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Synthesis of New Polyfused Heterocycles of Biological Importance by Means of Pd(0) Catalysis

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Abstract: A general synthetic methodology employing heteroaryl-aryl Suzuki coupling is reviewed, by which 15 heteroaromatic ring systems of biological interest have been prepared.

Keywords: Suzuki-coupling, indole alkaloids, total synthesis, pyridazine, intercalation

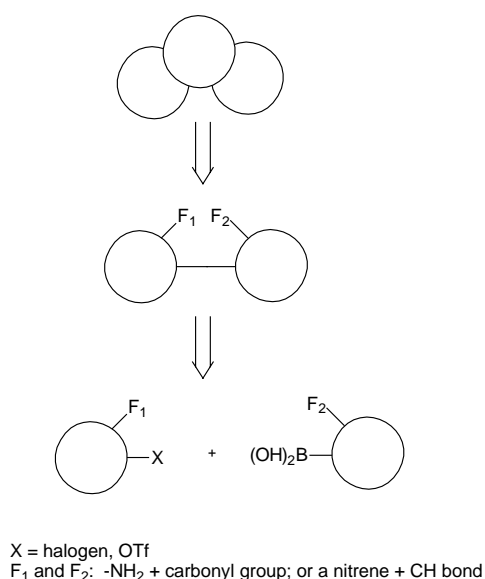
Introduction

Our ongoing interest in polyfused heteroaromatics as potential intercalating agents [1] and reverse transcriptase inhibitors [2] prompted us to elaborate new and economical reaction paths to such ring systems. In the course of these efforts we found [1,3] that the palladium(0)-catalyzed cross-coupling reaction may provide valuable biaryl compounds suitable to further ring closure reactions yielding the

desired polycycles. In this paper we review our activity in this field during the last five years and show that 15 different polycyclic systems have been synthesized by this methodology.

The general concept of the syntheses discussed here is depicted by the retrosynthetic analysis shown in Figure 1. This figure reveals that if the reaction partners participating in the Suzuki-reaction (by cross-coupling of the X and boronic acid functions) bear appropriate substituents F_1 and F_2 suitable for reactions to form new ring moieties, novel polycycles can be obtained. A large variety of combinations of the functional groups F_1 and F_2 is available, e.g. a condensation reaction (if $F_1 = \text{NH}_2$ and $F_2 = \text{CH=O}$ groups), insertion reaction (if $F_1 =$ a nitrene N-atom and $F_2 =$ a H atom) or nucleophilic substitution reaction (if $F_1 = \text{NH}_2$ and $F_2 =$ a halogen atom) can be carried out.

Figure 1. Retrosynthetic analysis of polyfused ring systems employing the Suzuki cross-coupling reaction

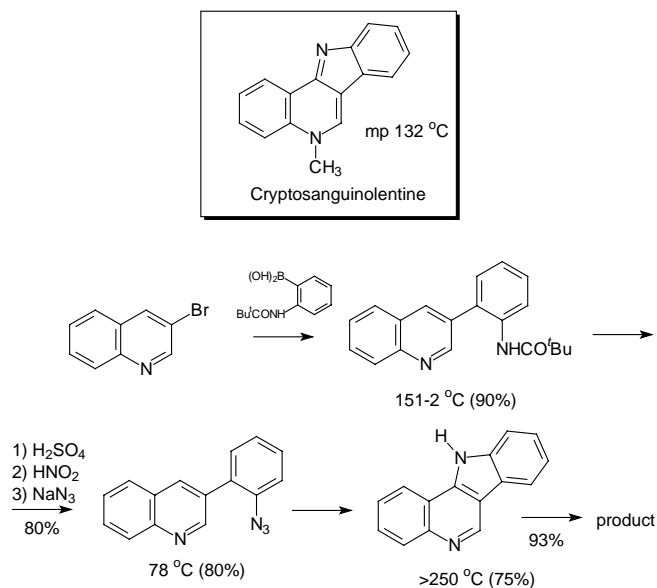


Results and Discussion

By application of the synthetic principle outlined in the Introduction above, new straightforward syntheses for three analogous compounds isolated from *Cryptolepis Sanguinolenta* have been elaborated. These reactions are depicted in Schemes 1-3.

