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Tuneable access to indole, indolone and cinnoline derivatives from a common 1,4-diketone Michael acceptor

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Abstract

A convergent strategy is reported for the construction of nitrogen-containing heterocycles from common substrates: 1,4-diketones and primary amines. Indeed, by just varying substrates, substituents or heating mode it is possible to selectively synthesize indole, indolone (1,5,6,7-tetradihydroindol-4-one) or cinnoline (5,6,7,8-tetrahydrocinnoline) derivatives in moderate to excellent yields.

Keywords

N-heterocycle; 1,4-diketone; indole; indolone; cinnoline.
Introduction

Nitrogen heterocycles are widespread in plenty of molecules of interest, either in materials science, optics, electronics or biology [1–4]. They are also very useful building blocks to create more sophisticated organic molecules. Therefore the search for efficient methods for the synthesis of nitrogen-containing heterocycles is crucial to both organic and medicinal chemists. Among these, indole, indolone (1,5,6,7-tetrahydroindol-4-one) and cinnoline (5,6,7,8-tetrahydrocinnoline) derivatives are an important class of functionalized compounds having biological and medicinal activities of interest (Figure 1) [5–8].

Figure 1: Examples of bioactive nitrogen-containing heterocycles (indole [9], indolone [10] and cinnoline [11] derivatives).

Indeed, indole ring-containing compounds have various biological and pharmacological activities and are part of many marketed drugs used as anticancer, antiemetics, antihypertensives, antidepressants, anti-inflammatory, or anti-HIV, among others [9]. In contrast, concerning indolone and cinnoline derivatives, there are very few marketed drugs but many molecules are under investigations for their activities as antibacterial, antifungal, anticancer, anti-inflammatory agents or even on the central nervous system [7,12,13].

Several routes have been reported to access these key compounds, the most developed being for the indole [14] derivatives with the Fischer indole synthesis involving sigmatropic rearrangements [15–18], nucleophilic and electrophilic cyclization [19–25] reductive and oxidative cyclization [26,27] and by using transition-metal catalysis [28–37]. There are fewer
ways to access indolone derivatives mainly based on the use of di- [12,38,39] or tri-ketones [10,13] and enaminones [40–43] as starting materials. For the synthesis of cinnoline derivatives, aryldiazenes and aryltriazenes are substrates of choice for transition-metal catalyzed (Rh, Pd, Cu) cross-coupling reactions followed by intramolecular cyclizations [44–47]. Moreover arylhydrazones and arylhydrazines/hydrazines can be used as well respectively as partners in 4+2 cyclization reaction [48–51] or by reacting mostly with carbonyl derivatives [52–55].

From the state-of-the-art, a strategy that promotes the synthesis of indole, indolone or cinnoline derivatives from the same starting material is not yet available. To reach this goal, the Michael reaction between 1,4-diketones and primary amines seems particularly attractive because of its straightforward, metal-free and under air character. Herein, we report our investigations on this reaction and we have shown that it can be selectively directed towards the synthesis of indole, indolone or cinnoline derivatives by just changing substrates, substituents or heating mode (Scheme 1).

**Scheme 1:** General strategy to access indole, indolone and cinnoline derivatives from 1,4-diketones.
Results and Discussion

The synthesis of the target compounds required the prior preparation of a panel of variously substituted 1,4-diketones 5. 1,4-Diketones 5 have been prepared either by a Nef reaction [56] from the corresponding nitroenone 3 or a Wittig reaction [57] from 1,2-cyclohexanedione and the corresponding ylide 4 (Scheme 2).

Scheme 2: Synthesis of 1,4-diketones 5a-k via Nef reaction or Wittig reaction

The nitrenones 3a-d were obtained in three steps from the appropriate commercially available cyclohexenones (Scheme 2). First, a Baylis-Hillman reaction between cyclohexanone and formaldehyde led to the formation of the corresponding Baylis-Hillman alcohols in good yield [58] followed by a DMAP-catalyzed acetylation of these alcohols gave the corresponding acetates [59]. Nitrenones 3a-d were finally obtained in acceptable yield by reacting the acetates derivatives with the appropriate nitroalkanes [60]. The next step was the
transformation of the nitro group of 3a-d via a Nef reaction using sodium ethoxide in ethanol, followed by hydrolysis with concentrated sulfuric acid at low temperature[56], leading to the corresponding new γ-diketones 5a-d in 61-87 % yields (Scheme 2).

Despite the efficiency of the Nef reaction, the diversity at the R1 position via this synthesis route remains limited in terms of chemical diversity as it dependent on the availability of the corresponding nitro derivative. It was thus decided to move to the Wittig reaction [57] offering a much more straightforward and efficient route to a panel of new diketones 5e-k from 1,2-cyclohexanedione and the corresponding Wittig ylides 4a-g (readily accessible from the corresponding halogenated derivatives) (Scheme 2). Indeed, the Wittig reaction leads exclusively to the isomerized product 5.

