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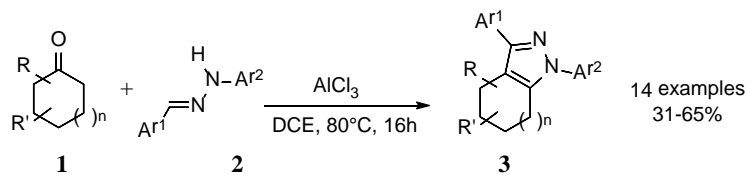
## Graphical Abstract

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### **AlCl<sub>3</sub>-catalyzed reaction of cycloalkanones with arylhydrazones: A convenient direct synthesis of 4,5,6,7-tetrahydro-1*H*-indazoles and analogues**

Rima Laroum, Fabienne Berrée, Thierry Roisnel, Bertrand Carboni and Abdelmadjid Debache

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## AlCl<sub>3</sub>-catalyzed reaction of cycloalkanones with hydrazones: A convenient direct synthesis of 4,5,6,7-tetrahydro-1*H*-indazoles and analogues

Rima Laroum,<sup>a</sup> Fabienne Berrée,<sup>b</sup> Vincent Dorcet,<sup>b</sup> Thierry Roisnel,<sup>b</sup> Bertrand Carboni<sup>b\*</sup> and Abdelmadjid Debache<sup>a\*</sup>

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### ABSTRACT

A AlCl<sub>3</sub>-catalyzed reaction of cycloalkanones with hydrazones is described. This approach provides a mild and operationally simple access to the synthesis of 2,3-diaryl-4,5,6,7-tetrahydro-1*H*-indazoles and analogues in good to moderate yields.

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### Introduction

Nitrogen-containing heterocycles represent one of the most important classes of organic compounds. They are amply present in natural products and, due to their wide range of biological properties, also constitute the major constituents of a variety of drugs [1]. Among the vast number of pharmacologically active heterocyclic compounds, 4,5,6,7-tetrahydro-1*H*-indazoles and analogues are of particular interest since they were identified as anti-inflammatory [2], antituberculosis [3], antiproliferative agents [4], interleukin-2 inducible T-cell kinase inhibitor [5], gamma secretase modulator [6] or cannabinoid-1 receptor inverse agonists [7]. In parallel, they were also used as ligands in gold, uranium, rhodium, iridium and palladium complexes [8]. With

regard to the synthetic aspect, these heterocycles were mostly prepared by reaction of aryl hydrazines with 1,3-diketones [2b,4c,9] or  $\alpha,\beta$ -unsaturated ketones [10], an approach that can be sometimes affected by regioisomer formation. Other important strategies for the creation of the tetrahydro-indazole ring consist of base-mediated addition of hydrazones to nitroolefins [11], metal-catalyzed cyclization of  $\beta$ -bromo- $\alpha,\beta$ -unsaturated ketones with arylhydrazines [12] or aminohydroxylation of allylic hydrazones [13], nitrilimine cycloaddition to enamines, [14] or iodine-mediated intramolecular amination [15]. Alternative approaches includes modification of a prebuilt bicyclic subunit, as oxidation of dihydroindazole [2a, 16], partial reduction of indazole [6], Pd(II)- or photoredox catalyzed C-3 arylation [17], or N-arylation reactions in the presence of Cu(I) [18].

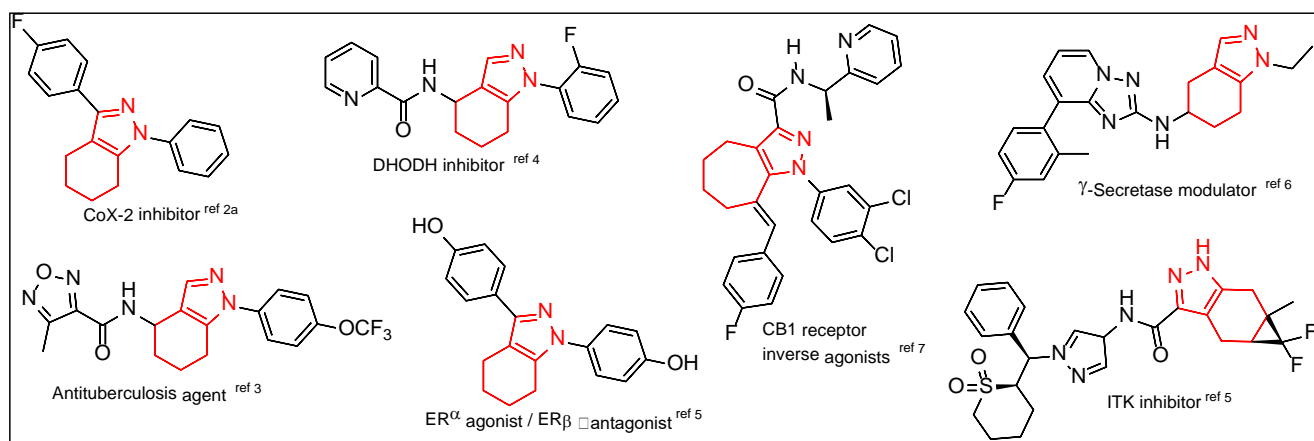
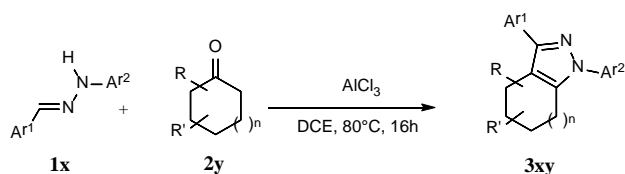


Figure 1. Some examples of bioactive 4,5,6,7-tetrahydro-1*H*-indazoles and analogues.

