A New Facile Approach to Isoindole and Pyrrole Derivatives

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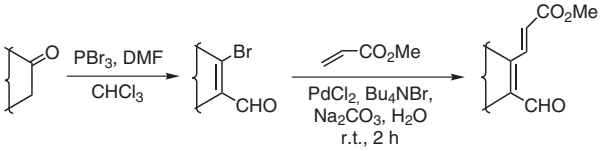
Abstract: A highly efficient protocol for the synthesis of N-substituted di-/tetrahydroisoindole derivatives and N-substituted pyrroles fused with seven-membered rings has been developed by reaction of amines with 3-(2-formyl-cycloalkenyl) α,β-unsaturated esters or nitriles, which, in turn, were prepared from β-bromovinyl aldehydes by a Pd(0)-catalyzed Heck reaction. Bisisoindoles were also achieved by this room-temperature procedure.

Key words: nitrogen heterocycles, isoindoles, pyrroles, synthetic method, amines

Among the nitrogen-containing heterocycles, pyrroles, indoles, and also their partial as well as completely reduced analogues occur widely in natural and synthetic biologically active molecules.[1] Although isoindoles and their derivatives are less common compared to pyrroles and indoles, still they have attracted interest from synthetic organic chemists due to their notable importance and applications. They can serve as inhibitors of cyclooxygenase isoenzyme (COX-2) and thrombin.[2] They also have broad applications as organic light-emitting devices (OLED) due to their fluorescence and electroluminescence properties[3] and also as the substrates for preparation of oligoacenes.[4] 4,5,6,7-Tetrahydroisoindoles are key structural moieties of porphyrins and some of their derivatives are biologically active.[5,6] Hydroxy derivatives of 2-aryl-substituted 4,5,6,7-tetrahydroiso (or methanoiso) indoles elicit sedative action on the central nervous system.[7]

Isoindoles are generally prepared based on the synthesis of pyrrole and their synthetic routes follow oxidation of pyrrolidine,[8] condensation of 1,4-dicarbonyl compounds and amines (the Paal–Knorr synthesis),[5a,6a,9] cyclization of enamino acids,[5c,6b,10] Diels–Alder reactions of 3-sulfolenes and alkenes,[11] cyclization of isocyanoacetates with vinyl sulfones or nitroalkenes,[12,13] phthalazine ring contraction,[6c] reactions of α,β-unsaturated imines with nitroalkanes catalyzed by samarium,[14] and hydrogenation of N-substituted isoindolines.[15] Herein, we wish to report a mild, noncatalytic, base- and additive-free room-temperature-route to N-substituted isoindole and pyrrole derivatives by addition of amines to 3-(2-formyl-cycloalkenyl)acrylic esters or 3-(2-formyl cycloalkenyl)acrylonitriles, which, in turn, were prepared from the corresponding β-bromovinyl aldehydes[16] by a Pd-catalyzed Heck reaction. This method has been further extended to the synthesis of bisisoindoles.

As part of our ongoing research efforts in the development and application of new methods for the synthesis of heterocycles[17] and carbocycles[18] exploiting the Pd-catalyzed intramolecular Heck reaction on substrates derived from β-bromovinyl aldehydes, we were interested in developing a general, simple, and effective method for the preparation of fused pyrrole derivatives from 3-(2-formyl-cycloalkenyl) α,β-unsaturated esters or nitriles. Recently, we have reported the synthesis of dihydrofuran and furan derivatives from the esters of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid.[19] Our approach to the synthesis of the starting materials involves the reaction of β-bromovinyl aldehydes with acrylic esters[20] catalyzed by Pd(0) nanoparticles in water at room temperature (Scheme 1) or with acrylonitrile in acetonitrile at 80 °C in the presence of $Pd(OAc)_2$ (Scheme 2). Recently, high yielding nanopalladium-catalyzed reactions have attracted considerable attention because of their high reactivity and selectivity.[21]



