Synthetic Methods

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Synthesis of Highly Substituted *N*-Hydroxyindoles through 1,5-Addition of Carbon Nucleophiles to In Situ Generated Unsaturated Nitrones**

K. C. Nicolaou, Anthony A. Estrada, Sang Hyup Lee, and Graeme C. Freestone*

We recently reported a new method for the construction of substituted *N*-hydroxyindoles through trapping of unsaturated nitrones by oxygen, sulfur, and nitrogen nucleophiles.[1] Substituted *N*-hydroxyindoles continue to be of considerable interest to us not only because of our efforts towards the total synthesis of the thiopeptide antibiotic nocathiacin I,[2] whose structure contains such a domain, but also due to the growing interest in their construction as a consequence of the proven biological properties of this unique structural motif.[3,4] Intrigued by the preference of phenolic substrates to react through their carbon, rather than their oxygen, centers,[1] we investigated the behavior of various carbon nucleophiles in that process. Herein, we report our findings in this area which constitute a new method for generating highly substituted *N*-hydroxyindoles through carbon–carbon bond formation involving 1,5-addition[5] to α,β-unsaturated nitrones.

Scheme 1 depicts the transformation involving a $SnCl_2{\cdot}2H_2O$-initiated cascade to facilitate conversion of nitroaromatic α,β-unsaturated ketoesters **I** into α,β-unsaturated nitrones **II**, with subsequent trapping of the latter, rather reactive species by various carbon nucleophiles to afford *N*-hydroxyindoles **III**.[6] To explore this reaction, nitroaromatic α,β-unsaturated ketoesters **3a**–**3e** were prepared from nitroaromatic systems **1a**–**1e** by a two-step process via intermediates **2a**–**2e** in good overall yield (Scheme 2). Bromo-substituted substrate **3a** was then employed in the new process with silyl enol ethers acting as

[*] Prof. Dr. K. C. Nicolaou, A. A. Estrada, Dr. S. H. Lee, Dr. G. C. Freestone
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

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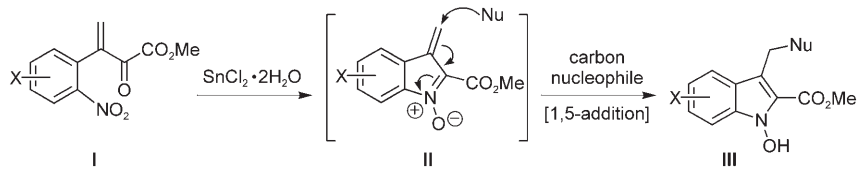
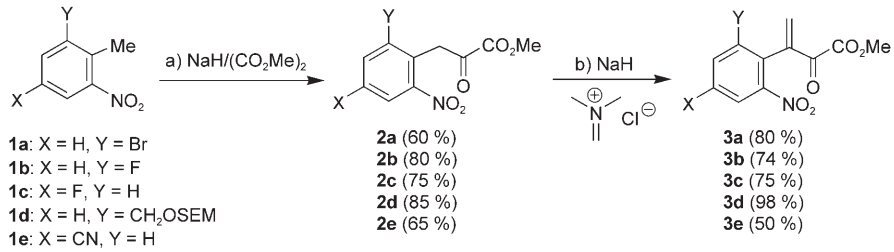


Scheme 1. General path for the construction of 3-substituted *N*-hydroxyindoles (**III**). Nu = carbon nucleophile.



Scheme 2. Synthesis of nitro ketoesters **3a–e**. Reagents and conditions: a) NaH (4.0 equiv), $(CO_2Me)_2$ (5.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 18 h, **2a** (60%), **2b** (80%), **2c** (75%), **2d** (85%), **2e** (65%); b) NaH (1.1 equiv), $CH_2{=}N^+Me_2Cl^-$ (3.0 equiv), THF, 0 °C, 1 h; then 25 °C, 12 h, **3a** (80%), **3b** (74%), **3c** (75%), **3d** (98%), **3e** (50%). DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, SEM = 2-(trimethylsilyl)ethoxymethyl.