In this context, it is still relevant to develop simple and direct approaches for facile synthesis of this class of heterocycles. Inspired by the work of Minunni [19] and Cecchi [20] and coworkers on the reaction of aldehydrazones with benzoylacetate esters, we hypothesized that a similar approach could constitute a direct access to 2,3-diaryl-4,5,6,7-tetrahydro-1*H*-indazoles and analogues starting from cycloalkanones and aryl hydrazones via an acid-catalyzed process (Scheme 1).

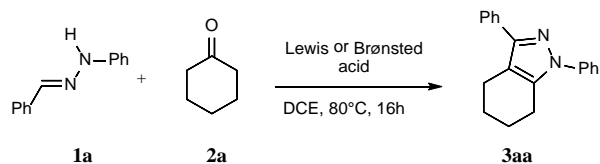


Scheme 1. 2,3-Diaryl-4,5,6,7-tetrahydro-1*H*-indazole synthesis

## Results and discussion

Our investigations were initiated with phenylhydrazone **1a** and cyclohexanone **2a** as model substrates to find optimal conditions for the formation of **3aa**, as depicted in Table 1. In the presence of  $\text{AlCl}_3$  in 1,2-dichloroethane, if no reaction occurred at room temperature, to our delight, the desired product was obtained in 49 % yield after heating 16 h at  $80^\circ\text{C}$  (Table 1, entry 1). Lower yields were observed with other Lewis acids, as  $\text{FeCl}_3$  or  $\text{Yb}(\text{OTf})_3$ , while the reaction failed with  $\text{TsOH}$  or  $\text{PhB}(\text{OH})_2$  (Table 1, entry 2-5). A short study of the influence of the relative amounts of **1a**, **2a** and  $\text{AlCl}_3$  showed that optimal yield was obtained with a 1/1.5/2 ratio (Table 1, entry 1, 6-8).

Table 1. Optimization of the reaction conditions



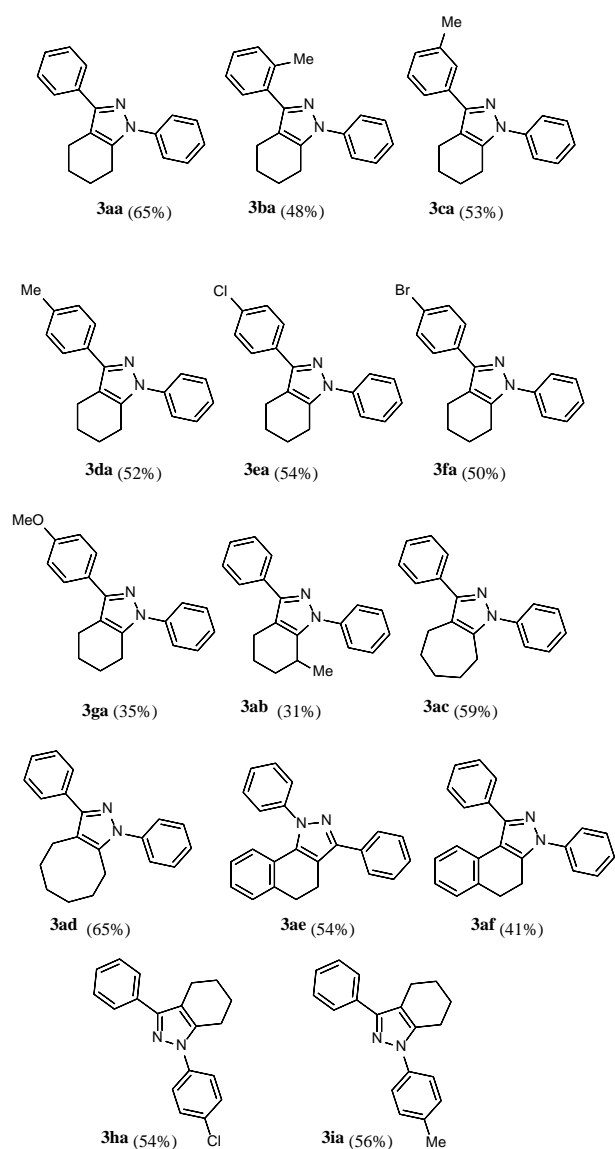
Entry	Catalyst	n equiv. <b>2a</b> <sup>a</sup>	n' equiv. cat. <sup>a</sup>	Yld (%) <sup>b</sup>
1	$\text{AlCl}_3$	1	1	49
2	$\text{FeCl}_3$	1	1	45
3	$\text{Yb}(\text{OTf})_3$	1	0.1	35