Scheme 1 Procedure A

The starting materials were prepared by treating β-bromovinyl aldehydes (1 mmol) with methyl acrylate (4 mmol) in the presence of $PdCl_2$ (10 mol%), Na_2CO_3 (4 mmol), and Bu_4NBr (1 mmol) in water (4 mL) at room temperature for 2 hours (procedure A), thereby, producing Pd(0) nanoparticles in situ.[22] In no case was the formation of any side product observed.[23] 3-(2-Formyl cycloalkenyl)acrylonitriles were prepared by the reaction of β-bromovinyl aldehydes (1 mmol) with acrylonitrile (4 mmol) in the presence of $Pd(OAc)_2$ (10 mol%), Et_3N (1.5 mmol), and Ph_3P (0.25 mmol) in acetonitrile (5 mL) at 80 °C for one hour (procedure B). Reaction of β-bromovinyl aldehydes with acrylonitrile using the $PdCl_2/Bu_4NBr/Na_2CO_3/H_2O$ system did not produce the desired 3-(2-formyl cycloalkenyl)acrylonitriles but afforded a mixture of decomposed products.

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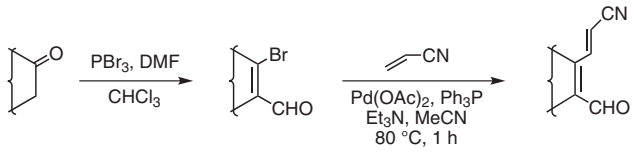


Scheme 2 Procedure B

Different 3-(2-formyl-cycloalkenyl) α,β-unsaturated esters[24] or nitriles[25] were then prepared following the above-mentioned procedures (A or B). In all cases, yields were excellent. The results are summarized in Table 1.

Table 1 Synthesis of 3-(2-Formyl-cycloalkenyl) α,β-Unsaturated Esters or Nitriles

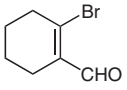
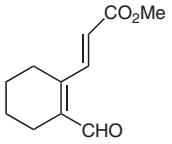
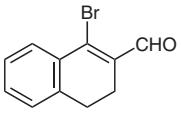
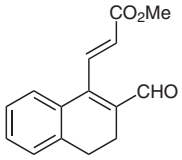
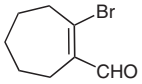
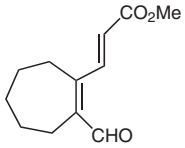
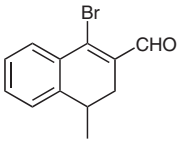
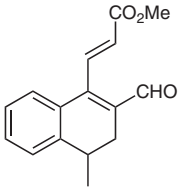
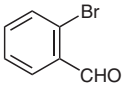
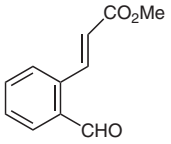
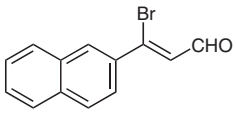
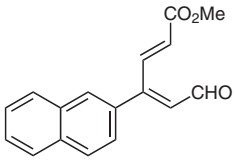
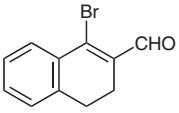
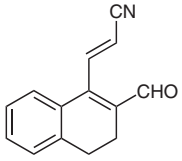
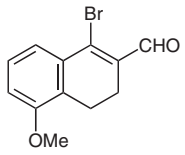
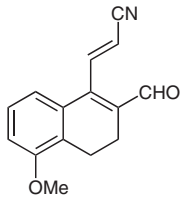
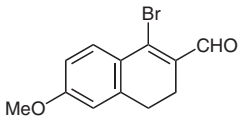
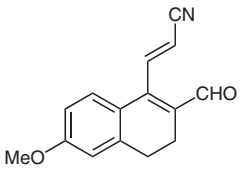
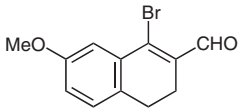
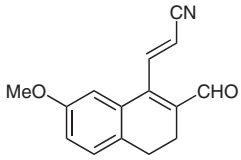
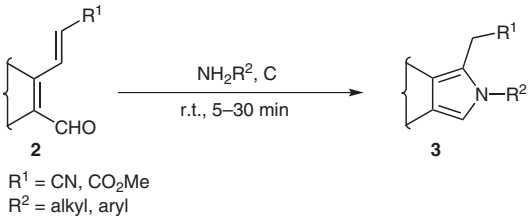
Entry	Procedure	β-Bromovinyl aldehyde	Formyl alkene	Yield (%)[a]
1	A	 **1a**	 **2a**	98
2	A	 **1b**	 **2b**	99
3	A	 **1c**	 **2c**	93
4	A	 **1d**	 **2d**	95
5	A	 **1e**	 **2e**	88
6	A	 **1f**	 **2f**	90
7	B	 **1b**	 **2g**	85

