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Total Synthesis of Nigellicine and Nigeglanine Hydrobromide

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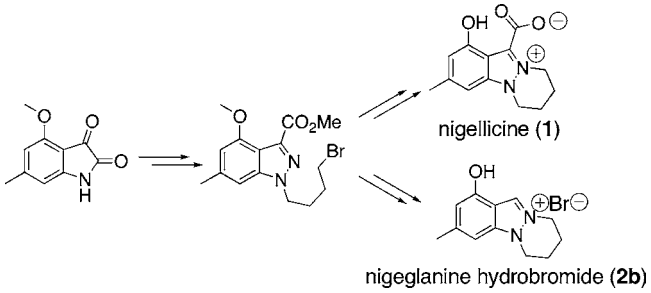
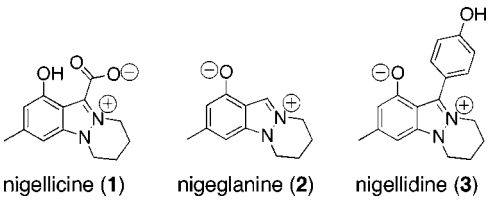
ABSTRACT



The first syntheses of the pyridazinoindazolium alkaloids nigellicine and nigeglanine hydrobromide via a common intermediate are described. Ortho-lithiation/acylation and the direct amination of an isatin ring system are the key steps in the synthesis.

The tricyclic pyridazino[1,2-*a*]indazolium ring system is rarely encountered. Apart from being the subject of one patent,[1] it has appeared in the literature only in the context of three natural products. The first member of the family, nigellicine (**1**), was isolated in 1985 from the seeds of *Nigella sativa*.[2] Subsequently, two additional alkaloids containing the same ring system, nigeglanine (**2**) and nigellidine (**3**), were isolated from *Nigella glandulifera*[3] and *Nigella sativa*,[4] respectively. Herein we report the first syntheses of any member of this natural product family[5,6] and the independent confirmations of the structures of **1** and **2**.



Retrosynthetic analysis (Figure 1) suggested that **1** might arise from the double alkylation of substituted indazole **4** with 1,4-dibromobutane. The indazole core structure was envisioned to come from the intramolecular cyclization of ketohydrazine **5**, potentially attainable via either direct amination or diazotization/reduction of the corresponding amine precursor. Finally, the synthesis was anticipated to proceed through aniline **6** via regiospecific ortho-lithiation[7] and quenching with a suitable oxalate derivative.

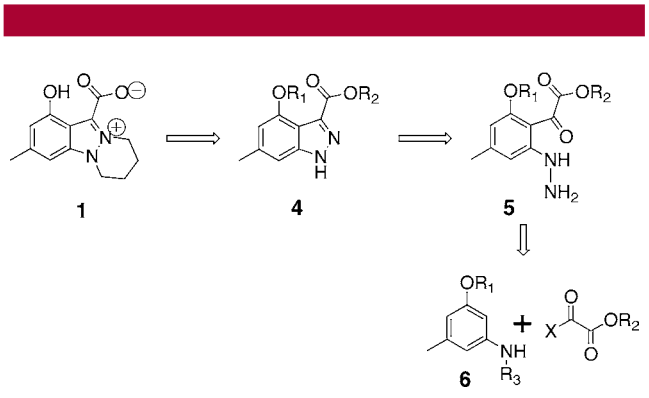


Figure 1. Retrosynthetic analysis of nigellicine (**1**).

With confidence that the total synthesis of nigellicine could be achieved in the above-mentioned manner, the preparation

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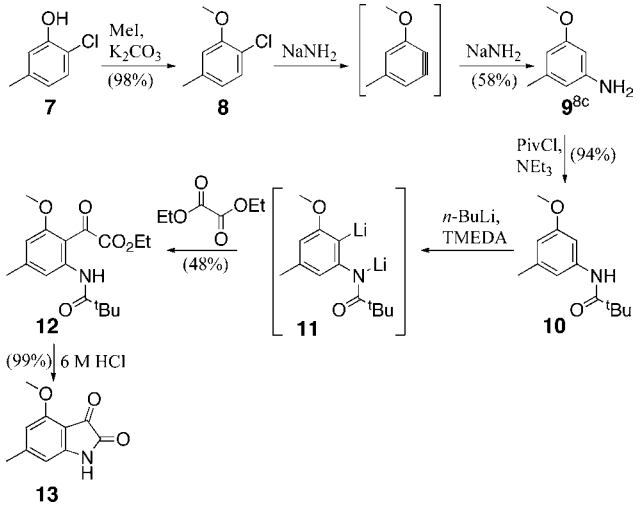
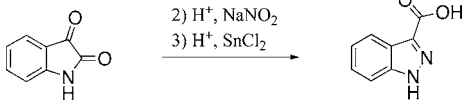
Scheme 1. Synthesis of Isatin **13**



