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Hypervalent Iodine Oxidation of 2-Aryl-1,2,3,4-Tetrahydro-4-Quinolones: An Expedient Route to Naturally Occurring 4-Alkoxy-2-Arylquinolines

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Abstract: Easily accessible 2-aryl-1,2,3,4-tetrahydro-4-quinolones are readily oxidized to the corresponding 4-alkoxy-2-arylquinolines using a relatively safe hypervalent iodine reagent, [hydroxy (tosyloxy)iodo]benzene (HTIB), in high yields, thus providing a concise route to an important class of naturally occurring alkaloids.

The leaves of *Lunasia amara*[1,2] and *Galipea longiflora*[3] (family *Rutaceae*) are a rich source of alkaloids bearing an alkoxylated 2-arylquinoline nucleus. Specifically, the 4-alkoxy-2-aryl-quinoline derivatives have attracted attention due to their biological activity.[1,3] Only a limited number of methods are available for the synthesis of these compounds, which require multiple steps[2,4] or toxic reagents.[5]

We have explored the application of hypervalent iodine reagents in the preparation of heterocyclic compounds *via* the oxidation of phenolic Schiff's bases[6] and *o*-aminochalcones.[7] Our general explorations in solventless reaction systems,[8] using microwave or ultrasound activation,[8a,b] have led to a concise route to tetrahydroquinolone derivatives on clay surface[8c] and a more efficient usage of the hypervalent iodine reagents, iodobenzene diacetate (IBD)[8d,e] and [hydroxy(tosyloxy)iodo]benzene (HTIB),[9] in solid state reactions. HTIB has been found to be an effective reagent for one step conversion of enolizable ketones to the corresponding α-tosyloxyketones.[10] However, the oxidation of tetrahydroquinolones with HTIB invariably results in the formation of corresponding quinolones in acetonitrile or alcoholic media.[11] In view of the importance of 4-alkoxy-2-aryl-quinoline derivatives as building blocks for the synthesis of naturally occurring alkaloids and our continued interest in the development of eco-friendly synthetic protocols,[8,9] herein we describe a concise route to 4-alkoxy-2-arylquinolines using HTIB in the presence of trialkyl orthoformate and a catalytic amount of perchloric acid.

In brief, the treatment of 2-aryl-1,2,3,4-tetrahydroquinolone with 1.2 equivalent of HTIB in trimethyl orthoformate and perchloric acid as a catalyst exclusively affords 2-aryl-4-

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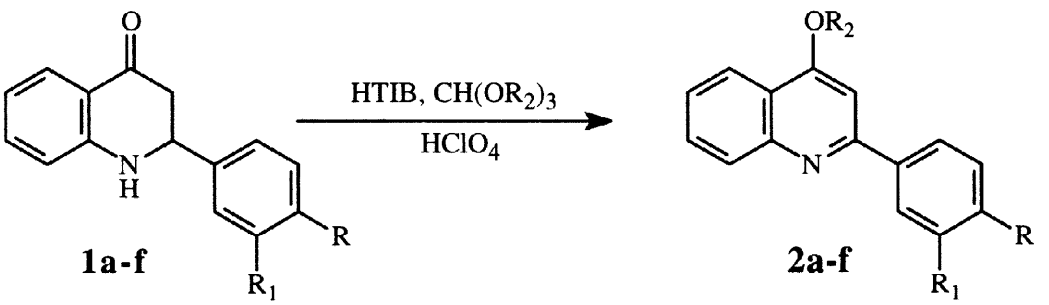
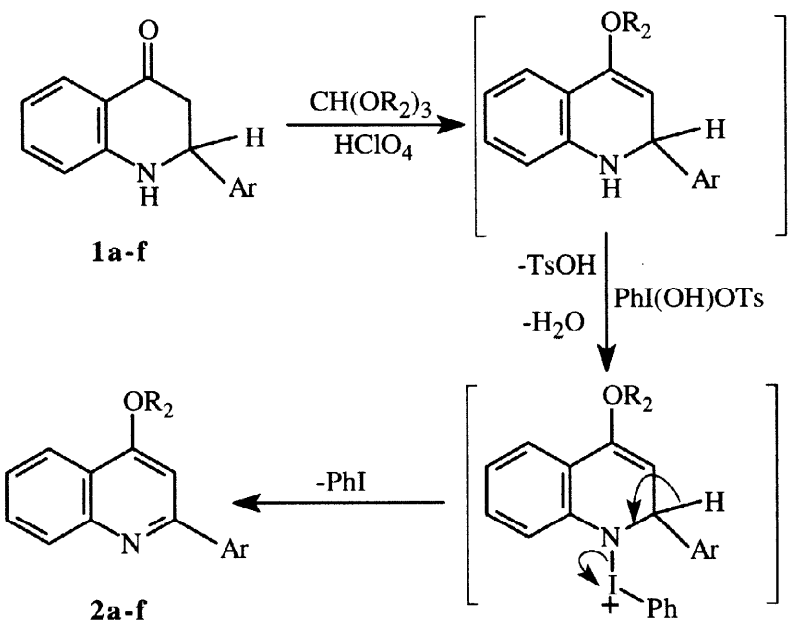
methoxyquinoline. In an analogous reaction, treatment with HTIB in triethyl orthoformate results in the formation of the corresponding 2-aryl-4-ethoxyquinoline. The generality of this HTIB oxidative synthetic approach is established by facile oxidation of a variety of substituted 2-aryl-1,2,3,4-tetrahydroquinolones (**1a-f**) to the corresponding 4-alkoxy-2-arylquinolines (**2a-f**) (**Scheme 1**), **2a** and **2f** being the alkaloids isolated from *Lunasia amara*.[1,2]



