



HAL
open science

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

Dalel El-Marrouki, Sabrina Touchet, Abderrahmen Abdelli, Hédi M'rabet, Mohamed Lotfi Efrit, Philippe C. Gros

► **To cite this version:**

Dalel El-Marrouki, Sabrina Touchet, Abderrahmen Abdelli, Hédi M'rabet, Mohamed Lotfi Efrit, et al.. Tuneable access to indole, indolone, and cinnoline derivatives from a common 1,4-diketone Michael acceptor. *Beilstein Journal of Organic Chemistry*, 2020, 16, pp.1722-1731. 10.3762/bjoc.16.144 . hal-02901438

HAL Id: hal-02901438

<https://hal.science/hal-02901438v1>

Submitted on 20 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Dalel El-Marrouki^{1,2}, Sabrina Touchet*¹, Abderrahmen Abdelli², Hédi M'Rabet², Mohamed Lotfi Efrit² and Philippe C. Gros*¹

Address: ¹Université de Lorraine, CNRS, L2CM, F-5400 Nancy, France and ²Université de Tunis El Manar, SOHES-LR17ES01, Tunis, Tunisie.

Email: Sabrina Touchet* - sabrina.touchet@univ-lorraine.fr and Philippe C. Gros* - philippe.gros@univ-lorraine.fr.

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-tetrahydroindol-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].

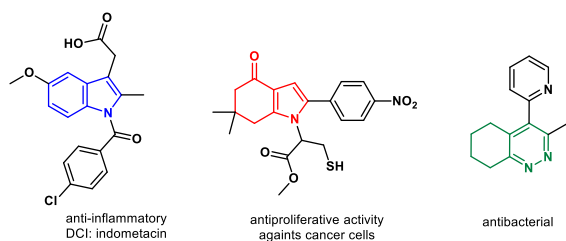


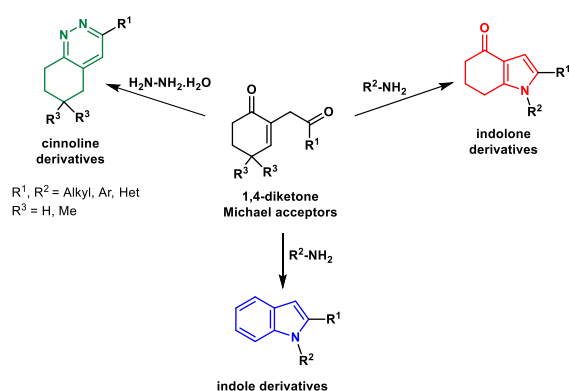
Figure 1: Examples of bioactive nitrogen-containing heterocycles (indole [9], indolone [10] and cinnoline [11] derivatives).

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 aryldiazones 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].

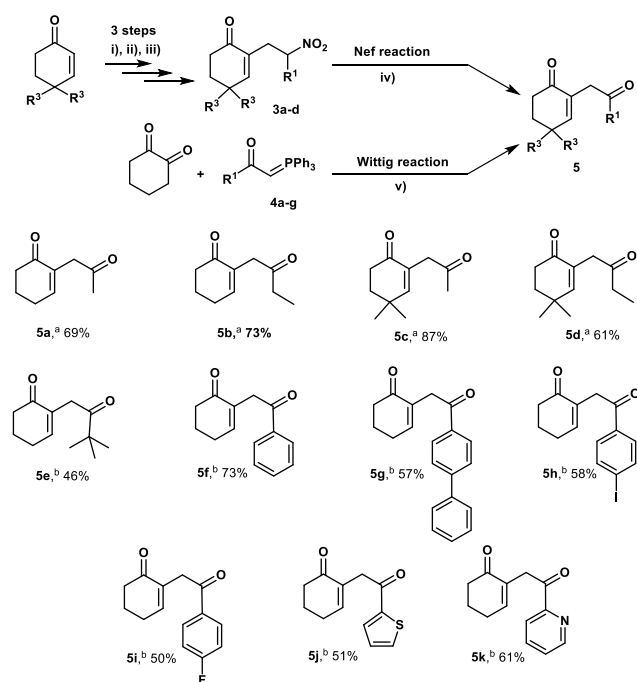
From the state-of-the-art, a strategy that promotes the synthesis of indole, indolone or cinnoline derivatives from the same starting material is not yet available. To reach this goal, the Michael reaction between 1,4-diketones and primary amines seems particularly attractive because of its straightforward, 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).