of a specific embodiment of synthon **5** was commenced (Scheme 1). In anticipation of the regiospecific ortho-lithiation reaction, it was necessary to protect the known aniline derivative **9**, accessible in two steps from commercially available 2-chloro-5-methylphenol (**7**),[8] with regiochemical realignment occurring via a benzyne intermediate.[8c] Thus, treatment of **9** with pivaloyl chloride yielded protected amine **10**. Subsequent reaction of **10** with 2.2 equiv of *n*-butyllithium at 0 °C effected ortho-lithiation to produce dianion **11**, which, upon quenching with diethyl oxalate, afforded **12** as a single regioisomer.[9] Attempts to aminate **12**, however, either directly[10] or via diazotization/reduction[11] met with failure. In the end, the only productive transformation that could be achieved was acidic cleavage of the pivaloyl group and subsequent cyclization to isatin **13**.

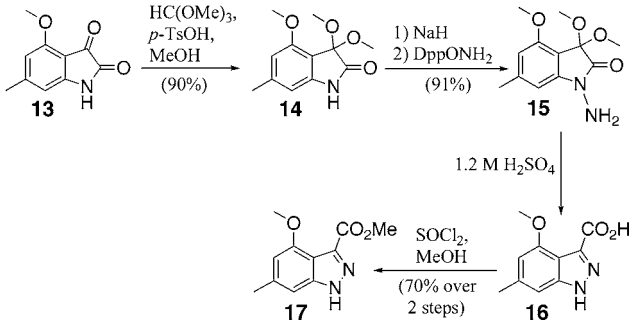
Conversion of **13** to the corresponding indazole via a hydrolysis/diazotization/reduction protocol (Scheme 2) failed,

Scheme 2. Isatin−Indazole Transformation



despite ample precedent.[12] Subsequent attempts to aminate **13**, either via diazotization/reduction or directly with an electrophilic aminating reagent, also failed. But protection of **13**'s reactive ketone functionality as the dimethyl acetal (→**14**) finally enabled (Scheme 3) direct *N*-amination via

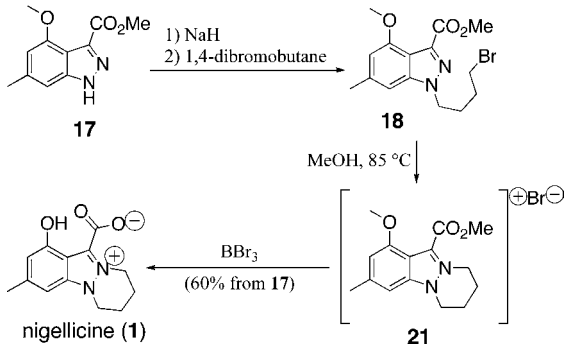
Scheme 3. Synthesis of Indazole **17**



deprotonation with sodium hydride and quenching with *O*-(diphenylphosphinyl)hydroxylamine (DppONH$_2$)[13] to afford isatin derivative **15**. Gratifyingly, treatment of **15** with aqueous sulfuric acid then produced the desired indazole core (**16**), which was most conveniently manipulated as its methyl ester (**17**).

The final ring-forming transformation was accomplished as shown in Scheme 4. Although a one-pot, double nucleo-

Scheme 4. Synthesis of **1**



philic displacement of dibromobutane by **17** was not successful, monoalkylation of **17** afforded regioisomer **18**[14] in good yield along with a small amount of both regioisomer **19** and double alkylation product **20**. Subsequent heating of **18** in anhydrous methanol effected cyclization of the third

(1) Chugai Pharmaceutical Co., Ltd., Japan, Japanese Patent 60004185, 1985; *Chem. Abstr.* **1985**, *102*, 220870.

(2) Atta-ur-Rahman; Malik, S.; He, C.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 2759−2762.

(3) Liu, Y.; Yang, J.; Liu, Q. *Chem. Pharm. Bull.* **2004**, *52*, 454−455.

(4) Atta-ur-Rahman; Malik, S.; Hasan, S. S.; Choudhary, M. I.; Ni, C. Z.; Clardy, J. *Tetrahedron Lett.* **1995**, *36*, 1993−1996.

(5) A SciFinder Scholar search leads to a Ph.D. thesis titled "The Total Synthesis of Three Natural Products: Nigellicine, Nigellidine, and Chilenone-A" (Guneratne, R. D., Cornell University, 1988), but the title is misleading since the thesis does not describe the synthesis of **1** nor **3**.

(6) For the synthesis of some monocyclic analogues of nigellicine, see: Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.* **2003**, *68*, 5977−5982.

(7) For a recent review see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.

