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One-pot reaction of pyranoindolones with phenylisocyanates: a simple and regioselective approach to β-carbolines

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ABSTRACT

A versatile, regioselective and novel approach towards 2-aryl-β-carbolin-3-ones from the reaction of pyranoindolones with phenylisocyanates is described.

Introduction

Pyrido[3,4-*b*]indoles, commonly known as β-carbolines, are the key structural motif of a variety of biologically important alkaloids of natural and synthetic origin.[1–4] β-Carboline alkaloids (Fig. 1) are widespread in both the plant and animal kingdom, mostly marine microorganisms, with high affinity for benzodiazepine, serotonin and dopamine receptor sites.[5–7] They also exhibit a vast diversity of biological activities, very often significant antitumor action,[8] by DNA intercalation,[9–11] DNA binding,[12,13] or DNA synthesis inhibition[14] among others. Very recently, tetrahydro-β-carboline derivatives demonstrated antileishmanial activity against the transgenic infrared fluorescent *Leishmania infantum* strain.[15] Furthermore, they have been utilized as antipsychotic and antihypertensive drugs (Reserpine, Serpasil®),[16–18] vasodilators (Vincamicine, Oxybral®)[19] or PDE5 inhibitors for the treatment of erectile dysfunction (Tadalafil, Cialis®).[20]

1-Oxo-β-carboline skeletons are also present in natural products (e.g., the alkaloid Bauerine C)[21] with remarkable biological and pharmacological activities,[21–23] and many of them have been patented and described as useful central nervous system depressants and kinase inhibitors.[24,25]

On the other hand, reports of 3-oxo-β-carbolines are quite limited and they are mainly synthesized by the reaction of 2-acylindoloacetic acid esters with primary amines.[12–15] The above-mentioned importance of this scaffold requires efficient synthetic methodologies, both for construction of the β-carboline system and for its functionalization.[26,27] Diels–Alder reactions of pyranoindolones with dienophiles are often employed as a key reaction for the synthesis of fused carbazoles[28,29] e.g., access to the alkaloids carbazomycins A and B.[30] Previously, we described synthetic methodologies towards the synthesis of β-carbolinones based on the reactions of pyranoindolones with phenylhydrazine or benzoylhydrazine[31] or utilizing *N,N′*-disubstituted ureas (PhBr, reflux)[32] (Scheme 1).

As a continuation of our interest in β-carbolines and the search for improved synthetic routes, herein, we describe a rapid and simple methodology based on the one-pot reaction of pyranoindolones with isocyanates for the preparation of a series of 2-aryl-β-carbolin-3-ones in good yields (Scheme 1).

Results and discussion

Our initial experiments focused on the reaction between pyranoindolone **1a** and phenylisocyanate **2a** (1:1 ratio) in bromobenzene at reflux. After 2 h, a mixture of the two regioisomers of β-carbolinones **3a** and **5a** (1:3 ratio) as well as the phenylisocyanate-derived trimer **6** was formed (Table 1, entry 1, see ESI

