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A Convenient and General Method for the Synthesis of Indole-2,3-dicarboxylates and 2-Arylindole-3-carboxylates

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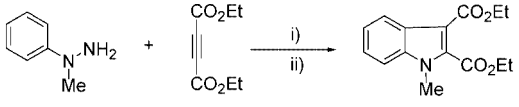
A transition-metal-free, simple and efficient one-pot method for the synthesis of indole-2,3-dicarboxylates and 2-arylindole-3-carboxylates is described. The corresponding products are obtained by a domino hydroamination/Fischer indole cyclization in good-to-excellent yields from easily available 1-alkyl-1-phenylhydrazines and acetylene carboxylates.

The catalytic addition of organic amines and their derivatives to alkenes and alkynes (hydroamination) to produce nitrogen-containing molecules is of significant importance for synthetic chemists in basic research as well as for those in the chemical industry.[1] Today intermolecular hydroaminations are known to be catalyzed by a variety of transition metals (d- and f-block metals),[2] alkali metals[3] and Brönsted and Lewis acids.[4] However, most of these catalysts are rather limited with respect to their substrate tolerance.

Various biologically active amine alkaloids, especially indoles, continue to attract the interest of organic chemists. Though many catalytic methods exist for the synthesis of indoles,[5] still the most famous synthesis for indoles and their derivatives constitutes the Fischer indole synthesis.[6] We have been interested for some time in the improvement and exploration of methodologies for the synthesis of indole heterocycles.[7] For example, we developed a one-pot synthesis of tryptamines and tryptopholes by a titanium-catalyzed hydrohydrazination of chloro- and silyloxo-substituted alkynes.[7a,8] In continuation of this work, we became interested in the hydrohydrazination reaction of acetylenedicarboxylates, which are easily available. Some related carboxy-2,3-disubstituted indole derivatives are known to be potent inhibitors of thromboxane synthase,[9] phospholipase-A_2,[10] cyclooxygenase-2,[11] steroid-5α-reluctase[12] and glycine/NMDA antagonists.[13] In addition to their biological activity, indole-2,3-dicarboxylate esters may serve as valuable synthetic intermediates for other indole derivatives and more complex indole heterocycles.[14]

On the basis of our previous hydroamination protocols, we initially investigated the reaction of *N*-methyl-*N*-phenylhydrazine (**1a**) with diethyl acetylenedicarboxylate (**2**) in the presence of 10 mol-% of $Ti(NEt_2)_4$ as the catalyst at 100 °C. Subsequent treatment of the reaction mixture with 3 equiv. of $ZnCl_2$ allowed the cyclization of the in-situ-generated hydrazone to give the corresponding diethyl 1-methylindole-2,3-dicarboxylate **3a** in 55% yield (Table 1, Entry 1).

Table 1. Reaction of 1-methyl-1-phenylhydrazine (**1a**) with diethyl acetylenedicarboxylate (**2**).[a]



1a **2** **3a**

Entry	Hydrazine **1a** [equiv.]	Alkyne **2** [equiv.]	Yield **3a** [%]
1[b]	1.0	1.0	55
2	1.0	1.0	63
3[c]	1.0	1.0	30
4[d]	1.0	1.0	60
5	1.5	1.0	66
6	1.0	1.5	78
7	1.0	2.0	87

[a] Reaction conditions: i) toluene, 100 °C, 24 h; ii) $ZnCl_2$ (3 equiv.), 100 °C, 24 h. [b] 10 mol-% $Ti(NEt_2)_4$, 20 mol-% 2,6-di-*tert*-butyl-4-methylphenol. [c] Reaction temperature 80 °C. [d] Reaction temperature 120 °C.