i) $(\text{HCHO})_{\text{aq}}$, DMAP, THF, r.t., 24h ii) Ac_2O , Et_3N , DMAP, 0°C then 2h r.t. iii) $\text{R}^1\text{-CH}_2\text{-NO}_2$, Et_3N , EtOH, reflux, 24h iv) EtONa , EtOH, r.t., 3h then H_2SO_4 , -50°C , 1h v) toluene or DCM reflux 48h then r.t. 2 days

^a via Nef reaction, ^b via Wittig-Horner reaction

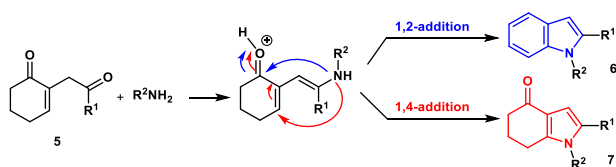
Scheme 2: Synthesis of 1,4-diketones **5a-k** via Nef reaction or Wittig reaction

The nitrenones **3a-d** were obtained in three steps from the appropriate commercially available cyclohexanones (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

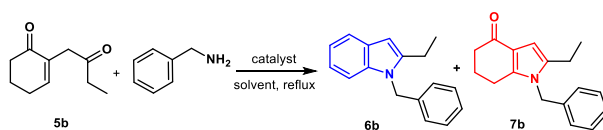
transformation of the nitro group of **3a-d** via a Nef reaction using sodium ethoxide in ethanol, followed by hydrolysis with concentrated sulfuric acid at low temperature[56], leading to the corresponding new γ -diketones **5a-d** in 61-87 % yields (Scheme 2).

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.

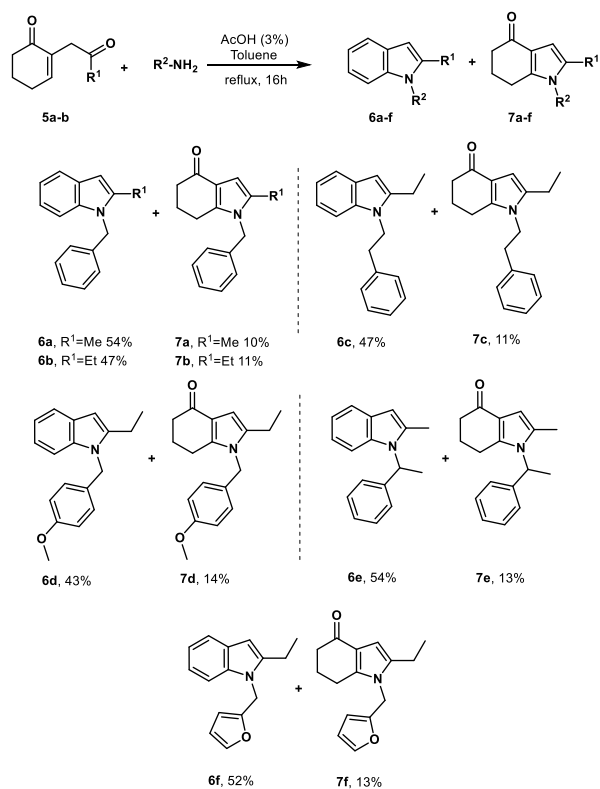
Table 1: Effects of solvent and heating mode on the **6b:7b** ratio.

