A new facile synthesis of 3-amidoindole derivatives and their evaluation as potential GSK-3β inhibitors†

Anahit Pews-Davtyan,[a] Annegret Tillack,[a] Anne-Caroline Schmöle,[b] Stefanie Ortinau,[b] Moritz J. Frech,[b] Arndt Rolfs*[b] and Matthias Beller*[a]

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3-Amidoindoles were synthesized from commercially available arylhydrazines and propargylamines over Zn-salt mediated one pot procedure in excellent regioselectivity and up to 94% yield.

The indole ring is a privileged structural motif present in a wide variety of natural and synthetic therapeutic products.[1,2] Among the numerous known derivatives, 3-amido and 3-amino-substituted indoles have been scarcely investigated. Few exceptions constitute δ-carbolines, quindolines, and cryptolepines, which have been isolated from different plants (Fig. 1).[3]

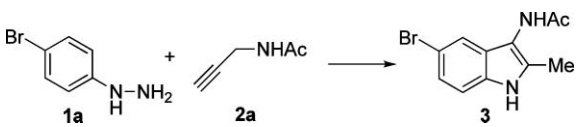
Fig. 1 δ-Carbolines and indoloquinoline alkaloids.

Notably, these compounds represent attractive pharmacological targets and show antimalarial, anti-muscarinic, anti-bacterial, anti-viral, anti-plasmoidal, and anti-hyperglycemic activities.[4] Furthermore, synthetic derivatives of 3-aminoindoles are known to be antagonists of different receptors such as CRTH2,[5] V1a,[6] mPGES-1,[7] NMDA[8] or valuable kinase inhibitors, *e.g.* COX-2[9] and are useful for treating hyper-proliferative disorders, diseases associated with angiogenesis,[10] inflammatory diseases, *e.g.* psoriasis, eczema, arthritis, neurodegenerative diseases,[8] *e.g.* Huntington's and Alzheimer's diseases, depressive disorders, and anxiety. Besides this pharmacological potential, 3-aminoindole derivatives have also been proposed as fungicides.[11]

So far, 3-aminoindoles have been prepared by multistep processes often including protection and deprotection steps of the indole nitrogen. In general, the heterocycle is constructed by reacting 2-aminobenzonitrile[8,9,12] or substituted phenylhydrazines[6,13] as *N*-nucleophiles with appropriate carbonyl-compounds (Fischer indole synthesis). More recently, 3-aminoindoles have been also synthesized *via* acid catalyzed multicomponent reaction between imines and isocyanides.[14] However, the most common approach to 3-aminoindoles is nitrosylation[15] or nitration[5,7,10,11,15,16] of a respective indole followed by reduction to the amino function and subsequent derivatizations. Few 3-aminoindoles were also prepared *via* amination of indoles with azodicarboxylates[17] or hydrolysis of isonitrosoindole.[18] Clearly, the known syntheses of this class of compounds possess several drawbacks and a more general and concise synthesis of 3-aminoindole derivatives will be a valuable tool for the further exploration of their chemistry and biology.

For some years we are interested in novel syntheses of biologically active indoles.[19] Here, we investigated especially intermolecular hydroamination reactions of alkynes with phenylhydrazines (hydrohydrazination) towards 2,3-disubstituted indoles. The concept of this domino alkyne-amination-Fischer-indole-sequence was first developed by Bergman *et al.* on a stoichiometric basis[20] and further improved by Odom and co-workers using titanium-based catalysts.[21,22] More recently, we showed that simple zinc salts are able to promote the intermolecular hydroamination of the arylhydrazines with alkynes, too. Subsequent [3.3]-sigmatropic cyclization led to the corresponding indoles.[19a,b,23,24] Advantageously, this protocol is conveniently performed on air and offers broad functional group tolerance. Based on this work, here we describe a new general and direct synthesis of 3-amidoindoles by zinc-promoted hydrohydrazination of *N*-acyl propargylamines. Furthermore, it is shown that some of the resulting products show

Table 1 Selected Zn-salts and solvents for indole synthesis[a]



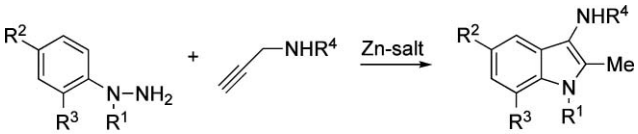
Entry	Zn-salt	Solvent	Yield [%][b]
1	$ZnCl_2$	Toluene	71
2	$ZnCl_2$	Dioxane	53
3	$ZnCl_2$	DME	73
4	$ZnCl_2$	Heptane	61
5	$ZnBr_2$	Toluene	73
6	$ZnBr_2$	Dioxane	55
7	$ZnBr_2$	DME	78
8	$ZnBr_2$	Heptane	56

[a] Reaction conditions: Alkyne (1 mmol), arylhydrazine (1.5 mmol), Zn-salt (3 mmol), solvent (3 mL), 110 °C, 20–22 h. [b] Isolated yield.

