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A practical and convenient method for synthesis of substituted 4-iodoquinolines☆

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Abstract

An efficient route toward substituted 4-iodoquinolines has been developed from tosyloxy quinolines using iodine, red phosphorous and glacial acetic acid at room temperature in good yields. This procedure avoids the use of transition metals and harsh reaction conditions.

Keywords: 4-Tosyloxy quinoline; Red P; Glacial acetic acid; I_2 crystals

Iodoquinolines [1] are key pharmacophores and versatile intermediates for the synthesis of biologically active compounds. Haloquinolines can undergo both electrophilic and nucloephilic substitutions and also serve as excellent starting materials for transition metal catalyzed carbon–carbon bond formation via cross-coupling such as Stille, Suzuki, and Heck protocols [2]. Particularly, 4-iodoquinolines are flexible intermediates for the construction of antimalarial drugs such as chloroquine, mefloquine. Our interest in recent years has been towards the synthesis of various halogen derivatives of quinolines to synthesize novel biologically active molecules incorporating quinoline moiety [3].

Common strategies for the synthesis of 4-iodoquinolines are limited to metal-promoted halide exchange [4]. Other literature methods like, direct iodination of hydroxyquinoline [5], diazotization of 4-aminoquinoline followed by phosphorus triodide [6] or via 4-trimethylstannyl derivatives [7], gave low yields of 4-iodoquinolines.

Moreover, these methods require the use of transition metals, harsh reaction conditions, longer reaction times, and elevated temperatures. In addition, use of polar solvents such as DMF or HMPA that might constitute a waste disposal problem in industrial scale synthesis. Moreover, the catalysts are expensive, corrosive and need to be prepared prior to use. So there is still scope to develop a mild and metal-free approach towards the synthesis of iodoquinolines. Herein we wish to report a facile method for the preparation of substituted 4-iodoquinolines in good yields by the reaction of 4-tosyloxy derivatives with iodine, red phosphorus and glacial acetic acid at room temperature.

The most important aspect of this method is the nucleophilic aromatic substitution of tosylates with iodine in quinoline nucleus has been achieved for the first time. The reaction was initially carried out by the treatment of 4-tosyloxy derivative **1a** with molecular iodine, red phosphorous in glacial acetic acid at ambient temperature. The reaction was completed in 1.5 h leading to the formation of 4-iodoquinoline **2a** in 89% yield (Scheme 1). In order to improve the yields, we performed reactions using different quantities of reagents. The best results are obtained with 10:28 mmol ratio of iodine, red phosphorus to convert 0.01 mol of tosyloxy quinoline into iodoquinoline. To study the generality of this process, several examples were studied and results are summarized in Table 1. The procedure is applicable to a wide range of substituted tosyloxy quinolines, proceeds at room temperature to give the corresponding 4-iodoquinolines in high yields. We also examined the possibility of bromination by using bromine in place of iodine in the same reaction and found that 4-bromoquinoline was obtained in good yield (Scheme 2).

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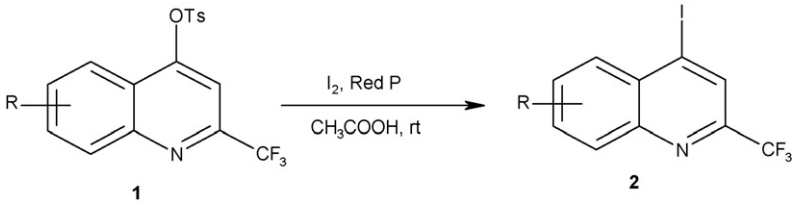


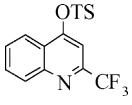
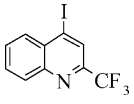
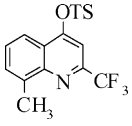
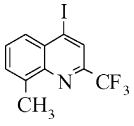
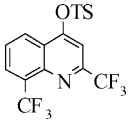
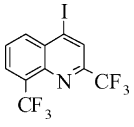
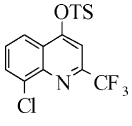
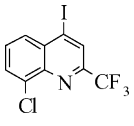
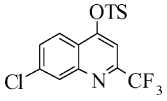
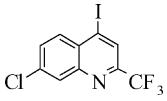
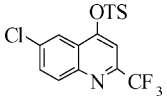
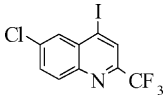
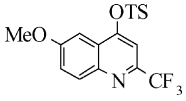
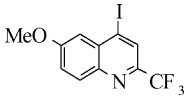
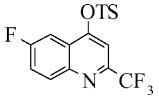
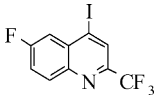
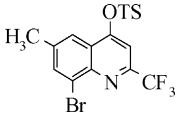
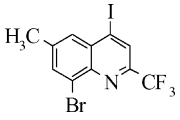
R= CH_3, OCH_3 Cl, Br

Scheme 1.

