



Reactivity of spiroanthraceneoxazolidines with cyclopropanes: An approach to the oxindole alkaloid scaffold

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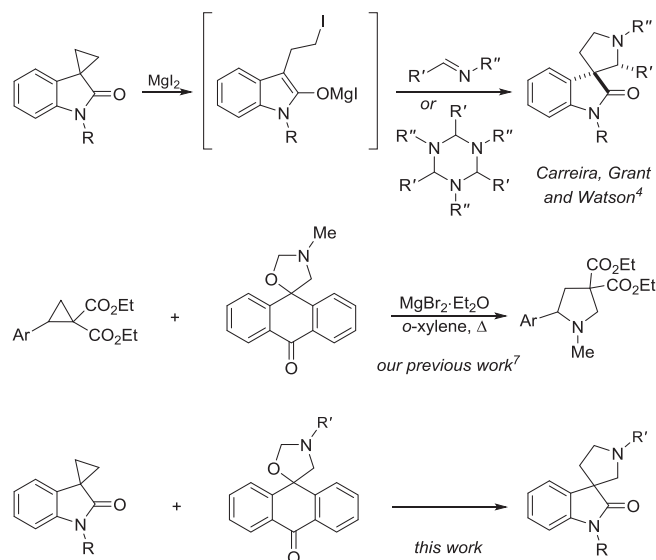
ABSTRACT

The reaction of *N*-methylspiro[anthracene-oxazolidine] with spiro[cyclopropane-3,3'-indolin]-2-ones in the presence of MgI_2 formed the corresponding spiro[pyrrolidine-3,3'-indolin]-2-ones in 42–65% yields. The use of *N*-benzylspiro[anthracene-oxazolidine] in this reaction led to the formation of a mixture of the corresponding *N*-methyl- and *N*-benzylpyrrolidines.

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The pyrrolidine core is one of the most important building blocks in organic synthesis and is a popular fragment in medicinal chemistry [1]. In particular, compounds which are spirofused at the 3-position of the indolin-2-one pyrrolidine ring constitute the basis for naturally occurring oxindole alkaloids [2]. The oxindole motif is present in the core of numerous biologically active compounds such as coerulescine and horsfiline (Fig. 1). The latter were isolated from the Malaysian medicinal plant *Horsfieldia superba* and have attracted significant attention as analgesic medicinal compounds [3].

Straightforward approaches for the synthesis of the oxindole framework based on a formal [3+2]-cycloaddition of imines to cyclopropanes were reported by the Carreira, Grant and Watson groups (Scheme 1) [4]. These works are based on the high strain



Scheme 1. Selected reactions of cyclopropanes.

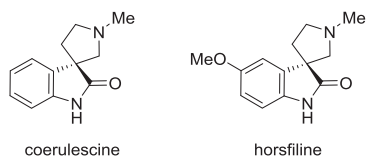


Fig. 1. Examples of naturally occurring alkaloids containing an oxindole framework.

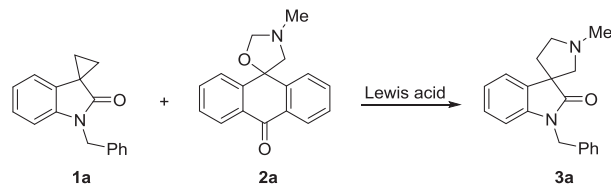
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energy of the cyclopropane ring which allows its facile ring-opening with formation of an iodide-enolate. The latter possesses a dipolar nature and successfully forms the pyrrolidine ring after reaction with imines or 1,3,5-triazinanes. It should be noted that such an approach has been effectively applied to the chemistry

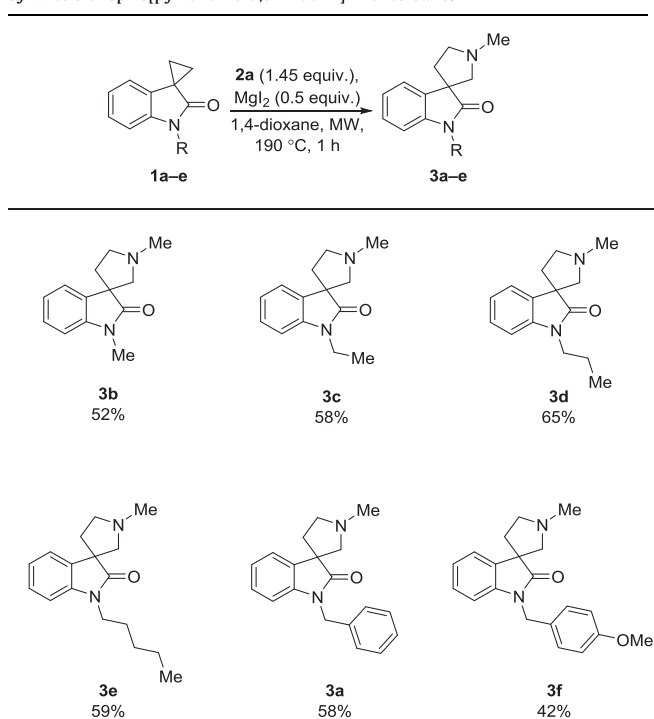
of donor–acceptor cyclopropanes, whose structure promotes an easier ring-opening of the cyclopropane ring [5]. In particular, previously we reported that the reaction of D-A cyclopropanes [6] with spiro[anthracene-oxazolidine] resulted in diethyl 5-arylpyrrolidine-3,3-dicarboxylates [7]. Thus, the spiroanthraceneoxazolidine system [8] unexpectedly appeared to be a synthetic equivalent of *N*-methylmethanimine. Herein, we report the reactivity of spiro[anthracene-oxazolidine] and its application in the synthesis of a valuable natural oxindole scaffold.