carbon nucleophiles under the reductive conditions provided by $SnCl_2{\cdot}2H_2O$ (2.5 equiv) in DME at 40 °C. The results from these experiments are summarized in Table 1. As seen, both cyclic (Table 1, entries 1–3) and acyclic (Table 1, entries 4–10) silyl enol ethers enter the reaction with good yields. The products include *N*-hydroxyindoles substituted at the 3-position with carbon chains containing α-substituted ketones with various groups. These appendages include aliphatic, aromatic, and heteroaromatic ketone functionalities. Of particular interest to pharmaceutical research are the fluoro-substituted compounds, which are also formed in good yields (Table 1, entries 8–10) under these conditions. Furthermore, as a result of their chemical properties, these compounds may serve as viable substrates for further manipulation. By-product **4** (Table 1 and Table 2) is also produced in many of these reactions through an intramolecular Michael addition as previously observed and mechanistically rationalized.[1]

We next tested the possibility of employing silicon- and tin-activated nucleophiles such as allyl silanes and stannanes in the *N*-hydroxyindole-forming reaction. Table 2 summarizes the results of this investigation, further demonstrating the power of this method to construct molecular complexity rapidly and efficiently from simple building blocks. Thus, allyl trimethylsilanes carrying a variety of structural motifs were shown to react smoothly with the α,β-unsaturated nitrone derived from the bromonitroaromatic ketoester **3a** to afford novel *N*-hydroxyindoles (Table 2, entries 1–4). Interestingly, when allyl trimethoxysilane was used (Table 2, entry 5), the methoxy group was transferred to the *N*-hydroxyindole to furnish the corresponding methoxy ether **19** (see Supporting Information) in good yield. In an attempt to complement this result, methoxytrimethylsilane (Table 2, entry 6) was subjected to the reaction conditions and produced, as expected, the same methoxy ether **19**. Further confirmation of the structure of product **19** was obtained by X-ray crystallographic analysis[7] (see Figure 1a). The employment of triethylsilane in the reaction resulted in reduction of the reactive nitrone species, leading to the 3-methyl-substituted product (Table 2, entry 7), while allenyl trimethylsilane furnished an acetylenic compound, **21**, albeit in low yield (20%; Table 2, entry 8). Allyl stannanes (Table 2, entries 9 and 10) also reacted with the nitrone derived from **3a**, leading to the desired products in varying yields. Compound **23** was analyzed by X-ray crystallography[7] (see Figure 1b).

To demonstrate the validity of the proposed method and the generality and scope of the reaction with regards to the nitroaromatic substrate, we explored the employment of substrates **3a–3e** in combination with silyl enol ethers **24** and **25**. Products **5**, **26a–29a**, **8**, and **26b–29b** were formed in moderate to good yields (see Table 3). Of particular interest is the survival of the aromatic nitrile functionality (Table 3, entry 5) under the reductive and nucleophilic conditions employed—an observation that stands as a testament to the mild nature of the process. From Table 3 it can also be seen that the method accommodates various substitution patterns around the aromatic nuclei, including a