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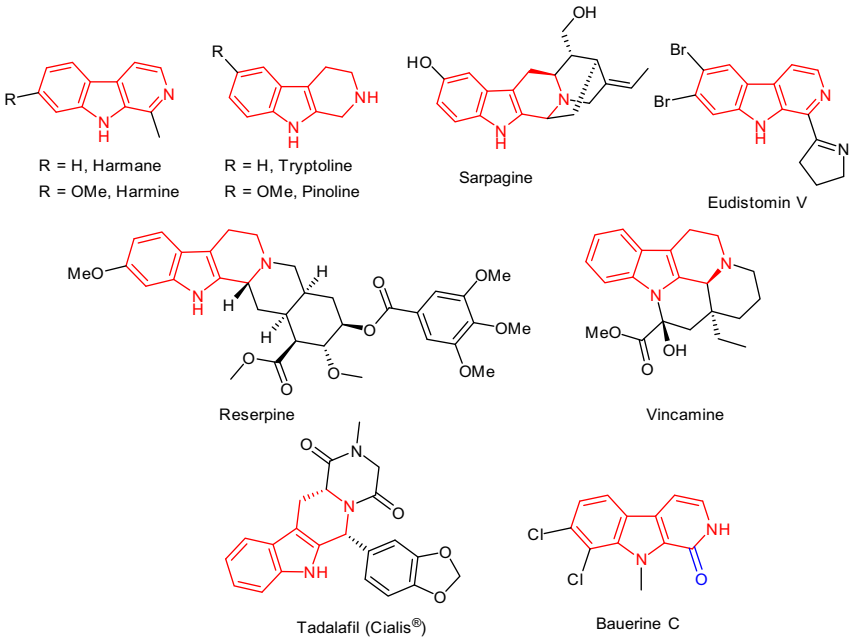
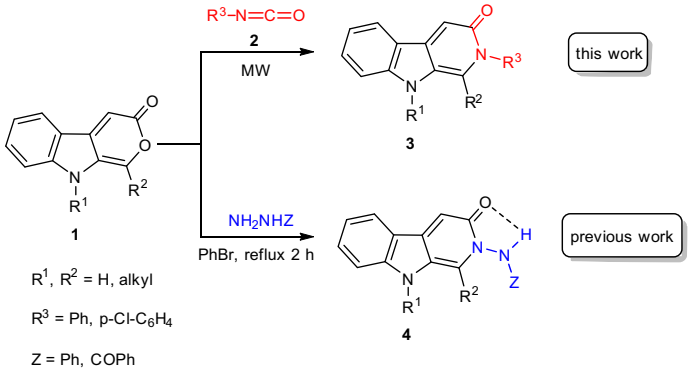


Figure 1. Selected examples of biologically important β-carbolines.



Scheme 1. One-pot reaction of pyranoindolones with isocyanates as well as previous reported approaches.

for NMR analysis of compounds **3a**, **5a** and **6**). Upon adjusting the reagent ratio, we observed that when 5.0 equiv of phenylisocyanate **2a** was used, a mixture of regioisomers **3a** and **5a** in a 3:1 ratio, as well as trimer **6** was obtained (entry 2). Unfortunately, after significant experimentation involving both the reaction time and the reagent equivalents, it was not possible to obtain increased regioselectivity, while a substantial amount of the starting material was trimerized.

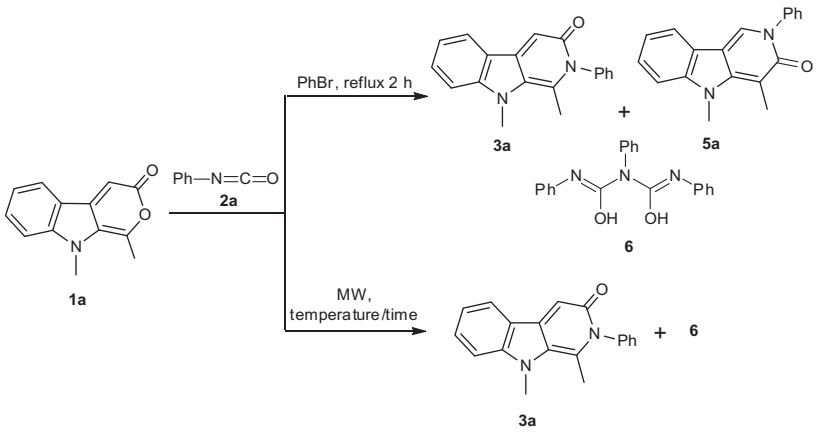
Microwave (MW) irradiation has shown prominent results in the condensation of phenylisocyanates and α-ketols for the regioselective synthesis of 4-oxazolin-2-ones.[33] Thus, 2-pyranoindolone (1.0 mmol) and phenylisocyanate (3.0 mmol) were irradiated in a microwave oven without solvent for 10 minutes (entry 3). To our delight, only the β-carbolinone regioisomer **3a** was formed in good yield which was easily purified by column chromatography. Upon using less equivalents of isocyanate **2a**, unreacted pyranoindolone **1a** was recovered (entry 4), whereas increasing the equivalents of **2a** and reducing the irradiation time (4 min) afforded better results (entry 5). The desired reaction conditions (temperature and time) were set as reported in entry 6, 160 °C/5 min (Table 1). After the reaction conditions were optimized, the generality of the reaction was investigated and the results showed that the reaction has a broad applicability.