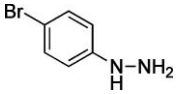
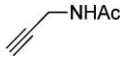
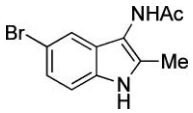
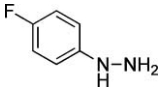
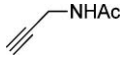
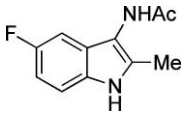
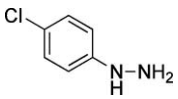
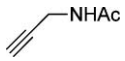
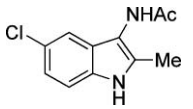
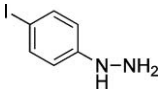
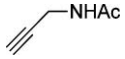
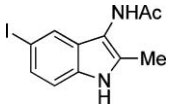
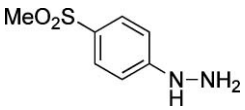
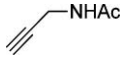
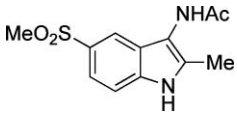
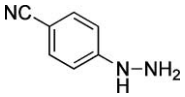
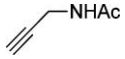
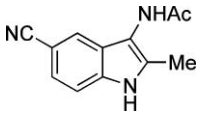
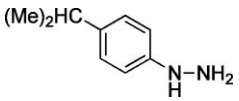
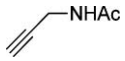
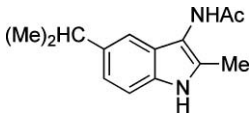
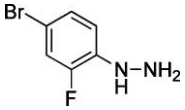
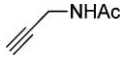
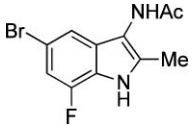
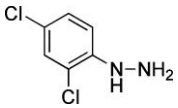
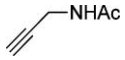
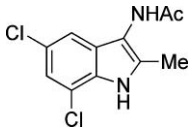
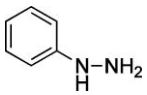
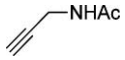
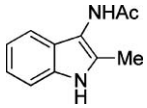
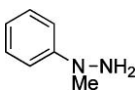
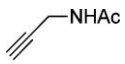
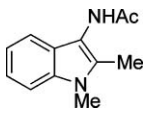
[a]*Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, D-18059, Rostock, Germany. E-mail: matthias.beller@catalysis.de; Fax: +49 381 1281 51113; Tel: +49 381 1281 113*
[b]*Albrecht-Kossel-Institute for Neuroregeneration, Center for Mental Health Disease, University of Rostock, Gehlsheimerstr. 20, D-18147, Rostock, Germany. E-mail: arndt.rolfs@med.uni-rostock.de; Fax: +49 381 494 4699; Tel: +49 381 494 9540*

† Electronic supplementary information (ESI) available: Procedures and characterisation data for all new compounds, scans of NMR spectra. See DOI: 10.1039/b920861e

Table 2 Hydrohydrazination of acylated propargylamines with different phenylhydrazines to 3-amidoindoles[a]