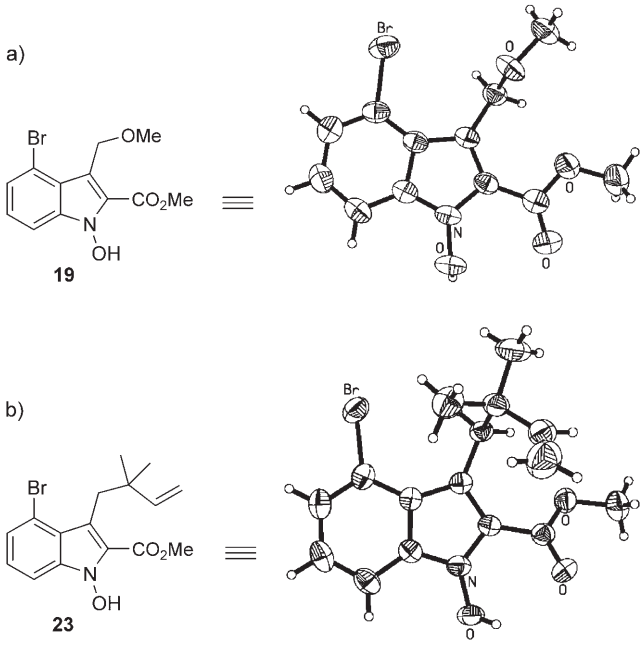
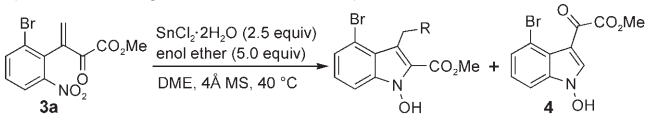
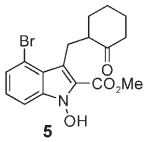
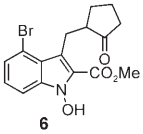
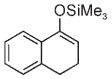
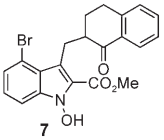
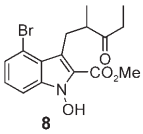
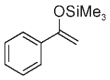
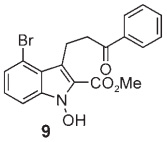
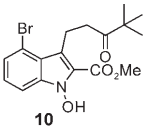
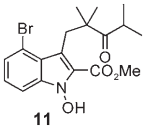
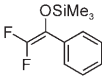
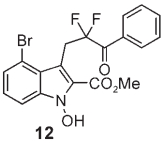
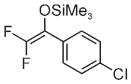
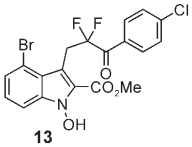
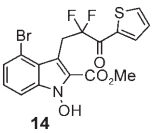


Figure 1. ORTEP drawings of compounds **19** (a) and **23** (b) drawn at the 50% probability level (only heteroatom labels shown).

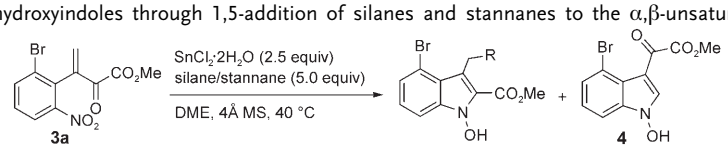
Table 1: Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers to the α,β-unsaturated nitrone derived from **3a**.[a]

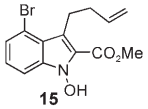
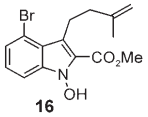
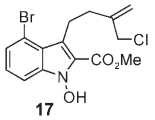
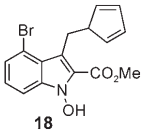
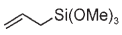
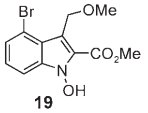
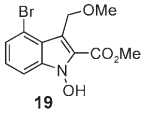
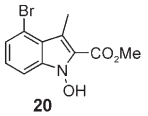
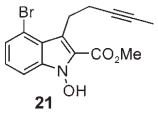
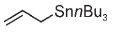
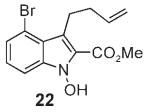
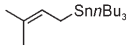
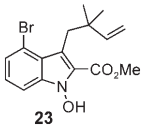


Entry	Enol ether	*t* [h]	Product	Yield [%][b]	Yield (**4**) [%][b]
1		1.5	 **5**	61	17
2		1.5	 **6**	70	17
3		1.2	 **7**	66	11
4		1.0	 **8**	73	10
5		1.3	 **9**	60	10
6		2.0	 **10**	63	10
7		1.0	 **11**	68	15
8		1.5	 **12**	75	[c]
9		1.5	 **13**	75	[c]
10		1.5	 **14**	63	[c]

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous 1,2-dimethoxyethane (DME; concentration: 0.12–0.16 M), and the products were purified by preparative TLC (silica gel). [b] Yield of isolated product. [c] Trace amounts not isolated.