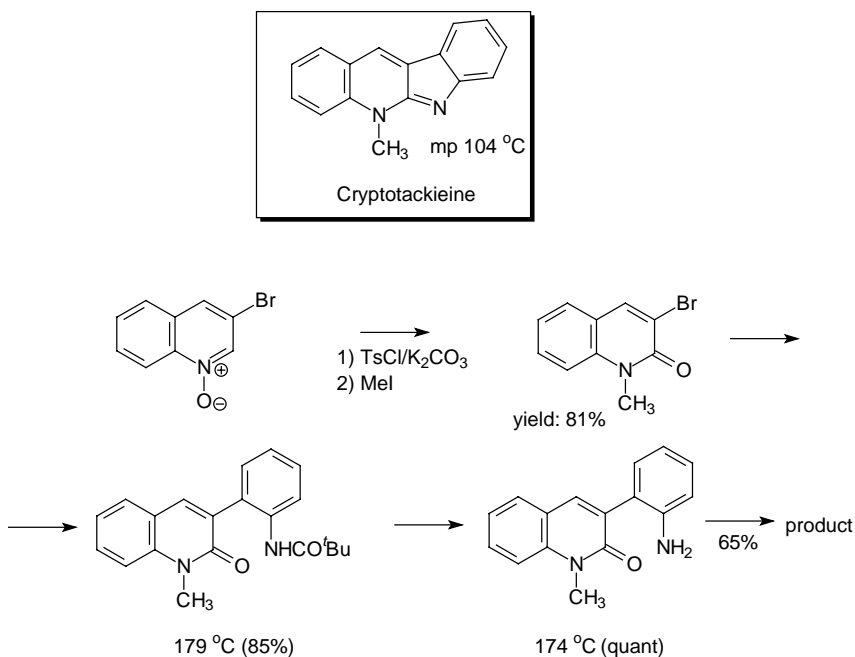
Thus, Cryptosanguinolentine (Scheme 1) was obtained from 3-bromoquinoline in 5 steps: the Suzuki-coupling to a phenylquinoline was followed by deprotection of the amino moiety and formation of an azide, which at higher temperature (*via* formation of a nitrene) underwent ring closure to the product in good yield [4].

Scheme 1.

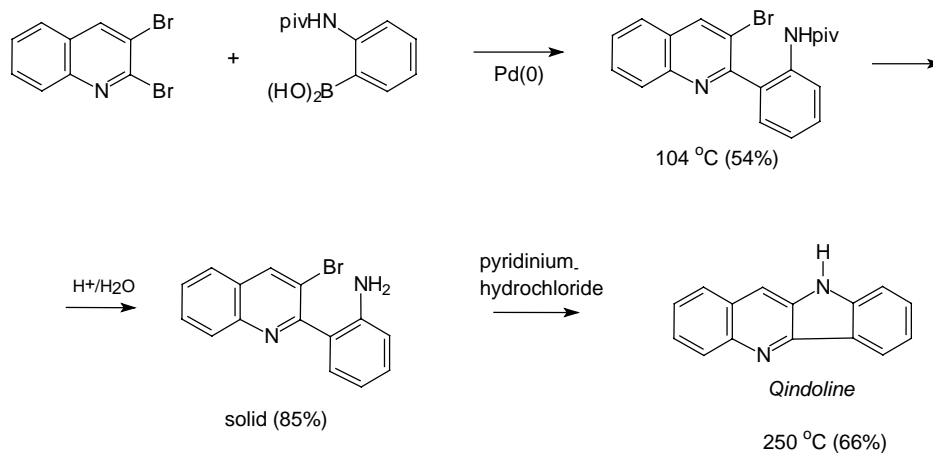


Cryptotackieine was synthesized starting from 3-bromoquinoline-N-oxide in 4 steps (Scheme 2) [4]. In contrast to the previous reaction, the final ring closure was accomplished by a condensation reaction of the amino moiety and the oxo function of the carbostyryl ring. The third related compound, Quindoline, was prepared from 2,3-dibromoquinoline *via* a selective cross-coupling of the 2-bromo atom to an amine followed by deprotection and intramolecular nucleophilic substitution. (Scheme 3) [5].

