Natural Product Synthesis

A Mild and Efficient Synthesis of Oxindoles: Progress Towards the Synthesis of Welwitindolinone A Isonitrile**

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Recently, Moore and co-workers reported the isolation and structural elucidation of several oxindole-containing natural products from blue-green algae. Termed the welwitindolinones, this structurally intriguing class of alkaloids displays diverse and valuable biological properties, including multiple drug resistance (MDR) reversing, insecticidal, and antifungal activities.[1] To date, ten congeners have been identified, nine of which contain a 3,4-bridged oxindole core as exemplified by *N*-methyl welwitindolinone C isothiocyanate (**1**). Welwitindolinone A isonitrile (**2**) accounts for the antifungal activity associated with the extracts and is the proposed biosynthetic precursor to welwitindolinones B–D.[1a] Motivated by its antifungal activity, topological complexity, and the possibility of accessing other welwitindolinones (e.g. **1**), we targeted **2** for total synthesis. Herein we report a novel method for the preparation of spiro-oxindoles and its application in a synthesis of an advanced intermediate that contains the complete welwitindolinone A carbon framework.[2]

Recognizing that the sensitive vinyl isonitrile region found in **2** could potentially derive from a ketone, we began devising a synthetic approach that targeted **3** as a key intermediate (Scheme 1). For the construction of **3** we envisioned routes that, in a retrosynthetic sense, involved disconnection of either the C3–C_{aryl} bond (Scheme 1, bond a), or the C3–$C_{carbonyl}$ bond (bond b). Although ring formation by closure of bond a (i.e., **4** → **3**) was well precedented in either radical[3] or metal catalyzed modes,[4] concern over the thermal stability of the proposed cyclobutene intermediate and the likelihood that bond formation would occur on the convex face (thus delivering the incorrect stereochemistry at C3) led us to focus on strategies involving formation of bond b (i.e., **5**→**3**). To this end, Pd-catalyzed carbonylative cyclization of aniline **5a** ($R = NH_2$)[5] or radical cyclization of isonitrile **5b** ($R = NC$)[6] held potential; however, remaining

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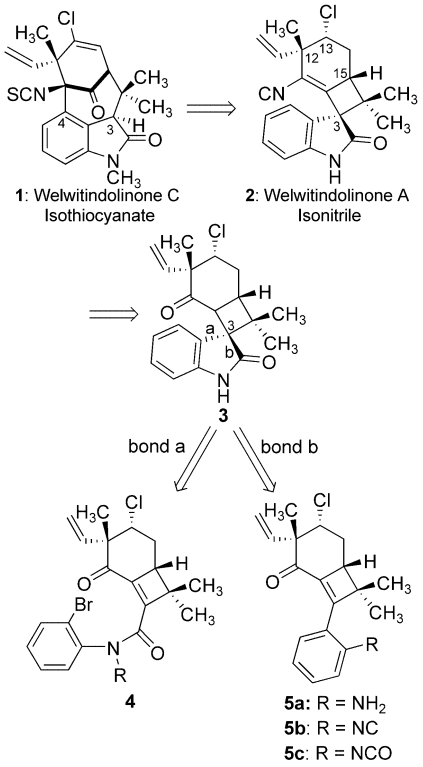
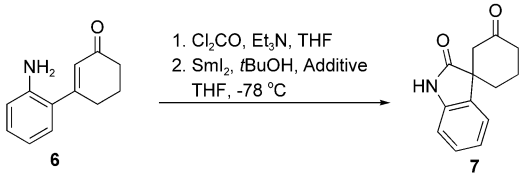


Scheme 1. Brief retrosynthetic analysis of welwitindolinone A isonitrile.

concerns regarding the stability of cyclobutenes to the prolonged heating required by these approaches led us to seek alternatives. Of particular interest in this regard was a recent report describing the SmI_2-mediated reductive coupling of acrylates with isocyanates to furnish amides.[7] In the context of a welwitindolinone synthesis, we anticipated that a similar reaction involving isocyanate **5c** would deliver spiro-oxindole **3** under reaction conditions that would be compatible with the sensitive cyclobutene.

To test the viability of the proposed SmI_2-mediated oxindole synthesis, aniline **6** was converted to its corresponding isocyanate and treated with SmI_2; unfortunately, only trace amounts of oxindole **7** were obtained (Table 1, entry 1).

