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Substitution and Cyclization Reactions Involving the Quasi-Antiaromatic 2*H*-Indol-2-one Ring System

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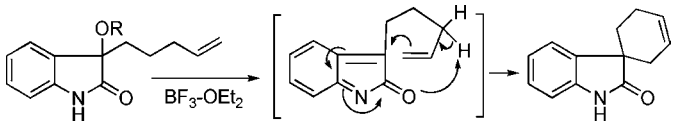
ABSTRACT



The quasi-antiaromatic 2*H*-indol-2-one ring system is readily generated by treating a 3-hydroxy-substituted 1,3-dihydroindol-2-one with a Lewis acid. Stepwise addition of various π-nucleophiles to the highly reactive 2*H*-indol-2-one system occurs smoothly to afford substituted oxindoles. The cyclization was also carried out in an intramolecular fashion to give spiro-substituted oxindoles in good yield.

Functionalized 1,3-dihydroindol-2-ones (oxindoles) represent the core structure of many important pharmacological agents and natural products.[1] For example, the oxindole motif is present in the anti-Parkinson's drug ropinirole,[2] in non-opioid nociceptin receptor ligands,[3] and in the growth hormone secretagogues.[4] In addition, the oxindole moiety constitutes a key structural element in several natural products,[5] including the antibiotic speradine[6] and the cytostatic welwistatin.[7] Consequently, the development of novel synthetic strategies leading to 3,3-disubstituted oxindole derivatives is of paramount importance. Various methods have been developed for the construction of this ring system. Among the techniques commonly used in their synthesis are derivatization of other heterocycles,[8] intramolecular Heck reactions,[9] arylation of amides,[10] and variants of the Stolle reaction.[11] The synthesis of oxindoles has also been carried out by using the Friedel−Crafts reaction,[12] the Gassman sulfonium ylide reaction,[13] photoinduced[14] and radical cyclizations,[15] as well as transition-metal-catalyzed reactions.[16] Even though a variety of methods are available, simple and efficient approaches toward 3,3-disubstituted oxindoles still remain scarce. In connection with our current studies dealing with

(1) (a) Akai, S.; Tsujino, T.; Akiyamna, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478. (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (c) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193. (d) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.

(2) Gallagher, G.; Lavanchi, P. G.; Wilson, J. W.; Hieble, J.; Demmarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533.

(3) Zaveri, N. T.; Jiang, F.; Olsen, C. M.; Deschamps, J. R.; Parrish, D.; Polgar, W.; Toll, L. *J. Med. Chem.* **2004**, *47*, 2973.

(4) Nagata, R.; Tokunaga, T.; Hume, W.; Umezone, T.; Okazaki, U.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H. *J. Med. Chem.* **2001**, *44*, 4641.

(5) Thiericke, R.; Tang, Y. Q.; Sattler, I.; Grabley, S.; Feng, X. Z. *Eur. J. Org. Chem.* **2001**, 261.

(6) Tsuda, M.; Mugishima, T.; Komatzu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Shiro, M.; Hirai, M.; Ohizumii, Y.; Kobayashi, J. *Tetrahedron Lett.* **2003**, *59*, 3227.

(7) Zhang, X.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288.

(8) Sundberg, R. J. *Indoles*; Academic Press: London, UK, 1996; Vol. 17, pp 152−154.

(9) (a) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8G. (b) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, *17*, 1807. (c) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

(10) (a) Kametani, T.; Ohsawa, T.; Ihara, M. *Heterocycles* **1980**, *14*, 277. (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (c) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546.

(11) Sumpter, W. C. *Chem. Rev.* **1945**, *37*, 443.

(12) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093.

(13) Gassman, P. G.; Gruetzmacher, G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5512.

(14) (a) Wolfe, J. F.; Sleevi, M. C.; Goehring, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 3646. (b) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435.

(15) (a) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657. (b) Bowman, W. R.; Heaney, H.; Jordon, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657. (c) Jones, K.; Wilkinson, J.; Edwin, R. *Tetrahedron Lett.* **1994**, *35*, 7673. (d) Cabri, W.; Candiani, I.; Colombo, M.; Franzii, L.; Bedeschi, A. *Tetrahedron Lett.* **1995**, *36*, 949.

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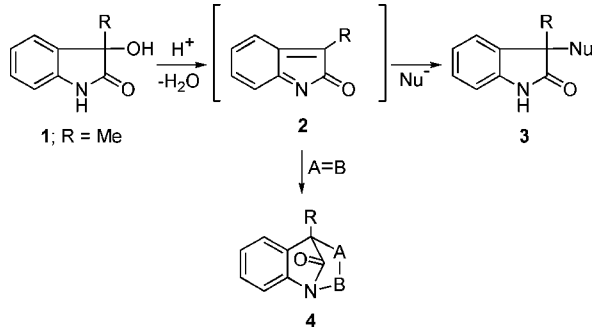
the synthesis of indole alkaloids,[17] we describe herein an approach to diversely functionalized oxindoles starting from the commercially available isatin.

