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Expedited synthesis of matrine analogues based on an oxidative cascade addition/double-cyclization radical process.

Simón Olguín-Uribe,[a][b] Marco V. Mijangos,[a] Yoarhy A. Amador-Sánchez,[a] Miguel A. Sánchez-Carmona[a] and Luis D. Miranda*[a]

Abstract: The addition of a nicotinate-xanthate derivative to *N*-allylindoles and *N*-allylpyrroles resulted in polycyclic heterocycle-fused pyrido-naphthyridines via a tandem radical intermolecular/intramolecular oxidative addition reaction sequence that creates three new C-C bonds and two new rings in a single event. Such polyheterocycles showcase the matrine alkaloid framework and are similar to indole-monoterpenoid natural products and are a resourceful strategy for cascade termination for the rapid synthesis of polycyclic motifs.[8][9]

Introduction

Natural products have an important place in medicinal chemistry as they are an ever-increasing source of bioactive molecules useful for drug development.[1] Given that natural product scaffolds and motifs are considered privileged starting points for drug discovery programs, there is a great demand for the development of strategies and methodologies for the rapid access to derivatives and analogues of these structures.[2] As an extension of our research program in diversity oriented synthesis,[3] we have focused our attention on the alkaloids matrine (**1**) and oxymatrine (**2**), which are the main alkaloids in the root of *Sophora flavescens* Aint (Figure 1).[4] These alkaloids feature a dipyrido-naphthyridine tetracyclic system and display a wide variety of biological activities such as anti-tumor activity,[5a] antiinflamoatory activity,[5b] as well as activity against the hepatitis B virus,[5c] among others.[5d] Interestingly although several derivatives of **1** have been prepared in different medicinal programs, most of them have been synthetized from the natural product itself and,[5d] to the best of our knowledge only five total synthesis can be found in the literature for this kind of alkaloid.[6] Among those synthesis, Zard and co-workers have described an elegant synthetic approach using an impressive tandem xanthate-based radical process to assemble the tetracyclic system in a single step from simple starting materials (Scheme 1a).[6e] In the process, three new C-C bonds and two new rings were created. Following this line of reasoning, we developed the idea that a small library of indole/pyrrole-matrine analogs (**9**) might be readily available through a similar cascade process starting from the corresponding *N*-allyl heterocycles (*e.g.*, **8**, Scheme 1b). In this case, the cascade radical termination would be an oxidative rearomatizing step,[7][8] rather than a xanthate transfer as occurs in the original process. As we have demonstrated, the xanthate-based oxidative radical substitutions on aromatic and heteroaromatic systems are efficient processes in both inter-[7] and intramolecular fashion,

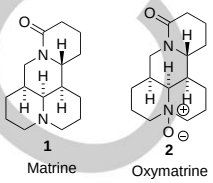
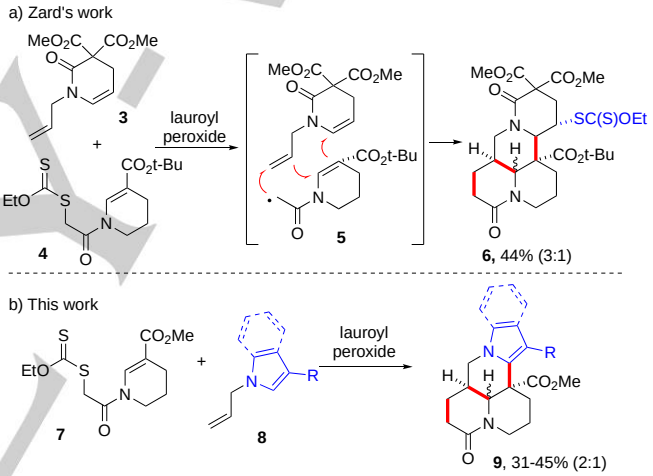


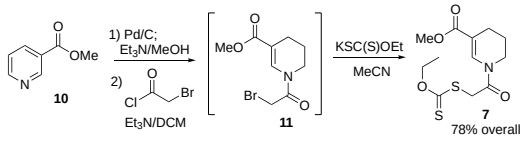
Figure 1. Matrine and oxymatrine structures



Scheme 1. A xanthate-based radical cascade process to assemble the tetracyclic matrine system.

Results and Discussion

The synthesis of the key xanthate **7** was carried out using the three-step protocol described below. First, catalytic hydrogenation of methyl nicotinate (**10**) followed by *N*-bromoacetylation yielded the bromoacetamide **11**, which was used crude and subjected to the nucleophilic substitution reaction to afford, after just one chromatographic purification, the pure xanthate **7** in 78% overall yield in gram scale (Scheme 2).



Scheme 2. Synthesis of xanthate **7**.