Entry ^a	Catalyst	Solvent	Time	6b (%) ^b	7b (%) ^b	6b:7b
1	TfOH (3%)	Toluene	16h	-	-	-
2	AgOTf (3%)	Toluene	16h	-	-	-
3	TFA (3%)	Toluene	16h	-	-	-
4	<i>p</i> TsOH (3%)	Toluene	16h	-	-	-
5	AcOH (3%)	Toluene	16h	47	10	83:17
6		Toluene	16h	33	8	80:20
7		CH ₂ Cl ₂	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
13 ^c		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.

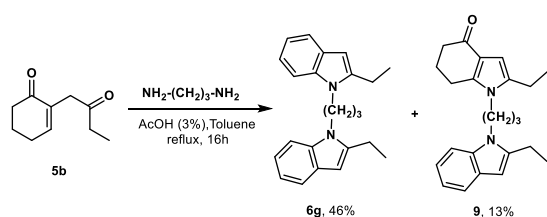
We first investigated the reactivity in the presence of a set of catalysts with different acidities (Entries 1-5 – Table 1). Among them only acetic acid afforded reaction products while the

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.



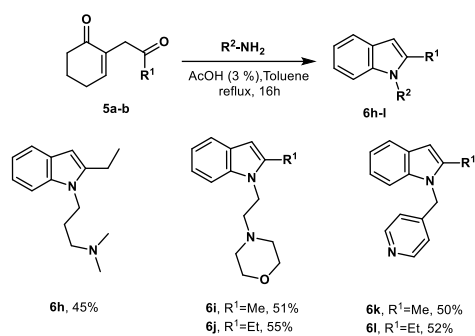
Scheme 4: Synthesis of indoles **6a-f** and corresponding side product indolones **7a-f**.

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.



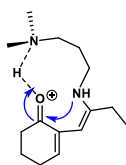
Scheme 5: Reaction of **5b** with a diamine.

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).



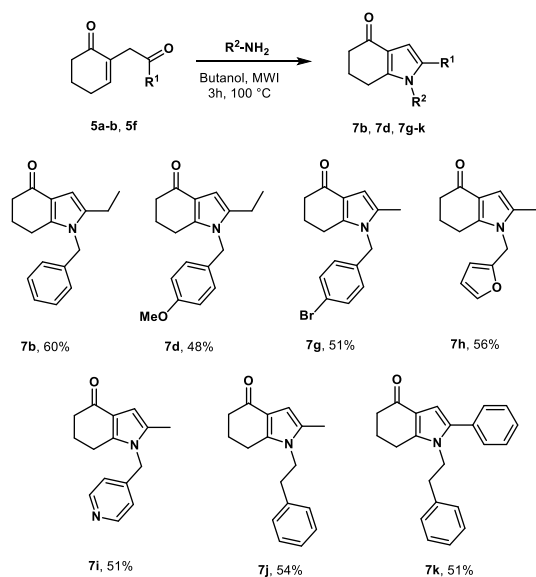
Scheme 6: Synthesis of indoles **6h-l**.

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).



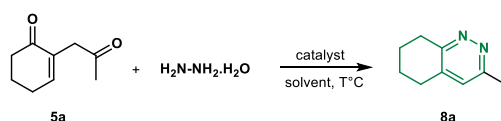
Scheme 8: Synthesis of indolone derivatives **7b**, **7d** and **7g-k**.

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).

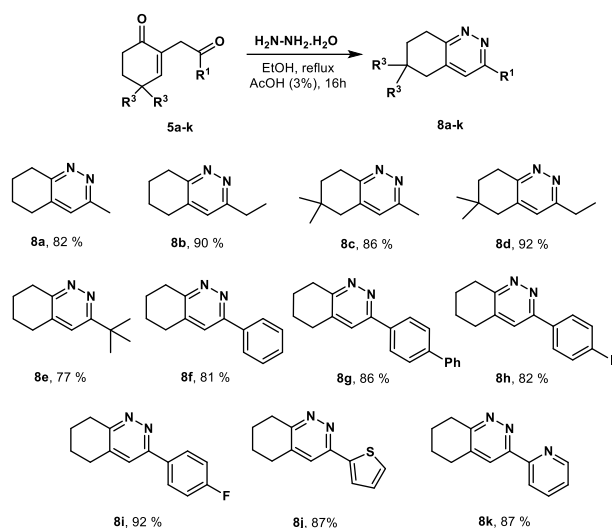
Table 2 Optimization of the reaction conditions for synthesis of cinnolines **8**.