Interestingly, the same reaction occurred in 63% yield when performed in the absence of any titanium catalyst (Table 1, Entry 2). This observation is in agreement with the previous work of Acheson[15] and Miki et al.[16] who prepared selected dimethyl indole-2,3-dicarboxylates in yields of 13–62%. Interestingly, in 1935 Diels and Reese had already described the condensation of 1-benzyl-1-phenylhydrazine with acetylenedicarboxylate; however, no product yield of the respective indole-2,3-dicarboxylate was given.[17]

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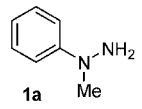
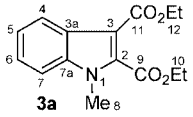
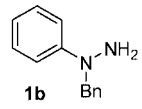
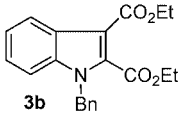
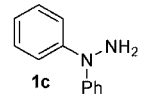
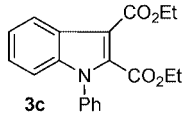
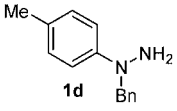
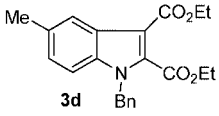
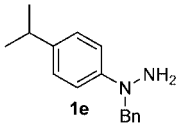
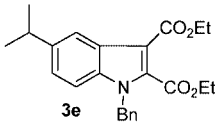
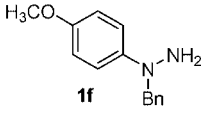
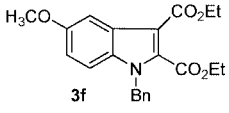
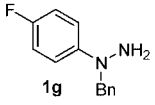
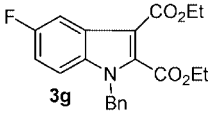
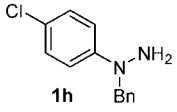
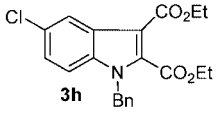
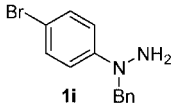
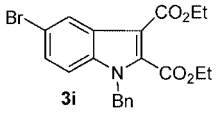
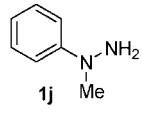
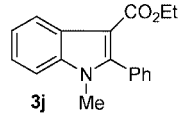
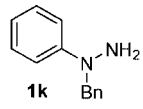
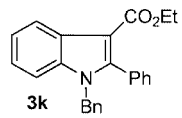
Because of the limited information available, we decided to perform a systematic study to improve the yield of this domino hydroamination/cyclization sequence. Selected experiments are shown in Table 1. The use of an excess amount of phenylhydrazine **1a** (1.5 equiv.) improved the yield of **3a** slightly. In contrast, a considerable increase in the yield of the corresponding indoledicarboxylate was observed when an excess of alkyne **2** was used. Hence, 1.5 and 2.0 equiv. of **2** gave 78 and 87% yield of **3a**, respectively. This is explained by oligomerization side reactions of **2**. We also examined the effect of temperature to improve the yield of the indole product. However, neither an increase in the

Table 2. Synthesis of indole-2,3-dicarboxylates.[a]

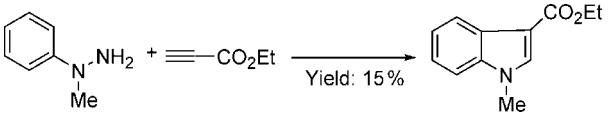
Entry	Hydrazine	Alkyne	Product	Yield [%][b]
1	 **1a**		 **3a**	87
2	 **1b**		 **3b**	67
3	 **1c**		 **3c**	60
4	 **1d**		 **3d**	65
5	 **1e**		 **3e**	60
6	 **1f**		 **3f**	55
7	 **1g**		 **3g**	75
8	 **1h**		 **3h**	40
9	 **1i**		 **3i**	26
10	 **1j**		 **3j**	55
11	 **1k**		 **3k**	60

[a] Reaction conditions: i) hydrazine (1 equiv.), acetylenedicarboxylate (2 equiv.), toluene, 100 °C, 24 h; ii) $ZnCl_2$ (3 equiv.), 100 °C, 24 h. [b] Yield of isolated products.

reaction temperature to 120 °C nor a lowering to 80 °C gave a better yield of **3a**. Also, attempts to improve the yield further by using different solvents such as benzene, methanol, THF, 1,4-dioxane and NMP were not fruitful. Noteworthy is that when $ZnCl_2$ was added in the beginning of reaction, the desired product was also obtained, albeit in lower yield.