With 1,4-diketones 5 in hand, we first investigated the synthesis of indole and indolone derivatives. The reaction mechanism shown in Scheme 3 involves the formation of an imine upon reaction of the primary amine with the most reactive carbonyl moiety (non-conjugated and exocyclic carbonyl function). Then, depending on the reaction conditions, the imine can react following a 1,2 or 1,4 addition process leading respectively to an indole 6 (after dehydration and aromatization) or an indolone 7. The reaction was first investigated by mixing diketone 5b as the Michael acceptor and benzylamine under various conditions (Table 1).

Scheme 3: Mechanism of formation of indole and indolone derivatives.
Table 1: Effects of solvent and heating mode on the 6b:7b ratio.

| Entry | Catalyst      | Solvent | Time | 6b (%) | 7b (%) | 6b:7b |
|-------|---------------|---------|------|--------|--------|-------|
| 1     | TfOH (3%)     | Toluene | 16h  | -      | -      | -     |
| 2     | AgOTf (3%)    | Toluene | 16h  | -      | -      | -     |
| 3     | TFA (3%)      | Toluene | 16h  | -      | -      | -     |
| 4     | pTsOH (3%)    | Toluene | 16h  | -      | -      | -     |
| 5     | AcOH (3%)     | Toluene | 16h  | 47     | 10     | 83:17 |
| 6     | Toluene       | Toluene | 16h  | 33     | 8      | 80:20 |
| 7     | CH₂Cl₂        | 16h     | -    | -      | -      | -     |
| 8     | THF           | 16h     | -    | -      | -      | -     |
| 9     | Ethanol       | 16h     | 13   | 16     | 45:55  |
| 10    | Propanol      | 16h     | 6    | 31     | 16:84  |
| 11    | Butanol       | 16h     | 10   | 43     | 19:81  |
| 12    | Pentanol      | 16h     | 7    | 28     | 20:80  |
| 13c   | Butanol       | MWI 3h  | -    | 60     | 0:100  |

*a reaction conditions: 5b (0.54 mmol), primary amine (0.81 mmol), 4 mL of solvent and catalyst (0.02 mmol) unless otherwise specified (in column 2 the catalyst percentage it is always reported and it exactly corresponds to 0.02 mmol); b isolated yield; c 13 mL of butanol, MWI 100°C.

We first investigated the reactivity in the presence of a set of catalysts with different acidities (Entries 1-5 – Table 1). Among them only acetic acid afforded reaction products while the
others only produced complex mixtures of degradation products. In the conditions of entry 5, indole 6b was isolated in 47% and indolone 7b was also formed concomitantly in 10% yield. Entries 6-11 were next performed with the aim to favour the 1,4-addition process and thus the formation of indolone 7b. Removing the acid catalyst from the reaction mixture (Entry 6) did not affect the 6b:7b ratio obtained in entry 5. While in aprotic solvents, other than toluene (Entries 7-8), the reaction produced complex mixtures of degradation products, using alcohols had a notable impact on the reaction contents. Indeed, going from ethanol to propanol and thus increasing the refluxing temperature led to indolone 7b as the main product, the best yield being obtained in butanol (43%, Entry 11) with however the formation of 6b in 10% yield. Switching to a microwave irradiation formed exclusively 7b in 60% yield after 3h (Entry 13). Note that to check the effect of a shorter reaction time on the reaction outcome, we have reduced the time to 3h also under the classical refluxing conditions of entry 11 and obtained a partial conversion of the starting diketone 5b. Despite the side formation of indolone 7b in entry 5, these conditions were applied to several amines producing the corresponding substituted indoles 6a and 6c-f in 41-52% yields (Scheme 4). The yield of indolones 7a and 7c-f was found almost constant (10-14%) whatever the amine involved. It is worthy of note that the two compounds were easily separated using usual chromatographic techniques.
Scheme 4: Synthesis of indoles 6a-f and corresponding side product indolones 7a-f.

The reaction was also applied to a diamine (Scheme 5). When 1,3-diaminopropane was used the bis-indole 6g was isolated in 46% yield. Interestingly, the mixed indolone/indole compound 9 was also obtained as the side product. However no traces of the bis-indolone derivative were detected.

Scheme 5: Reaction of 5b with a diamine.

We then succeeded in directing the reaction exclusively towards the indole formation by reacting the diketone with substrates combining a primary and a tertiary amine separated by several spacer arms (Scheme 6).
Scheme 6: Synthesis of indoles 6h-l.

Under these conditions, the functional indoles 6h-l were obtained exclusively in 45-55% yield. We assumed that the tertiary amine would interact with the protonated intermediate, thus promoting the 1,2-addition (Scheme 7).

