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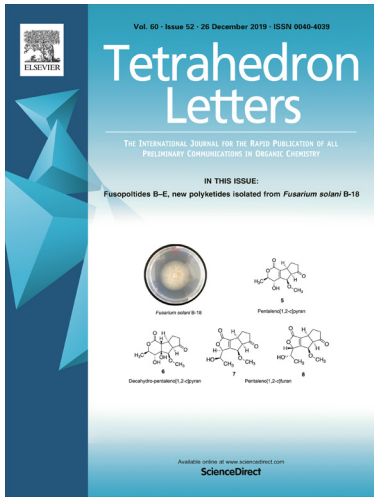

A short divergent approach to highly substituted carbazoles and β-carbolines *via in situ*-generated diketoindoles

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A short and divergent approach to highly substituted carbazoles and β–carbolines *via in-situ* generated diketoindoles

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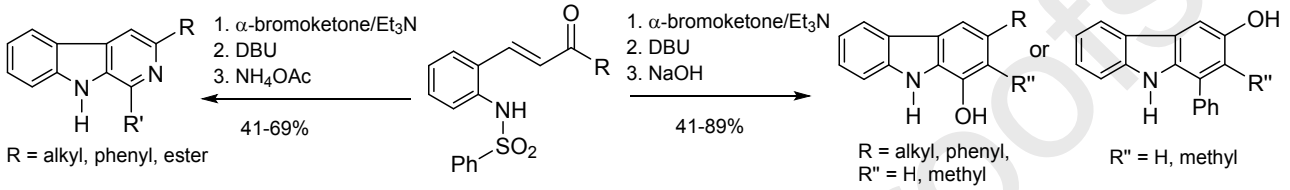

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A short divergent approach to highly substituted carbazoles and β-carbolines *via in situ*-generated diketoindoles

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ABSTRACT

Based on an aza-alkylation/Michael addition cascade reaction developed by Kim and co-workers we have developed divergent cascade reactions leading to either highly substituted 1-hydroxycarbazoles, 3-hydroxycarbazoles or β-carbolines, starting from readily accessible *ortho*-arylsulfonylaminobenzaldehydes. Olefination of the aldehyde functionality by aldol condensation or Wittig olefination gave reactive enone intermediates, which underwent the cascade reactions, either in two steps or in one-pot conversions, to give hydroxycarbazoles or complex β-carbolines.

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1. Introduction

The β-carbolines are a large class of secondary metabolites, occurring in various living organisms, such as plants, marine invertebrates, and microorganisms, and a broad spectrum of biological activities (e.g. antimicrobial, antiviral, neuropharmocological, antitumor) has been demonstrated for them.[1] The carbazoles, formal 2-desaza analogues of the β-carbolines, are also widely distributed in Nature and have attracted considerable interest in organic and medicinal chemistry.[2] Hence, considerable effort has been undertaken for the development of synthetic approaches to these two chemotypes of natural products.

Whereas the synthesis of β-carbolines bearing various residues at C-1, in combination with substituents on ring C, is easily achieved starting from tryptamine or tryptophan using the Pictet-Spengler, Bischler-Napieralski and related reactions (reviewed in the literature),[3] *via* Pd-catalyzed cross-coupling reactions of 1-halogenated β-carbolines,[4] or by reaction of 1,9-dimetalated β-carboline with electrophiles[5] β-carbolines bearing additional residues at C-3 are far less accessible (except for residues that can be derived from the carboxylate group originating from tryptophan.[6] Tryptamines bearing additional residues in the side chain are available *via* electrophilic substitution of indoles at C-3 with appropriately substituted nitroalkenes over several steps.[3] Alternative approaches to 1,3-disubstituted β-carbolines utilize tryptamine derivatives obtained by functionalization of gramine[7] or Pd-catalyzed cyclization of 3-alkynyl-2-acylindoles.[8] Additional approaches to ring A-substituted β-carbolines have also been reported.[9]

