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New Spirocyclic Oxindole Synthesis Based on a Hetero Claisen Rearrangement

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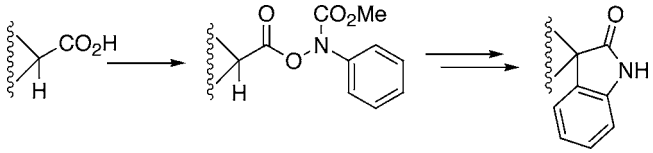
ABSTRACT



A new method for preparing spirocyclic oxindoles is presented. Featuring a [3,3]-sigmatropic enolate rearrangement, the three-step process converts carboxylic acid starting materials to oxidnole products in overall yields of 52−76%. The enolate rearrangement step occurs at −78 °C and provides easy access to oxindole products that have previously been difficult to prepare.

Incorporating the oxindole substructure into relevant alkaloids can be accomplished by several different general strategies. In some cases, particularly when an existing indole alkaloid is being converted to a related oxindole alkaloid in a semisynthetic process, it is sometimes possible to effect an oxidative ring contraction as was done in the conversion of the indole alkaloid gardnerine to the oxindole alkaloid gelsemicine.[1] In true total syntheses, some investigators have chosen to incorporate elements of the oxindole moiety into early-stage synthetic intermediates,[2] while other investigators have relegated the bulk of the oxindole construction to a late stage in their synthetic program.

1 **2**

With regard to the latter, such an approach can often require the net conversion of a cyclic ketone to a spirocyclic oxindole as illustrated by the conversion of tetracyclic ketone **1** to the alkaloid gelsemine (**2**). In fact, this specific transformation has been accomplished only once in a conceptually elegant but relatively inefficient manner.[3] Fleming has reported several other approaches to this problem, although their direct application to gelsemine or other oxindole alkaloids has not appeared.[4]

While considering alternative strategies to solve this problem, we were attracted by the possibility that a [3,3] sigmatropic rearrangement of an intermediate such as **3** (M = metal, $SiMe_3$) would produce a substituted aniline derivative such as **4** suitable for cyclization to spirocyclic product **5**. Formally related to the Fischer indole synthesis[5] and the Brunner oxindole synthesis,[6] this 3-aza-4-oxa-[3,3] sigma-

(1) (a) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1573−1578. (b) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327−1336.

(2) See, for example, (a) Fukyama, T.; Liu, G. *J. Am. Chem. Soc.* **1996**, *118*, 7426−7427. (b) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812−9824.

(3) (a) Sheikh, Z.; Steel, R.; Tasker, A. S.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 763−764. (b) Dutton, J. K.; Steel, R. W.; Tasker, A. S.; Popsavin, V.; Johnson, A. P. *J. Chem. Soc., Chem. Commun.* **1994**, 765−766.

(4) (a) Fleming, I.; Loreto, M. A.; Michael, J. P.; Wallace, I. H. M. *Tetrahedron Lett.* **1982**, *23*, 2053−2056. (b) Clarke, C.; Fleming, I.; Fortunak, J. M. D.; Gallagher, P. T.; Honan, M. C.; Nuebling, C. O.; Raithby, P. R.; Wolff, J. J. *Tetrahedron* **1988**, *44*, 3931−3944.

(5) (a) Fischer, E.; Jourdan, F. *Ber.* **1883**, *16*, 2241−2245. (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227−250.

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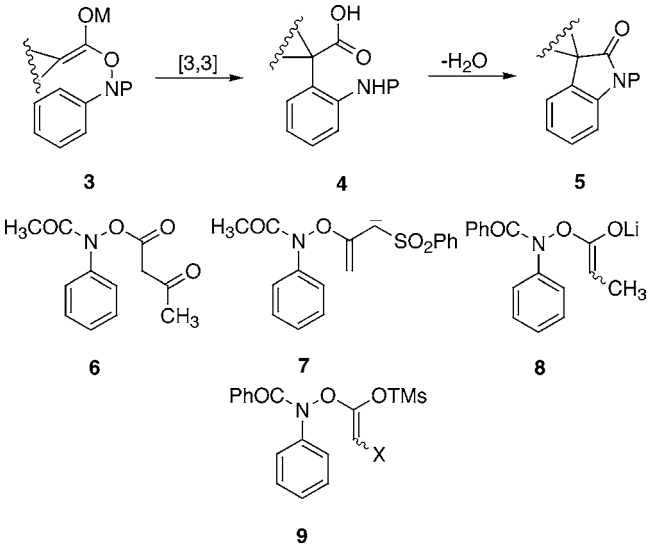
tropic process[7] is expected to be particularly facile because of anion acceleration when M = metal and the weak N−O bond.[8]