Thus, two readily available phenylisocyanates **2a–b** were reacted with the easily obtained[34,35] pyranoindolones **1a–d** having different substitution patterns, in all cases yielding only the desired regioisomer of the corresponding 2-aryl-β-carbolin-3-ones **3a–h** in moderate to good yield (Scheme 2).

Full assignment of the ^{1}H and ^{13}C NMR chemical shifts of the new compounds **3**, **5** and **6** was achieved. Regarding the structure of the isolated β-carbolines **3**, the assignment of **3d** is described based on rigorous spectroscopic analysis including IR, 2D NMR, MS and elemental analysis data (ESI).

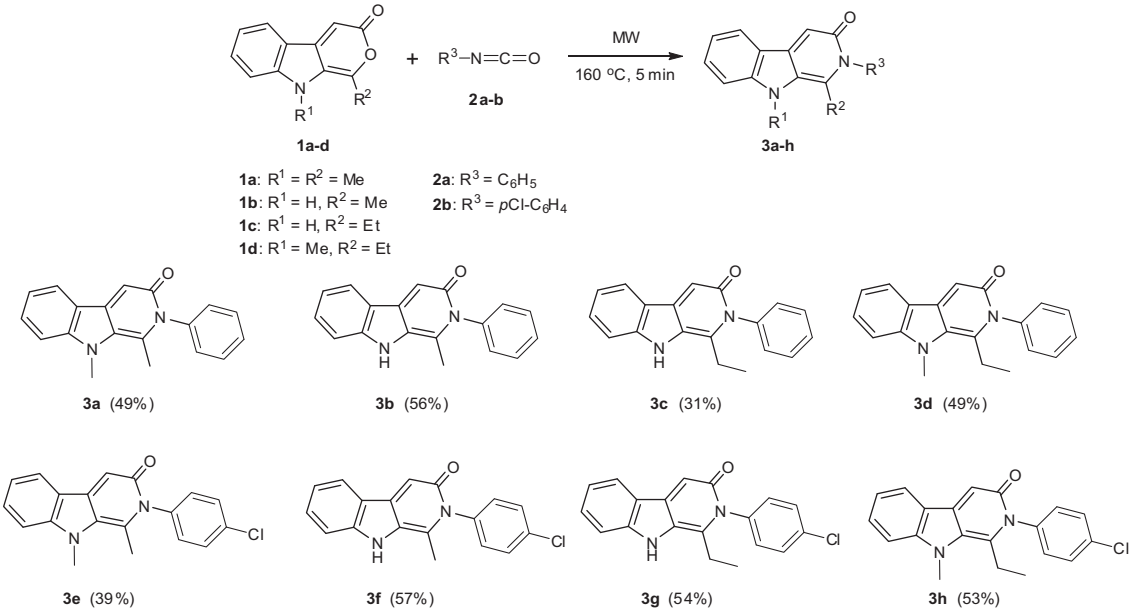
The presence of the four indole aromatic protons appeared in a characteristic pattern, resonating as a doublet of doublets at $\delta = 7.88$ (5-H),[36] a double doublet of doublets at $\delta = 7.10$ (6-H), a double doublet of doublets at $\delta = 7.53$ (7-H) and as a doublet of doublets at $\delta = 7.17$ (8-H), with their carbons resonating at $\delta = 122.8$, 119.3, 130.8, and 108.9 ppm, respectively. Moreover, the 4-position proton appeared as a singlet at $\delta = 7.03$. The presence of the phenyl moiety was identified from the two characteristic proton multiplets at $\delta = 7.26–7.31$ (2′,6′-H) and 7.46–7.56

Table 1
Optimization of the conditions: conventional heating versus microwave irradiation



Entry	**2a** (equiv)	Conditions	**3a** (%)	**5a** (%)	**6** (%)
1	1.0	PhBr, reflux, 2 h	12	34	52
2	5.0	PhBr, reflux, 2 h	35	11	49
3	3.0	MW, 160 °C, 10 min	45	–	10
4[a]	1.0	MW, 160 °C, 4 min	29	–	21
5	3.0	MW, 160 °C, 4 min	48	–	5
6[b]	3.0	MW, 160 °C, 5 min	49	–	5

[a] Unreacted starting material recovered.
[b] Optimized conditions are highlighted.



