

α -Iodination of Enaminones with Bis(pyridine)iodonium(I) Tetrafluoroborate

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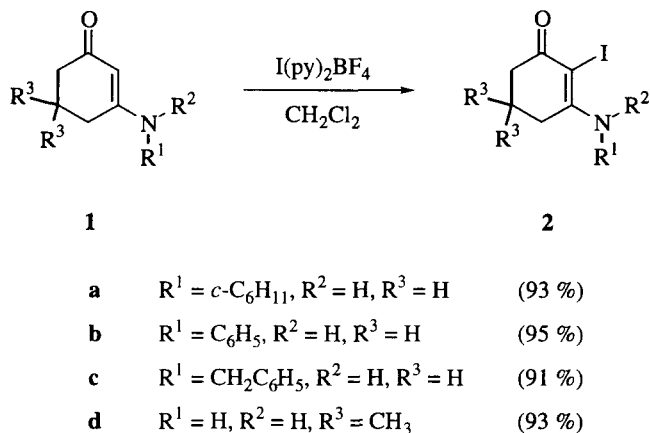
Abstract: Primary, secondary and tertiary enaminones react with bis(pyridine)iodonium(I) tetrafluoroborate in methylene chloride at room temperature to give α -iodo enaminones in almost quantitative yields. The reported reaction is the first known example of direct iodination of tertiary enaminones.
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α -Iodo enaminones have recently been described as useful synthetic intermediates for the preparation of biologically active heterocyclic compounds.¹ However, the iodination of enaminones cannot be considered a simple procedure based on methods currently available. In fact, only a few particular methods are known^{1b,2} and these prove to be inadequate for the preparation of tertiary α -iodo enaminones.^{1,2}

In previous papers we have described the preparation and reactivity of bis(pyridine)iodonium(I) tetrafluoroborate [I(py)₂BF₄] towards several unsaturated substrates.³ In particular, I(py)₂BF₄ allows the iodofunctionalization of 1-hetero-1,3-butadienes in good yields.⁴ These facts prompted us to study the reaction of I(py)₂BF₄ with enaminones.

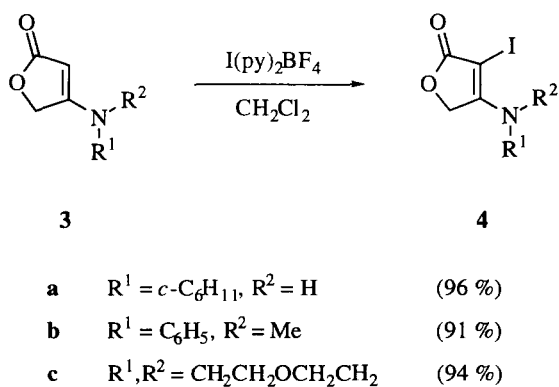
We therefore treated the enaminone **1a** (prepared by reaction of 1,3-cyclohexanedione and cyclohexylamine)⁵ with bis(pyridine)iodonium(I) tetrafluoroborate in CH₂Cl₂ at room temperature. The complete consumption of starting material (2 hours) was confirmed by ¹H NMR spectroscopy. After the usual work-up procedure,⁶ the resulting crude (g.c. purity > 95 %) was the α -iodo enaminone **2a**, as confirmed by the spectroscopic data (¹H and ¹³C NMR) and mass spectrometry (Scheme 1). In a similar way, the

corresponding iodo-derivatives **2b-2d** are obtained from the enaminones **1b-1d**, respectively, and no iodination of the phenyl ring was detected (**1b** and **1c**).



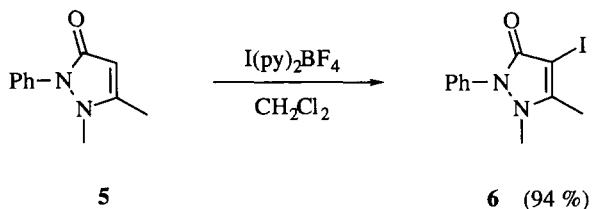
Scheme 1

We have also examined the iodination of enaminones derived from tetronic acid. Scheme 2 shows the results obtained in this study. The formation of α -iodo enaminones **4b** and **4c** from the reaction of **3b** and **3c**, respectively, with $\text{I(py)}_2\text{BF}_4$ is particularly noteworthy as it constitutes the first known example of direct iodination of tertiary enaminones.



Scheme 2

Finally, in order to assess the suitability of this reaction for the iodination of tertiary enaminone skeleton compounds with pharmacological activity, we used antipyrine **5** as the starting material. The reaction leads to the formation of the iodoantipyrine **6** in almost quantitative yield (Scheme 3). The iodinated product **6** can be used as a versatile starting material in the synthesis of antipyrine derivatives which show antipyretic, hypnotic and analgesic properties since halogen-containing compounds provide a further avenue for structural elaboration.



Scheme 3

In conclusion, the reaction of enaminones with bis(pyridine)iodonium(I) tetrafluoroborate allows the preparation of α -iodo enaminones in almost quantitative yields. Due to the mild nature of the reaction and its simplicity, cleanness and quickness, we anticipate that this procedure will prove to be widely applicable. In addition, since this reaction is suitable for the iodination of tertiary enaminones, it can be used to prepare iodinated heterocyclic compounds that can be further functionalized to give derivatives with pharmacological activity.

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6. Typical experimental procedure:

To a solution of bis(pyridine)iodonium(I) tetrafluoroborate (1 mmol, 0.372 g) in methylene chloride (15 ml) at room temperature, was added the corresponding enaminone⁷ (1 mmol). After stirring for two hours, the solution was filtered, washed with sodium bicarbonate solution, and extracted with methylene chloride. The organic phase was dried over anhydrous sodium sulphate. Removal of solvents *in vacuo* gave the corresponding α -iodo enaminone as a solid which was essentially pure (g.c. purity > 95 %).
7. Enaminones **1a-1c** and **3a-3c** were synthesized as described in reference 5. **1d** and **5** were purchased from Aldrich Chemical Company.

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