JOC*Note*

Efficient Preparation of 2-Indolyl-1-nitroalkane Derivatives Employing Nitroalkenes as Versatile Michael Acceptors: New Practical Linear Approach to Alkyl 9*H*-β-Carboline-4-carboxylate

Giuseppe Bartoli,† Marcella Bosco,† Sandra Giuli,‡ Arianna Giuliani,‡ Laura Lucarelli,‡ Enrico Marcantoni,*,‡ Letizia Sambri,† and Elisabetta Torregiani†

Dipartimento di Scienze Chimiche, Università di Camerino, via S. Agostino 1, I-62032 Camerino (MC), Italy, and Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, viale Risorgimento 4, I-40136 Bologna, Italy

enrico.marcantoni@unicam.it

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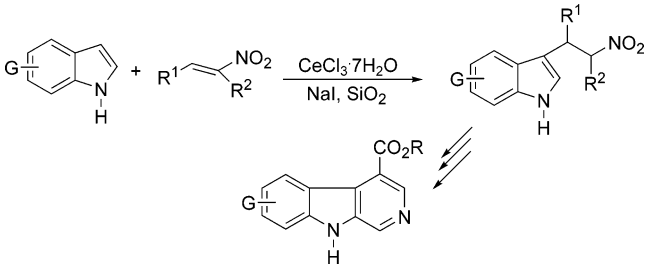
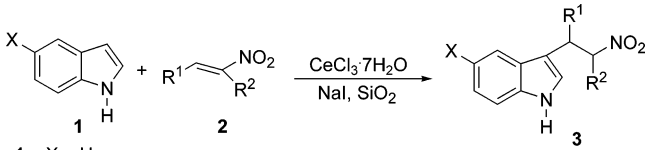


The combination of cerium(III) chloride heptahydrate and sodium iodide supported on silica gel is known to promote Michael-type additions. Continuing our work on solvent-free conditions, the $CeCl_3 \cdot 7H_2O-NaI-SiO_2$ system catalyzes the addition of a variety of indoles and nitroalkenes, giving 2-indolyl-1-nitroalkane derivatives in good yields. Development of this method has resulted in a new protocol for the synthesis of 4-substituted β-carbolines.

We reported recently that indoles react with α,β-unsaturated ketones in the presence of cerium(III) chloride heptahydrate and sodium iodide supported on silica gel leading to good yields of indoles alkylated at the 3-position.[1] The reaction may be regarded as a Friedel–Crafts-type conjugated addition of indoles[2] in solvent-free conditions.[3] However, several Michael acceptors[4] failed to react under our conditions, including vinyl sulfones, α,β-unsaturated esters, and acrylonitrile.

Although the Michael addition of nucleophilic indoles[7] to nitroalkenes has been well studied,[8] the area is far from fully explored. The use of $CeCl_3 \cdot 7H_2O-SiO_2$ as "friendly" Lewis acid promoter[9] in Michael reactions with poorly reactive indoles has not been reported previously. Among the strongest Michael acceptors,[5] nitroalkenes are also attractive because the nitro group can serve as a masked functionality. This *synthetic chameleon* can be transformed after the Michael addition has taken place.[6]

SCHEME 1



1 **2** **3**

1a: X = H
1b: X = OCH_3
1c: X = OH
1d: X = CN

Results and Discussion

It is well established that our $CeCl_3 \cdot 7H_2O-NaI$ combination supported on SiO_2 is optimal in suppressing polymerization of electron-rich heteroaromatic rings (such as indoles) under acid-catalyzed conditions.[10] Our procedure could find many other useful applications in Michael conditions. In our study of the addition of indoles to nitroalkenes (Scheme 1), treatment of indole (**1a**) with *trans*-β-nitrostyrene[11] in the presence of 0.3 equiv of $CeCl_3 \cdot 7H_2O$ and 0.3 equiv of NaI supported on SiO_2 (0.5 g/mmol of nitroalkene) gives a heterogeneous mixture that affords, after simple workup, the corresponding

* To whom correspondence should be addressed. Phone: +39 0737 402255. Fax: +39 0737 402297.
† Università di Bologna.
‡ Università di Camerino.