Classical approaches to substituted carbazoles include variations of the Fischer indole synthesis[10] and transition metal-catalyzed cyclizations of diarylamines and related precursor.[11] Furthermore, Knölker and co-workers' approach starting from anilines and cyclcohexadienyl-tricarbonyliron complexes has found broad application,[2,12] amongst other more recent approaches.[13]

In continuation of our recent work on bioactive β-carbolines[14] (e.g. inhibitors of the protein kinases CLK1, DYRK1A, PIM1) and carbazoles[14b,15]) we were interested in the development of a flexible approach to both β-carbolines and carbazoles with variable substitution patterns on rings A. This aim was most likely achievable with a protocol which includes *de-novo* construction of the respective A rings (pyridine in β-carbolines, benzene ring in carbazoles) from appropriately substituted, readily available precursors. A literature search revealed that Duval and Cuny[16] described a divergent approach to both β-carbolines and carbazoles starting from diketoindole precursors of type **A** in 2004. Treatment with base gave, depending on the nature of the substituents, 1-hydroxy- (**B**) or 3-hydroxycarbazoles (**C**), whereas incorporation of ammonia led to 1-substituted 3-alkyl-β-carbolines (**D**). However, this protocol is hampered by the fact that the synthesis of the required diketoindoles **A** requires a considerable number of steps, including utilization of organometallic building blocks (Fig. 1a).

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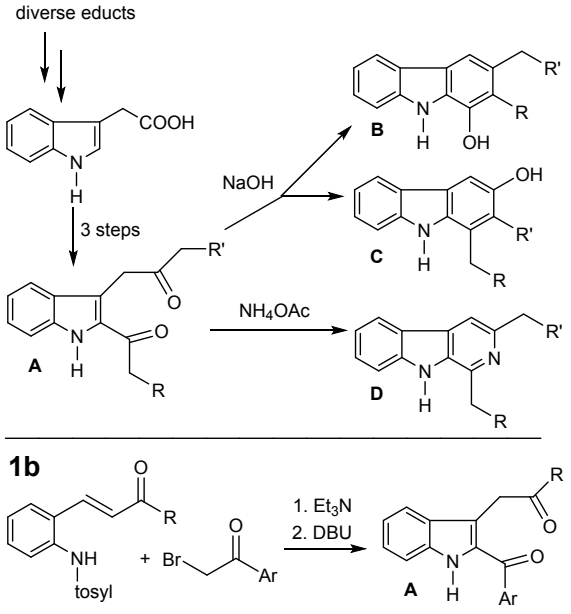


Figure 1: a) Multistep approach to hydroxycarbazoles and β-carbolines published by Duval and Cuny.[16] **b)** Kim and co-workers'[17] aza-alkylation/Michael addition approach to 2,3-disubstituted indoles.

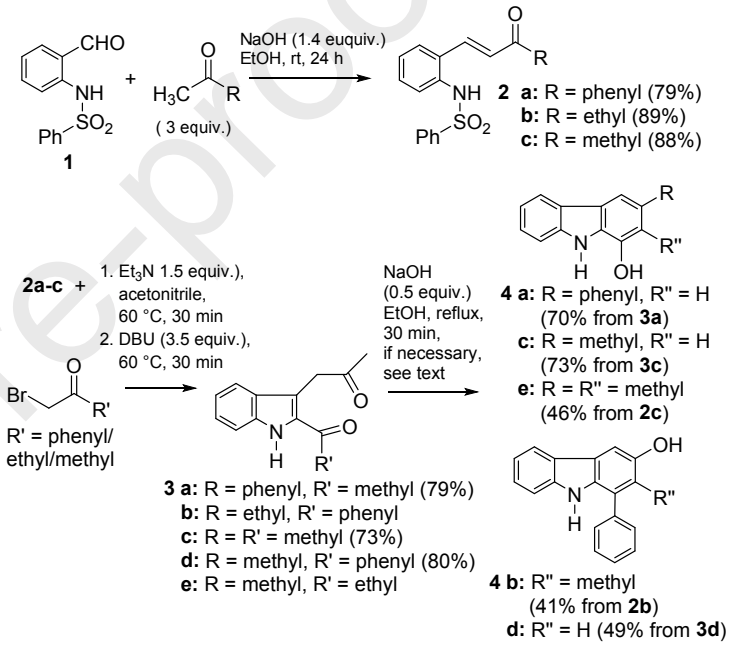
This prompted us to develop an improved protocol involving a significantly shorter approach to the central diketoindole intermediates **A** and direct processing of these intermediates into either β-carbolines or carbazoles. For the construction of the central building blocks **A** we selected a domino aza-alkylation/Michael addition cascade reaction of 2-(sulfonylamino)-substituted vinylogous ketones that had been previously developed by Kim and co-workers[17] for the preparation of 3-substituted 2-aroylindoles (Fig. 1b).