Scheme 2.

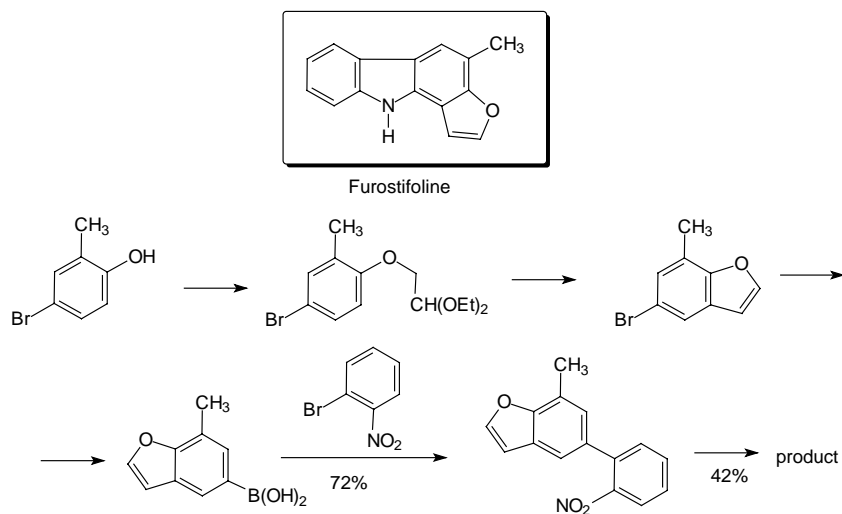


Scheme 3.



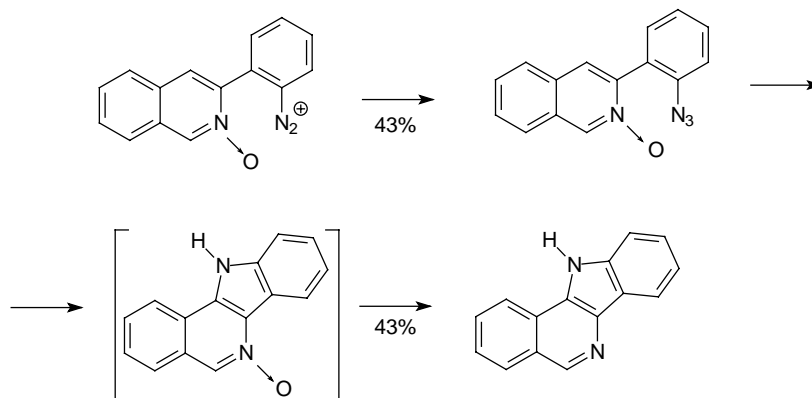
Our ring closure methodology has also been successfully applied in the area of indole-fused ring systems. Thus, we have reported recently that the alkaloid Furostifoline can conveniently be synthesized by our protocol as outlined in Scheme 4 [6]. In this case the cross-coupling was carried out by the reaction of a heterocyclic boronic acid and o-bromonitrobenzole and, then the nitro group was transformed to a nitrene to yield the tetracyclic end product.

Scheme 4.