Scheme 2. Synthesis of 2-aryl-β-carbolin-3-ones by the reaction of the pyranoindolones **1a–d** with isocyanates **2a–b**.

(3′,5′-H, 4′-H), with their carbons resonating at δ = 128.9, 129.6, and 128.6 ppm, respectively. Finally, the 9-methyl group appeared as a singlet at δ = 3.77 with its carbon resonating at δ = 32.6 ppm, whereas the 1-ethyl group appeared as a triplet and quartet at δ = 1.10 and 2.80, respectively.

Conclusion

In conclusion, we have developed a rapid and simple method[37] for the synthesis of a series of 2-phenyl-β-carbolin-3-ones **3** in good yields from the reaction of pyranoindolones with phenylisocyanates. All compounds, to the best of our knowledge, are novel and in the near future they will be tested against various biological targets. In addition, a thorough NMR analysis with full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been unambiguously achieved which will be useful for similar scaffolds e.g., indole alkaloids.

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Supplementary data

Supplementary data (physicochemical properties, spectroscopic data of ^{1}H and ^{13}C NMR spectra of the new compounds, 2D NMR, LC–MS and IR data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.075.

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37. *General procedure for the reaction of phenylisocyanates (**2a**–**b**) with pyrano[3,4-b]indol-3(9H)-ones (**1a**–**d**).* A mixture of the corresponding pyranoindolone **1a**–**d** (1.0 mmol) and the phenylisocyanate **2a**–**b** (3.0 mmol) was irradiated in a microwave oven for 5 min at 160 °C. The resulting residue was subjected to column chromatography on silica gel using petroleum ether–EtOAc (1:1) as eluent, slowly increasing the polarity up to pure EtOAc to give the desired compounds **3a**–**i**. *1-Ethyl-9-methyl-2-phenyl-2H-pyrido[3,4-b]indol-3(9H)-one (**3d**)* Yield: 0.148 g (49%); brown crystals; mp 241–243 °C. IR (nujol): 1686 (NC=O) cm^{-1}. ^{1}H NMR: δ = 1.10 (t, *J* = 7.5 Hz, 3H, 1-Me), 2.80 (q, *J* = 7.5, 2H, 1-CH_2), 3.77 (s, 3H, 9-Me), 7.03 (s, 1H, 4-H), 7.10 (ddd, *J* = 1.1, 7.4, 7.5 Hz, 1H, 6-H), 7.17 (dd, *J* = 1.1, 8.4 Hz, 1H, 8-H), 7.26–7.31 (m, 2H, 2′,6′-H), 7.46–7.56 (m, 3H, 3′, 4′, 5′-H), 7.53 (ddd, *J* = 1.2, 7.5, 8.4 Hz, 1H, 7-H), 7.88 (dd, *J* = 1.2, 7.4 Hz, 1H, 5-H). ^{13}C NMR: δ = 14.8 (1-Me), 22.5 (1-CH_2), 32.6 (9-Me), 104.4 (C-4), 108.9 (C-8), 119.3 (C-6), 120.9 (C-4b), 122.8 (C-5), 126.6 (C-9a), 128.6 (C-4′), 128.9 (C-2′,6′), 129.6 (C-3′,5′), 130.8 (C-7), 133.4 (C-1), 139.4 (C-1′), 140.6 (C-4a), 148.0 (C-8a), 161.9 (C-3). LC–MS (ESI, 1.65 eV): *m*/*z* (%) = 357 (32) [M^{+}+Na +MeOH], 325 (68) [M^{+}+Na) 303 (100) [M^{+}+1]. Anal. Calcd for $C_{20}H_{18}N_2O$ (302.14): C, 79.44; H, 6.00; N, 9.26%. Found: C, 79.35; H, 5.89; N, 9.24%.