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PAPER

Efficient and simple zinc-mediated synthesis of 3-amidoindoles†

Anahit Pews-Davtyan and Matthias Beller*

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A general synthesis of 3-amidoindoles from easily available arylhydrazines and acylated propargylamines is described. In the presence of inexpensive Zn salts, alkyne amination and subsequent Fischer indole-cyclization took place in good yields with excellent regioselectivity providing an interesting scaffold for potentially bio-active compounds.

The indole ring is a privileged structural motif present in a variety of natural and synthetic therapeutic products.[1,2] Among the various indole derivatives 3-amino- and 3-amido-substituted indoles have been scarcely investigated, except of δ-carbolines and their derivatives,[3] which show a wide range of biological activities (Fig. 1).[4]

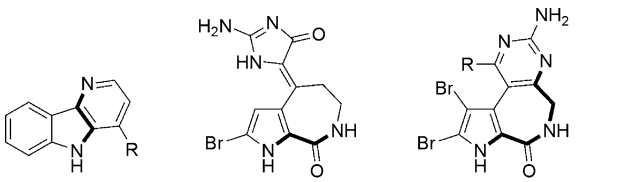


Fig. 1 δ-Carbolines, marine alkaloids hymenialdisine and latonduines A and B.

Furthermore, synthetic derivatives of 3-aminoindoles are known to be valuable kinase inhibitors and are useful for treating hyperproliferative disorders, diseases associated with angiogenesis,[5] inflammation and neurodegeneration,[6] depressive disorders, and anxiety.

Other biologically and synthetically interesting marine sponge alkaloids are hymenialdisine,[7] and recently isolated latonduines[8] A and B (Fig. 1). Hymenialdisine derivatives are known to inhibit various protein kinases,[9] whereas latonduine related molecules are useful for treatment of cystic fibrosis.[10] Notably, also indole-based natural[11] and synthetic[12] analogues bearing the highlighted structural motives (Fig. 1) as well as related sulfur and oxygen heterocycles show significant biological activity.[12c,13]

Based on our continuing interest in novel syntheses of biologically active indoles, we had the idea to prepare potentially bioactive 3-amidoindoles bearing biogenic heterocyclic amide fragments, marked in Fig. 1. To the best of our knowledge such compounds have not been synthesized before. Except for our recent work,[14] 3-amidoindoles have been prepared *via* multistep processes,[15] which often include protection and deprotection steps of the indole nitrogen. Clearly, such syntheses possess several drawbacks and a more general and concise synthesis of 3-amidoindole derivatives would be a valuable tool for the further exploration of their chemistry and biology.

In 2008, we developed a simple and general zinc-mediated intermolecular hydroamination reaction of alkynes with phenylhydrazines (hydrohydrazination) to give 2,3-disubstituted indoles.[16]

The concept of this domino alkyne-amination-Fischer-indole-sequence was first demonstrated by Bergman *et al.* on a stoichiometric basis[17] and further improved by Odom and co-workers using titanium-based catalysts.[18,19] Unfortunately, both the titanium-mediated and -catalyzed reactions showed only limited functional group tolerance and did not allow for the preparation of free indoles.

On the other hand, we have recently shown that the zinc-promoted intermolecular hydroamination of alkynes with arylhydrazines has a broad substrate scope. Hence, protected propargyl alcohols and amines as well as other sensitive alkynes can be used as substrates.[16a,b,20,21]

Advantageously, our protocol can be performed on air and all starting materials are commercially available or can be easily prepared by one step multigramm synthesis. For the performance of domino sequence it was proved that $ZnCl_2$ and $ZnBr_2$ are the best Zn-sources using aprotic solvents at 110 °C.

For the further exploration of our methodology, initially we choose commercially available unprotected electron-rich and electron-poor phenylhydrazines along with protected phenylhydrazines **1a–i** to investigate their impact on the reaction outcome (Fig. 2).

The applied propargylamides **2a–l** (except **2c**, which is commercially available) were synthesized straightforward from the propargyl amine and the corresponding acyl chloride (Fig. 3).[22]

In agreement with previous investigations the hydroamination reaction of the alkyne proceeds with excellent Markovnikov selectivity (>99%) to give 2,3-disubstituted indoles in good yields.[23]

Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str., 29a, D-18059, Rostock, Germany. E-mail: matthias.beller@catalysis.de; Fax: +49 381 1281 51113; Tel: +49 381 1281 113

† Electronic supplementary information (ESI) available: Procedures and characterisation data for all new compounds, scans of NMR spectra. See DOI: 10.1039/c1ob05576c

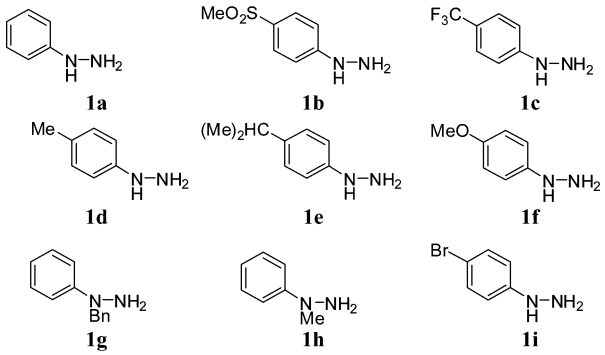


Fig. 2 Used phenylhydrazines.