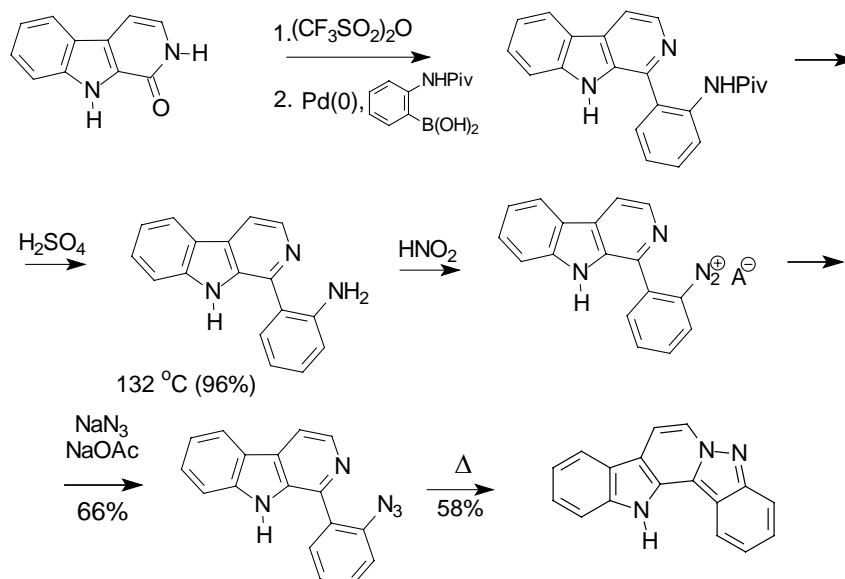
The continuation of our studies with 3-substituted arylisoquinolines [1] also led to the synthesis of a novel indole-fused ring. We found that o-azidophenylisoquinoline-N-oxide, obtained from the corresponding diazonium salt by an aza transfer reaction, undergoes ring closure at position 4 in the isoquinoline ring and, after a spontaneous deoxygenation, yields the indolo[3,2-c]isoquinoline skeleton as shown in Scheme 5 [7].

Scheme 5.



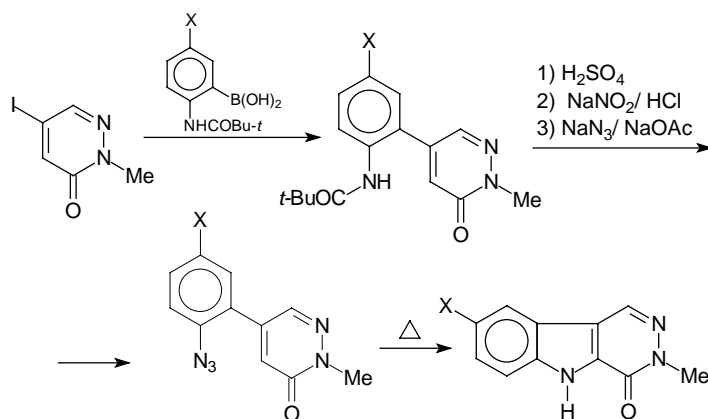
As summarized in Scheme 6, a new synthetic pathway to the indazolo[3,2-*a*]-β-carboline ring system has been elaborated. In this case the cross-coupling reaction was carried out with β-carboline-1-triflate to yield a protected amine, which was transformed similar to some related cases to the new pentacyclic ring system [8].

Scheme 6.



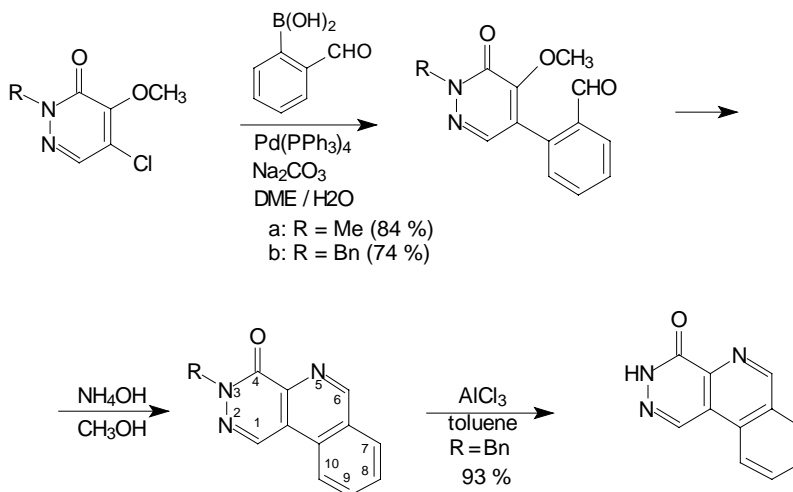
Our most recent investigation with halopyridazines revealed that some iodo and chloro derivatives of 2-alkylpyridazin-3-ones are suitable starting compounds for cross-coupling reactions. Thus, Scheme 7 shows that the starting 5-iodo derivative can be converted in 5 reaction steps to pyridazino[4,5-*b*]-indoles [9] in good yield

