Indole Synthesis

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Zinc-Promoted Hydrohydrazination of Terminal Alkynes: An Efficient Domino Synthesis of Indoles**

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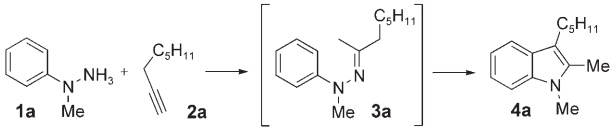
There is continuing interest in the development of improved methods for the synthesis of indoles owing to their importance as one of the most represented building block in natural bioactive products and marketed drugs.[1,2] Thus, indole and its derivatives have been termed "privileged pharmacological structures" as they bind to many biological receptors with high affinity.[3]

In recent years, domino sequences in particular have provided efficient complementary access to various indoles.[4] Such sequences start in general from easily available substrates. A reactive intermediate is generated with the aid of a catalyst, which is subsequently transformed to the desired indole. For example, the domino hydroformylation–Fischer indole sequence has evolved into a direct method for the one-pot construction of complex indoles from olefins.[5,6] More recently, Ackermann and Born reported the use of a combination of $TiCl_4$ and $tBuNH_2$ as catalyst for the domino hydroamination–Fischer indole cyclization.[7] In 1991, Bergman et al. reported the first zirconium-mediated synthesis of indoles by trapping a hydrazidozirconocene complex with alkynes and subsequent addition of hydrochloric acid.[8] Then, Odom and co-workers described the first titanium-catalyzed intermolecular hydroamination of arylhydrazines with alkynes.[9,10] The arylhydrazones obtained have been used further in the Fischer indole reaction to provide *N*-alkyl and *N*-aryl indoles in high yield. Based on this elegant approach, we have developed the titanium-catalyzed synthesis of functionalized tryptamines and tryptamine homologues, and tryptophol and tryptophol derivatives, starting from commercially available arylhydrazines and alkynes.[11] A problem which prevents widespread use of this reaction is the sensitivity of the titanium complexes towards functional groups, and the necessity for hydrazine protection and indole deprotection steps.

Our continuing interest in indole syntheses led us to look for alternative catalysts for the intermolecular hydrohydrazination. Herein we report the intermolecular zinc-mediated and -catalyzed hydroamination reactions of alkynes which provide a general synthesis of indoles.[12,13]

Our initial investigations involved studying the effect of different metal complexes on the model reaction of *N*-methyl-*N*-phenylhydrazine **1a** with 1-octyne **2a** (Table 1). The

Table 1: Variation of different metal salts for the indole synthesis.[a]



Entry	Metal salt	Equiv	Conversion[b] [%]	Yield[b] [%]
1[c]	$Ti(NEt_2)_4$/L/$ZnCl_2$	0.05/0.1/3	100	85
2	$Zn(OTf)_2$	1	100	>99
3	$ZnCl_2$	1	78	66
4	$FeCl_3 \cdot 6H_2O$	1	8	0
5	$HAuCl_4$	1	97	0
6	$H_2PtCl_6 \cdot 6H_2O$	1	100	<5
7	$IrCl_3$	1	100	0
8	$Sc(OTf)_3$	1	<5	<5
9	$Yb(OTf)_3$	1	10	<5
10	$Zn(OTf)_2$	0.5	96	94
11	$Zn(OTf)_2$	0.25	72	70
12	$Zn(OTf)_2$	0.1	36	30
13	$ZnCl_2$	3	100	97
14	$ZnBr_2$	1	79	55
15	$Zn(OAc)_2$	1	<5	0

[a] Reaction conditions: 1 mmol octyne, 1.3 mmol *N*-methyl-*N*-phenylhydrazine, 2 mL THF, 100°C, 24 h. [b] Determined by GC with hexadecane as internal standard. [c] For hydroamination: 5 mol% $Ti(NEt_2)_4$, 10 mol% 2,6-di-*tert*-butyl-4-methyl-phenol (L), 2 mL toluene, 100°C, 24 h. For Fischer indole cyclization: 3 mmol $ZnCl_2$, 100°C, 24 h.

