

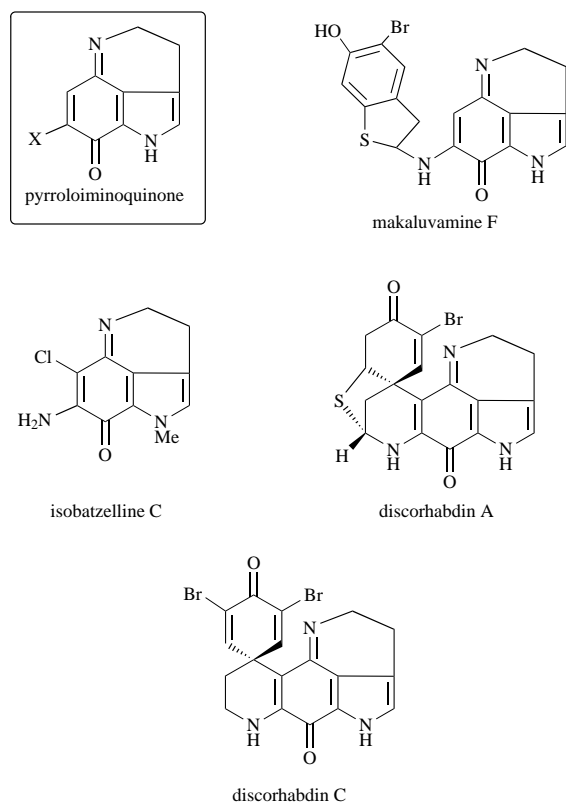
Novel and efficient synthesis of pyrroloiminoquinones using a hypervalent iodine(III) reagent

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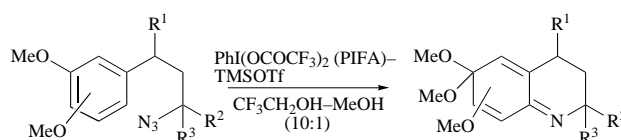
A novel and efficient route involving an intramolecular cyclization of 3-(azidoethyl)indole derivatives using a hypervalent iodine(III) reagent has been developed for the synthesis of pyrroloiminoquinones.

The pyrroloiminoquinone system is an essential component of a number of recently isolated marine alkaloids such as makaluvamines,¹ isobatzelline C² and discorhabdins³ which possess potent biological activities (e.g. cytotoxicity towards human tumor cell lines and inhibition of topoisomerase II). Because of their potent biological activities and their highly fused structures, pyrroloiminoquinone alkaloids have been challenging targets for synthetic chemists for years.



So far several groups, including ours, have reported diverse approaches for pyrroloiminoquinone derivatives: (i) intramolecular imine formation between the indoloquinone and the terminal amino group of the side-chain,⁴ (ii) intramolecular coupling reaction between the 4-amino group of the indole and the terminal activated ester group or leaving group of the side-chain,⁵ and (iii) formation of the pyrrole ring from 5-amino-4-formyltetrahydroquinone.⁶ We have previously reported the total synthesis of discorhabdin C *via* route (i).^{4a} In our con-

tinuing studies on hypervalent iodine(III) oxidation of phenol derivatives,⁷ we recently reported on the direct and efficient synthesis of quinone imine monoacetals using a combination of phenyliodine(III) bis(trifluoroacetate) (PIFA) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 1).⁸



Scheme 1

We report here a novel and efficient synthesis of pyrroloiminoquinones from indoles bearing an alkyl azido side-chain using the activated hypervalent iodine(III) reagent, PIFA-TMSOTf in (CF₃)₂CHOH-H₂O.

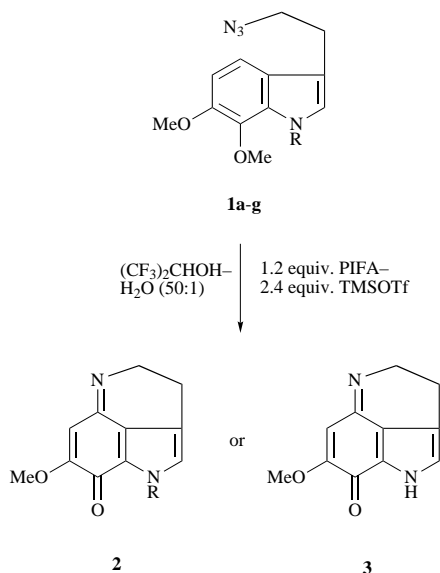
The starting indoles were prepared as follows. The treatment of 6,7-dimethoxyindole⁹ with oxalyl chloride followed by LAH reduction gave 3-(hydroxyethyl)indole (95% yield) which was converted to 3-(azidoethyl)indole (**1a**) *via* 3-(iodoethyl)indole in 65% yield. Other 3-(azidoethyl)indole derivatives (**1b-g**) were readily prepared from **1a** by standard alkylation and acylation methods. First we examined the reaction of **1a** with PIFA-TMSOTf. However, a complex mixture was obtained. The reactions of **1b** (R = Me) and **1c** (R = SiPr^t₃) with PIFA-TMSOTf also gave complex mixtures due to side reactions which can occur at the 1- or 3-positions of the indole nucleus. In fact, several groups had already reported that 1-, 2- or 3-substituted indole derivatives were obtained from the reaction of indoles with iodobenzene diacetate.¹⁰ Therefore we then examined the reactions of 1-protected indoles (**1d-g**) with PIFA-TMSOTf in the presence of H₂O. We found that the corresponding pyrroloiminoquinones (**2d, e**) or 1-deprotected pyrroloiminoquinone (**3**) could be obtained in moderate yields when the indoles were treated with PIFA-TMSOTf in (CF₃)₂CHOH-H₂O (50:1) † and when they were protected by electron-withdrawing groups such as acetyl, benzoyl, tosyl or benzyloxycarbonyl groups.

In conclusion, a facile and direct synthesis of pyrroloiminoquinones has been developed. This work will be applied to the syntheses of various types of quinone imine alkaloids containing pyrroloiminoquinones.

† Typical experimental procedure is as follows; to a stirred solution of **1** (0.1 mmol) in (CF₃)₂CHOH-H₂O (50:1) (2 ml), TMSOTf (0.24 mmol), then PIFA (0.12 mmol) as a solid were added sequentially at 0 °C. The mixture was stirred for 1 h under the same conditions. After aqueous work-up with saturated aqueous NaHCO₃, purification by preparative TLC gave pure **2** or **3**. All newly isolated compounds gave satisfactory spectroscopic data.

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Run	Starting Material (1)	Yields (%)	
		2	3
1	1a : R = H	— ^a	— ^a
2	1b : R = Me	— ^a	— ^a
3	1c : R = SiPr ₃	— ^a	— ^a
4	1d : R = Ts	2d : 61	—
5	1e : R = Cbz	2e : 47	—
6	1f : R = Ac	—	51
7	1g : R = Bz	—	47

^a Complex mixture.

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