4	$\text{PhB}(\text{OH})_2$	1	1	0
5	$\text{TsOH}$	1	1	0
6	$\text{AlCl}_3$	1.5	2	72
7	$\text{AlCl}_3$	1	2	53
8	$\text{AlCl}_3$	2	2	45

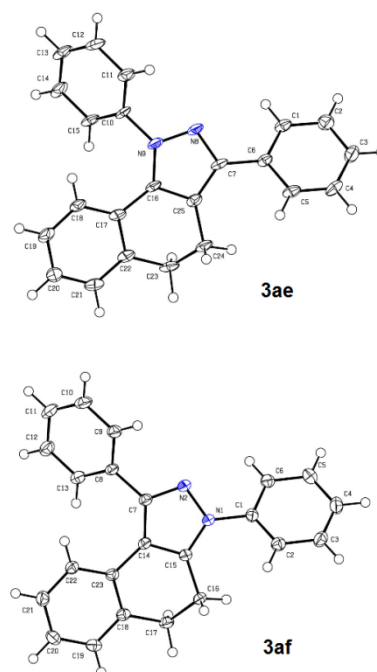
<sup>a</sup> Conditions: **1a** (1 mmol), cyclohexanone **2a** (n mmol), Lewis or Brønsted acid (n' mmol), 1,2-dichloroethane (5 mL),  $80^\circ\text{C}$ , 16 h. <sup>b</sup> The yield was calculated on the  $^1\text{H}$  NMR of the crude product with 1,3,5-trimethoxybenzene as internal standard.

The scope of the reaction was then evaluated under the previously optimized conditions. A range of arylhydrazones **1** derived from phenylhydrazine and aromatic aldehydes were first engaged in this process using cyclohexanone **2a** as model partner (Scheme 1, Table 2). Various electron-donating or withdrawing substituents on the aromatic moiety were tolerated with no significant influence of their nature or location. The lower yield observed for **3ga** was attributed to a partial demethylation due to the presence of the catalyst. The introduction of a substituent at the C-2 position of the cyclohexanone notably decreased the yield (**3aa** versus **3ab**), no product being observed with a more hindered substrate as menthone. By contrast, cycloheptanone and cyclooctanone are also good partners to access 4,5,6,7-tetrahydro-1*H*-indazoles, as  $\alpha$ - and  $\beta$ - tetralone. In the latter case, a single regioisomer **3af** was formed. Finally, similar yields were obtained with hydrazones prepared from *para*-substituted benzaldehydes.

Table 2. Scope of the  $\text{AlCl}_3$ -catalyzed reaction of cycloalkanones with hydrazones

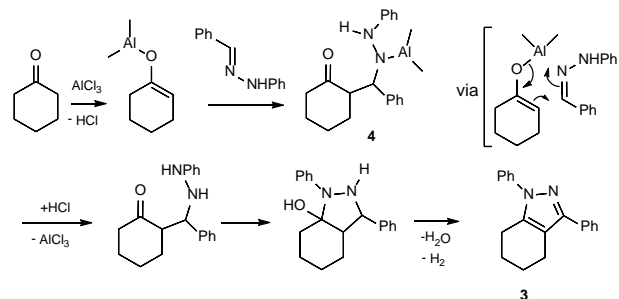


Compounds **3** were fully characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, and mass spectroscopy with experimental data in full agreement with the proposed formula (see ESI). Additionally, the structures of compounds **3ae** and **3af** were confirmed by single crystal X-ray analysis (Figure 2) [21].



**Figure 2.** X-Ray crystallographic structures of 4,5,6,7-tetrahydro-1H-indazoles **3ae** and **3af**.

A plausible mechanism was depicted in Scheme 2. The formation of an aluminum enolate would be followed by the addition of hydrazone to afford the hydrazoneketone **4** [22]. Intramolecular cyclization and aromatization provides the corresponding 4,5,6,7-tetrahydro-1H-indazole by elimination of water and hydrogen.



**Scheme 2.** Suggested mechanism for the formation of **3**

## Conclusion

A series of 4,5,6,7-tetrahydro-1H-indazoles and analogues was synthesized by  $\text{AlCl}_3$ -catalyzed reaction of cycloalkanes with hydrazones. Even if yields are only good to moderate yields, this direct approach offers the major advantage of not requiring the usual preliminary functionalization of the starting ketone or hydrazone. Scope and limitations, as a probable mechanistic hypothesis, were presented.

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This work was supported by the University of Rennes 1 and the Centre National de la Recherche Scientifique (CNRS). RL gratefully acknowledges le Ministère de l'Enseignement Supérieur et de la Recherche Scientifique (Algeria) for financial support (Profas program).

## Appendix A. Supplementary data

Experimental procedures for the preparation of compounds **3** and the copies of their  $^1\text{H}/^{13}\text{C}$  NMR spectra) can be found online at .....

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