Scheme 1

A plausible mechanistic pathway for the reaction presumably involves the formation of enol ether upon refluxing **1** in trialkoxy orthoformate in the presence of perchloric acid. The subsequent attack of HTIB on the nitrogen atom results in dehydrogenation to afford **2** as shown in **Scheme 2**.



Scheme 2

In conclusion, we have developed a practical oxidative protocol that provides a general route to an important class of naturally occurring alkaloids, alkoxylated 2-arylquinolines, from easily accessible tetrahydroquinolones and the relatively benign oxidant [hydroxy (tosyloxy)iodo]benzene (HTIB).

Experimental

The melting points are uncorrected. ^1H NMR spectra were recorded on a JEOL 300 MHz spectrometer using TMS as an internal standard. Mass spectra were recorded on a Hewlett Packard 5890 mass spectrometer (70 eV) using a GC/MS coupling or direct inlet system. The 2-aryl-1,2,3,4-tetrahydro-4-quinolones were obtained from readily available starting materials, 2'-aminochalcones, according to literature procedures.[8c, 12,13].

General Procedure:

Synthesis of 4-methoxy-2-(*p*-methylphenyl)quinoline (2c): The preparation of 4-methoxy-2-(*p*-methylphenyl)quinoline, **2c**, is representative of the general procedure employed. A solution of **1c** (1 mmol) in trimethyl orthoformate (5 mL) was refluxed in the presence of two drops of perchloric acid for 30 min. [Hydroxy (tosyloxy)iodo]benzene (1.2 mmol) was then added slowly, in portions, and the reaction mixture stirred for another 1 hour at room temperature until the completion of the reaction as followed by TLC examination. Trimethyl orthoformate was removed by distillation under reduced pressure and water was added to the residue. The product was extracted into methylene chloride (3 x 20 mL) and dried over anhydrous sodium sulfate. The removal of the solvent gave crude product which was further purified by passing it over a bed of silica gel to afford **2c**: yield: 86%; mp 92-93 °C; ^1H NMR($CDCl_3$) δ: 2.44 (3H, s, CH_3), 4.10 (3H, s, OCH_3), 7.15 (1H, s, H_3), 7.31 (2H, dd, 9.00 Hz, 2.56 Hz, $H_{3'}$, $H_{5'}$), 7.43-7.49 (1H, m, H_6), 7.66-7.71 (1H, m, H_7), 8.01 (2H, dd, 8.58 Hz, 2.50 Hz, $H_{2'}$, $H_{6'}$), 8.09 (1H, dd, 8.22 Hz, 2.46 Hz, H_8), 8.17 (1H, dd, 8.25 Hz, 2.60 Hz, H_5); ^{13}C NMR($CDCl_3$) δ: 21.40 (CH_3), 55.69 (OCH_3), 97.85 (C_3), 120.45 (C_{4a}), 121.68 (C_5), 125.60 (C_6), 127.51 ($C_{2'}$ & $C_{6'}$), 129.16 (C_8), 129.54 ($C_{3'}$ and $C_{5'}$), 129.98 (C_7), 136.56 ($C_{4'}$), 139.75 ($C_{1'}$), 149.79 (C_{8a}), 158.52 (C_2), 163.06 (C_4); MS: m/z 249 (M^+, 100), 220 (58), 190 (6), 178 (8), 128 (4), 102 (10), 89 (9), 63 (7), 51 (5).

Table: Synthesis of 2-aryl-4-alkoxyquinoline derivatives (2a-f)[a]

Entry	R	R_1	R_2	Yield (%)[b]	m. p. (°C)	
					Observed	Reported
2a	H	H	Me	86	67-68	66-67[1]
2b	Cl	H	Me	88	111-112	111-112[5]
2c	Me	H	Me	86	92-93	–
2d	OMe	H	Me	78	93	94-95[5]
2e	Cl	H	Et	75	108	106-107[5]
2f		$-OCH_2O-$	Me	76	116-117	116-117[1]

[a]Products exhibited physical and spectral properties in accord with the assigned structures. [b]Yields refer to the isolated pure products.

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