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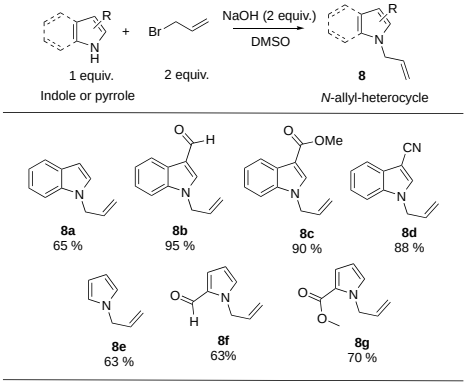
On the other hand, *N*-allyl heterocyclic derivatives were also easily synthetized by the alkylation of different substituted indole and pyrrole derivatives with allyl bromide using NaOH as a base in DMSO, at room temperature in an open flask (Table 1).

Table 1. Synthesis of *N*-allyl heterocycles.



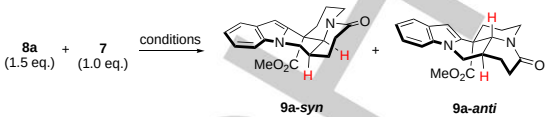
We then proceeded to test our proposal using *N*-allylindole **8a** as the model substrate. When performing the reaction with 1.5 equiv. of heterocycle **8a** and 1 equiv. of xanthate **7** in the presence of dilauroyl peroxide (DLP, 1.2 eq. added portionwise) in refluxing 1,2-dichloroethane (DCE), we were pleased to observe the expected pentacyclic indolo-matrine analog **9a** as the major product, and isolated it in 34% yield as a 2:1 mixture of *syn*:*anti* diastereomers as indicated by NMR analysis (Entry 1, Table 2). The coupling constant for ring-fused methine hydrogens was of particular importance for the stereochemical assignment, resulting in ^3J = 3.8 Hz for the **9a-*syn*** diastereomer, and ^3J = 10.9 Hz for the **9a-*anti*** diastereomer.

In an effort to perform the reaction at room temperature, this radical cascade process was also studied using Et_3B/O_2 as both initiator and oxidant. Under these conditions, only decomposition of starting xanthate **7** was observed by thin layer chromatography (Entry 2, Table 2).

Finally, when the reaction was carried out under microwave assistance, the yield of the diastereomeric mixture **9a-*syn*/*anti*** was increased to 43%, retaining the same diastereomeric ratio (*i.e.*, *syn*:*anti* = 2:1) and the reaction time was greatly reduced from 6 to 1.5 hours (Entry 3, Table 2). We decided to establish the latter conditions as optimal.

With the optimal conditions set, the scope of this tandem intermolecular/intramolecular oxidative radical addition was examined using supplementary **8b-g** *N*-allyl heterocycles. Thus, indolo-matrine analogs bearing a *C*-3-substitued indole ring (**9b-d**) were obtained in comparable yields (31-45%), with moderate selectivity toward the *syn*-diastereomer in all cases (Table 3). Similarly, when the *N*-allylpyrroles **8e-g** were coupled with xanthate **7**, the corresponding tetracyclic pyrrolo-matrine analogs were obtained in moderate yields (33-41%) for both unsubstituted and *C*-2-substituted pyrrole derivatives. In the same manner, as with the indole derivatives, the *syn* diastereomer was slightly favored (Table 3). It is important to mention that physical separation of both diastereomers via preparative TLC was successful only with the indolo-matrines **9a-c**.[11] All diastereomeric ratios were determined by ^{1}H NMR. Structures of **9b-*syn*** and **9d-*anti*** were further corroborated by single-crystal X-ray analysis (Table 3).[12]

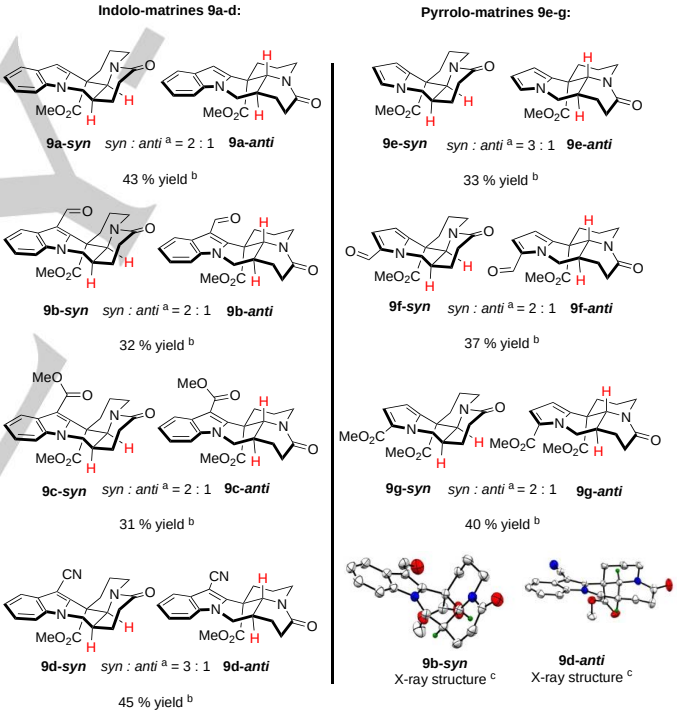
Table 2. Optimization of tandem radical process



entry	reagent	conditions[b]	time[c]	Yield (%)	*syn*:*anti*
1	DLP	DCE/Reflux	6	34	2:1
2	Et_3B	DCM/O_2/r.t.	6	trace	n.d.
3	DLP	DCE/M.W.	1.5	43	2:1

a) All reactions were carried out in dry solvents. b) Determined by ^{1}H NMR. r.t. = room temperature; M.W. = microwaves.

