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First hetero-Diels–Alder reaction with indoloquinone in the presence of hydrogen and palladium

Jacques Gentili and Roland Barret*

EA 3741, Ecosystèmes et molécules bio actives, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, 8 Avenue Rockefeller, 69373 Lyon Cedex 08, France

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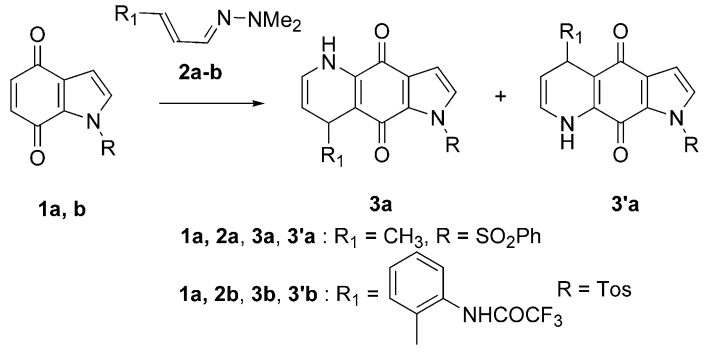
Abstract—*N*-Sulfonyl-indoloquinone and heterodienes react under a pressure of hydrogen in the presence of palladium to give piperidino-indoloquinones.

1. Introduction

The hetero-Diels–Alder reaction is now well documented.[1] It is an appropriate way for building aza-hetero ring units. Recently, we described the use of aza-diene **2a** with indoloquinone **1a** to obtain dihydropyridinoindoles **3a** and **3′a**.[2] With **1b** and **2b**, however, this reaction leads to very poor yields[3] (Scheme 1).

The piperidino-indoloquinone core is present in marine alkaloids such as discorhabdin **4**.[4] Analogs **5** of discorhabdin were synthesized from phenylethylamino quinones by spiroannulation with PIFA[4] (Scheme 2). The piperidino-indoloquinone structure can be obtained by hetero-Diels–Alder reaction to give **3** and **3′** followed by hydrogenation of the double bond, but the condensation step leads to several products: oxidation of the dihydropyridine unit into pyridine, addition of dimethylamine to the quinone.[5,6] We sought to obtain in one step the piperidino-indoloquinone structure by a hetero-Diels–Alder reaction and hydrogenation of the double bond in the same medium.

The piperidino-indoloquinones **6a** and **6′a** were synthesized directly from **1a** and **2a** under hydrogen (10 bars) in the presence of palladium. The alcoholic solution



Scheme 1.

Keywords: Diels–Alder reaction; Indoloquinone; Piperidino-indoloquinone.
* Corresponding author. Tel.: +33 04 78 77 75 42; fax: +33 04 78 77 75 49; e-mail: barret@rockefeller.univ-lyon1.fr

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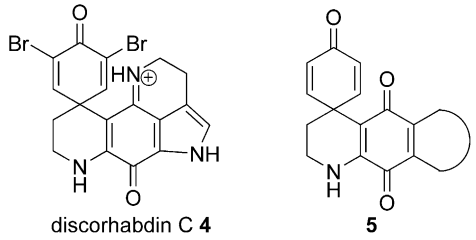

Scheme 2.

was stirred overnight under pressure of hydrogen. After filtration, the clear solution was stirred 2 h under air to re-oxidize the hydroquinones into quinones. The purple solution was concentrated and the residue was purified by chromatography over alumina.[7]

The regiochemistry of this reaction was established by 2D-NMR experiments on **3a** and **3′a** obtained by hetero-Diels–Alder reaction in the absence of hydrogen and after hydrogenation of both compounds into **6a** and **6′a**. The results show that **3a** and **6a** were the major isomers. Regioisomers **3′a** and **6′a** were very minor components of the reaction.

Different heterodienes **2c–g** were tested (Table 1, Scheme 3). All these reactions led to the [1,5]-isomers **6a**,**c–g**; the corresponding [1,8]-isomers **6′a**,**c–g;** were isolated in very minor amounts.

2. Limitation of this reaction

We observed the importance of the structure of the indole and the benzenesulfonyl group. When the benzenesulfonyl group was replaced by a hydrogen atom or when the indole was replaced by naphthoquinone, the reduction of the quinone into hydroquinone was faster than the condensation reaction and no cycloaddition was observed. With $R_1 = CO_2Et$, $R_2 = H$, reduction of the heterodiene was the major reaction and a complex mixture was formed.

