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Efficient one-pot synthesis of tryptamines and tryptamine homologues by amination of chloroalkynes

Vivek Khedkar, Annegret Tillack, Manfred Michalik and Matthias Beller*

Leibniz-Institut für Organische Katalyse (IfOK) an der Universität Rostock e.V., Buchbinderstr. 5-6, D-18055 Rostock, Germany

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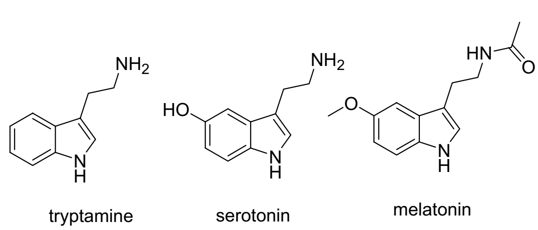
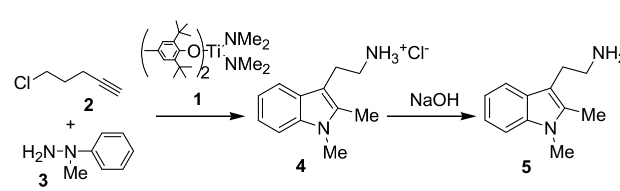
Abstract—A new method was developed for the one-pot synthesis of substituted 3-(2-aminoethyl)- and 3-(3-aminopropyl)indoles from commercially available aryl hydrazines and chloroalkylalkynes. Various tryptamine derivatives were prepared directly in good yield with excellent regioselectivity. The method involves a new domino reaction sequence consisting of a titanium-catalyzed amination of the chloroalkylalkyne, [3+3]-rearrangement of the resulting aryl hydrazone, and nucleophilic substitution of the chloride by ammonia.

There is a continuing interest in the development of new methods for the synthesis of indoles due to their importance as building blocks for pharmaceuticals and natural products.[1] Among the numerous indole derivatives with biological activity tryptamine and its derivatives such as the neurotransmitter serotonin, and the tissue hormone melatonin constitute especially important examples (Scheme 1).[2]

Although many synthetic approaches have been developed, the Fischer indole reaction remains the most important method to substituted indoles.[3] In this benchmark reaction aldehydes or ketones react with aryl hydrazines to give the corresponding hydrazones, which subsequently undergo a [3,3]-sigmatropic rearrangement to yield indoles in the presence of a Brønstedt or Lewis acid. Despite its versatility the Fischer indole reaction with aldehydes constitutes a two-step procedure, which sometimes proceeds in low yield. For example, the direct synthesis of tryptamine-like compounds[4] is sometimes troublesome due to side reactions of the free amino group with the aldehyde or ketone. Recently, Odom and co-workers described an interesting new titanium amide-catalyzed reaction of aryl hydrazines with alkynes.[5] The obtained aryl hydrazones have been further used in the Fischer indole reaction, which allows for an elegant two-step (one-pot) synthesis of substituted indoles. Based on our long standing interest in catalytic hydroamination reactions of olefins[6] and alkynes[7] we studied the regioselective attack of aryl hydrazines on terminal alkynes with respect to the catalyst. During these investigations we discovered a new domino process using 1-chloro-4-pentyne and *N*-methyl-*N*-phenylhydrazine as substrates. As shown in Scheme 2 and Table 1 the titanium-catalyzed hydroamination of 1-chloro-4-pentyne leads directly to the hydrochloride salt of *N*-methyl-2-methyltryptamine (2-(1,2-dimethyl-1*H*-indol-3-yl)ethylamine hydrochloride) in good yield. This unusual one-pot conversion involves first a titanium-catalyzed



Scheme 1. Examples of biologically active indoles.



Scheme 2. A new domino process to tryptamines.

* Corresponding author. Tel.: +49-381-4669313; fax: +49-381-4669-324; e-mail: matthias.beller@ifok.uni-rostock.de

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Table 1. Reaction of 1-chloro-4-pentyne with *N*-methyl-*N*-phenylhydrazine[a]

Entry	Catalyst	Catalyst (mol%)	Time (h)	Temperature (°C)	Yield (%)[b]	
					4	**5**
1	**1**	2.5	52	60	<5	<5
2	**1**	2.5	16	80	61	59
3	**1**	2.5	4	100	79	78
4	**1**	2.5	1.5	120	77	67
5	**1**	5	4	100	84	80
6	**1**	5	24	100	86	82
7[c]	**1**	5	24	100	62	58
8	$Ti(NMe_2)_4$	5	24	100	33	24
9	$(\eta^5\text{-}Cp)_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$	10	24	100	64	54

[a] Reaction conditions: 1.1 mmol 1-chloro-4-pentyne, 1.4 mmol *N*-methyl-*N*-phenylhydrazine, 2 mL toluene.
[b] Isolated yield based on 1-chloro-4-pentyne.
[c] 2 mL Tetrahydrofuran.