Scheme 7: Proposed intermediate to promote the 1,2-addition.

We next examined the preparation of a set of indolones under the microwave conditions determined in entry 13 of Table 1. These conditions were applied to several amines producing the exclusively the corresponding substituted indolones 7d and 7g-k in 48-56% yields (Scheme 8).
Scheme 8: Synthesis of indolone derivatives 7b, 7d and 7g-k.

Here again, the amount of indolone was found almost constant whatever the amine involved, suggesting that the reaction is not dependant of the nature of the amine. It is worth notice that, in case of a substrate combining a primary and a tertiary amine separated by a spacer arm only the indolone derivative is obtained in those conditions as well (compound 7i –Scheme 8).

Based on these results, we found it important to check that indole 6b resulted from a 1,2-addition and not from a degradation of indolone 7b. For this purpose, indolone 7b was refluxed overnight with acetic acid in toluene under the conditions producing mainly the indole (Table 1, entry 5). The indolone 7b was found unchanged, with no trace of indole 6b detected (see Supporting Information File 1 – I), indicating that the indole was formed intramolecularly by 1,2-addition of the intermediately formed imine to the Michael acceptor (Scheme 3).

We then investigated the synthesis of cinnoline derivatives by mixing diketone 5a and hydrazine monohydrate under various conditions (Table 2). We first investigated the reactivity in ethanol as protic solvent, at room temperature (entry 1 – Table 2). Under these
conditions, the expected cinnoline 8a was obtained in low yield of 20 % that could be increased up to 40% upon refluxing the mixture (entry 2 – Table 2). Switching to toluene (entry 3 – Table 2) did not improve the reaction outcome. However, the addition of a catalytic amount of acetic acid in refluxing ethanol while shortening the reaction time, dramatically increased the yield of 8a up to 82% (entry 4 – Table 2).

**Table 2** Optimization of the reaction conditions for synthesis of cinnolines 8.

| Entry | Catalyst | Solvent   | T°C      | time (h) | 8a (%)<sup>b</sup> |
|-------|----------|-----------|----------|----------|---------------------|
| 1     | -        | EtOH      | r.t.     | 48       | 20                  |
| 2     | -        | EtOH      | reflux   | 48       | 40                  |
| 3     | -        | Toluene   | reflux   | 48       | 35                  |
| 4     | AcOH (3%)| EtOH      | reflux   | 16       | 82                  |

<sup>a</sup> reaction conditions: 5a (1 mmol), hydrazine monohydrate (1.5 mmol), solvent (6 mL) and a catalyst (0.03 mmol) unless otherwise specified (in column 2 the reported catalyst percentage exactly corresponds to 0.03 mmol). <sup>b</sup> isolated yield.

These optimized conditions were then applied to the previously synthesized 1,4-diketones 5a-k (Scheme 9). As a general observation, the reaction was found efficient producing the expected cinnoline derivatives 8a-k in good to excellent yields (77 – 92 %) and tolerate alkyl, aromatic and heteroaromatic group at R<sup>1</sup> position.
Scheme 9: Synthesis of cinnoline derivatives 8a-k.

The success of our convergent strategy here can be explained through the mechanism suggested in Scheme 10. The synthetic pathway leading to the formation of indolone 7 starts with an imine formation between the secondary amine and the non-conjugated carbonyl from the 1,4-diketone. After an imine-enamine equilibrium, an intramolecular 1,4-addition to the Michael acceptor part of the molecule occurs, followed by a prototropy, leading to an intermediate enol which, after a keto-enol equilibrium and aromatization, gives the indolone 7. For indole 6 and cinnoline 8, the synthesis starts with the protonation of the oxygen of the conjugated carbonyl of the 1,4-diketone followed by an imine formation between the secondary amine and the non-conjugated carbonyl. Next, an intramolecular 1,2-addition to the Michael acceptor part of the molecule, previously activated by acid catalysis, takes place (after an imine-enamine equilibrium in the case of the indole pathway), followed by a prototropy, release of a water molecule, recovery of the proton catalyst and atmospheric oxygen aromatization, leads to indole 6 or cinnoline 8.
Conclusion

In summary, we have successfully developed a straightforward and metal-free strategy for the synthesis of nitrogen-containing heterocycles moieties of biological interested; indole 6, indolone 7 and cinnoline 8 derivatives; starting from common substrates: 1,4-diketones 5 and primary amines. The protocols developed here use mild conditions, are functional-group tolerant, transition metal-free, proceeds in moderate to good yields and therefore can be easily used in medicinal chemistry projects for rapid access to a wide range of variously substituted compounds for structure-activity relationship studies. The biological activity of the molecules is currently being studied.

Supporting Information

Experimental procedures, characterization data and copies of spectra of all compounds.

Supporting Information File 1:

File Name: Supporting Information BJOC

File Format: pdf

Title: Experimental data
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