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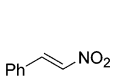
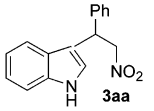
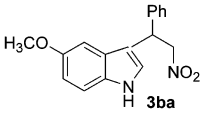
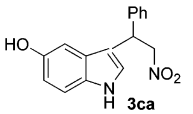
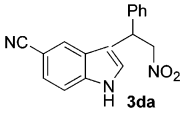
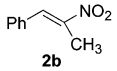
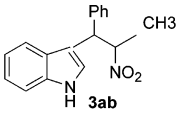
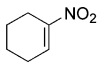
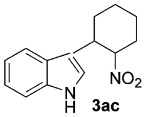
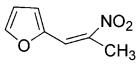
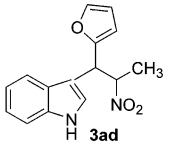
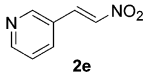
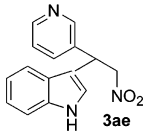
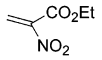
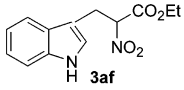
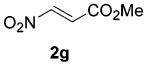
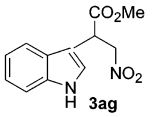
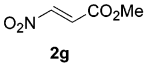
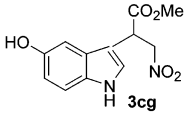
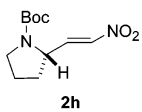
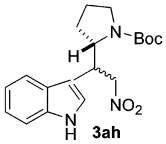
2-indolyl-1-nitroalkane (**3aa**) in good yield. Encouraged by this result, we have carried out the addition of a variety of indoles and nitroalkenes, summarized in Table 1. This synthetic approach allows the facile introduction of 2-nitroethyl-functionalized substituents into the 3-position of indole nucleus, possibly serving as a source for the corresponding amino compounds.[12] These derivatized indole stock compounds would be valuable intermediates for the preparation of molecules of biological interest.[13]

It has been observed that the electronic properties of the aromatic ring have an effect on the rate of this Michael reaction. The rate is accelerated if an electron-donating group is present on the indole nucleus (Table 1, entry 2). Even indole substrates bearing an electron-withdrawing group such as 5-cyanoindole (**1d**) afford the corresponding adduct[14] in satisfactory yield (Table 1, entry 4). In the case of an indole derivative containing a hydroxyl group (**1c**), our catalyzed Michael addition ran cleanly and in good yields (**3ca** and **3cg**). Direct reaction of hydroxyindoles is generally problematic, often resulting in low Michael adduct yields due to interaction of the indolyl hydroxyl group with the Lewis acid catalyst.[15] Unfortunately, where the pyrrole moiety of indole carries electron-withdrawing substituents such as a carbomethoxy or a benzenesulfonyl group, synthesis of the corresponding Michael adducts has not been successful. The presence of electron-withdrawing groups in pyrrole ring reduces the overall nucleophilicity.

With nitroalkenes substituted in the α- or *β*-position, the reaction proceeds with good yields. Moreover, with α,*β*-disubstituted nitroalkenes we observed low diastereoselectivity and approximately equal parts of syn and anti products. Only in the case of nitrocyclohexene (**2c**) as a Michael acceptor we have obtained moderate diastereoselectivity (Table 1, entry 6) in 2-indolyl-1-nitrocyclohexane (**3ac**). Moreover, Michael addition of indole to 1-furyl-2-nitropropene **2d** and 1-(3-pyridyl)-2-nitroethene **2e** gave the corresponding adducts **3ad** and **3ae** without any interference of the sensitive heterocyclic nucleus (Table 1, entries 7 and 8). Furthermore, we have investigated the use of our $CeCl_3{\cdot}7H_2O$−NaI−SiO_2 system to add indoles to the α-carbon atom of α,*β*-unsaturated carbonyl compounds having a strongly electron-withdrawing group at the *β*-carbon.[16] The readily available *trans*-*β*-nitroacrylate (**2g**)[17] gave very good yields in all cases (Table 1, entries 10 and 11). Upon oxidative removal of the nitro group, this is a useful, high-yielding method for synthesizing indoles having a malonate moiety at the 3-position.[18] Finally, our conditions can lead to the nitro indole **3ah**.[19] Indole reacts with nitroalkene

TABLE 1. Michael Addition of Indoles to Nitroalkenes Catalyzed by $CeCl_3{\cdot}7H_2O$−NaI Combination Supported on SiO_2[a]

Entry	Indole	Nitroalkene	Time/h	Product[b]	Yield (%)[c]
1	**1a**	 **2a**	8.0	 **3aa**	96
2	**1b**	**2a**	4.0	 **3ba**	92
3	**1c**	**2a**	24.0	 **3ca**	74
4	**1d**	**2a**	18.0	 **3da**	85
5	**1a**	 **2b**	15.0	 **3ab**	88[d]
6	**1a**	 **2c**	24.0	 **3ac**	87[e]
7	**1a**	 **2d**	16.0	 **3ad**	80[d]
8	**1a**	 **2e**	10.0	 **3ae**	93
9	**1a**	 **2f**	4.0	 **3af**	79
10	**1a**	 **2g**	4.0	 **3ag**	91
11	**1c**	 **2g**	8.0	 **3cg**	86
12	**1a**	 **2h**	22.0	 **3ah**	89[d]

[a] Reactions performed in the presence of 30 mol % $CeCl_3{\cdot}7H_2O$ and 30 mol % NaI supported on silica gel. [b] All products were identified by their IR, NMR, and GC/MS spectra. [c] Yields of products isolated by flash chromatography. [d] As a mixture of two diastereomers in about 1:1 ratio. [e] Calculated syn/anti ratio (78:22) on the mixture of diastereomers isolated by column chromatography.