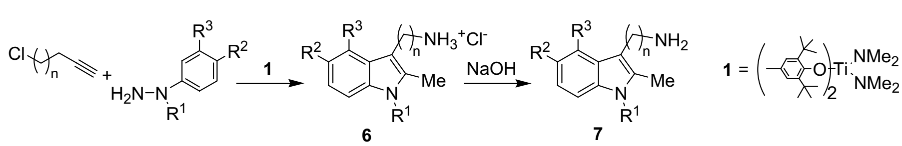
hydroamination of the alkyne to give the *N*-aryl-*N*-chloro-alkylhydrazone, then a [3,3]-sigmatropic rearrangement to the corresponding indole takes place and finally nucleophilic substitution of the halide by the liberated ammonia occurs.[8] Advantageously, the in situ generated hydrochloride acid acts as an efficient catalyst for the Fischer indole reaction.

As catalyst for the amination reaction bis(2,6-di-*tert*-butyl-4-methylphenoxo)-bisdimethylamide titanium **1** was used. **1** is easily synthesized from commercially available 2,6-di-*tert*-butyl-4-methylphenol and $Ti(NMe_2)_4$ in one step in good yield (72%),[9] and has been introduced by us very recently as a highly chemo- and regioselective hydroamination catalyst for terminal and internal alkynes with primary and secondary aliphatic amines, benzylamines, and anilines.[10]

Due to the highly selective Markovnikov reaction of the alkyne with the hydrazine, only the 2,3-disubstituted indole is produced. As shown in Table 1 the model reaction proceeds in good yield in toluene in the presence of 2.5–5 mol% of catalyst at 80–120 °C (Table 1, entries 2–6). Below 80 °C basically no conversion is observed. Interestingly, in the amination step in all reactions using **1** as catalyst excellent regioselectivities (>99%) toward the Markovnikov product (internal regioisomer) are obtained. The importance of the aryloxo ligand is clearly shown by comparing reactions in the presence of **1** and $Ti(NMe_2)_4$ as catalysts (Table 1, entry 6 vs 8). Also, a well-known titanocene-type catalyst $(\eta^5\text{-}Cp)_2Ti(\eta^2\text{-}Me_3SiC_2SiMe_3)$[11] leads to a significant lower yield of the indole.

Next, we were interested in the compatibility of our new procedure with different aryl hydrazones (Table 2).[12] Apart from *N*-methyl-*N*-phenylhydrazine seven different aryl hydrazines with Me-, Cl-, F-, and MeO-substituents were reacted with 1-chloro-4-pentyne and 1-chloro-5-hexyne.

Table 2. Reaction of chloroalkylalkynes with various aryl hydrazines[a]



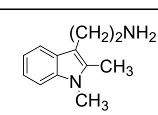
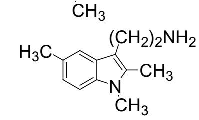
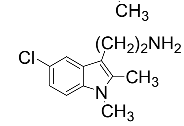
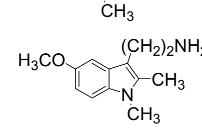
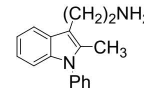
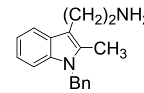
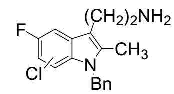
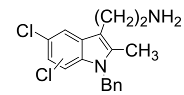
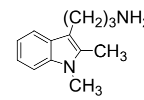
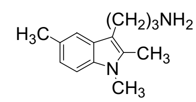
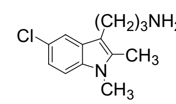
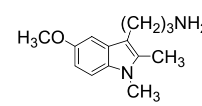
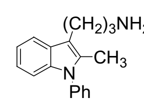
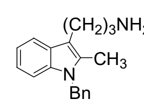
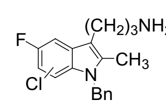
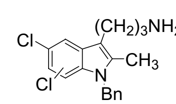
Entry	Alkyne (*n*)	Aryl hydrazine			Catalyst (mol%)	Time (h)	Product **7**	Yield (%)[b]	
		R_1	R_2	R_3				**6**	**7**
1	2	CH_3	H	H	5.0	24		86	82
2	2	CH_3	CH_3	H	5.0	24		65	60
3	2	CH_3	Cl	H	5.0	24		70	68
4	2	CH_3	OCH_3	H	5.0	24		71	69