Scheme 7.



Halomethoxypyridaziones also proved to be suitable derivatives for ring closure reactions as shown by Scheme 8. Suzuki coupling of the chlorine atom with appropriately substituted phenylboronic acid and subsequent ring closure – *i.e.* intramolecular nucleophilic substitution – gave rise to new pyridazoquinolinones [10]. In the case of the N-benzyl substituted derivative preparation of the unsubstituted pyridazoquinolinone could also be accomplished

Scheme 8.

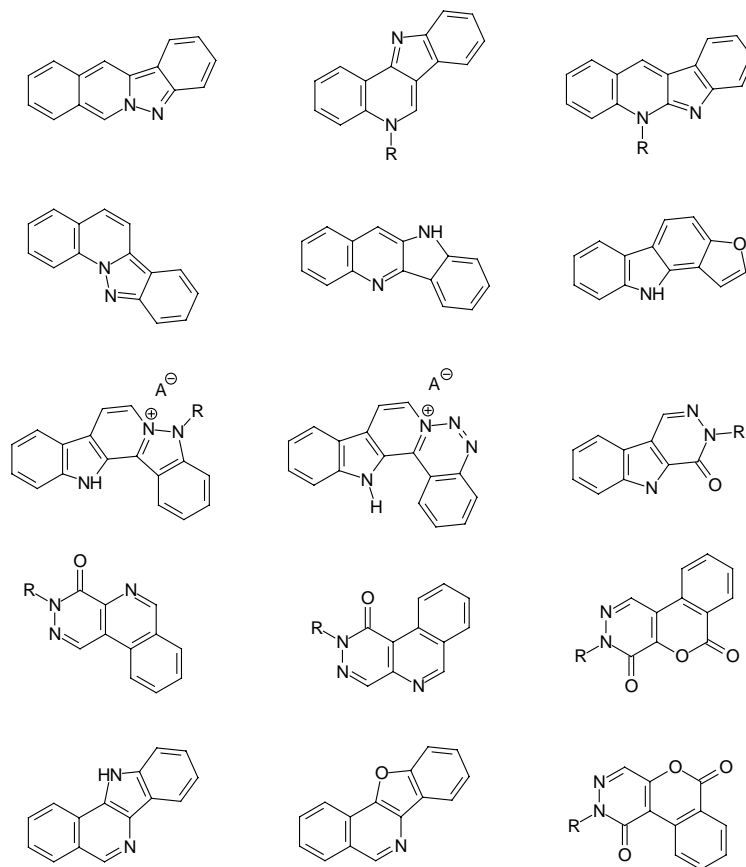


Biological tests on selected polycyclic derivatives revealed that some of these heterocyclic derivatives behave valuable reverse transcriptase inhibitory [1] and intercalating [8, 11] properties.

Conclusions

Straightforward syntheses of 15 different polyfused heterocycles (Scheme 9) have been elaborated by a general ring closure principle including Suzuki-coupling. Extension of these investigations to novel ring systems is in progress.

Scheme 9.



Acknowledgments

Financial support from the National Research Fund OTKA T 33105 and MediChem 1/047 NKFP as well as EU fund QLK2-CT-2002-90436 is gratefully acknowledged.

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