amination reaction proceeds smoothly in the presence of 5 mol% of known titanium catalysts. Subsequent addition of 3 equivalents of $ZnCl_2$ to promote the Fischer indole cyclization furnished the desired indole in good yield (85%; Table 1, entry 1). Surprisingly, the overall reaction sequence also proceeds in good to excellent yield without any titanium catalyst. Only in the presence of $Zn(OTf)_2$ and $ZnCl_2$ (Table 1) is **4a** obtained in >99 and 66% yields, respectively (Table 1, entries 2 and 3). Thus, simple zinc salts promote both the intermolecular hydroamination of the arylhydrazine **1** with the terminal alkyne **2** to the corresponding arylhydrazone **3** and subsequently initialize the [3,3]-sigmatropic cyclization to the corresponding indole **4**.

Owing to the highly selective Markovnikov reaction[14] of the alkyne with the hydrazine, only the 2,3-disubstituted

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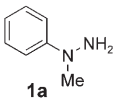
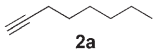
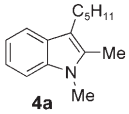
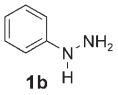
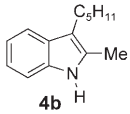
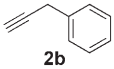
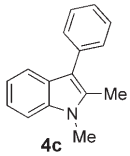
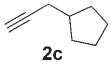
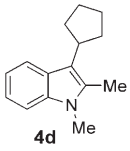
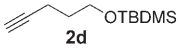
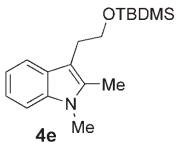
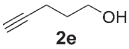
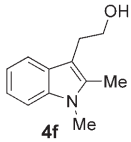
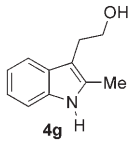
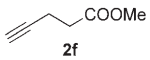
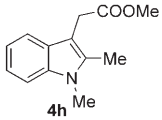
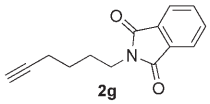
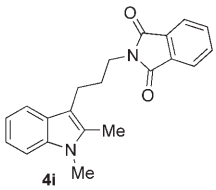
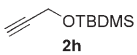
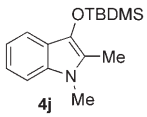
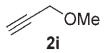
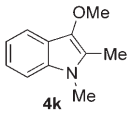
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2: Reaction of *N*-methyl-*N*-phenylhydrazine or *N*-phenylhydrazine with various substituted alkynes.[a]

Entry	Lewis acid	Arylhydrazine **1**	Alkyne **2**	Indole **4**	Yield[b] [%]
1	$ZnCl_2$	 **1a**	 **2a**	 **4a**	94
2	$ZnCl_2$	 **1b**	**2a**	 **4b**	91
3	$ZnCl_2$ $Zn(OTf)_2$	**1a**	 **2b**	 **4c**	81 96
4	$ZnCl_2$ $Zn(OTf)_2$	**1a**	 **2c**	 **4d**	95 94
5	$ZnCl_2$	**1a**	 **2d**	 **4e**	82
6	$ZnCl_2$	**1a**	 **2e**	 **4f**	97
7	$ZnCl_2$	**1b**	**2e**	 **4g**	97
8	$Zn(OTf)_2$	**1a**	 **2f**	 **4h**	58
9	$ZnCl_2$	**1a**	 **2g**	 **4i**	50
10	$ZnCl_2$	**1a**	 **2h**	 **4j**	60
11	$Zn(OTf)_2$	**1a**	 **2i**	 **4k**	53