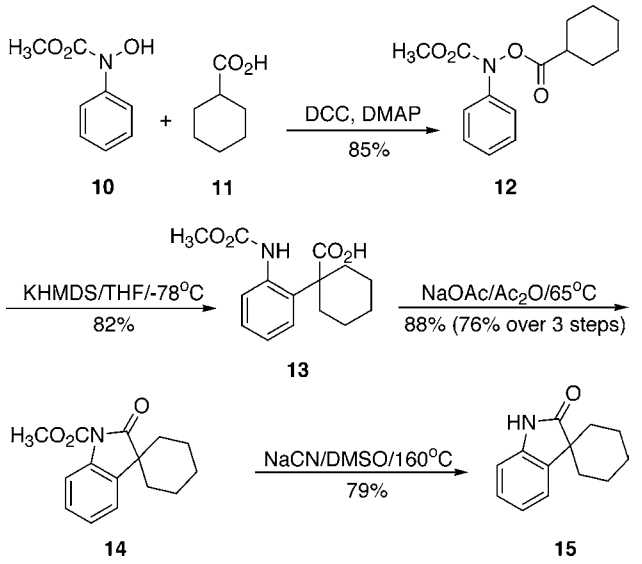


In fact, similar rearrangements have been previously reported. For instance, in 1977, Coates described the successful rearrangement of compound **6** at 110 °C (presumably through the enol tautomer),[9] and in 1984, Blechert reported a similar room-temperature rearrangement of stabilized anion **7**.[10] More recently, Endo has published the results of similar processes of which substrate **8** is typical.[11] Similarly, Prabhakar has reported the rearrangement of substrates such as **9**.[12] In the latter case, the authors suggested that the rearrangement worked best when the enolate X group could stablize an anion (Ph, SPh, double bond). None of the previous investigators, however, developed the reaction as a general route to spirocyclic oxindoles.

With the above as background, we have prepared a series of N,O-diacylated phenyl hydroxylamine derivatives designed to determine the feasibility of using this 3-aza-4-oxa [3,3] sigmatropic rearrangement to prepare spirocyclic oxindole derivatives. The overall transformation is illustrated for the conversion of cyclohexane carboxylic acid (**11**) to protected spiro oxindole **14** (Scheme 1).

Thus, DCC condensation of hydroxamic acid **10**[13] with cyclohexane carboxylic acid (**11**) afforded the O-acylated

Scheme 1



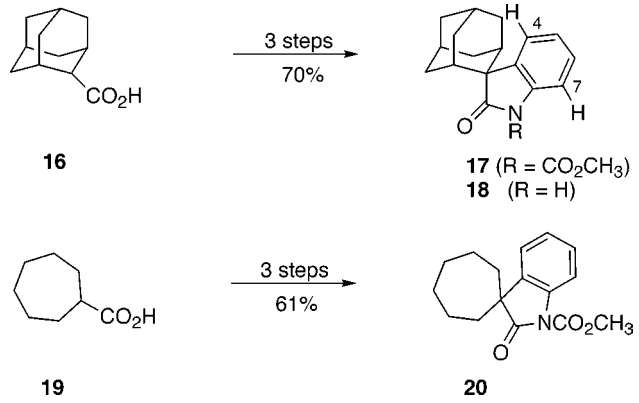
carbamate **12**. Treatment of **12** with potassium hexamethyldisilazide (KHMDS; 1.1 equiv) in THF at −78 °C followed by warming to room temperature afforded an 82% yield of a new product that was assigned the desired rearranged structure **13** on the basis of its spectral characteristics. Treatment of **13** with sodium acetate/acetic anhydride at 60−70 °C for 3 h then gave protected spirocyclic oxindole **14**. Carbonyl absorptions at 1794, 1762, and 1731 cm^{-1} are consistent with the assigned structure.[14] A one-proton doublet at δ 7.87 (J = 8.0 Hz) is assigned to the proton at position 7 of the protected spirocycle. Confirmation of the structure was obtained by removing the carbamate protecting group to afford lactam **15**, whose analytical characteristics were identical to those previously reported for this material.[4,15]