Table 2 (*continued*)

Entry	Alkyne (*n*)	Aryl hydrazine			Catalyst (mol%)	Time (h)	Product **7**	Yield (%)[b]	
		R_1	R_2	R_3				**6**	**7**
5	2	Ph	H	H	5.0	24		50	49
6	2	Bn	H	H	5.0	24		90	89
7[c]	2	Bn	F	Cl	2.5	4		84	80
8[c]	2	Bn	Cl	Cl	2.5	4		85	82
9	3	CH_3	H	H	5.0	24		63	60
10	3	CH_3	CH_3	H	5.0	24		78	67
11	3	CH_3	Cl	H	5.0	24		64	60
12	3	CH_3	OCH_3	H	5.0	24		81	68
13	3	Ph	H	H	5.0	24		57	50
14	3	Bn	H	H	5.0	24		64	55
15[c]	3	Bn	F	Cl	5.0	24		65	52
16[c]	3	Bn	Cl	Cl	5.0	24		61	55

[a] Reaction conditions: 1.1 mmol chloroalkylalkyne, 1.4 mmol aryl hydrazine, 100 °C, 2 mL toluene.
[b] Isolated yield.
[c] Two isomers (4-Cl:6-Cl) were obtained in a 2:1 ratio.

In all cases the conversion was >95% and the yield of the corresponding indole hydrochloride salt was good (50–90%). In general, the indole was isolated as the sole product in excellent regioselectivity.

However, by using disubstituted aryl hydrazines (Table 2, entries 7–8 and 15–16) cyclization to the indole nucleus gave a mixture of two regioisomers, which is well known for other Fischer indole reactions, too.

In conclusion, a new, one-pot method for the synthesis of functionalized tryptamines and tryptamine homologues has been developed. Starting from commercially available aryl hydrazines and chloroalkylalkynes a variety of potentially active indoles are obtained highly selectively in the presence of a catalytic amount of **1**. We believe that the presented approach constitutes the most efficient access for the here shown substituted tryptamines and tryptamine homologues. Further investigations of this method using other titanium catalysts are currently under way in order to allow the synthesis of indoles, which are not substituted at the 2-position.

Acknowledgements

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12. Typical reaction procedure: (Table 2, entry 2): In an Ace-pressure tube under an argon atmosphere a solution of catalyst **1** in 2 mL toluene was added to a mixture of 110 µL (113 mg, 1.1 mmol) 1-chloro-4-pentyne and 190 µL (191 mg, 1.4 mmol) *N*-methyl-*N*-(4-tolyl)hydrazine. The reaction mixture was heated at 100 °C for 24 h. During this time the corresponding 2-(1,2,5-trimethyl-1*H*-indol-3-yl)ethylamine hydrochloride precipitated. The mixture was diluted with 5 mL hexane and the precipitate was filtered off. Yield 170 mg (65%). For isolation of the free 2-(1,2,5-trimethyl-1*H*-indol-3-yl)ethylamine, the hydrochloride was dissolved in 20 mL water and NaOH was added until the solution reached a pH of 9. Then 20 mL CH_2Cl_2 were added and the organic layer was separated. The aqueous phase was washed twice with 10 mL CH_2Cl_2 and the combined organic phases were dried over anhydrous $MgSO_4$. After evaporation of the solvent 2-(1,2,5-trimethyl-1*H*-indole-3-yl)ethylamine was obtained as brown oil. Yield 133 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (s, 1H), 7.10 (d, $J = 8.3$ Hz, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 3.57 (s, 3H), 2.91 (t, $J = 6.4$ Hz, 2H), 2.82 (t, $J = 6.4$ Hz, 2H), 2.43 (s, 3H), 2.32 (s, 3H), 1.32 (bs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 134.9$, 133.5, 127.9, 127.7, 121.9, 117.6, 108.1, 107.7, 42.8, 29.3, 28.5, 21.3, 10.2. MS (EI, 70 eV): m/z (rel. intensity) = 202 (16, $M^{+\cdot}$), 172 (100), 157 (8), 128 (3), 115 (6), 91 (3), 77 (2), 51 (2), 30 (6). IR (neat, cm^{-1}): 3340, 3250, 3161, 1577, 1462, 1373, 785. HRMS Calcd. for $C_{13}H_{18}N_2$: 202.14700. Found: 202.14733. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, and IR spectroscopy. New compounds were further characterized by HRMS (high-resolution mass spectrometry).