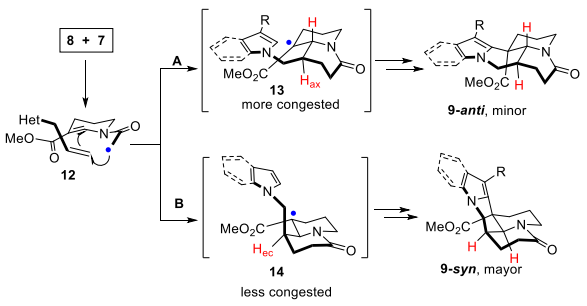
Table 3. Scope of the tandem oxidative radical addition



a) All diastereomeric ratios were determined by ^{1}H NMR. b) Yields refer for the isolated mixture of *syn*/*anti* diastereomers. c) For clarity, hydrogens (green atoms) are only shown in the fused rings.

Bearing in mind the cascade nature of this process, where three new C-C bonds are created together with two new rings by means of four tandem steps, *i.e.*, an intermolecular radical addition followed by two consecutive intramolecular radical additions and a final oxidation-rearomatization step, we considered the yields (31-45%) as good. For instance, for the 3-cyanoindole-derivative **9d** with the highest yield (45%), we estimated an 82 % yield per step in the cascade. In the same

way, for 3-carboxymethylindole-derivative **9c** with the lowest global yield (31%), the estimated yield per step was 75%. The moderate selectivity for the *syn*-diastereomer in all cases can be rationalized by analysis of the plausible transition states **13** and **14** (Scheme 3). The proposed transition state **13** with the pendant heterocycle side chain in the pseudo-equatorial position is more sterically congested than its counterpart transition state **14** with the heterocyclic side chain in a pseudo-axial disposition which would ultimately lead to the **9-*syn*** as the mayor diastereomer. These results are in complete accordance with Zard's observation.[6e]



Scheme 3. Stereochemical rationalization.

Conclusions

We have disclosed a strategy for the rapid synthesis of new polycyclic indole/pyrrole-matrine analogs **9-*syn/anti*** via an oxidative radical cascade coupling between simple *N*-allylic heterocycles **8** and readily available xanthate **7** in good preparative yields and moderate diastereoselectivity. In the process three new C-C bonds (including an all-carbon quaternary center) and two new rings are created in a single synthetic step. Furthermore, the oxidative rearomatizing termination step of this cascade allowed the straightforward incorporation of the indole and pyrrole aromatic nucleus into the matrine framework and avoid the xanthate transfer in the product. We anticipate that these conjugated polyheterocycles could be of interest for medicinal chemistry, as they share the biologically active matrine-framework and resemble indole monoterpenoid alkaloids, which are also biologically relevant.[10] Given the modular nature of this cascade reaction, new polyheterocycles might be readily available by switching the radical acceptor partner with other suitable *N*-allylic heterocycles to expeditiously populate and explore further the chemical space. These studies are currently underway in our laboratory and will be published in due course.

Acknowledgements

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Keywords: free radical • cascade process • matrine • indole • xanthate

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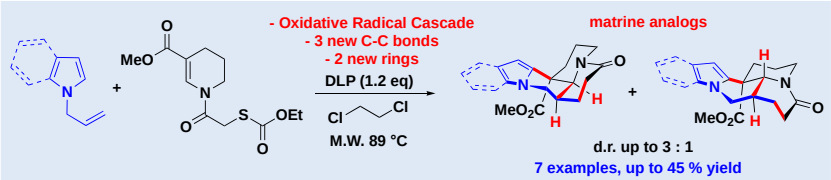
[11] In the cases of compounds 9c, 9f and 9g, complete purification could not be accomplished by flash cromatography, and where obtained along with a minor amount (< 4% by ^{1}H NMR) of an unknown impurity.

[12] The crystal structures were deposited in the Cambridge Crystallographic Data Centre (CCDC): 1531989 (**9b-*syn***) 1532012 (**9d-*anti***).

COMMUNICATION



The addition of a nicotinate-xanthate derivative to *N*-allylindoles and *N*-allylpyrroles resulted in polycyclic matrine analogs, via an oxidative cascade addition/double-cyclization radical process.

Cascade process *

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