Substituted 3-hydroxyindolin-2-ones can readily be prepared by treating 2,3-indolinediones (isatins) with a variety of organometallic reagents.[18,19] We reasoned that treatment of these compounds (i.e., **1**) with a Lewis acid would result in an overall dehydration and afford a transient 2*H*-indol-2-one (i.e., **2**) as a species that could be reactive toward various nucleophiles to give 3,3-disubstituted oxindoles of type **3** (Scheme 1). We were particularly interested in

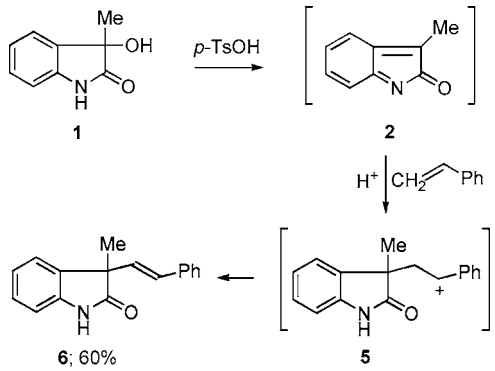
Scheme 1



trapping the labile quinone methide imine **2** with activated dienophiles with the hope that a Diels−Alder cycloadduct of type **4** would be obtained. Such a [4+2]-cycloaddition has recently been suggested to be involved in the biosynthesis of the alkaloid communesin B.[20,21] Since there have been no other reported examples of the Diels−Alder reaction of 2*H*-indol-2-ones in the literature,[22] we thought it would be worthwhile to study this intriguing and potentially useful cycloaddition reaction.

Our initial investigations involved the use of styrene as the added 2π-substrate. Heating a sample of **1** (R = Me) with a 10 M excess of styrene in toluene at reflux in the presence of catalytic *p*-toluenesulfonic acid afforded 3-methyl-3-styryl-1,3-dihydroindol-2-one (**6**) in 60% yield as the only isolable product (Scheme 2). The formation of **6** is best rationalized by addition of the terminal π-bond of styrene

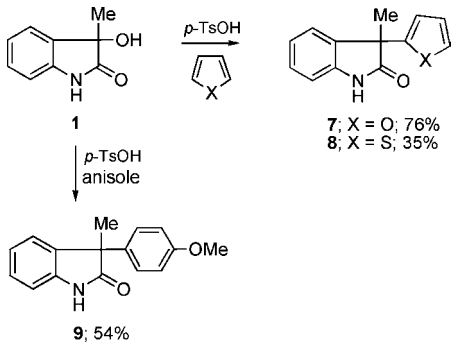
Scheme 2



onto the highly reactive 2*H*-indol-2-one intermediate **2** followed by a deprotonation of the resulting carbocation intermediate **5**.[23]

Apparently, the stepwise addition of the olefinic π-bond to the quasi-antiaromatic 2*H*-indol-2-one species is preferred over the [4+2]-cycloaddition reaction. A series of additional experiments showed that this electrophilic-induced substitution reaction proceeds with a variety of substrates containing activated π-bonds. Thus, we were pleased to find that an analogous substitution reaction occurred using furan, thiophene, and anisole as added nucleophilic π-substrates. Oxindoles **7**, **8**, and **9** were isolated in good yields for these three systems (Scheme 3).

Scheme 3



Spirocyclic compounds correspond to systems containing one carbon atom common to two rings and are structurally quite interesting entities.[24] Among them, the heterocyclic spiro-oxindole framework is an important structural motif in biologically relevant compounds as both natural products and pharmaceuticals.[25] Due to our ongoing interest in the chemistry of indole alkaloids,[17] we decided to expand the

(16) (a) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017. (b) Ali, B. E.; Okura, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264. (c) Brown, D. S.; Elliott, M. C.; Moody, C. J.; Mowlem, T. J.; Marino, J. P., Jr.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 2447. (d) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.

(17) Mejía-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275.

(18) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 3198.

(19) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem. Chim. Ther.* **1981**, 373.

(20) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203.

(21) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068.

(22) (a) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637. (b) Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449.

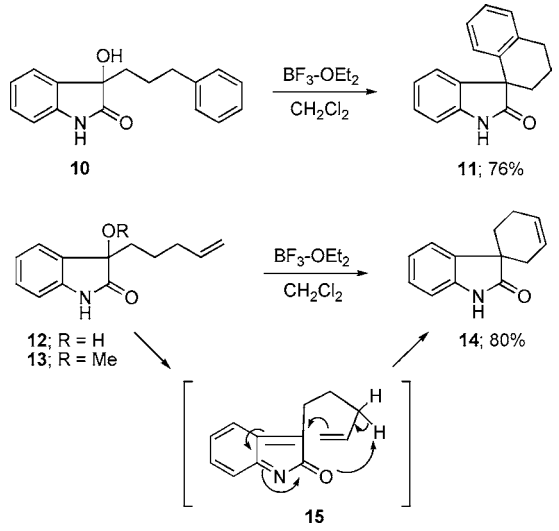
(23) A reviewer has pointed out that while the mechanism shown in Scheme 2 is not unreasonable, there is no real evidence for the proposed electrophilic addition of **2** to alkenes. An alternative possibility could involve an initial dehydration of **1** with acid to produce a reactive benzylic cation that would then undergo stepwise addition of styrene to eventually give **6**. We found, however, that the *N*-methyl analogue of **1** did not undergo the substitution reaction with styrene and this observation provides good support for the requirement of a 2*H*-indol-2-one intermediate (i.e. **2**).

