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The Use of Sulfur Ylides in the Synthesis of Substituted Indoles

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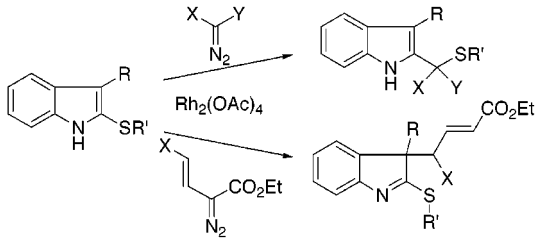
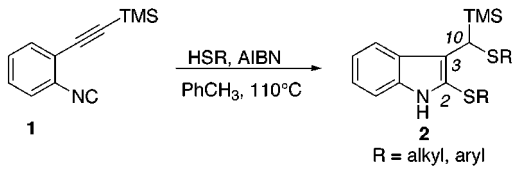
ABSTRACT

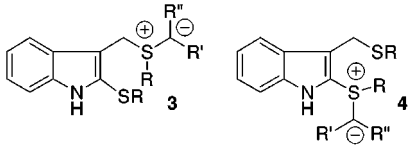


This letter describes the insertion of rhodium carbenoids into thioindoles. C-10 thioindoles undergo fragmentation–coupling reactions when exposed to rhodium carbenoids. In an analogous fashion, ketoester- and malonate-substituted carbenoids have been found to insert into C-2 thioindoles. In contrast, vinylogous carbenoids were found to alkylate C-2 thioindoles at C-3.

The presence of highly substituted indoles in a number of architecturally and biologically interesting natural and non-natural products[1] continues to inspire chemists to develop new and improved routes to their synthesis.[2] Our contribution to this area has been the synthesis of 2,10-dithioindoles from aryl isonitrile free radical cyclizations.[3]



We became fascinated with the notion that dithioindoles (**2**) might serve as versatile precursors to highly functionalized indole ring systems. As an illustration of this, we recently described the use of **2** in fragmentation−coupling reactions with active hydrogen compounds.[4] In an effort to further demonstrate the synthetic potential of **2**, we became interested in other thioether coupling protocols.[5] Among the possibilities, the selective formation of a sulfur ylide (e.g., **3** or **4**) seemed appealing, as it might lead to the insertion of a carbon atom into the C−S bond.[6,7] The possibility of generating the ylide using metal carbenoid chemistry made this proposal all the more attractive to us, as it presented us with the possibility of carrying out these transformations in an asymmetric fashion.[8,9] Described herein are our investigations laying the foundation for the use of dithioindoles in sulfur ylide rearrangement reactions.



To simplify our initial investigations we opted to focus our efforts on the intramolecular ylide chemistry of a

(1) (a) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155.
(2) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.
(3) Rainier, J. D.; Kennedy, A. R.; Chase, E. *Tetrahedron Lett.* **1999**, *40*, 6325.
(4) Rainier, J. D.; Kennedy, A. R. *J. Org. Chem.* **2000**, *65*, 6213.
(5) We have recently utilized KF and 18-C-6 to couple dithioindoles with active hydrogen compounds. Rainier, J. D.; Kennedy, A. R., unpublished work.
(6) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for the Synthesis with Diazo Compounds*; Wiley: New York, 1998.
(7) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223.
(8) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.
(9) Davies, H. M. L. *Eur. J. Org. Chem* **1999**, 2459.

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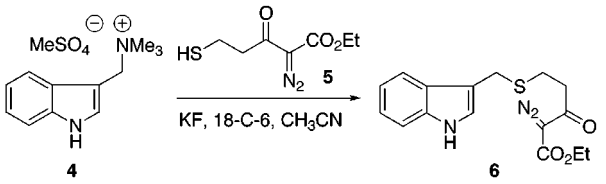
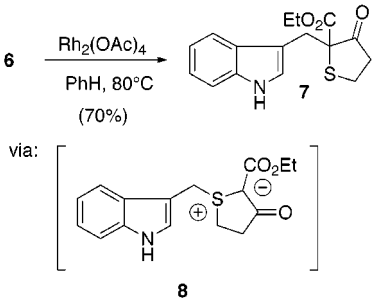
substrate lacking the C-2 thioether and settled upon **6**. Diazoketoester **6** was generated from the coupling of methylated gramine with thiol **5**[10] by employing KF and 18-C-6. Exposure of **6** to $Rh_2(OAc)_4$ resulted in diazo decomposition and the formation of coupled product **7** in 70% yield.

