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Heck Reaction to a New Heterocyclic System: pyrido[2',3'-d']pyridazino[2,3-a]indole

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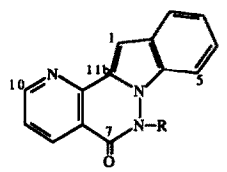
Abstract: *Starting from a judiciously substituted N-aminoindole, the Heck reaction led to a new class of heterocyclic compounds pyrido[2',3'-d']pyridazino[2,3-a]indole.*

Within the framework of our research program concerning new indole analogs of pharmacological interest, we were interested in the synthesis of pyrido[2',3'-d']pyridazino[2,3-a]indole **1**, a new heterocyclic system.



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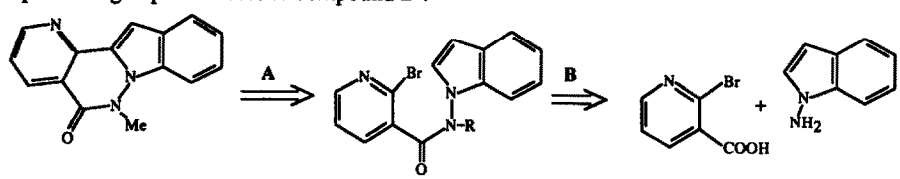
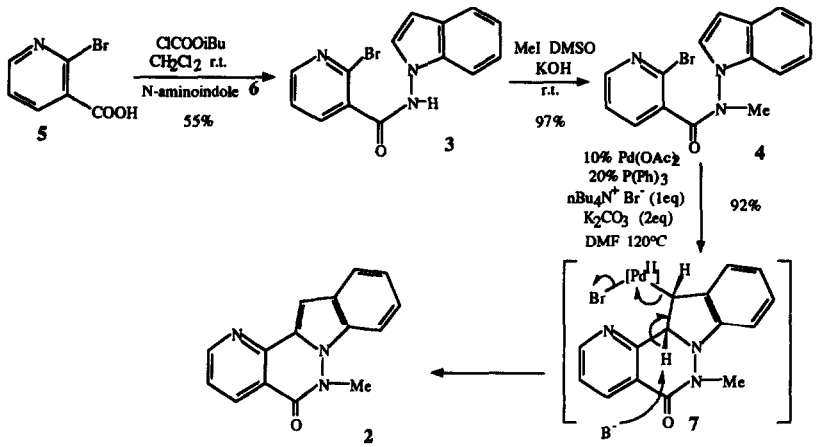
Our retrosynthetic approach to **1** was based on the biarylic coupling illustrated in scheme 1. Since radical-based cyclization experiments were unsuccessful (nBu_3SnH, AIBN), we turned our attention to the use of the Heck reaction[1]. Few examples of its application in the indole field exist[1c-d-e]. However, this ring closure method proved highly suitable for our purpose. Herein we reported the successful realization of steps **A** and **B** permitting a quick access to compound **2**[2].



2 **3** R = H; **4** R = Me **5** **6**

Scheme 1

Formation of the amide bond between N-aminoindole **6** (prepared in 60% yield[3] from indole and O-diphenyl-phosphinylhydroxylamine) and acid **5**[4] proved troublesome. Neither the nicotinic acylchloride route nor the use of classical coupling reagents (carbonyldiimidazole, DCCI, CMC) or Mukaiyama's reagent afforded the hydrazide **3** in better than 20% yield. Fortunately, activation of acid **5** using isobutyl chloroformate provided **3** in 55% yield (scheme 2).



Scheme 2

Because of the basicity of organopalladium compounds, protection of the nitrogen function in **3** was necessary. In fact, cyclization of amine **3** under the Heck reaction conditions led to a complex mixture of unidentified compounds. On the other hand, cyclization of the N-methylhydrazide **4** under the same reaction conditions provided the desired tetracycle in a 92% yield[2b]. Pd(0) was generated *in situ* from $Pd(OAc)_2$ and $P(Ph)_3$ [1], the presence of K_2CO_3 renders the reaction catalytic. In compound **7**, [Pd] and H-11b are in *trans*-relationship, also the classical β-elimination (*cis*) doesn't occur. We suggest that [Pd] reductive elimination is base assisted.

This direct and original Heck reaction led to the desired tetracycle, first representative of a new class of pyridopyridazinoindole based heterocycles.

Acknowledgments

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