The [3,3] rearrangement takes place at low temperature. Thus, when the potassium enolate derived from **12** was allowed to stir at −78 °C for 1.5 h followed by quenching with cold methanol at that temperature, the only material observed in the ^{1}H NMR of the crude product mixture was rearranged **13**. Careful inspection of the crude spectra revealed no remaining starting material. Without purification of the two intermediate compounds, the three-step conversion of acid **11** to **14** was accomplished in 76% overall yield.

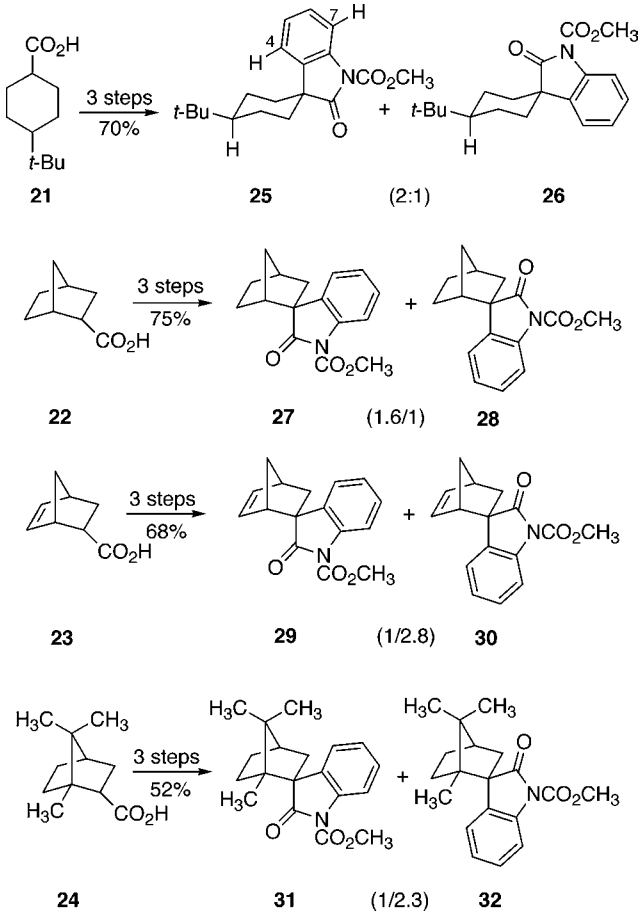
In a similar fashion, adamantane carboxylic acid (**16**) was converted in three steps to spirocyclic oxindole **17** (70% yield, unoptimized) and cycloheptane carboxylic acid (**19**) was smoothly transformed into the corresponding oxindole **20** (61% yield, unoptimized) (Scheme 2). In the case of the adamantane derivative, removal of the methyl carbamate (NaCN/DMSO; 160 °C; 2 h)[14b] afforded the previously reported lactam **18**.[4]

(6) Brunner, K. *Monatsh. Chem.* **1896**, *17*, 479−490.
(7) For a review of similar hetero [3,3] rearrangements, see: Blechert, S. *Synthesis* **1989**, 71−82.
(8) The bond dissociation energy of the N−O bond has been estimated to be approximately 43 kcal/mol (180 kJ/mol). Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 162.
(9) Coates, R. M.; Said, I. M. *J. Am. Chem. Soc.* **1977**, *99*, 2355−2357.
(10) Blechert, S. *Tetrahedron Lett.* **1984**, *25*, 1547−1550.
(11) (a) Endo, Y.; Hizatate, S.; Shudo, K. *Tetrahedron Lett.* **1991**, *32*, 2803−2806. (b) Uchida, T.; Endo, Y.; Hizatate, S.; Shudo, K. *Chem. Pharm Bull.* **1994**, *42*, 419. (c) Endo, Y.; Uchida, T.; Hizatate, S.; Shudo, K. *Synthesis* **1994**, 1096−1105.
(12) (a) Almeida, P. S.; Prabhakar, S.; Lobo, A. M.; Marcelo-Curto, M. J. *Tetrahedron Lett.* **1991**, *32*, 2671−2674. (b) Lobo, A. M.; Prabhakar, S. *Pure Appl. Chem.* **1997**, *69*, 547−552. (c) Santos, P. F.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Heterocycles* **2001**, *55*, 1029−1043.
(13) Aresta, M.; Berloco, C.; Quaranta, E. *Tetrahedron* **1995**, *51*, 8073−8088.
(14) (a) Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 11375−11380. (b) Morales-Rios, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron* **1996**, *52*, 5339−5348.
(15) Moore, R. F.; Plant, S. G. P. *J. Chem. Soc.* **1951**, 3475−3478.