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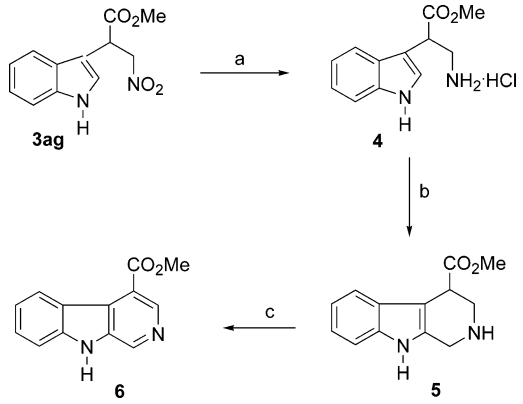
derivative (**2h**), giving a mixture of diastereomers that we have not been able to separate. This mixture is, however, easily converted to the enantiomerically pure alkaloid (−)-(*S*)-brevicolline.[20] The chiral nitroalkene synthon **2h** has been obtained starting from natural amino acid (*S*)-proline.[21]

The present methodology can be applied widely. The preparation of 3-(2-aminoethyl)-1*H*-indole, tryptamine and its derivatives, the neurotransmitter serotonin, and the tissue hormone melatonin constitute especially important examples.[22] In general, the tryptamines are an important class of compounds frequently used as building blocks in the construction of numerous indole alkaloids with useful biological activity,[23] but they are not very stable. Therefore, syntheses have been designed to pass through stable intermediates likely 3-(2-nitroethyl)indolyl derivatives, and subsequently transformed to the amino compounds. Synthetic routes to tryptamines via reduction of the nitro compounds[24−26] have been demonstrated. Our novel synthetic approach using the Lewis acid promoter cerium(III) salt provides an easy and convenient method of making tryptamines by Michael addition of indoles to nitroalkenes. One of the most important aspects in this methodology is that the solvent-free conditions suppress any polymerization phenomena of the acid-sensitive substrates.

The β-carbolines represent a large group of biologically active alkaloids widespread in nature.[27−29] A number of central nervous system pharmacological effects have been attributed to such alkaloids.[30] Synthesis of pyrido[3,4-b]-indoles, the β-carbolines (Scheme 2), was examined to further evaluate the general utility of silica gel-supported

SCHEME 2 [a]



[a] Reagents and conditions: (a) (i) H_2 (1 atm), Raney nickel, room temp for 16 h; (ii) 4 N HCl−dioxane, 78%. (b) (i) 37% aq HCHO, MeOH, room temp for 18 h; (ii) 6% aq K_2CO_3, EtOAc, room temp, 1 h; 90%. (c) Pd/C, xylenes, refluxing for 4 h, 83%.

cerium(III) chloride heptahydrate and sodium iodide. While β-carbolines can be synthesized via tryptamines[31] (vide supra), 4-substituted β-carbolines lacking substitution at the 3-position are not well represented in the literature. We have been especially interested in demonstrating the value of our present procedure by synthesis of methyl 9*H*-β-carbolines-4-carboxylate (**6**). Busacca's method[32] of derivatization of an intermediate to generate a diverse group of 4-substituted β-carbolines requires N-protection, whereas our linear approach involves introduction of the 4-substituent in the first synthetic step. Toward this goal, we began with Michael addition of indole (**1a**) to methyl β-nitroacrylate (**2g**) under our conditions (Table 1, entry 10). The reaction affords indole **3ag** in excellent yield, and the nitro group has been efficiently reduced by hydrogenation in the presence of Raney nickel to give the β-substituted tryptamine derivative **4**.[33] The hydrochloride of **4** was converted in modest yield under protic conditions according to the standard procedure[34] into the 4-substituted 1,2,3,4-tetrahydro-β-carboline **5** by condensation with formaldehyde followed by Pictet−Spengler cyclization of the imine. By compari-

(19) (2-Nitroethyl)indolyl derivative **3ah** was obtained under Michael conditions using indole-anion but in 47% yield and the use of bulky protecting groups in the 1-position was needed; see: Mahboobi, S.; Wiegrebe, W.; Popp, A. *J. Nat. Prod.* **1999**, *62*, 577−579.

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In conclusion, we have demonstrated that the readily available and economical $CeCl_3 \cdot 7H_2O-NaI-SiO_2$ system is a viable means for Lewis acid-promoted Michael addition of indoles with functionalized nitroalkene Michael acceptors. The results show that our present synthetic methodology can be applied widely and especially to the synthesis of β- carbolines that are difficult to make by other means. These cerium(III)-promoted reactions in solvent-free conditions are expected to be of use in the synthesis of a range of indole alkaloids.

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Supporting Information Available: Detailed description of experimental procedures for the compounds **3**, product characterization data and ^1H and ^{13}C NMR peak listing for compounds not reported previously, and additional details on the reaction methodology and the isolation and characterization of products **4**–**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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