Entry ^a	Catalyst	Solvent	T ^o C	time (h)	8a (%) ^b
1	-	EtOH	r.t.	48	20
2	-	EtOH	reflux	48	40
3	-	Toluene	reflux	48	35
4	AcOH (3%)	EtOH	reflux	16	82

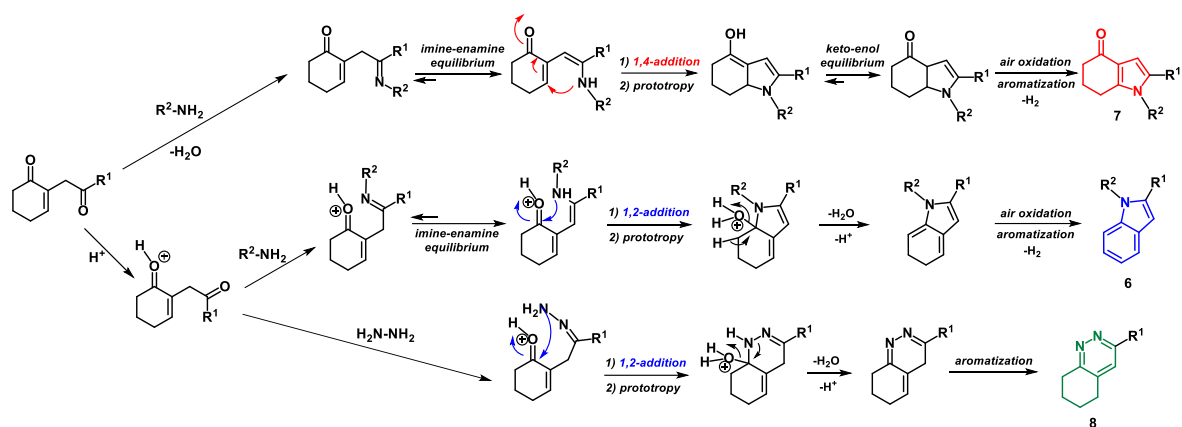
^a reaction conditions: **5a** (1 mmol), hydrazine monohydrate (1.5 mmol), solvent (6 mL) and a catalyst (0.03 mmol) unless otherwise specified (in column 2 the reported catalyst percentage exactly corresponds to 0.03 mmol). ^b isolated yield.

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 R¹ 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**.



Scheme 10: Proposed mechanism for the preparation of compounds **6**, **7** and **8**.

Conclusion

In summary, we have successfully developed a straightforward and metal-free strategy for the synthesis of nitrogen-containing heterocycles moieties of biological interest; 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, proceed 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

Acknowledgements

The authors would like to thank François Dupire (UMR 7053 – L2CM) and Fabien Lachaud (UMR 7053 – L2CM) for the HRMS and GC-MS experiments and related discussions. They thank also the Université de Lorraine and the CNRS for their support. The University of Tunis El Manar and the Tunisian Ministry of Higher Education and Scientific Research are also acknowledged for a grant to D.M.