1a-k 2a-d 3-17

Entry	Arylhydrazine		Alkyne		Zn-salt	Solvent	Product		Yield [%][b]
1		**1a**		**2a**	$ZnBr_2$ $ZnCl_2$	DME Toluene		**3**	78 71
2		**1b**		**2a**	$ZnCl_2$ $ZnCl_2$	DME Toluene		**4**	72 71
3		**1c**		**2a**	$ZnBr_2$ $ZnCl_2$	DME DME		**5**	89 77
4		**1d**		**2a**	$ZnCl_2$ $ZnBr_2$	Toluene DME		**6**	70 46
5		**1e**		**2a**	$ZnBr_2$ $ZnCl_2$	DME DME		**7**	89 86
6		**1f**		**2a**	$ZnCl_2$ $ZnBr_2$	DME DME		**8**	80 69
7		**1g**		**2a**	$ZnBr_2$ $ZnCl_2$	DME DME		**9**	94 71
8		**1h**		**2a**	$ZnCl_2$ $ZnBr_2$	DME DME		**10**	66 65
9		**1i**		**2a**	$ZnCl_2$ $ZnBr_2$	Toluene DME		**11**	77 71
10[27]		**1j**		**2a**	$ZnBr_2$ $ZnCl_2$	DME DME		**12**	91 69
11		**1k**		**2a**	$ZnCl_2$ $ZnBr_2$	DME DME		**13**	55 53

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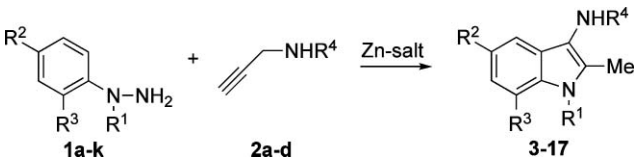
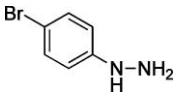
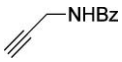
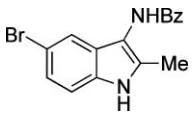
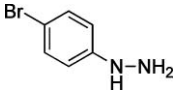
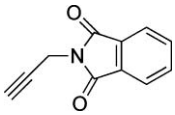
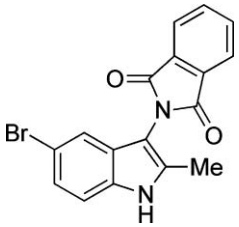
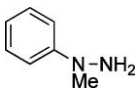
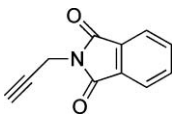
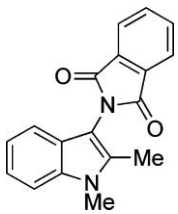
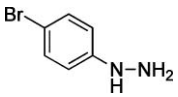
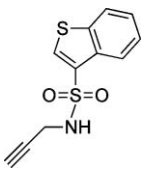
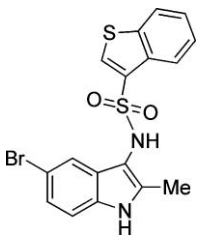


Entry	Arylhydrazine		Alkyne		Zn-salt	Solvent	Product		Yield [%][b]
12		**1a**		**2b**	$ZnBr_2$ $ZnCl_2$	DME DME		**14**	74 60
13[c]		**1a**		**2c**	$ZnBr_2$ $ZnCl_2$	DME Toluene		**15**	67 54
14[c]		**1k**		**2c**	$ZnBr_2$ $ZnCl_2$	DME DME		**16a**	52 (19[d]) 48 (10[d])
15[e]		**1a**		**2d**	$ZnCl_2$ $ZnBr_2$	Toluene DME		**17**	51 <10

[a] Reaction conditions: alkyne (1 mmol), arylhydrazine (1.5 mmol), Zn-salt (3 mmol), solvent (5 mL), 110 °C, 20–22 h. [b] Yield of isolated product. [c] Zn-salt (5 mmol). [d] Yield of anti-Markovnikov product **16b**. [e] 80 °C, 24 h.

promising accumulation of β-Catenin in cell assays, which makes them potential candidates as novel GSK-3β inhibitors.

Our previous synthetic investigations have shown that the success of a domino sequence is strongly dependent on the selection of the Zn-source, temperature, and solvent. Hence, we performed some test reactions to indentify optimal reaction conditions using *N*-acetylpropargylamine[25] and *N*-phenylhydrazines. The initial hydroamination reaction of the alkyne proceeds with high Markovnikov selectivity (>99%) to give 2,3-disubstituted indoles in good yield.[26] Testing different Zn salts like $ZnCl_2$, $ZnBr_2$, ZnI_2, $Zn(OTf)_2$, $Zn(OAc)_2$ in several solvents (THF, DMF, DME, NMP, toluene, heptane, acetonitrile, 1,4-dioxane) at temperature 80 to 120 °C proved that $ZnCl_2$ and $ZnBr_2$ are the best Zn-sources in aprotic solvents at 110 °C. In Table 1 selected results of the reaction of (4-bromophenyl)hydrazine (**1a**) and *N*-acetylpropargylamine (**2a**) are shown. Next, the optimized reaction conditions were used to demonstrate the scope and limitations of our protocol. As shown in Table 2 a variety of 4-substituted phenylhydrazines and acylated propargylamines gave the desired products in good to excellent yield. To our delight unprotected phenylhydrazines react well making protection/deprotection steps unnecessary (Table 2, entries 1–10, 12, 13 and 15).