Scheme 2



Scheme 3

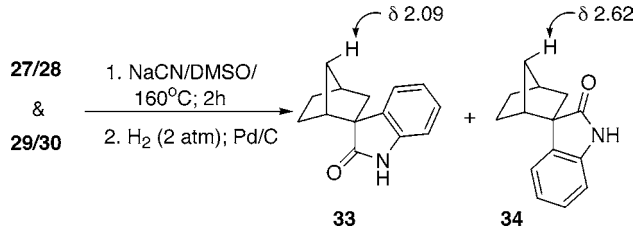


The stereochemistry of the spiroannelation process was next investigated. Carboxylic acids **21**−**24** (mixtures of isomers) were exposed to the three-step process described above for cyclohexane derivative **11** (Scheme 3). In all cases, the yields of the protected spirocyclic oxindoles were 50% or greater. *tert*-Butylcyclohexane derivative **21** was converted to a 2.0:1 mixture of spirocyclic isomers **25** and **26**, the ratio determined by the weights of the individual isomers isolated after flash chromatography.[16] The stereochemistry of the major isomer, **25**, was tentatively assigned to the isomer with an axial aryl substituent on the basis of the comparison of its ^{1}H NMR spectrum with that of adamantane derivative **17**.

A consistent feature of the ^{1}H NMR spectra of all of the carbamate-protected spirocycles reported herein is a one-proton doublet in the δ 7.8−8.0 range assignable to the H-7 proton of the aromatic oxindole ring. In adamantane derivative **17**, this doublet occurrs at δ 7.91 and is accompanied by a second one-proton doublet at δ 7.79 assignable to the H-4 proton. Situated proximate to and bifurcating two adamantane 1,3-diaxial protons, the H-4 proton of **17** is apparently significantly deshielded compared to those of **14** and **20**, which occur at ca. δ 7.35.

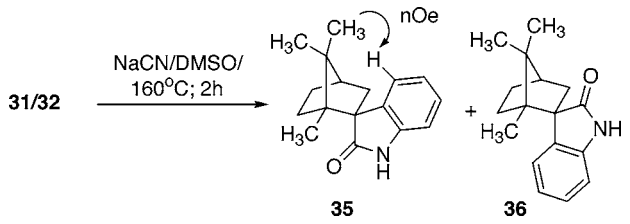
In the *tert*-butylcyclohexane series, the corresponding H-4 proton of the major isomer **25** is similarly situated with respect to two 1,3-diaxial cyclohexane protons, and as expected, the doublet for this proton occurs downfield at δ 7.52. The corresponding H-4 proton in minor isomer **26** is seen at δ 7.20, in accord with the H-4 doublets at δ 7.31 and 7.39 for oxindoles **14** and **20**, respectively.

Norbornane derivatives **22** and **23** also underwent efficient three-step spiroannelation processes to produce two pairs of diastereomers, **27**/**28** and **29**/**30**, respectively. In the case of norbornane carboxylic acid **22**, the major oxindole isomer **27** is the result of a [3,3] sigmatropic process occurring from the less hindered top face of the norbornane ring, while the major rearrangement isomer **30** from norbornene carboxylic acid **23** is the result of the [3,3] process occurring from the less hindered bottom face. The ratios of the diastereomers in these two cases were determined by converting each diastereomeric pair to the known unprotected spirooxindoles **33** and **34** that had been previously reported individually and unambiguously by Fleming.[4] Integration of ^{1}H NMR signals of the 7-syn protons in the two isomers (doublets, J = 10 Hz) provided the ratios reported above.