Table 1 Synthesis of 3-(2-Formyl-cycloalkenyl) α,β-Unsaturated Esters or Nitriles (continued)

Entry	Procedure	β-Bromovinyl aldehyde	Formyl alkene	Yield (%)[a]
8	B	 **1g**	 **2h**	85
9	B	 **1h**	 **2i**	78
10	B	 **1i**	 **2j**	80

[a] Isolated yields after purification by column chromatography.

Next, pyrrole formation[26] was investigated. A variety of N-substituted di-/tetrahydroisoindole derivatives and N-substituted pyrroles was synthesized (Table 2) by treating 3-(2-formyl-cycloalkenyl)-acrylic esters or 3-(2-formyl cycloalkenyl)acrylonitriles with different amines in CH_2Cl_2 at room temperature for 5–30 minutes (Scheme 3).



Scheme 3 Synthesis of pyrrole derivatives

Aliphatic amines reacted very rapidly and the reactions were complete within 5 minutes to give almost quantitative yields of the products. Aromatic amines with alkyl, alkoxy and halogen substituents at *ortho*, *meta*, or *para* positions gave good to excellent yields. The reaction rate was slightly faster with electron-donating substituents.

Table 2 Synthesis of Pyrroles[a]

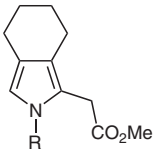
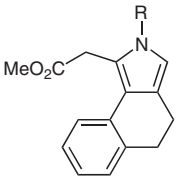
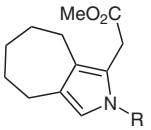
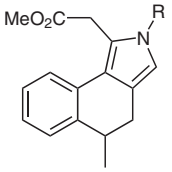
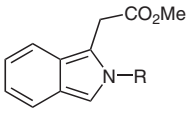
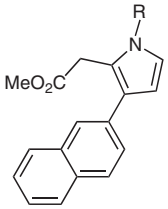
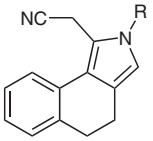
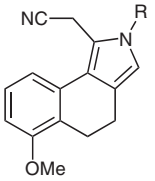
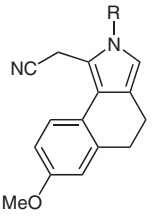
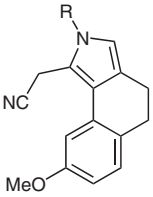
Entry	Alkene **2**	Pyrrole **3**		Time (min)	Yield (%)[b]
1	**2a**		**3a** R = Ph	20	90
2			**3b** R = 4-$MeOC_6H_4$	18	92
3			**3c** R = Bn	5	98
4			**3d** R = 4-FC_6H_4	30	83
5			**3e** R = 2-MeC_6H_4	25	85
6	**2b**		**3f** R = *n*-Bu	5	97
7			**3g** R = Bn	5	95
8			**3h** R = 2-ClC_6H_4	25	88
9			**3i** R = 2-C_6H_4N	30	80
10	**2c**		**3j** R = Bn	6	93
11			**3k** R = 3,5-$Cl_2C_6H_3$	30	85
12			**3l** R = *n*-Bu	5	96

Table 2 Synthesis of Pyrroles[a] (continued)

Entry	Alkene **2**	Pyrrole **3**		Time (min)	Yield (%)[b]
13	**2d**		**3m** R = 4-MeC_6H_4	20	89
14	**2e**		**3n** R = Bn	5	90
15	**2f**		**3o** R = Bn	5	85
16	**2g**		**3p** R = 3-$MeOC_6H_4$	10	91
17	**2h**		**3q** R = 4-$MeOC_6H_4$	20	90
18	**2i**		**3r** R = 4-$MeOC_6H_4$	20	90
19	**2j**		**3s** R = *n*-Bu	5	93