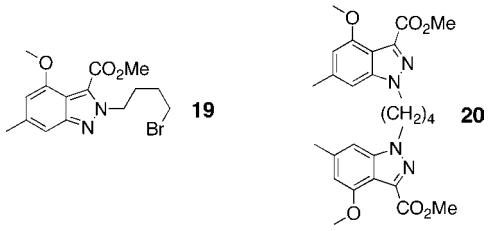
(8) (a) Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5397−5400. (b) Claudi F.; Giorgioni, J. G.; Di Stefano, A.; Abbracchio, M. P.; Paoletti, A. M.; Balduinio. W. *J. Med. Chem.* **1992**, *35*, 4408−4414. (c) Saari, W. S. (Merck), U.S. Patent 3671636, 1972; *Chem. Abstr.* **1972**, *77*, 88083.

(9) Regiochemistry confirmed by nOe difference spectra (see Supporting Information).

(10) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 3133−3135. (b) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205−213.

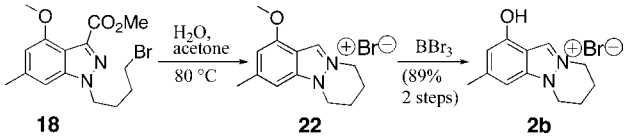
(11) Coleman, G. H. *Org. Synth.* **1964**, *I*, 442−445.

and final ring in the nigellicine core to afford bromide **21**. Removal of both methyl protecting groups from **21** with BBr_3 completed the total synthesis of **1**, with an overall yield of 18% in 12 steps from commercially available starting materials. The spectral properties (^1H NMR, ^{13}C NMR, and UV−vis) and melting behavior of synthetic **1** are in excellent agreement with those reported for the natural product.[15]



Originally, it was anticipated that **1** could be converted into **2** by heat-induced decarboxylation.[16] Attempts to achieve this transformation have, as yet, been unsuccessful.[17] It was discovered serendipitously, however, while attempting to convert **18** to **21** by heating in aqueous acetone, that not only did the expected cyclization occur (Scheme 5), but hydrolysis and decarboxylation also happened, to yield **22** directly. Demethylation of **22** with BBr_3 in refluxing methylene chloride afforded the hydrobromide salt **2b** in 89% yield from **18**. The ^1H, ^{13}C, and HMBC spectra of synthetic **2b** are in excellent agreement with those reported for naturally derived material.[18]

Scheme 5. Synthesis of Nigeglanine Hydrobromide (**2b**)



In summary, the present work provides the first synthesis of nigellicine and affirms the structure originally reported. This work also affords the first synthetic access to the nigeglanine alkaloid family and affirms its tricyclic core structure.

Acknowledgment. We thank Dr. J. Clardy[2,4] for helpful exchange of information.

Supporting Information Available: General information and experimental details and selected spectra for **8**, **9**, **12**−**18**, **21**, **1**, **22**, and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050769M

(12) (a) Snyder, H. R.; Thompson, C. B.; Hinman, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 2009−2012. (b) Buu-Hoi, N. P.; Hoeffinger, J. P.; Jacquignon, P. *J. Heterocycl. Chem*. **1964**, *1*, 239−241.

(13) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236−6239.

(14) Regiochemistry confirmed by 1D-NOESY (see Supporting Information).

(15) Some differences were noted between the IR spectrum of synthetic **1** and the IR of the natural product. An authentic sample of natural **1** was not available. See the Supporting Information for a tabulated comparison of the spectra of synthetic **1** and the natural material.

(16) For examples of the thermal decarboxylation of indazole-3-carboxylic acids see: (a) Behr, L. C.; Fusco, R.; Jarboe, C. H. In *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles, and Condensed Rings*; Wiley, R. H., Ed.; Chemistry of Heterocyclic Compounds, Vol. 22; Wiley: New York, 1967. (b) Borsche, W.; Diacont, K. *Justus Liebigs Ann. Chem.* **1934**, *510*, 287−296. (c) von Auwers, K. *Chem. Ber.* **1922**, *55*, 1141−1157.

(17) Unreacted starting material is recovered upon heating under neutral conditions up to 200 °C in a variety of solvents, at which point nonproductive decomposition occurs. Heating in 1 M HCl, on the other hand, yields unreacted starting material up to 150 °C, at which point nonproductive decomposition occurs.

(18) There is apparently a significant effect of the counterion and pH of **2** on spectra of this material. The ^1H NMR, ^{13}C NMR, and HMBC spectra of synthetic **2** as its HBr salt most closely match (and are in excellent agreement with: see the Supporting Information) the spectra reported for naturally derived **2**·H_2O. Despite that compelling congruence, the IR and UV−vis spectra of synthetic **2** are different (see the Supporting Information) from those reported for the natural material. Unfortunately, we have been unable to obtain an authentic sample of the natural material or spectra thereof, despite repeated acknowledged requests.