We have extended the scope of this diketoindole synthesis to aliphatic acyl residues at C-2 of **A** and developed a protocol for the subsequent direct conversion into either β-carbolines or hydroxycarbazoles.

2. Results and Discussion

Various protocols have been published for the synthesis of the required (ring-substituted) *ortho*-arenesulfonylamino enone starting materials, either from 2-functionalized anilines or nitrobenzenes, and construction of the enone moiety is conveniently accomplished either from 2-formyl derivatives (*via* Wittig olefination[18] or aldol condensation with methyl ketones[19]) or from 2-halogenated derivatives *via* Heck-type olefinations with enones or allylic alcohols.[20] In our hands, aldol condensation of aldehyde **1**, readily available from commercially available 2-aminobenzyl alcohol *via* one-pot *N*-sulfonylation/PCC oxidation,[21] with methyl ketones (acetone, 2-butanone, acetophenone) proved to be most convenient, and enones **2a-c** were obtained in 79-89% yield. Utilizing Kim and co-workers'[17a] aza-alkylation/Michael addition cascade reaction protocol, intermediates **2a-c** were reacted with aliphatic and aromatic α-bromoketones in presence of trimethylamine to achieve *N*-alkylation, directly followed by treatment with DBU to terminate the cascade reaction (intramolecular Michael addition, aromatization by desulfonylation). Diketoindoles **3a**, **3c** and **3d** were isolated in high yields (73-80%), whereas the a high tendency for undergoing immediate intramolecular aldol condensation under the basic reaction conditions[22] to give the 3-hydroxycarbazole **4b** and the 1-hydroxycarbazole **4e** in moderate yields. Compound **4b** is easily converted into the marine alkaloid hyellazole (O-methyl derivative of **4b**) by O-methylation,[16] hence our approach favorably compares with previously published multi-step total syntheses of hyellazole, which typically afford either indole- or benzene-derived intermediates with complex substitution patterns.[23]

Diketoindoles **3a**, **3c** and **3d** were converted into the hydroxycarbazoles **4a**, **4c** and **4d** by treatment with sodium hydroxide in ethanol-water in 46-73% yield. The moderate yields of some of the obtained 1- and 3-hydroxycarbazoles are in part due to the sensitivity of the hydroxycarbazoles to air oxidation.[16,24,25] As previously observed by Duval and Cuny,[16] diketoindoles bearing two enolizable keto groups had a clear preference for the formation of the 1-hydroxycarbazoles (Scheme 1).



Scheme 1: Three-step cascade synthesis of carbazoles starting from sulfonamides **2a-c**.

With the respective diketoindoles **3a**/**3c**/**3d** in hand, 1,3-disubstituted β-carbolines **5a**/**5c**/**5d** were accessible by treatment with ammonium acetate in glacial acetic acid. However, the above described tendency for **3b** and **3e** to cyclize directly to the hydroxycarbazoles prevented the option for synthesizing the β-carbolines **5b**/**5e**. Fortunately, undesired carbazole formation could be circumvented by adding excess ammonium acetate immediately after DBU-mediated generation of the diketoindoles. After heating the reaction mixtures in a sealed tube, β-carbolines **5b**/**5e** were obtained directly from enones **2b**/**2c** in a four-step cascade reaction in 41% and 58% yield (Scheme 2).