From these facts, a mechanism for this reaction can be proposed, consisting first of a hetero-Diels–Alder reaction followed by hydrogenation of the Diels–Alder adducts. The *N*-sulfonyl-indoloquinones and diene-hydrazones are stable to the hydrogenation conditions whereas the *N*-unsubstituted indoloquinone is reduced into hydroquinone before the Diels–Alder reaction and no cycloaddition is observed.

Table 1. Hetero-Diels–Alder reaction under hydrogen pressure and palladium over charcoal

R_1	R_2	%	Heterodiene	**6a**,**c–g**/**6′a**,**c–g**
CH_3	H	68	**2a**	95/5
C_2H_5	H	49	**2c**	60/40
H	H	43	**2d**	60/40
C_6H_5	H	30	**2e**	86/14
H	C_2H_5	40	**2f**	70/30
H	CH_3	55	**2g**	100/0

3. Conclusion

To our knowledge, this work describes the first example of a Diels–Alder reaction under hydrogen pressure in the presence of palladium to obtain directly the reduction products. We are currently extending this approach to other quinones and heterodienes.

References and notes

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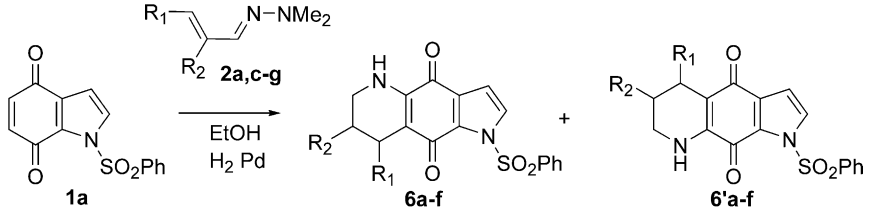
7. Selected data: A solution in ethanol (10 mL) of quinone **1a** (0.200 g, 0.690 mmol), heterodiene **2a** (0.330 g, 2.76 mmol) was stirred with 10% Pd·C (0.020 g) under hydrogen pressure (10 bars) overnight. The excess pressure was vented and the reaction mixture was filtered on Celite®. Then, the clear solution was stirred under the air for 2 h. The resulting purple solution was evaporated to dryness under vacuum and the crude residue was purified by chromatography over alumina to give **6a** (0.158 g, 0.445 mmol) and **6′a** (0.008 g, 0.023 mmol). **6a**: blue crystal; mp: 95 °C; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.0 (CH_3, d, J = 6 Hz), 1.6 (CH_2–CH_2, m), 3.0 (CH–CH_3, m), 3.3 (CH_2–



Scheme 3.

N, m), 5.6 (NH, m), 6.6 (3-H, d, $J = 5$ Hz), 7.6 (2-H, d, $J = 5$ Hz), 7.4–7.6 (3H arom, m), 8.1 (2H *ortho*, d, $J = 12$ Hz). ^{13}C NMR (DMSO-d_6), δ (ppm): 14.1, 23.0, 26.4, 36.2, 106.9, 126.6, 126.9, 128.6, 128.7, 130.0, 133.0, 134.2, 137.5, 142.4, 173.0, 178.8. MS: 356 ($M^{+\cdot}$), 341, 215 (100%), 198. HRMS: calculated for $C_{18}H_{16}N_2O_4S$: 356.08307, found: 356.08170.

6′a: blue crystal; mp: 97 °C; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.1 (CH_3, d, $J = 6$ Hz), 1.6 (CH_2–CH_2, m), 3.1 (CH–CH_3, m), 3.3 (CH_2–N, m), 5.5 (NH, m), 6.7 (3-H, d, $J = 5$ Hz), 7.7 (2-H, d, $J = 5$ Hz), 7.4–7.6 (3H arom, m), 8.1 (2H *ortho*, d, $J = 12$ Hz). MS: 356 ($M^{+\cdot}$), 341, 339, 215 (100%), 200, 199, 198. HRMS: calculated for $C_{18}H_{16}N_2O_4S$: 356.08307, found: 356.08213.