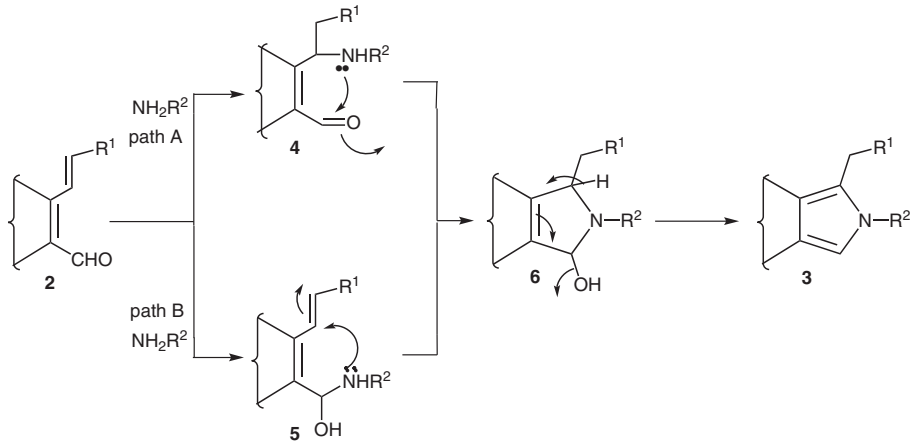
[a] Reaction was carried out with formyl alkene **2** (1.0 mmol) and amine (1.1 mmol) in CH_2Cl_2 at r.t. for 5–30 min.
[b] Isolated yields after purification by column chromatography.

The reaction was unsuccessful with nitroanilines but it proceeded smoothly with 2-aminopyridine to afford the *N*-pyridinylbenzoisoindole derivative (entry 9). Isoindole **3n** was also achieved from substrate **2e** (entry 14). Compound **3n** gradually underwent decomposition in $CDCl_3$. A pyrrole derivative **3o** was also obtained from substrate **2f** in excellent yield (entry 15).

One of the noteworthy advantages of these reactions is that no workup is needed, and the reaction mixture can be directly loaded for column chromatography. To examine any solvent effect, different solvents were screened. THF, MeCN, and toluene gave almost similar results to those with CH_2Cl_2. Addition of Lewis acids such as BF_3-OEt_2 or $TiCl_4$ prior to the addition of the amine failed to afford the desired product presumably due to the sequestering of the amine by the Lewis acid.

We propose the following mechanistic rationale for the synthesis of fused pyrroles **3** (Scheme 4).

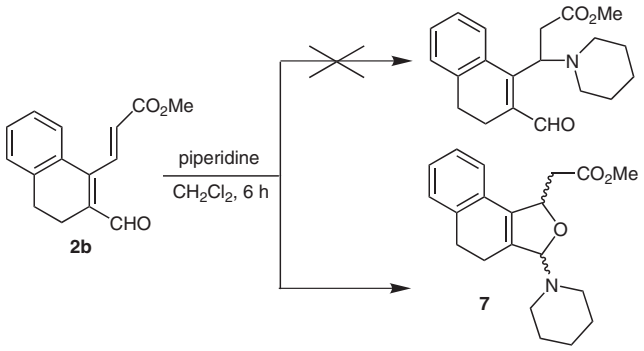
In path A, aza-Michael addition of the amine followed by intramolecular attack at the aldehyde and subsequent



Scheme 4 Proposed mechanism of fused pyrrole synthesis

elimination of water leads to the pyrrole. Another possible mechanistic explanation for the transformation of **2** to **3** is the formation of intermediate **5**, obtained by the attack of the amine on the aldehyde which eventually leads to the pyrrole via intermediate **6** (path B). In either case, aromatization is the driving force.

The reaction was so fast that intermediates could not be isolated. Thus, we hypothesized that if we were to use a secondary amine then the reaction could be stopped at intermediate **4** if indeed the reaction proceeds through path A, assuming that a secondary amine reacts analogously to primary amine used previously. To verify this idea, compound **2b** was treated with piperidine (Scheme 5).