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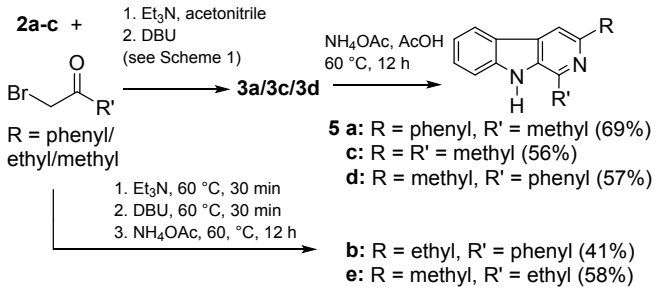
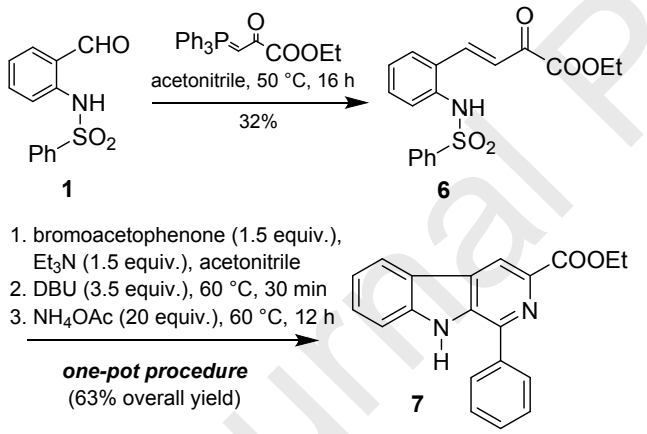


Scheme 2: Three-step cascade synthesis of β-carbolines starting from sulfonamides **2a-c**.

This cascade reaction was further applied to the synthesis of a 3-alkoxycarbonyl β-carboline. Preparation of the required intermediate **6** could not be accomplished with the standard aldol condensation of aldehyde **1** and ethyl pyruvate, and Lewis acid–mediated condensation using BF_3/acetic anhydride[26] was also not successful. Hence, the required enone moiety was built up by Wittig olefination of aldehyde **1** with a pyruvate-derived phosphorane. Upon conversion of the obtained α-ketoester intermediate **6** with bromoacetophenone under the conditions described above for diketoindole synthesis, the desired indole was accompanied by poorly separable side-products. It was again found that a one-pot procedure involving addition of excess ammonium acetate immediately after DBU-mediated generation of the diketoindole was most convenient, and 1-phenylindole-3-carboxylate **7** was obtained in 63% yield (Scheme 3).



Scheme 3: Wittig olefination to give vinylogous ketoester **6**, followed by one-pot conversion into β-carboline-3-carboxylate **7**.

3. Conclusion

In conclusion, we have, based on valuable previous work on both the preparation of diketoindole intermediates[17] and their further conversion into tricyclic heterocycles,[16] developed novel short cascade reactions leading to either highly substituted 1-hydroxycarbazoles, 3-hydroxycarbazoles or β-carbolines starting from readily accessible *ortho*-arylsulfonylaminobenzaldehydes. Olefination of the aldehyde functionality by aldol condensation or Wittig olefination gave reactive enone intermediates, which underwent cascade reactions, either in two steps or in one-pot conversions giving either hydroxycarbazoles or complex β-carbolines. This divergent and straightforward approach should ve carbazole and β-carboline derivatives.

Supplementary Material

Experimental section and copies of NMR spectra are available as supplementary data.

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since they prepared the diketoindole intermediates by Friedel-Crafts-type acylation of 3-substituted indole precursors under acidic conditions.

Highlights

- divergent approach to highly substituted carbazoles and β-carbolines
- cascade reactions starting from readily available building blocks
- target compounds achieved in one- or two-pot reactions
- high variability of substituents
- very short approach to the carbazole alkaloid hyellazole

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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