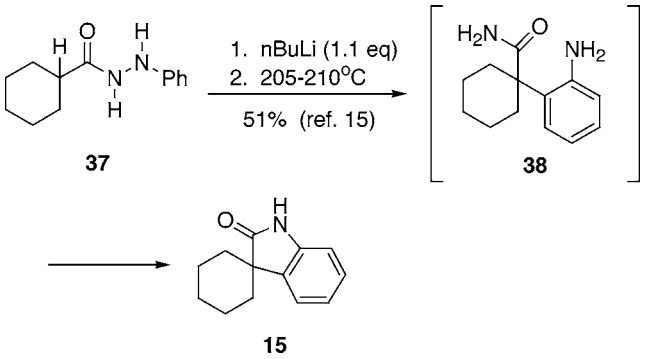
Exposure of the more sterically demanding camphor carboxylic acid **24** (mixture of endo and exo isomers) to the same sequence of reactions afforded the spiroannelated oxindoles **31** and **32** in 52% yield for the three steps. As with the norbornane isomers discussed above, the identities and relative amounts of the two product stereoisomers were determined by removal of the carbamate protecting group followed by careful chromatographic separation and weighing of the individual parent oxindoles **35** and **36**.

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.



Although oxindoles **35** and **36** have been previously reported,[17] neither had been isolated in pure form. Moreover, the previous structure assignments based on ^{1}H NMR experiments were ambiguous. Accordingly, each pure isomer was analyzed in an attempt to arrive at a secure structural assignment. Of particular interest was the observation that irradiation of the δ 1.45 methyl singlet (7-syn) in the minor isomer **35** led to significant NOE enhancement of the indole H-4 doublet at δ 7.26 (J = 7.6 Hz). This result is consistent with structure **35**, the result of [3,3] rearrangement from the more hindered exo face of the camphor molecule. No such NOE enhancements were observed on irradiation of the remaining five methyl singlets in major and minor isomers **35** and **36**. The major isomer **36**, therefore, arises as expected from a rearrangement process that occurs from the less hindered endo face of the camphor molecule.

It is interesting to compare the formation of spirocyclic oxindoles by the [3,3] sigmatropic rearrangement process described herein with the related Brunner oxindole synthesis. First reported in late nineteenth century,[6] the Brunner oxindole synthesis involves the treatment of acyl phenyl hydrazides with strong bases such as calcium oxide, calcium hydride, and sodium amide, among others, followed by heating to temperatures of 200 °C or higher.[18] For instance, in an optimized experimental procedure, the phenyl hydrazide of propanoic acid was mixed with calcium hydride and then heated to 230 °C to give a 41−44% yield of 3-methyloxindole.[19] In a more recent study of the reaction, it was reported that heating the preformed lithium salts (^{n}BuLi) of phenyl hydrazides to 205−210 °C led to improved yields in some cases.[17] Under these conditions, the spirooxindole **15** from cyclohexane carboxylic acid phenyl hydrazide **37** was formed in 51% yield.



By contrast, the [3,3] sigmatropic rearrangement reactions described here occur at −78 °C, nearly 300 °C lower than those of the Brunner oxindole reaction. In the synthesis of complex targets such as gelsemine (**1**), the more gentle reaction conditions are clearly preferred.

In summary, the rearrangements of the potassium enolates of N-protected *O*-acyl phenyl hydroxylamines occurs under mild conditions and with good efficiencies. The products are easily cyclized to spirocyclic oxindoles. The method is suitable for application to complex target molecules.

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Supporting Information Available: Typical experimental procedures and structural characterization data for compounds **12**−**14**, **17**, **20**, **25**−**32**, and **35**−**36** and ^{1}H NMR spectra for other compounds related to **12** and **27**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Wolff, J.; Taddei, M. *Tetrahedron* **1986**, *42*, 4267−4272.

(18) Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, 1970; p 362.

(19) Endler, A. S.; Beeker, E. I. *Org. Synth.* **1957**, *37*, 60−62.