We commenced our study with optimization of the reaction conditions using the model reaction of *N*-benzyloxindole cyclopropane **1a** with spiroanthraceneoxazolidine **2a** (Scheme 2). Unfortunately, it was discovered that the previously developed conditions for the reactions of D-A cyclopropanes (*o*-xylene, MgBr₂·Et₂O, reflux, 3.5 h) [7] were not appropriate (Table 1, entry 1). The same experiment at higher temperature (210 °C) in a microwave reactor led to the desired *N*-benzylcoerulescine (**3**) in low yield with an admixture of starting oxazolidine **2** (Entry 2). As mentioned above, Carreira and co-workers reported the successful reaction of oxindole cyclopropane with 1,3,5-trimethyl-1,3,5-triazinane catalyzed by MgI₂ in THF at 125 °C [4b]. Nevertheless, we found that under the same conditions spiroanthraceneoxazolidine **2a** did not lead to the formation of product **3a**, and the crude mixture was contaminated with oxazolidine **2** (Entry 3). At this stage, it was clear that the reaction of spirooxazolidine **2** requires higher temperatures than the reactions of imines and 1,3,5-triazinanes. For this reason, we chose higher boiling 1,4-dioxane and after variation of the reaction temperature and equivalents of MgI₂ (Entries 4, 7) we found optimal conditions for this process: heating the reagents in



Scheme 2. Synthesis of spiropyrrolidine **3a**.

Table 2
Synthesis of spiro[pyrrolidine-3,3'-indolin]-2-ones **3a–e**.



1,4-dioxane with MgI₂ (0.5 equiv.) in a microwave reactor at 190 °C for 1 h (Entry 10). At the same time, attempts to use other solvents or Lewis acids did not improve the yield (Entries 5, 6, 8, 9).

Further efforts were directed toward an extension of the starting substrates. For this purpose, we synthesized a number of cyclopropanes **1** from commercially available isatin. The first stage was alkylation of isatin with an alkyl halide in the presence of K₂CO₃ in DMF, the second, Wolff–Kishner reduction of *N*-substituted isatin at reflux in hydrazine-hydrate (65% water solution). The third stage was the ethylenation of oxindoles by treatment with 1,2-dibromoethane and NaH in DMF (see ESI for details). With the optimized

Table 1
Optimisation of the reaction conditions.^a

Entry	Conditions	Solvent	Lewis acid (equiv.)	Yield 3a (%) ^b
1	2a (1.7 equiv.), reflux, 4 h	<i>o</i> -xylene	MgBr ₂ ·Et ₂ O (1.0)	– ^c
2	2a (2.25 equiv.), MW, 210 °C, 2 h	<i>o</i> -xylene	MgBr ₂ ·Et ₂ O (1.0)	25 ^d
3	2a (1.1 equiv.), MW, 120 °C, 30 min	THF	MgI ₂ (0.1)	recovered 2a
4	2a (1.3 equiv.), MW, 170 °C, 1 h	1,4-dioxane	MgI ₂ (0.2)	29 ^d
5	2a (1.45 equiv.), MW, 210 °C, 1 h	DMF	MgI ₂ (0.2)	27 ^d
6	2a (1.2 equiv.), MW, 150 °C, 15 min	THF	BBT ₃ (1.0)	– ^c
7	2a (1.2 equiv.), MW, 170 °C, 1 h	1,4-dioxane	MgI ₂ (1.1)	40 ^d
8	2a (1.3 equiv.), MW, 170 °C, 1 h	THF	MgBr ₂ (0.2)	30 ^d
9	2a (1.2 equiv.), MW, 170 °C, 1 h	1,4-dioxane	MgBr ₂ (1.1)	27
10	2a (1.45 equiv.), MW, 190 °C, 1 h	1,4-dioxane	MgI ₂ (0.5)	58

^a Reactions were performed on a 0.8 mmol scale.

^b Isolated yields of product **3a** based on cyclopropane **1a**.

^c Complex mixture of products.

^d NMR yield: product was contaminated by the starting oxazolidine.

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