References

1. Kumar, D.; Jain, K. S. *Curr. Med. Chem.* **2016**, *23*, 4338–4394.
2. Liu, J.-C.; Suresh, N.; Kang, Z.; Wen, Z. *Mini Rev Med Chem.* **2019**, *19*, 1517–1530.
3. Wang, S.-Y.; Shi, X.-C.; Laborda, P. *Eur. J. Org. Chem.* **2020**, *185*, 111847.
4. Rubina, B.; Dharam, P.; Garima, K.; Ravi, K.; Manni, D. *IJPER* **2019**, *53*, 1–16.
5. Singh, T. P.; Singh, O. M. *Mini Rev Med Chem.* **2018**, *18*, 9–25.
6. Thanikachalam, P. V.; Maurya, R. K.; Garg, V.; Monga, V. *Eur. J. Med. Chem* **2019**, *180*, 562–612.
7. Lewgowd, W.; Stanczak, A. *Arch. Pharm. (Weinheim)* **2007**, *340*, 65–80.
8. Awad, E. D.; El-Adadelah, M. M.; Matar, S.; Zihlif, M. A.; Naffa, R. G.; Al-Momani, E. Q.; Mubarak, M. S. *Molecules* **2012**, *17*, 227–239.
9. Kaushil, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662.
10. Martínez, R.; Clara-Sosa, A.; Ramírez Apan, Ma. T. *Bioorg. Med. Chem.* **2007**, *15*, 3912–3918.
11. Yuvaraj, T. V.; Unnissa, S. H.; Surendiran, N. S.; Ur rahman, M. A.; Binumon, V. *AJRC* **2010**, *3*, 853–858.
12. Batchu, H.; Batra, S. *Eur. J. Org. Chem.* **2012**, *2012*, 2935–2944.

13. Khalafy, J.; Badparvar, F.; Mariani, A. P. *J. Chil. Chem. Soc.* **2016**, *61*, 3112–3115.
14. Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, No. 7, 1045–1075.
15. Vuong, H.; Duarte, S.; Klumpp, D. A. *Top Catal* **2018**, *61*, 685–688.
16. Ghiyasabadi, Z.; Bahadorikhalili, S.; Saeedi, M.; Karimi-Niyazagheh, M.; Mirfazli, S. S. *J Heterocyclic Chem* **2020**, *57*, 606–610.
17. Irgashev, R. A.; Steparuk, A. S.; Rusinov, G. L. *Tetrahedron Letters* **2019**, *60*, 151185.
18. Yu, J.; Xu, J.; Yu, Z.; Jin, Y.; Li, J.; Lv, Y. *Journal of Flow Chemistry* **2017**, *7*, 33–36.
19. Chesnokov, G. A.; Agheshina, A. A.; Topchiy, M. A.; Nechaev, M. S.; Asachenko, A. F. *Eur. J. Org. Chem.* **2019**, *2019*, 4844–4854.
20. Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985–9989.
21. Zhao, H.; Yuan, H.; Zhang, Y.; Li, R.; Li, W. *Org. Lett.* **2019**, *21*, 6557–6561.
22. Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037–1040.
23. Chen, Y.; Cho, C.-H.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802–6811.
24. Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62–69.
25. Zhao, G.; Roudaut, C.; Gandon, V.; Alami, M.; Provot, O. *Green Chem.* **2019**, *21*, 4204–4210.
26. Sathishkumar, P. N.; Prabha, P. S.; Bhuvanesh, N. S. P.; Karvembu, R. *Journal of Organometallic Chemistry* **2020**, *908*, 121087.
27. Rode, N. D.; Abdalghani, I.; Arcadi, A.; Aschi, M.; Chiarini, M.; Marinelli, F. *J. Org. Chem.* **2018**, *83*, 6354–6362.
28. He, Y.; Wu, H.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 2105–2109.
29. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Iazzetti, A.; Marinelli, F. *Org. Biomol. Chem.* **2013**, *11*, 545–548.
30. Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5170–5174.
31. Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12992–12996.