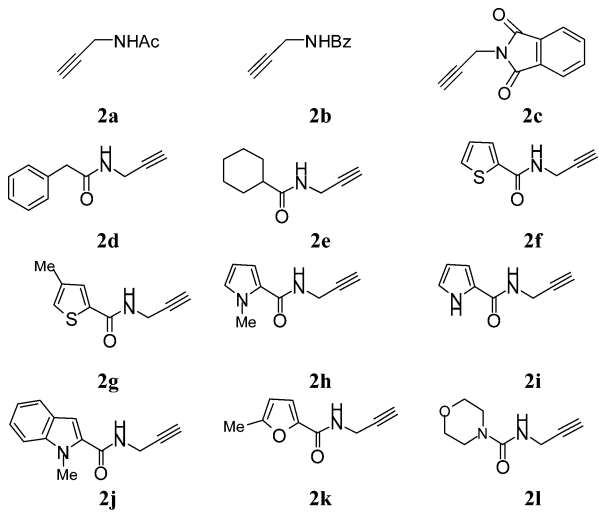
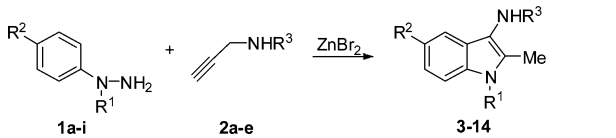


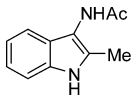
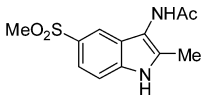
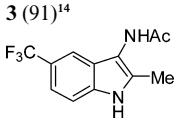
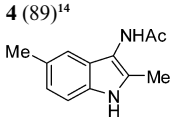
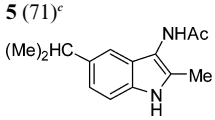
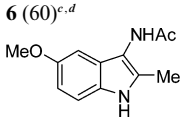
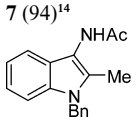
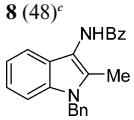
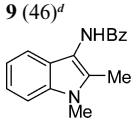
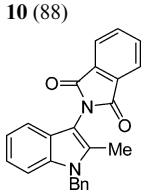
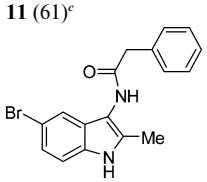
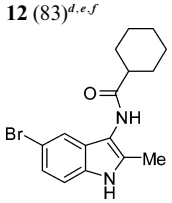
Fig. 3 Used propargylamides.

We have already shown excellent yields and high selectivity in the synthesis of compounds **3**, **4** and **7** (Table 1, entries 1, 2 and 5). Further experiments demonstrated that other activated (Fig. 1, compounds **1d** and **1f**) and deactivated (Fig. 1, compounds **1c** and **1i**) phenylhydrazines or protected ones (Fig. 1, compounds **1g** and **1h**) gave the desired products in moderate to good yields (Table 1, entries 6 and 7). Obviously substituents with a stronger positive inductive effect at the indole nitrogen or aromatic ring are not favourable for the construction of the 3-aminoindole moiety. Apparently, such substrates are activated for the electrophilic attack at different positions resulting in unwanted side reactions. Interestingly, hydrohydrazination of *N*-propargylphthalimide (**2c**) let not only to the expected minor *anti*-Markovnikov and main Markovnikov products, but also to its structural isomer in minor amounts (Table 1, entry 10).

Next, phenylhydrazines **1a**, **1b** and **1e** were used for the hydrohydrazination of more challenging heterocyclic propargylamides (Table 2). However, the previously optimized reaction conditions were not easily transferable to these more demanding substrates (Fig. 2, compounds **2f–2l**). Using three equivalents of Lewis acid gave detrimental results for nitrogen heterocycles because of decomposition of the heterocycle. To our delight, decreasing the catalyst amount ensured good yields with both electron-rich and electron-poor phenylhydrazines (Table 2). Additionally, switching from conventional heating to microwave irradiation, allowed us to decrease the reaction time with improved selectivities.

Table 1 Hydrohydrazination of acylated propargylamines with different phenylhydrazines to 3-amidoindoles[a]

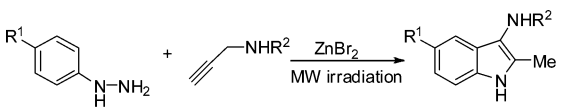


Entry	Product (yield[b], %)	Entry	Product (yield[b], %)
1	 **3** (91)[14]	2	 **4** (89)[14]
3	 **5** (71)[c]	4	 **6** (60)[c,d]
5	 **7** (94)[14]	6	 **8** (48)[c]
7	 **9** (46)[d]	8	 **10** (88)
9	 **11** (61)[c]	10	 **12** (83)[d,e,f]
11	 **13** (60)[g]	12	 **14** (64)[g]

[a] Reaction conditions: Alkyne 1 mmol, arylhydrazine 1.5 eq., $ZnBr_2$ 3 eq., solvent: DME 5 mL, 110 °C, 20–22 h, conventional heating in pressure tube. [b] Yield of isolated product. [c] $ZnCl_2$ was used. [d] Toluene was used. [e] Zn–salt 5 eq. [f] Mixture of isomers (55% isolated product **12** along with the 28% of unseparatble mixture of two other isomers). [g] Microwave irradiation, 110 °C, 1 h.