Table 2: Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silanes and stannanes to the α,β-unsaturated nitrone derived from **3a**.[a]



Entry	Silane/ stannane	*t* [h]	Product	Yield [%][b]	Yield (**4**) [%][b]
1		2.5	 **15**	57	20
2		1.5	 **16**	61	15
3		3.5	 **17**	50	11
4		15	 **18**	57	15
5		1.5	 **19**	53	12
6		2.0	 **19**	50	15
7		3.5	 **20**	50	16
8		28	 **21**	20	[c]
9		30	 **22**	25	15
10		4.5	 **23**	62	14

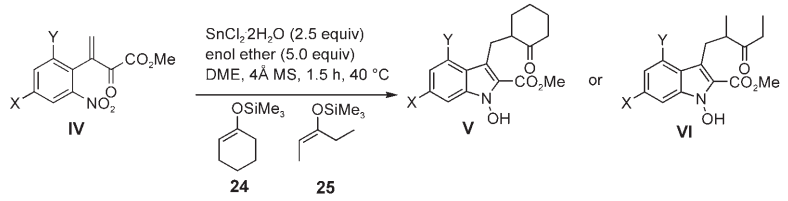
[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by preparative TLC (silica gel). [b] Yield of isolated product. [c] Trace amounts not isolated.

fluorine residue (Table 3, entries 2 and 3), which often exhibits unique pharmacological properties.

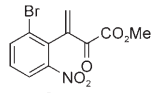
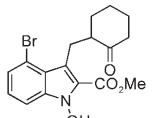
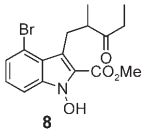
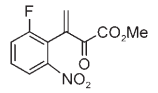
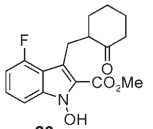
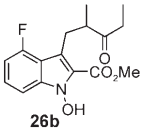
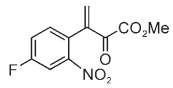
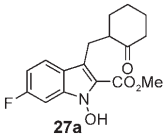
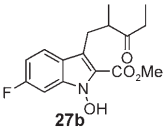
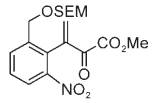
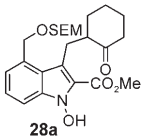
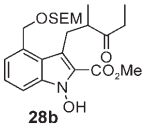
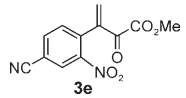
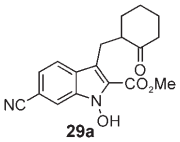
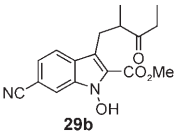
Finally, to demonstrate the effect of varying the stoichiometry of the reaction, bromonitroaromatic ketoester **3a** and difluorosilyl enol ether derived from 2,2,2-trifluoroacetophenone[8] were subjected to the standard conditions (Table 1, entry 8), but using 1, 3, 5, or 10 equivalents of the nucleophile. The results (50, 59, 75, and 74% yield, respectively) demonstrate that this method may also be applied to more complex systems where a large excess of the nucleophile may not be acceptable.

The chemistry described herein expands the repertoire of carbon–carbon bond-forming reactions and provides facile and direct entry to a variety of highly substituted *N*-hydroxyindoles. The method is expected to find applications in chemical synthesis in general and in the construction of

Table 3: Synthesis of 3-alkyl-*N*-hydroxyindoles through 1,5-addition of silyl enol ethers **24** and **25** to substituted α,β-unsaturated nitrones **IV**.[a,b]



IV, V, VI, 24, 25

Entry	α,β-Unsaturated nitro ketoester	Product **V**	Yield [%][c]	Product **VI**	Yield [%][c]
1	 **3a**	 **5**	61	 **8**	73
2	 **3b**	 **26a**	44	 **26b**	61
3	 **3c**	 **27a**	45	 **27b**	61
4	 **3d**	 **28a**	57	 **28b**	46
5	 **3e**	 **29a**	43	 **29b**	40

[a] Reactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by preparative TLC (silica gel). [b] In each case, a minor by-product corresponding to compound **4** was formed (see Table 1 and Table 2), but not isolated. [c] Yield of isolated product.

molecular complexity and diversity for biological and pharmaceutical purposes in particular.

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