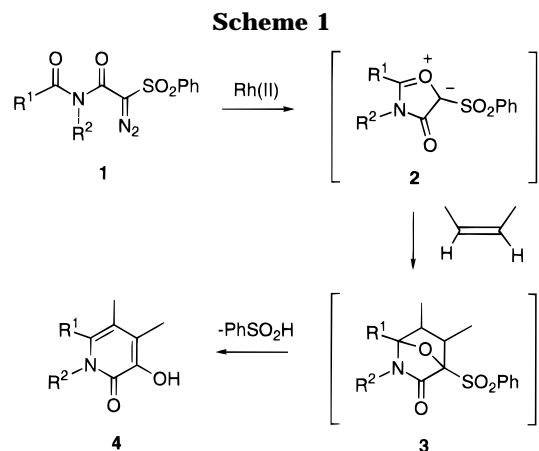
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Six-membered nitrogen heterocycles comprise the backbone of many biologically and structurally interesting alkaloids.<sup>1,2</sup> The 3-hydroxy-2(1*H*)-pyridone (**4**) ring system is a valuable building block in natural product synthesis,<sup>3</sup> as it can act as a common intermediate for the preparation of a wide variety of piperidine, pyridine, quinolizidine, and indolizidine alkaloids.<sup>2,4</sup> Only a few methods of preparing 3-hydroxy-2(1*H*)-pyridones have been reported, and they typically involve harsh conditions that preclude the presence of sensitive functional groups.<sup>5</sup> We envisaged a convenient route to these pyridones by a [3 + 2]-cycloaddition of a phenylsulfonyl-substituted isomünchnone intermediate<sup>6</sup> (i.e., **2**) with an alkene, followed by a subsequent elimination of phenyl sulfonic acid (Scheme 1).

By appropriate selection of the diazo precursor **1** and the dipolarophile, various groups can be introduced into the N-1 and C-4, C-5, C-6 positions. Moreover, substituents can be subsequently introduced at C-3 by conversion of the hydroxyl functionality to a triflate group,<sup>7</sup> followed by a palladium-catalyzed cross-coupling reaction.<sup>8</sup> In this paper, we report on some model studies leading to the regioselective synthesis of various 3-hydroxy-2(1*H*)-pyridones utilizing this novel cascade process. Also presented are the results of the palladium-mediated transformation of the corresponding triflate to various pyridone derivatives, as well as an application



of the method to the synthesis of the indolizidine alkaloid (±)-ipalbidine (**18**).<sup>9,10</sup>

The preparation of the requisite diazoimide **5** was accomplished by a diazo transfer reaction<sup>11</sup> of 1-[(benzenesulfonyl)acetyl]pyrrolidin-2-one with *p*-acetamidobenzenesulfonyl azide and triethylamine. Formation of the isomünchnone ring was achieved by the reaction of **5** with Rh<sub>2</sub>(OAc)<sub>4</sub> to give a rhodium carbenoid species that undergoes an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic dipole (Scheme 2). Bimolecular trapping of the dipole with *N*-phenylmaleimide, methyl acrylate, and vinyl sulfone proceeded in high yield. The initially formed cycloadducts (i.e., **3**) were not isolable or observed, as they all readily underwent ring opening to give the 3-hydroxy-2(1*H*)-pyridones **6–8**.

Cycloadduct **8** was easily converted to the corresponding triflate **9** by treatment with *N*-phenyltrifluoromethanesulfonamide and triethylamine.<sup>12</sup> The synthetic potential of vinyl triflates has been well established over the last decade,<sup>7</sup> and these compounds have been shown to be suitable substrates in various types of coupling reactions, including Stille couplings<sup>8</sup> and Heck reactions.<sup>13</sup> In contrast to the numerous examples of cross-coupling reactions with simple vinyl triflates, there are no ex-

† Dedicated to the memory of Paul Dowd (1936–1996), a valued friend and exceptional scientist.