As already described by Acheson et al.[15] we were also able to isolate the intermediate hydrazone of the reaction between *N*-methyl-*N*-phenylhydrazine (**1a**) and acetylenedicarboxylate **2** in the absence of $ZnCl_2$. After 24 h at 100 °C in toluene, a hydrazone/indole ratio of 83:17 was found. The hydrazone immediately underwent Fischer indole cyclization in the presence of the Lewis acid. At this point it is noteworthy that Schwesinger et al. demonstrated that the reaction of phenylhydrazine and acetylenedicarboxylate also yielded the corresponding hydrazone.[18] However, as a result of the strong intramolecular hydrogen bond, subsequent Fischer indole cyclization to yield the indole-2,3-dicarboxylate was prevented. Apparently, the presence of two substituents at the hydrazine nitrogen atom facilitates the Fischer indole cyclization. Thus, we next applied the improved hydroamination–cyclization protocol to indole products **3a**–**k** (Table 2).

However, lower yields (26–40%) were obtained for the reaction of *N*-(4-bromophenyl)- and *N*-(4-chlorophenyl)-*N*-benzylhydrazine, presumably owing to the lower reactivity in the Fischer indole cyclization step. Notably, the methodology is also applicable to other activated acetylenecarboxylic acid derivatives. Hence, the regioselective synthesis of 2-arylindolecarboxylate derivatives is possible from ethyl 3-phenyl-1-propynecarboxylate in 55–60% yield (Table 2, Entries 10 and 11). To the best of our knowledge these are the first examples of such a direct synthesis of 2-arylindole-3-carboxylates. Moreover, by applying the more labile ethyl propiolate, 15% of the desired product was obtained under similar reaction conditions (Scheme 1). Here, the lower product yield can be explained by the increased propensity of ethyl propiolate to undergo self condensation.



Scheme 1. Reaction with ethyl propiolate.

In conclusion, we presented the synthesis of various diethyl indole-2,3-dicarboxylates by a domino hydroamination/Fischer indole cyclization synthesis. The corresponding products are obtained easily from commercially available substrates in general in good yield. We believe that this methodology constitutes the most convenient access to this class of compounds.

Experimental Section

Representative Procedure: An Ace pressure tube under an argon atmosphere was charged with 1-methyl-1-phenylhydrazine (0.366 g, 3.0 mmol), diethyl acetylenedicarboxylate (1.02 g, 6.0 mmol) and dry toluene (5 mL). The pressure tube was fitted with a Teflon cap and heated at 100 °C for 24 h in an oil bath. Then, the reaction mixture was cooled to r.t. and anhydrous $ZnCl_2$ (1.22 g, 9.0 mmol) was added. The reaction mixture was further heated at 100 °C for 24 h. The excess toluene was distilled off under reduced pressure, and the residue was purified by chromatography on silica gel (hexane/ethyl acetate, 9:1) to afford **3a** as a gummy liquid. Isolated yield: 0.717 g (87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (br. d, $^3J_{4,5}$ = 8.0 Hz, 1 H, 4-H), 7.37–7.33 (m, 2 H, 6,7-H), 7.28 (m, 1 H, 5-H), 3.83 [s, 3 H, Me(8)], 4.48 [q, ^3J = 7.3 Hz, 2 H, CH_2(10)], 4.38 [q, ^3J = 7.2 Hz, 2 H, CH_2(12)], 1.42 [t, ^3J = 7.3 Hz, 3 H, Me(10)], 1.40 [t, ^3J = 7.2 Hz, 3 H, Me(12)] ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 164.1 (C-11), 162.8 (C-9), 136.8 (C-7a), 135.0 (C-2), 125.4 (C-3a), 124.3 (C-6), 122.3, 122.5 (C-4,5), 110.0 (C-7), 108.0 (C-3), 62.3 [CH_2(10)], 60.2 [CH_2(12)], 31.3 [Me(8)], 14.0 [Me(10)], 14.4 [Me(12)] ppm (numbering according to Table 2, Entry 1). IR (neat): $\tilde{\nu}$ = 3055, 2982, 2938, 2905, 1733, 1717, 1700, 1615, 1539, 1471, 1444, 1412, 1379, 1273, 1247, 1210, 1157, 1103, 1034, 1014, 860, 788, 753, 742 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 275 (100) [M]$^+$, 230 (40), 229 (30), 203 (28), 202 (91), 200 (20), 158 (18), 157 (22), 89 (6). HRMS (EI): calcd. for $C_{15}H_{17}NO_4$ 275.1153; found 275.1152.

Acknowledgments

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