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LETTERS

First halogen-dance reaction in quinoline series: application to a new synthesis of quindoline.

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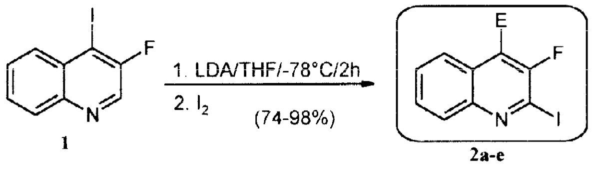
Abstract:

The first halogen-dance reaction in quinoline series is described as well as a new convergent synthesis of quindoline, a natural benzo-δ-carboline.

Keywords : Halogen and compounds, Metalation, Polycyclic heterocyclic compounds, Coupling reactions.

In 1993, we established that metalation [1] of iodopyridines by LDA at low temperature was feasible if the pyridine nucleus bears a second halo (chloro or fluoro) substituent and a halogen-dance reaction was observed [2]. We wish to report here the first halogen-dance reaction in quinoline series as well as an application to a new convergent synthesis of quindoline **5** (scheme 2). Quindoline is a benzo-δ-carboline isolated in 1977 by Dwuma-Badu *et al.* [3] from *Cryptolepis sanguinolenta*, and is the purpose of very recent works as its alkylated analogues possess antimalarial activities [4, 5].

Treatment of the iodoquinoline **1** [6] with LDA at –75°C followed by quenching with electrophiles led to the corresponding 4-substituted 3-fluoro-4-iodoquinolines **2a-e** in good to high yields (scheme 1, table 1).



Scheme 1

Table 1

Entry	E$^+$	E	% Yield*	Product
1	H_2O	H	95	**2a**
2	I_2	I	98	**2b**
3	CCl_3CCl_3	Cl	74	**2c**
4	CH_3CHO	$CH_3CH(OH)$	79	**2d**
5	PhCHO	PhCH(OH)	75	**2e**

* : isolated yield

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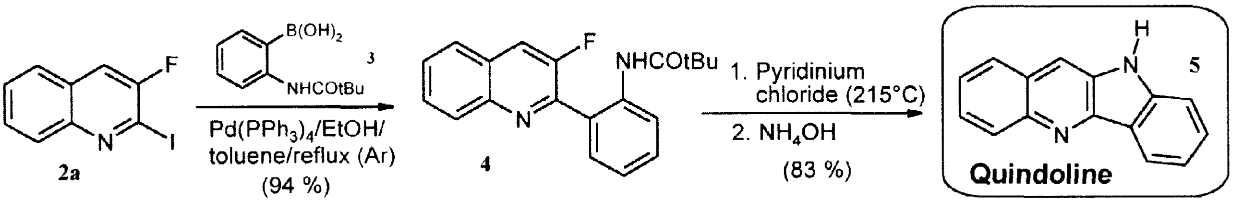
Identification of compounds **2a-e** were infered from the ^1H and ^{13}C NMR spectra (strong shielding of the carbon bearing the iodo atom). The behaviour of iodoquinoline **1** towards LDA is very similar to that observed in pyridine series, i.e. fluoro-directed metalation of the more acidic 2-position under kinetic control, followed by the fast isomerization to the more stable 4-lithioquinoline (thermodynamic product). It should be pointed out that it was not possible to introduce an alkyl chain at the C-4 position of the quinoline ring. This problem is under investigation as well as mechanistic studies of this new halogen-dance reaction.

Palladium-catalyzed cross-coupling reaction between boronic acid **3** [7] and iodoquinoline **2a** using a Suzuki procedure [8], afforded the biaryl **4** in a very good yield. Cyclization to quindoline **5** was best achieved by treatment with boiling pyridinium chloride (scheme 2).



Scheme 2

For the first time, a halogen-dance reaction was observed in quinoline series. Lithiation is ortho-directed by fluorine at the C-2 position of the quinoline ring but the most stable lithio derivatives at C-4 position is rapidly and quantitatively formed. This reaction allowed us to synthesize quindoline **5** in 3 steps from 3-fluoro-4-iodo-quinoline **1** with an interesting 74 % overall yield [9].[‡] It can be noted that it is the first fully regioselective synthesis of a benzo-δ-carboline starting from a quinoline derivative.

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[‡] The main physical data of compound **5** are identical to those of the natural product [9]: mp: 254-256°C; pale yellow powder. IR (KBr): 3054, 1614, 1398, 1223, 737 cm^{-1}. ^1H NMR (500 MHz, DMSO) 7.27 (ddd, 1H, H7, J=1.8, 6.5, 7.7); 7.54 (m, 1H, H2); 7.55 (m, 1H, H9); 7.61 (m, 1H, H8); 7.64 (m, 1H, H3); 8.09 (dd, 1H, H1, J=1.2, 8.0); 8.19 (dd, 1H, H4, J=0.6, 8.0); 8.27 (s, 1H, H11); 8.35 (d, 1H, H6, J=7.7); 11.4 (s, 1H, NH). ^{13}C NMR (DMSO) 111.6 (C9); 113.1 (C11); 119.4 (C7); 121.0 (C5b); 121.4 (C6); 124.9 (C2); 126.1 (C3); 126.8 (C11a); 127.6 (C1); 128.8 (C4); 129.8 (C8); 132.5 (C10a); 143.4 (C4a); 144.1 (C9a); 145.7 (C5a). Anal. Calcd for $C_{15}H_{11}N_2$ (219.3) C 82.2%, H 5.1%, N 12.8. Found: C 82.1%, H 4.9, N 12.5.