A critical feature of this method is that the entering iodine substituent always replaces tosyloxy group at the same position on the quinoline ring. Noteworthy, we observed that under the present reaction conditions 4-hydroxy quinolines do not produce the corresponding 4-iodoquinolines. Moreover, the iodination of the 4-tosyloxy quinoline without CF_3 group at second position does not provide the product. Thus, highly electron-withdrawing nature of CF_3 functional group at the second position of the quinoline nucleus has been responsible for the iodination of the tosyloxy quinolines. We presume that the reaction occur through acid halide generated in situ is responsible for this transformation. This was confirmed by the preparation of 4-chloroquinoline from tosyloxy derivative with acetyl chloride in the same reaction condition in 60% yield. 4-Hydroxy quinolines and tosyl derivatives were prepared following the literature procedures [8].

In conclusion we have demonstrated a simple and convenient method for the synthesis of 4-iodoquinolines under mild conditions. This method avoids the use transition metals, higher temperatures, and polar solvents. The experimental simplicity, inexpensive reagents and high yields have ensured positive impact on the economy of reaction, which may have a wide application in laboratory and industrial practice.

Table 1
Synthesis of substituted 4-iodoquinolines

Entry	Substrate **1**	Product[a] **2**	Time (h)	Yield[b] (%)
a			1.5	89
b			2.0	90
c			2.5	80
d			1.5	85
e			2.5	88
f			3.0	79
g			3.0	72
h			2.5	78
i			3.0	76

[a] All products were characterized by ^{1}H NMR and MS.
[b] Isolated and unoptimized yields after column chromatography.

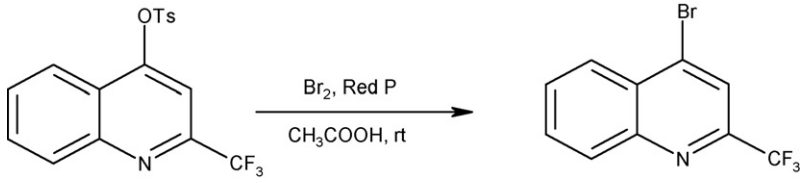
1. Experimental

1.1. Experimental procedure for the preparation of substituted 4-iodoquinolines

To a stirring suspension of red P (0.9 g, 28 mmol) in glacial acetic acid 25 ml, I_2 crystals (2.54 g, 10 mmol) were added portion wise slowly in a span of about 20 min and the reaction mixture stirred at 20 °C for 1 h. Then, 2-trifluoro 8-methyl-4-tosyloxy quinoline (3.81 g, 0.01 mol) was added portion wise to the iodinating mixture and stirred at room temperature for appropriate time. After completion of the reaction, chloroform (25 ml) was added to the reaction mixture and washed with aqueous sodium metabisulfite (10%), sodium bicabonate (10%), and finally with water. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh ethyl acetate–hexane (1:9)) to afford pure product.

The spectral (^{1}H NMR and MS) data of some representative products are given below:

1. Compound **2b**: mp 68–69 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.81 (s, 3H), 7.50–7.72 (m, 3H), 8.23 (s, 1H). EIMS: *m/z*: 337 (M^+).
2. Compound **2h**: mp 111–112 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.55–7.65 (dt, 1H, J = 9.1, 2.1 Hz), 7.72–7.80 (dd, 1H, J = 9.1, 2.1 Hz), 8.16–8.23 (dd, 1H, J = 9.1, 5.8 Hz), 8.28 (s, 1H). EIMS: *m/z*: 341 (M^+).



Scheme 2.

3. Compound **2i**: mp 136–137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.68 (s, 3H), 7.76–7.78 (d, 1H, J = 1.6 Hz), 8.0–8.06 (d, 1H, J = 1.6 Hz), 8.27 (s, 1H). EIMS: m/z: 416 (M^+).

Acknowledgements

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