[a] Reaction conditions: 1.5 mmol alkyne, 1.95 mmol *N*-methyl-*N*-phenylhydrazine or *N*-phenylhydrazine, 3 equiv $ZnCl_2$ or 1 equiv $Zn(OTf)_2$, 4 mL THF, 100 °C, 24 h. TBDMS = *tert*-butyldimethylsilyl. [b] Yield of isolated product.

indole is produced in excellent yield. Other typical Lewis acids, such as $FeCl_3$ and rare earth triflates, are not active in this reaction (Table 1, entries 4, 8, and 9). Furthermore, $HAuCl_4$, H_2PtCl_6, and $IrCl_3$, which are active in electrophilic aromatic substitutions, gave no desired product (Table 1, entries 5, 6, and 7).[15] Instead, oligomers of the alkyne are mainly formed as side products.

We investigated whether the reaction also proceeds in the presence of catalytic amounts of $Zn(OTf)_2$. Indeed, with 0.5 and 0.25 equivalents of Lewis acid, the indole is obtained in 94 and 70% yield, respectively (Table 1, entries 10 and 11). However, a further decrease to 0.1 equivalents led to lower yields (Table 1, entry 12).

Variation of the reaction conditions demonstrated that the model reaction of *N*-methyl-*N*-phenylhydrazine with 1-octyne proceeds in high yield in polar solvents, such as tetrahydrofuran, dioxane, and dimethylformamide. Notably, toluene, which is the commonly used solvent in titanium-catalyzed hydrohydrazinations, gave only a low yield of 21% (24 h, 100 °C, 3 equiv $ZnCl_2$). To achieve full conversion and high yield, a slight excess of *N*-methyl-*N*-phenylhydrazine is advantageous.

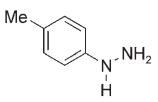
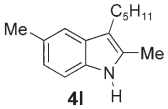
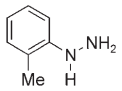
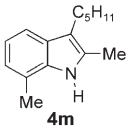
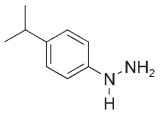
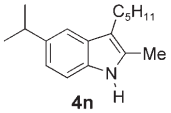
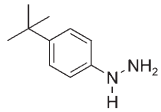
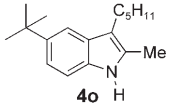
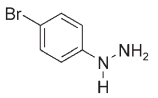
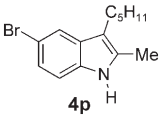
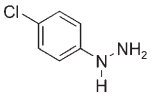
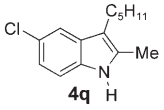
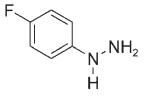
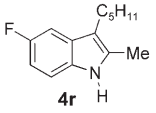
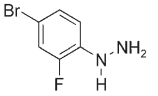
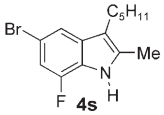
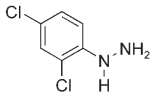
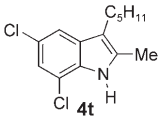
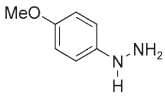
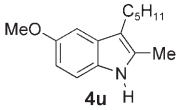
We were interested in the scope and limitations of the procedure with different alkynes (Table 2). For this purpose, we studied the reaction of *N*-methyl-*N*-phenylhydrazine and *N*-phenylhydrazine with various alkynes in the presence of $Zn(OTf)_2$ and $ZnCl_2$. Notably, applying the unprotected hydrazine together with 1-octyne, the free indole **4b** is formed in high yield (91%; Table 2, entry 2). This is the first example of free indole formation by hydrohydrazination of alkynes. Apart from 1-octyne other alkynes, for example 3-phenyl-1-propyne and 3-cyclopentyl-1-propyne, also gave the corresponding indoles **4c** and **4d** in up to 96% yield (Table 2, entries 3 and 4). We developed a synthesis for pharmaceutically relevant tryptophol