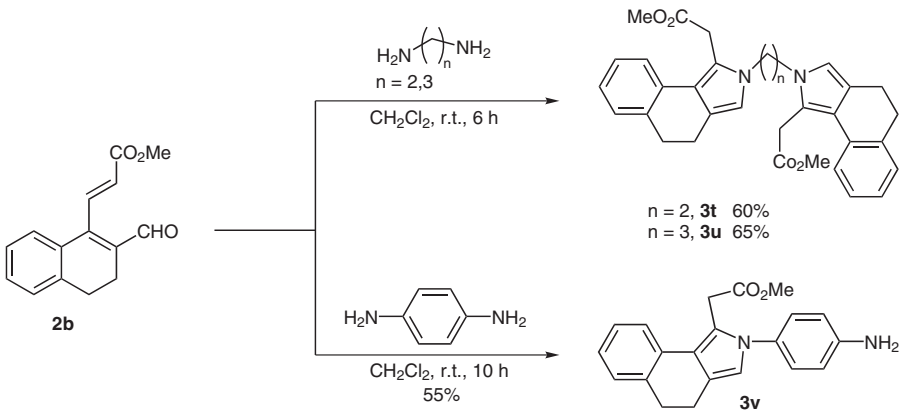


Scheme 5 Reaction of substrate **2b** with piperidine

{3-Piperidin-1-yl-1,3,4,5-tetrahydronaphtho[1,2-*c*]furan-1-yl}acetic acid methyl ester **7** was obtained as a diastereomeric mixture (Scheme 5). This observation supports that the reaction proceeds through pathway B and rules out the possibility of aza-Michael attack prior to the attack at aldehyde (path A).

To study the scope of this methodology, substrate **2b** was reacted with diamines. As expected we obtained bispyrrole derivatives when 0.5 equivalent ethylenediamine or propane-1,3-diamine were reacted with the substrate **2b**. However, 1,4-diaminobenzene yielded monopyrrole derivative **3v** which contained a free NH_2 group even after stirring for 10 hours (Scheme 6).

In conclusion, we have developed a new efficient method towards N-substituted pyrrole derivatives. This procedure provides a general methodology for the synthesis of pyrroles from easily available starting materials and is applicable for synthesis of bispyrroles also. The notable advantages of this methodology are: mild reaction conditions, rapid reaction, minimal workup thereby preventing loss of products, excellent overall yields, and general applicability. Further studies on the synthetic applications of these starting materials are currently in progress.



Scheme 6 Reaction of substrate **2b** with diamine

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(24) **General Procedure for the Heck Reaction in Water (Procedure A)**
β-Bromovinyl aldehyde (1 mmol), Na_2CO_3 (4 mmol), Bu_4NBr (1 mmol), $PdCl_2$ (10 mol%), and H_2O (5 mL) were placed in a two-neck round-bottom flask. Methyl acrylate (4 mmol) was added, the mixture stirred for 2 h, diluted with aq NH_4Cl solution and extracted with Et_2O (3 × 25 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and then concentrated. The product was purified by column chromatography using EtOAc–PE as eluent.

(25) **General Procedure for the Heck Reaction in Acetonitrile (Procedure B)**
β-Bromovinyl aldehyde (1 mmol), Ph_3P (0.25 mmol), Et_3N (1.5 mmol), and dry MeCN (5 mL) were placed in a two-neck round-bottom flask fitted with a condenser. The solvent was degassed with N_2 and then $Pd(OAc)_2$ (10 mol%) and acrylonitrile (4 mmol) were added. The mixture was heated at 80 °C for 1 h, cooled; solvent was evaporated, diluted with H_2O and extracted with Et_2O (3 × 25 mL). The organic layers were combined, washed with brine, dried over

Na_2SO_4, and then concentrated. The product was purified by column chromatography using EtOAc–PE as eluent.

(26) **General Procedure for the Preparation of Pyrroles**
To a solution of 3-(2-formyl cycloalkenyl)acrylic ester (0.5 mmol) or 3-(2-formyl cycloalkenyl)acrylonitrile (0.5 mmol) in CH_2Cl_2 (3 mL), amine (0.5 mmol) was added and stirred at r.t. for 5–30 min. The solvent was evaporated, and then the product was purified by column chromatography using EtOAc–PE as eluent.