In addition to *N*-acetylated and *N*-benzoylated propargylamines, *N*-propargylphthalimide (**2c**) gave the corresponding indole also in high yield. However, in this case for full conversion a larger excess of Lewis acid was necessary (Table 2, entries 13 and 14). Notably, reacting alkyne **2c** with 1-methyl-1-phenylhydrazine (**1k**) formation of anti-Markovnikov product was also observed (Table 2, entry 14). To demonstrate the possibility to attach pharmacologically important heterocycles onto the indol, the sulfonylated propargylamine **2d** was synthesized. Applying this substrate domino alkyne hydroamination and *in situ* Fischer indole cyclization proceeded at lower temperature and at temperatures >100 °C only decomposition of the starting materials occurred.

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*-acetylated 3-aminoindoles exist as 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.

To prove their biological activity, the newly synthesized compounds were tested in a cellular assay towards the inhibition of GSK-3β. GSK-3β is the key enzyme in the canonical Wnt signalling. Deregulation of GSK-3β is linked to several diseases such as bipolar disorders, Alzheimer's disease, and diabetes,[28] as well as to the differentiation of progenitor cell into cells with neuronal phenotype. Therefore, GSK-3β is an important current pharmacological target. Inhibition of GSK-3β, either by activating canonical Wnt signalling or by specific GSK-3β-inhibitors results in a disrupture of the β-catenin degradation complex. β-Catenin is stabilized in the cytosol and translocated to the nucleus where it binds to the TCF/LEF complex and regulates the transcription of Wnt specific target genes.[29] Several inhibitors have been described yet, together with different mechanisms of action. Most of them act either ATP- or Mg-competitive. The most prominent ones are Paullones (Kenpaullone and Alsterpaullones), Indirubines (6-bromoindirubin-3′-oxime, aka BIO) or lithium salts. The disadvantage of these substances is that they inhibit other kinases as well (Indirubines and Paullones) or have high K_i-concentrations (lithium salts). In contrast, anilinomaleimides (SB-216763, SB-415286) show high specificity combined with low IC_{50}-concentrations.[30] Here, the prepared 3-amidoindoles were tested on their impact on total β-catenin accumulation using an ELISA test specific for total β-catenin. As model system we used the human neural progenitor cell line ReNcell VM.[31] Briefly, cells were treated for 2 h with the new synthesized compounds under differentiation. Then, the cells were lysed and the protein was extracted. To our delight several of the newly developed substances showed a significant increase of β-catenin. This clearly indicates that they are able to inhibit GSK-3β (Fig. 2). Notably, the iodo-substituted compound **6** was even able to reach the inhibition level of Kenpaullone, a prominent GSK-3β inhibitor.

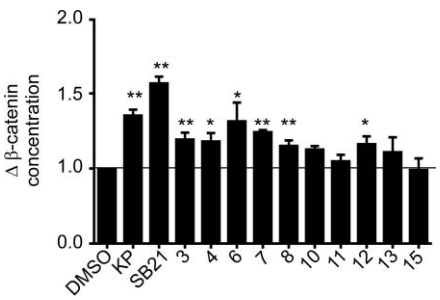


Fig. 2 Total β-catenin in ReNcell VM cells after treatment with new synthesized substances.[32]

In conclusion, we have developed an effective, general, and one-step approach for the Zn-mediated synthesis of 3-amidoindoles from commercially available hydrazines and terminal alkynes. These are the first examples of a *one-pot* synthesis of 3-amido-substituted indoles without the necessity for indole protection. Advantageously, broad functional group tolerance is observed and the resulting products are highly stable compared to other known 3-aminosubstituted indoles. Some of the synthesized compounds show significant inhibition of GSK-3β. Further studies will investigate the biological impact of the new designed 3-amidoindoles on the canonical Wnt signalling in detail, especially their mechanism of action towards GSK-3β inhibition.

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