32. Zhao, G.; Bignon, J.; Levaique, H.; Dubois, J.; Alami, M.; Provot, O. *J. Org. Chem.* **2018**, *83*, 15323–15332.
33. Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153–2167.
34. Ho, H. E.; Oniwa, K.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2016**, *18*, 2487–2490.
35. Sperança, A.; Godoi, B.; Menezes, P.; Zeni, G. *Synlett* **2013**, *24*, 1125–1132.
36. Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 942–945.
37. Filatova, E. A.; Pozharskii, A. F.; Gulevskaya, A. V.; Ozeryanskii, V. A. *J. Org. Chem.* **2015**, *80*, 872–881.
38. Heravi, M. M.; Baghernejad, B.; Oskooie, H. A.; Hekmatshoar, Rahim. *Tetrahedron Lett.* **2008**, *49*, 6101–6103.
39. Wu, S.; Fluxe, A.; Janusz, J. M.; Sheffer, J. B.; Browning, G.; Blass, B.; Cobum, K.; Hedges, R.; Murawsky, M.; Fang, B.; Fadayel, G. M.; Hare, M.; Djandjighian, L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5859–5863.
40. To, Q. H.; Lee, Y. R.; Kim, S. H. *Tetrahedron* **2014**, *70*, 8108–8113.
41. Lan, X.-C.; Chen, T.-T.; Zhao, Y.; Wu, Y.; Wang, J.; Tu, S.-J.; Jiang, B.; Hao, W.-J. *Tetrahedron Lett.* **2017**, *58*, 1519–1522.
42. Jiang, B.; Yi, M.-S.; Shi, F.; Tu, S.-J.; Pindi, S.; McDowell, P.; Li, G. *Chem. Commun.* **2012**, *48*, 808–810.
43. Jiang, B.; Li, Q.-Y.; Zhang, H.; Tu, S.-J.; Pindi, S.; Li, G. *Org. Lett.* **2012**, *14*, 700–703.
44. Zhu, C.; Yamane, M. *Tetrahedron* **2011**, *67*, 4933–4938.
45. Zhao, D.; Wu, Q.; Huang, X.; Song, F.; Lv, T.; You, J. *Chem. Eur. J.* **2013**, *19*, 6239–6244.
46. Muralirajan, K.; Cheng, C.-H. *Chem. Eur. J.* **2013**, *19*, 6198–6202.

47. Danilkina, A. N.; Bukhtiiarova, S. N.; Govdi, I. A.; Vasileva, A. A.; Rumyantsev, M. A.; Volkov, A. A.; Sharaev, I. N.; Povolotskiy, V. A.; Boyarskaya, A. I.; Korniyakov, V. I.; Tokareva, V. P.; Balova, A. I. *Molecules* **2019**, *24*, 1420–3049.
48. Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusano, S. *Org. Lett.* **2009**, *11*, 309–312.
49. South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *Tetrahedron Lett.* **1996**, *37*, 1351–1354.
50. South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem.* **1996**, *61*, 8921–8934.
51. South, M. S.; Jakuboski, T. L. *Tetrahedron Lett.* **1995**, *36*, 5703–5706.
52. Chang, M.-Y.; Lu, Y.-J.; Cheng, Y.-C. *Tetrahedron* **2015**, *71*, 6840–6845.
53. Fukumoto, S.; Imamiya, E.; Kusumoto, K.; Fujiwara, S.; Watanabe, T.; Shiraishi, M. *J. Med. Chem.* **2002**, *45*, 3009–3021.
54. Khalafy, J.; Rimaz, M.; Ezzati, M.; Marjani, A. P. *Curr. Chem. Lett.* **2013**, *2*, 43–48.
55. Altomare, C.; Cellamare, S.; Summo, L.; Catto, M.; Carotti, A.; Thull, U.; Carrupt, P.-A.; Testa, B.; Stoeckli-Evans, H. *J. Med. Chem.* **1998**, *41*, 3812–3820.
56. Chamakh, A.; M'hirsi, M.; Villiéras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, *2000*, 295–299.
57. Mawaziny, S.; Lawny, A. M. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2000**, *163*, 99–120.
58. Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965–5966.
59. Rezgui, F.; El Gaied, M. M. *Tetrahedron* **1997**, *53*, 15711–15716.
60. Mhasni, O.; Rezgui, F. *Tetrahedron Lett.* **2010**, *51*, 586–587.