(24) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

(25) (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz Chem. Soc.* **2001**, 273.

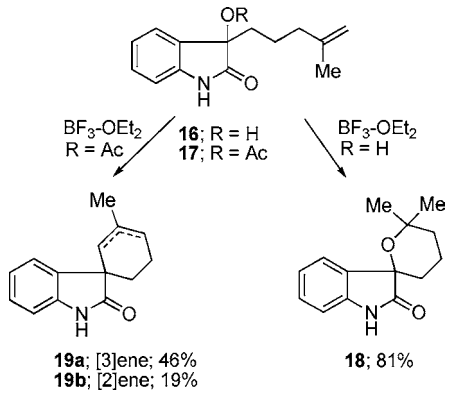
scope of the synthetic methodology outlined above and apply the method toward the cyclization of several 3-hydroxy-substituted oxindoles bearing unsaturated side chains. The exploitation of cationic π-cyclizations for the construction of polycyclic ring systems has been the object of intense study since the early 1950s.[26] Initial forays into this arena demonstrated the syntheses of fused ring terpenoid-type systems, and later efforts were also carried out for the syntheses of spiro and bridged ring carbocyclic systems.[27] For our methodological studies into the formation of spiro-oxindoles, we selected to investigate some very simple core systems. Our initial inquiry was the study of the cyclization reaction of 3-hydroxy-3-(3-phenylpropyl)-1,3-dihydroindol-2-one (**10**). We found that **10** could be converted into spiro-oxindole **11** in 76% yield upon heating with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at reflux.[28] A related acid-catalyzed cyclization with 3-hydroxy-3-pent-4-enyl-1,3-dihydroindole-2-one (**12**) also proceeded under similar conditions. Most interestingly, a single cyclized product was obtained in 80% isolated yield. Extensive NMR studies showed that the product corresponded to spiro-oxindole **14** (Scheme 4). One possibility

Scheme 4



to account for the high specificity associated with this particular cyclization is that the reaction occurs via a pseudo-ene type process that involves 2*H*-indol-2-one **15**. This pathway avoids the formation of a highly reactive secondary carbocation intermediate. Such an intermediate would have been expected to produce a mixture of regioisomeric spiro-oxindoles (vide infra). The identical cyclized product (i.e., **14**) was also formed from the acid-catalyzed reaction of the corresponding methyl ether **13**. Interestingly, the reaction of (4-methylpent-4-enyl)indolone **16** with $BF_3{\cdot}OEt_2$ did not produce the expected spirocyclic oxindole **19**, giving instead the cyclic tetrahydro-2*H*-pyran **18** in 81% yield as the exclusive product (Scheme 5). In retrospect, this result is

Scheme 5



not totally unexpected as protonation of the more activated olefinic π-bond leads to a stable tertiary carbocation and this path occurs in preference to formation of the 2*H*-indol-2-one intermediate. However, if **16** is first converted into the corresponding acetate **17**, the spiro-substitued oxindole **19** is indeed formed (65%) by a pathway involving attack of the olefinic π-bond onto the transient indol-2-one intermediate. In this case, a 2.5:1 mixture of regioisomeric alkenes (**19a**/**19b**) is produced and this result is consistent with a mechanism for cyclization proceeding via a distinct tertiary carbocation intermediate.

In summary, we have demonstrated the utility of the quasi-antiaromatic 2*H*-indol-2-one system for the synthesis of substituted oxindole derivatives. The highly reactive indol-2-one behaves more like an electrophilic π-acceptor than a reactive diene. The mechanistic details of the π-cyclization reaction seem to depend on the nucleophilicity of the attacking olefin. When a 4-pentenyl group is attached to the lactam ring, the cyclization seemingly proceeds in an ene-like fashion with assistance from the amide carbonyl group and this leads to a single cyclized spiro-oxindole as the product. The formation of a mixture of regioisomeric products from a tethered 4-methylpent-4-enyl group is more consistent with the involvement of a distinct carbocation intermediate. Further investigations are currently underway to exploit 2*H*-indol-2-ones as useful substrates for alkaloid synthesis and our future findings will be reported in due course.

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Supporting Information Available: Complete description of experimental details and product characterization of all new compounds together with photocopies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Sutherland, J. K. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 3, p 341.

(27) (a) Haring, S. R.; Livinghouse, T. *J. Org. Chem.* **1997**, *62*, 6388. (b) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765.

(28) Identical products were obtained in essentially the same yield by carrying out the intramolecular cyclization reaction with catalytic *p*-toluenesulfonic acid in toluene at 100 °C.