Table 1: SmI_2-mediated synthesis of spiro-oxindoles.[a]



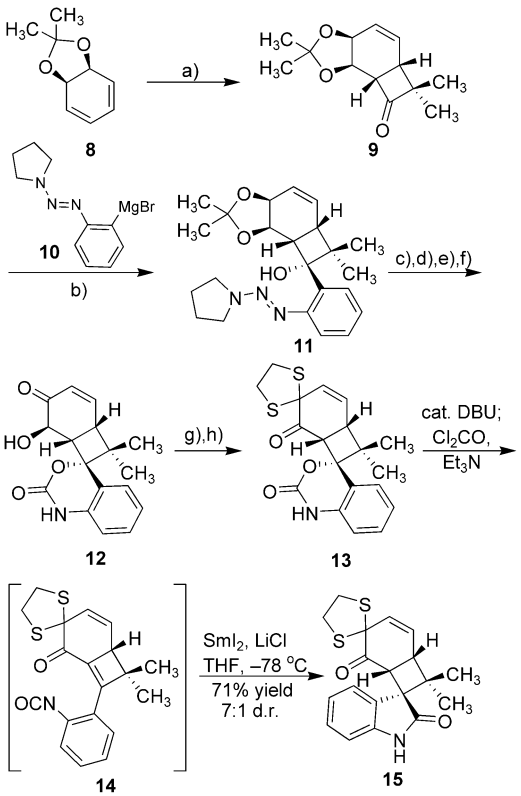
Entry	Additive	Yield [%][b]
1	None	5
2	NiI_2[c]	15
3	HMPA[d]	32
4	LiBr[e]	47
5	LiCl[e]	88

[a] Reactions carried out with 1 equiv **6**, 1 equiv *t*BuOH and 2.1 equiv SmI_2. [b] Yield of isolated product. [c] 0.05 equiv. [d] 6.2 equiv. [e] 8.4 equiv.

In an effort to improve the chemical yield, the effects of additives known to modulate the activity of SmI_2 were examined.[8] In contrast to conventional additives such as NiI_2 and HMPA (hexamethyl phosphoramide; entries 2,3), simple, nontoxic lithium salts provided substantially improved yields (entries 4,5). Thus, brief exposure (2 min) of the isocyanate derived from **6** to a mixture of SmI_2, LiCl, and *t*BuOH at −78 °C furnished the corresponding oxindole in 88% isolated yield (entry 5).[8c,9–11]

Having developed a new method for the synthesis of spiro-oxindoles, we turned towards preparing a fully elaborated cyclobutene-containing substrate that would be poised for conversion to **2**. As the point of departure, the readily available cyclohexadiene acetonide **8** was found to participate in an exquisitely stereo- and regioselective [2+2] cycloaddition that furnished **9** in excellent yield (Scheme 2).[12] Diastereoselective introduction of the requisite aryl amine was achieved through the aegis of ortho-metallated aniline **10**,[13] which proved uniquely effective for this transformation as attempts with numerous other aryl metal species led to enolization or decomposition.[14]

In ongoing studies, Grignard addition product **11** was routinely converted to α,β-unsaturated ketone **12** on multigram scale by an efficient four step sequence involving chemoselective reduction of the triazene, protection of the



Scheme 2. a) Isobutyryl chloride, Et_3N, THF (85% yield). b) **10**, THF, −78%°C (88% yield). c) Raney Ni, MeOH. d) 4-Nitrophenyl chloroformate, $NaHCO_3$, MTBE; 1 M NaOH. e) 60% AcOH/H_2O, reflux. f) Bu_2SnO, MeOH, reflux; NBS, $CHCl_3$ (73% yield, 4 steps). g) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, 0 °C. h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to −20 °C (46% yield, 2 steps). MBTE = methyl *tert*-butyl ether, NBS = *N*-bromosuccinimide, Cat. = catalyst.

resultant amino alcohol, acetonide removal, and selective oxidation of the allylic alcohol.[15] Although the derived ketone **12** provides a potential branch point for several synthetic end-games, our initial efforts have focused on applying our recently developed oxindole synthesis to this fully elaborated system.

To this end, protection of **12** as the corresponding dithiolane followed by oxidation of the secondary alcohol provided the masked cyclization substrate **13**.[16] Addition of 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU, 0.4 equiv) to a solution of **13** in THF effected the smooth elimination of CO_2 and provided an unstable β-(2-aminophenyl)-α,β-unsaturated ketone, which was converted to isocyanate **14** in the same reaction vessel (Cl_2CO, Et_3N). After removal of HCl salts by filtration, the isocyanate was exposed to a mixture of SmI_2 and LiCl at −78 °C. Chromatographic purification on silica gel furnished a 71 % yield of **15** as an inseparable 7:1 mixture of diastereomers. The major diastereomer was determined by NOE analysis to be appropriately configured for conversion to **2** (Scheme 1) and is consistent with bond formation on the less hindered, convex face of **14**.

Inspired by the unique and challenging structural features presented by the welwitindolinone alkaloids, we have discovered and developed a new SmI_2-mediated synthesis of spiro-oxindoles. This stereoselective reaction, in conjunction with a highly regio- and diastereoselective [2+2] cycloaddition provides efficient access to the carbon skeleton of welwitindolinone A isonitrile. These reactions serve as key steps in our ongoing total synthesis of this important natural product. The new reductive cyclization constitutes a significant expansion of the scope of SmI_2-mediated reactions, and suggests that other intramolecular cyclizations of α,β-unsaturated ketones may by possible. Results related to both areas of inquiry will be reported in due course.

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