Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 121–129

Synthesis of novel 1-methyl-1*H*-pyridazino[3,4-*b*]indoles

Zsuzsanna Riedl,[a,*] Katrien Monsieurs,[b] Gábor Krajsovszky,[c] Petra Dunkel,[c] Bert U. W. Maes,[b] Pál Tapolcsányi,[c] Orsolya Egyed,[a] Sándor Boros,[c] Péter Mátyus,[c] Luc Pieters,[d] Guy L. F. Lemière[b] and György Hajós[a]

[a]*Chemical Research Center, Institute of Biomolecular Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, PO Box 17, Hungary*
[b]*Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerpen, Belgium*
[c]*Department of Organic Chemistry, Semmelweis University, 'Szentágothai János Tudásközpont', H-1092 Budapest, Hőgyes E. u. 7., Hungary*
[d]*Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerpen, Belgium*

Received 8 July 2005; revised 14 September 2005; accepted 29 September 2005

Available online 26 October 2005

Cordially dedicated to Professor András Lipták on the occasion of his 70th birthday.

Abstract—New synthetic pathways have been elaborated to 1-methyl-1*H*-pyridazino[3,4-*b*]indoles starting from halopyridazin-3(2*H*)-ones. Suzuki cross-coupling reaction of chloro, iodo, dichloro, and dibromo substituted pyridazin-3(2*H*)-ones with 2-pivaloylaminophenylboronic acid followed by hydrolysis of the amide and subsequent ring closure via condensation gave fused indoles. Some of these compounds showed biological activity as antitrypanosomal agents.

1. Introduction

As a continuation of our earlier investigations, novel efficient pathways were developed for substituted 1-methyl-1*H*-pyridazino[3,4-*b*]indoles starting from halopyridazin-3(2*H*)-ones.[1] The area of these methylated pyridazino-fused indoles seemed particularly interesting as we have noticed some structural similarity between neocryptolepine (**A**) and the 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**B**) ring system (Fig. 1).

Naturally occurring tetracyclic indolo[3,2-*b*]quinoline alkaloid cryptolepine as well as its [2,3-*b*] fused isomer neocryptolepine, isolated from a decoction of the root of *Cryptolepis sanguinolenta*,[2a,b] showed antitrypanosomal and antiplasmodial activity and have been used as lead compounds for new therapeutic agents.[2c] Introduction of halogen or nitro substituents has resulted in more active and/or more selective antiplasmodial agents.[3] Importantly, the 'debenzo' derivative of cryptolepine, that is, 1-methyl-δ-carboline, showed a much better selectivity index (cytotoxicity/antiplasmodial activity) than cryptolepine itself.[4] This finding prompted us to make efforts to synthetize substituted 1-methyl-1*H*-pyridazino[3,4-*b*]indoles and to investigate their antiplasmodial and antitrypanosomal activity.

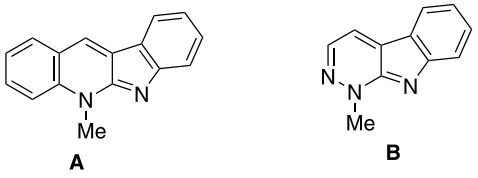


Figure 1. The structural similarity of neocryptolepine (**A**) and 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**B**) ring systems.

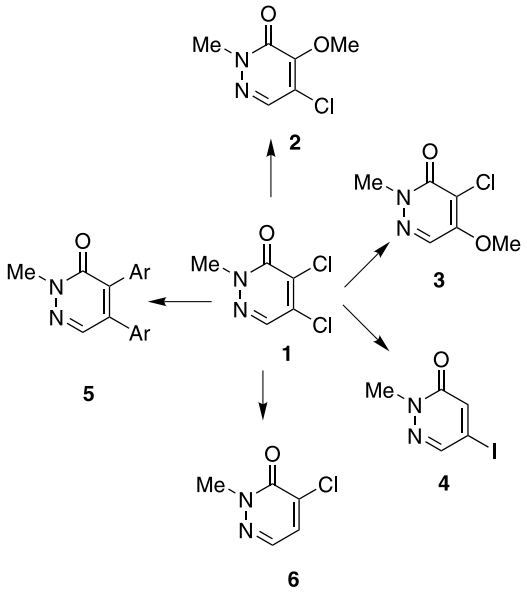
2. Discussion

Earlier we found that 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones undergo non-selective Suzuki cross-coupling reaction with arylboronic acids under classical Suzuki conditions resulting in a mixture of mono- and diaryl-substituted pyridazin-3(2*H*)-ones.[5] Recently, on 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**1**) a C-5 selectivity was observed in the coupling reaction with phenylboronic acid using $Pd(PEt_3)_2Cl_2$ as precatalyst and 1 M Na_2CO_3 as base in DMF.[6] Unfortunately, the general applicability of

Keywords: Fused pyridazines; Fused indoles; Ring closure; Suzuki coupling; Antitrypanosomal activity.
* Corresponding author. Tel.: +36 1 3257550; fax: +36 1 3257863; e-mail: zriedl@chemres.hu

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.136

these optimized reaction conditions remain unknown. Alternatively, in order to achieve selective arylation we earlier introduced the strategy of 'provisionally masked functionalities' (PMFs).[1] For this purpose **1** was converted into chloro-methoxy substituted pyridazin-3(2*H*)-ones (**2**, **3**)[7] by nucleophilic substitution and into 5-iodo-2-methyl-pyridazin-3(2*H*)-one (**4**)[8] by halogen exchange followed by hydrodeiodination (Scheme 1).