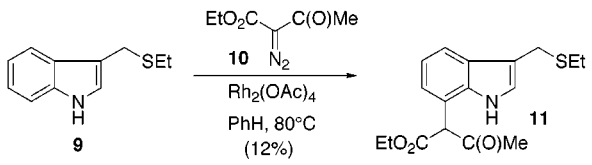


Presumably **7** is the result of the intramolecular formation of sulfur ylide **8** followed by a subsequent elimination−coupling reaction. Alternatively, **7** could result from a Stevens-type [1,2]-shift of **8**.[11]

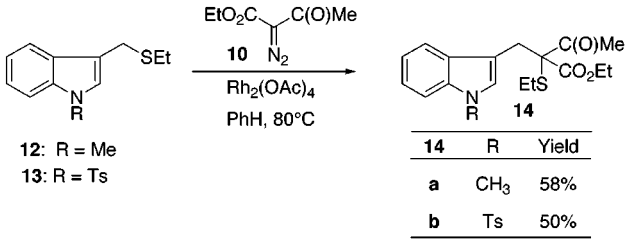


Having demonstrated the feasibility of our approach in an intramolecular sense, we decided to pursue the analogous intermolecular reactions. As 3-ethylthiomethylindole had been found to be immune to traditional fragmentation−coupling conditions,[12] the success of these experiments would allow us and others to utilize indoles other than gramine and methylated gramine in fragmentation−coupling reactions.[13]

In the event, exposure of C-10 thioether **9** to diazoketoester **10**[14] and $Rh_2(OAc)_4$ resulted in a low yield of the C-7 C−H insertion product **11**.[15]

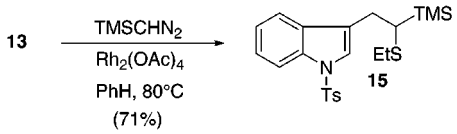


From the notion that the indole nitrogen was interfering with the formation of a C-10 sulfur ylide, we synthesized the corresponding *N*-methylindole **12**. When **12** was exposed to **10** and $Rh_2(OAc)_4$, we isolated coupled product **14a** in an unoptimized 58% yield. In an analogous fashion, we isolated **14b** in 50% yield when sulfonamide **13** was exposed to **10** and $Rh_2(OAc)_4$.

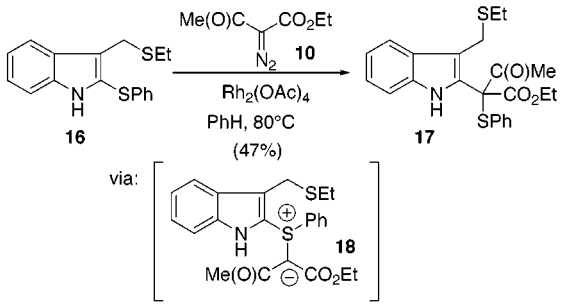


14	R	Yield
a	CH_3	58%
b	Ts	50%

Similarly, we isolated indole **15** in 71% yield when **13** was subjected to TMS diazomethane and $Rh_2(OAc)_4$. These experiments clearly demonstrate that unactivated C-10 thioindoles are amenable to fragmentation−coupling reactions when sulfur ylides are involved.

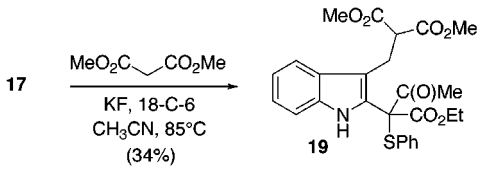


With the success of our experiments with the C-10 thioindoles, we turned our attention to 2,10-dithioindoles. We synthesized dithioindole **16** with the notion that the C-2 thioether would be much less reactive than the corresponding C-10 thioether in intermolecular ylide forming reactions.[16] That is, since the lone pairs on the C-2 sulfur are conjugated with both the indole and the phenyl group, we reasoned that they should be less available for attack onto the Rh carbenoid. Therefore, we were surprised to isolate the C-2 insertion product **17** in 47% yield as the only identifiable product when **16** was exposed to diazo-β-ketoester **10** and $Rh_2(OAc)_4$. Presumably, **17** results from the formation of sulfur ylide **18** followed by a subsequent Stevens-type [1,2]-alkyl shift.



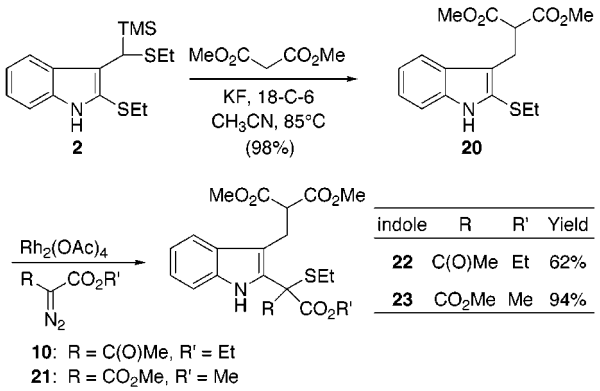
To illustrate the potential that these reactions and substrates bring to the synthesis of substituted indoles, we carried out an elimination−coupling reaction on **17** with dimethyl malonate using our KF, 18-C-6 conditions. This resulted in the formation of the highly substituted indole **19**.