Nitrogen- as well as sulfur- and oxygen-containing heterocycles did not show significant differences in their reactivity towards phenylhydrazines. Notably, at lower temperature than 100 °C along with indole significant amounts of oxazole were formed by a competetive Zn-catalyzed cyclization of the alkynes. At elevated temperature indolization reaction is faster and only minor amounts of corresponding oxazoline (or oxazole) were detected by GC-MS. Further experiments showed that known cyclizations of propargylamides[22b] to oxazolines (main product) and oxazoles (minor product) are simply catalyzed by zinc triflate without any

Table 2 Scope of hydrohydrazination of heterocyclic propargylamides with different phenylhydrazines[a]



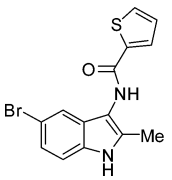
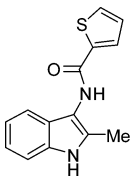
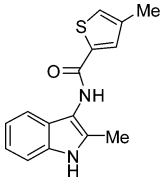
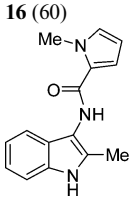
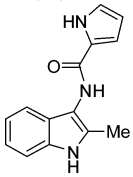
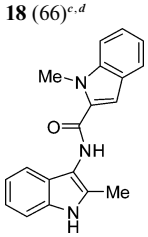
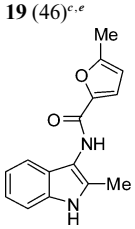
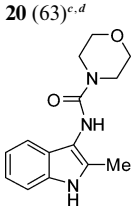
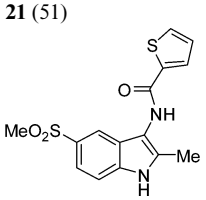
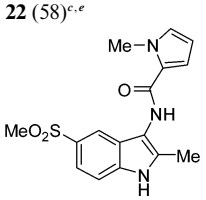
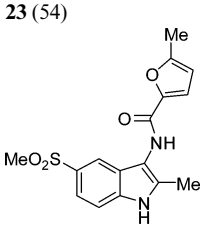
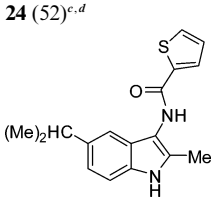
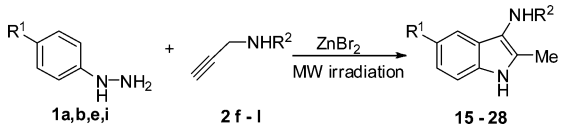
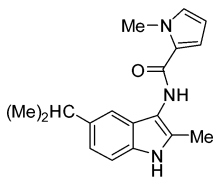
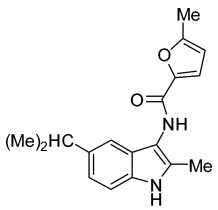
Entry	Product (yield[b],%)	Entry	Product (yield[b],%)
1		2	
	15 (59)		**16** (60)
3		4	
	17 (59)		**18** (66)[c,d]
5		6	
	19 (46)[c,e]		**20** (63)[c,d]
7		8	
	21 (51)		**22** (58)[c,e]
9		10	
	23 (54)		**24** (52)[c,d]
11		12	
	25 (52)		**26** (62)

Table 2 (*Contd.*)



Entry	Product (yield[b],%)	Entry	Product (yield[b],%)
13		14	
	27 (54)[c,d]		**28** (61)

[a] Reaction conditions: Alkyne 1 mmol, arylhydrazine 1.5 eq., $ZnBr_2$ 2 eq., solvent: DME 2 mL, 120 °C, 1 h, microwave irradiation. [b] Yield of isolated product. [c] $ZnBr_2$ 1 eq. [d] 130 °C. [e] 110 °C. [e] 100 °C.

noble metal catalysts at ambient temperature in good to excellent yields.

It is important to note that all new compounds are crystalline, stable materials, which make their storage, handling, and further transformations easy. In solution, the *N*-acylated 3-aminoindoles exist as mixture of rotamers. In polar aprotic solvents, like DMSO or acetone rotation is very fast and only minor signals of the second rotamer in NMR were detectable (see ESI†).

In conclusion, we have developed a general, effective and one-step approach to the synthesis of biogenic 3-amidoindoles. The Zn-mediated synthesis starts from commercially available phenylhydrazines and acylated propargylamines without the necessity of indole protection. Advantageously, no expensive catalysts need to be used and broad functional group tolerance is achieved. Biological tests of new products are ongoing.

Acknowledgements

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