Scheme 1.

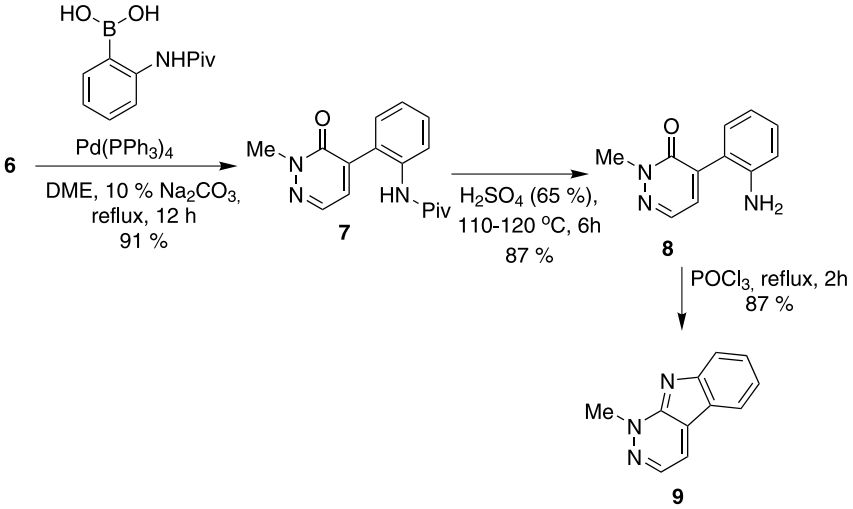
In this paper our efforts towards the synthesis of substituted 1-methyl-1*H*-pyridazino[3,4-*b*]indoles starting from (substituted) mono- and dihalopyridazin-3(2*H*)-ones are summarized. To the best of our knowledge, only very limited literature data are available for derivatives of the 1*H*-pyridazino[3,4-*b*]indole ring system.[9]

First, we attempted the synthesis of the unsubstituted 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**9**) starting from 4-chloro-2-methylpyridazine-3(2*H*)-one (**6**). Compound **6**[10a] was synthesized from **1** via reaction with hydrazine followed by hydrodehydrazination of 4-chloro-5-hydrazino-2-methyl-pyridazin-3(2*H*)-one with $CuSO_4$, a procedure that has successfully been applied for the analogous demethyl derivative.[10b] This compound reacted with 2-pivaloylaminophenylboronic acid under the Gronowitz reaction conditions,[11] that is, in a mixture of dimethoxyethane and 10% aqueous sodium carbonate solution using tetrakis(triphenylphosphine)palladium as catalyst. The cross-coupling reaction afforded the pivaloyl protected compound **7**[12] in high yield (91%). Compound **7** was hydrolyzed to the aminophenyl derivative **8** under reaction conditions previously reported by us.[13] This compound—due to the proximity of the amino and oxo functions—underwent smooth condensation reaction in boiling phosphoryl chloride yielding the desired 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**9**) as red crystals (Scheme 2).[13]

4,5-Dichloro-2-methylnitropyridazin-3(2*H*)-one (**10**) was synthesized from **1** by a nitration reaction.[14] Also on this substrate we observed that cross-coupling reaction with phenylboronic acid gave some diphenyl-substituted pyridazin-3(2*H*)-one (**11**) indicating the non-selective nature of the reaction. In order to realize the desired C-4 selective phenylation we used 4-iodo-2-methyl-6-nitropyridazin-3(2*H*)-one (**12**) which can be simply prepared from 4,5-dichloro-2-methyl-6-nitropyridazin-3(2*H*)-one (**10**) by reaction with sodium iodide in refluxing DMF.[8b]

When **12** was subjected to cross-coupling with 2-pivaloylaminophenylboronic acid and 5-chloro-2-pivaloylaminophenylboronic acid, 2-methyl-4-(2-pivaloylaminophenyl)-6-nitropyridazin-3(2*H*)-one (**13a**) and 2-methyl-4-(5-chloro-2-pivaloylaminophenyl)-6-nitropyridazin-3(2*H*)-one (**13b**), respectively, were obtained in good yield (Scheme 3). After hydrolytic removal of the pivaloyl protecting group the corresponding anilino compounds (**14a**,**b**) were obtained. These compounds were cyclized by the procedure described above for the synthesis of derivative **9** to yield 1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (**15a**) and 6-chloro-1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (**15b**).

Interestingly, 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones (**17a**,**b**) could also be prepared starting



Scheme 2.