(10) Moyer, M. P.; Feldman, P. L.; Rappaport, H. *J. Org. Chem.* **1985**, *50*, 5223.
(11) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1988**, *29*, 6005.
(12) Poppelsdorf, F.; Holt, S. J. *J. Chem. Soc.* **1954**, 4094.
(13) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* **1981**, *16*, 941.
(14) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.
(15) The remainder of the identifiable material from the reaction consisted of starting material (47%) and what we have tentatively assigned as the C-2 C−H insertion product (ca. 3%).
(16) Compound **16** comes from the coupling of EtSH with the corresponding 2-thiophenyl-3-phenylthiomethylindole.



As the generation of **17** and **19** represents a novel and potentially important entry into 2,3-disubstituted indoles, we decided to further examine the C-2 thioether insertion chemistry. To best utilize both the C-2 and C-10 thioethers, we decided to reverse the order of the C−C bond-forming reactions. The coupling of **2** with dimethyl malonate using KF and 18-C-6 resulted in the formation of **20** in 98% yield. As an aside, this experiment illustrates the importance of the C-2 thioether in elimination−coupling reactions. The reaction of **17** with dimethyl malonate using the same conditions was much less efficient. Thioether **20** was exposed to diazocarbonyls **10** and **21**[14] in the presence of $Rh_2(OAc)_4$. In both instances sulfur ylide formation was followed by a Stevens-type [1,2] shift to provide C−S insertion products **22** and **23** respectively.

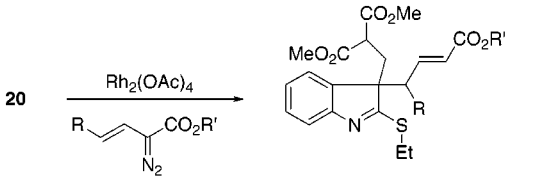
Scheme 1



indole	R	R'	Yield
22	C(O)Me	Et	62%
23	CO_2Me	Me	94%

In addition to ketoester- and malonate-substituted diazo compounds, we have examined the reactions of vinyl diazoacetates **24**,[17] **25**,[20] and **26**[18] with **20**. Interestingly, when decomposed with $Rh_2(OAc)_4$ these provided thioimidates **27**, **28**, and **29**, respectively. Thioimidates **28** and **29** were both formed as a 2:1 mixture of diastereomers. These reactions caught our attention as they might represent a novel entry into bioactive indoles containing quaternary substitution at C-3 (e.g., amouramine, spirotryprostatins).

Scheme 2



24: R = H, R' = *t*-Bu

25: R = Me, R' = Et

26: R = CO_2Et, R' = Et

Thioimidate	R	R'	Yield
27	H	*t*-Bu	88%
28	Me	Et	93%
29	CO_2Et	Et	82%

Presumably, **27**−**29** result from either the conjugate addition of **20** onto the respective rhodium carbenoids[19] or from the formation of an intermediate sulfur ylide followed by a [3,3]-sigmatropic rearrangement. These transformations are reminiscent of the vinylogous rhodium carbenoid couplings with electron-rich olefins that have emanated from the Davies laboratories.[20]

From the experiments that have been outlined in this manuscript, it is clear that thioindoles are valuable substrates in synthetic chemistry. We had previously demonstrated this through novel elimination−coupling reactions. This letter has described a continuation of these studies and several interesting transformations. These include the use of C-2 and C-10 thioethers in C−S insertion reactions with rhodium carbenoids. We have also found that C-2 thioethers undergo alkylation reactions at C-3 with vinylogous rhodium carbenoids. Our current investigations in this area are focused on optimizing the reactions that we have discovered, utilizing asymmetric carbenoids in these reactions, and using the products of these transformations in the synthesis of bioactive indole-containing natural products.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Davies, H. M. L.; Hougland, P. W.; Cantrell, W. R., Jr. *Synth. Commun.* **1992**, *22*, 971.

(18) Davies, H. M. L.; Clark, D. M.; Alligood, D. B.; Eiband, G. R. *Tetrahedron* **1987**, *43*, 4265.

(19) We quantitatively reisolated starting material when **20** was subjected to unsubstituted vinyl diazoester **24** in the absence of $Rh_2(OAc)_4$.

(20) (a) Davies, H. M. L.; Hu, B.; Saikali, E.; Bruzinski, P. R. *J. Org. Chem.* **1994**, *59*, 4535. (b) Davies, H. M. L.; Saikali, E.; Young, W. B. *J. Org. Chem.* **1991**, *56*, 5696.