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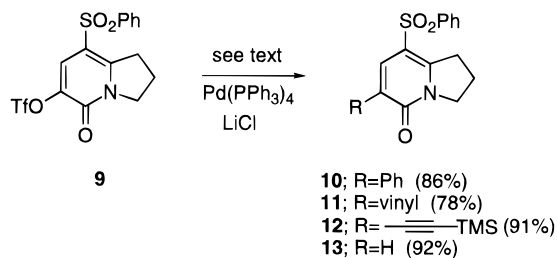
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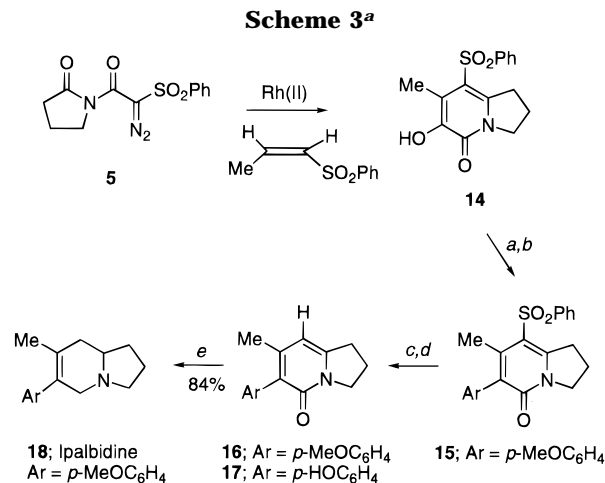
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amples of similar reactions with pyridone-derived triflates such as **9**. To test the reactivity of this new class of triflates, we subjected **9** to coupling reactions with various organometallic reagents.<sup>14</sup> Reaction of **9** with tributylphenyltin in the presence of lithium chloride (3 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) gave the phenyl-substituted pyridone **10** in 86% yield. A related Stille coupling with vinyltributyltin afforded pyridone **11** in 78% yield. (Trimethylsilyl)acetylene underwent palladium-catalyzed coupling with triflate **9** to provide acetylene **12** in 91% yield. Conversion of the triflate into the unsubstituted 2-pyridone (R = H) was achieved *via* a palladium(0)-catalyzed formate reduction<sup>15</sup> to afford **13** in 92% yield.



Our interest in establishing **9** as a useful building block for indolizidine synthesis prompted us to use similar methodology for the preparation of ( $\pm$ )-ipalbidine.<sup>10,16</sup> A short synthesis of this alkaloid was carried out as depicted in Scheme 3. Reaction of  $\alpha$ -diazomide **5** with *cis*-1-(phenylsulfonyl)-1-propene and a catalytic quantity of Rh(II) acetate in benzene at 80 °C provided the



<sup>a</sup> Reagents: (a) (TfO)<sub>2</sub>NPh, NEt<sub>3</sub>; (b) MeOC<sub>6</sub>H<sub>4</sub>SnBu<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, LiCl; (c) Ra-Ni, EtOH (65 °C); (d) 48% HBr, reflux; (e) LiAlH<sub>4</sub>, AlCl<sub>3</sub>.

expected 3-hydroxy-2(1*H*)-pyridone **14** in 51% isolated yield. Conversion of **14** to the corresponding vinyl triflate (86%), followed by Stille coupling with tributyl(4-methoxyphenyl)tin,<sup>17</sup> gave the aryl-substituted 2-pyridone **15** in 72% yield. Desulfonylation of **15** was effected using Raney nickel to give 2-pyridone **16** in 90% yield. Heating a sample of **16** in 48% HBr afforded phenol **17** in 97% yield. Reduction of **17** with alane (LiAlH<sub>4</sub>, AlCl<sub>3</sub>)<sup>10</sup> gave ( $\pm$ )-ipalbidine (**18**) in eight steps in 17% overall yield.

In summary, we have successfully prepared novel 3-hydroxy-2(1*H*)-pyridones from the [3 + 2]-cycloaddition reaction of isomünchnone dipoles and studied the palladium-catalyzed coupling reactions of the corresponding triflates with various organometallic reagents. This methodology has proved to be applicable for the synthesis of the indolizidine alkaloid ( $\pm$ )-ipalbidine.

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**Supporting Information Available:** Experimental details for the preparation of, as well as spectroscopic data for, all new compounds (10 pages).

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