homologues by reaction of silyl-protected (2- and 3-hydroxyalkyl)alkynes with *N*,*N*-disubstituted arylhydrazines.[11b] The yield of this reaction using simply $ZnCl_2$ is 82% (Table 2, entry 5). The particular advantage of this reaction is that by using $ZnCl_2$, there is no need for protecting groups at the alkyne or the hydrazine unit. Thus, the tryptophol homologue **4g** is obtained in excellent yield (97%) by reacting *N*-phenylhydrazine with pentyn-1-ol in the presence of $ZnCl_2$ (Table 2, entry 7). Moreover, the reaction of *N*-methyl-*N*-phenylhydrazine with methyl pent-4-ynoate gave the indomethacin analogue **4h** (Table 2, entry 8). Similarly, the phthalimide-protected 6-aminohexyne afforded the tryptamine homologue **4i** (Table 2, entry 9). Even sensitive electron-rich 3-silyloxyindoles **4j**[16] and 3-methoxyindole **4k** were obtained, although only in moderate yields because of decomposition. To our knowledge, the latter reaction is the first example of a hydroamination of a propargylalkylether. In addition, we carried out some initial trials with internal alkynes, for example 1-phenyl-1-propyne and diphenylacetylene. However, these substrates resulted only in traces of the respective indoles under the optimized conditions, and in these cases, further work is necessary.

We explored the reaction of 1-octyne with various substituted arylhydrazines **2** in the presence of $Zn(OTf)_2$. Again, a protection of the arylhydrazine is not necessary, and the free indole is obtained in good to excellent yields (Table 3). Comparing *ortho*-and *para*-methylphenylhydrazine, the former is less reactive. Arylhydrazines substituted with electron-withdrawing groups required higher temperatures and more $Zn(OTf)_2$ for complete conversion (Table 3, entries 5–9), which is in agreement with the Fischer indole cyclization of aldehydes. Applying these conditions, all monohalophenylhydrazines gave product yields of $>95\%$. In the case of dihalosubstituted arylhydrazines, somewhat lower yields were observed (Table 3, entries 8 and 9).

In conclusion, we have developed a convenient one-pot method for the synthesis of various substituted indoles. Starting from commercially available arylhydrazines and terminal alkynes, a range of pharmaceutically relevant indole building blocks are obtained selectively in the presence of either $Zn(OTf)_2$ or $ZnCl_2$. No expensive catalyst is required for this novel environmentally friendly reaction, and for the first time free indoles, for example, tryptophol derivatives, are directly available from alkynes.

Table 3: Reaction of 1-octyne with various substituted arylhydrazines.[a]

Entry	Hydrazine **1**	Indole **4**	Yield[b] [%]
1		 **4l**	97
2		 **4m**	82
3		 **4n**	95
4		 **4o**	67
5[c]		 **4p**	97
6[c]		 **4q**	97
7[c]		 **4r**	96
8[c]		 **4s**	80
9[c]		 **4t**	52
10		 **4u**	97

[a] Reaction conditions: 1.5 mmol 1-octyne, 1.95 mmol arylhydrazine, 1 equiv $Zn(OTf)_2$, 4 mL THF, 100°C, 24 h. [b] Yield of isolated product. [c] 2 equiv $Zn(OTf)_2$, 4 mL THF, 120°C, 24 h.

Experimental Section

General procedure: $ZnCl_2$ (4.5 mmol, 545.3 mg) or $Zn(OTf)_2$ (1.5 mmol, 613.3 mg) were dissolved in THF in an ACE pressure tube under an argon atmosphere. Arylhydrazine (1.95 mmol) and alkyne (1.5 mmol) were then added to this solution. The pressure tube was sealed and the reaction mixture was heated at 100°C for 24 h. After removal of the solvent in vacuo, the indole product was purified by column chromatography (hexane/ethyl acetate).

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