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Extending Pummerer Reaction Chemistry. Application to the Oxidative Cyclization of Indole Derivatives

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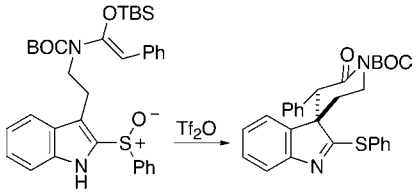
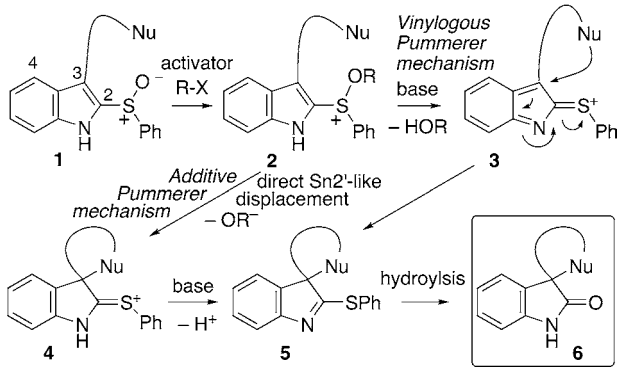
ABSTRACT



Treatment of 2-(phenylsulfinyl)indoles bearing a pendant nucleophile at C(3) with Tf_2O/lutidine triggers a Pummerer-like cyclization to furnish 3,3-spirocyclic-2-(phenylthio)indolenine products, which can, in turn, be hydrolyzed to 3,3-spirocyclic oxindoles.

The development of a new strategy for the synthesis of 3,3-spirosubstituted oxindoles **6** via regioselective cyclization of 3-substituted 2-(phenylsulfinyl)indoles **1** is described, Scheme 1. This indirect oxidative cyclization sequence evolved from the recognition that direct oxidative cyclization onto C(3) of the indole nucleus is often frustrated by low yields, insufficiently controlled regiochemistry, and product over-oxidation.[1] A new twist on the venerable Pummerer reaction[2] serves as the pivotal transform that both enforces complete regioselectivity upon cyclization and ensures that the oxidation-sensitive product survives unscathed. Oxidation is confined to the sulfur atom in the sulfide precursor to **1**, and since oxidation and cyclization are now two separate events, there is no possibility for undesired product (over)-oxidation. A priori, two limiting mechanisms, termed vinylogous and additive,[3] can be posited for this sequence. These pathways differ principally by whether the leaving group OR in **2** is discharged prior to (vinylogous), or simultaneously

Scheme 1. Extended Pummerer-Mediated Functionalization of Indole C(3): A New Approach to 3,3-Disubstituted Oxindoles



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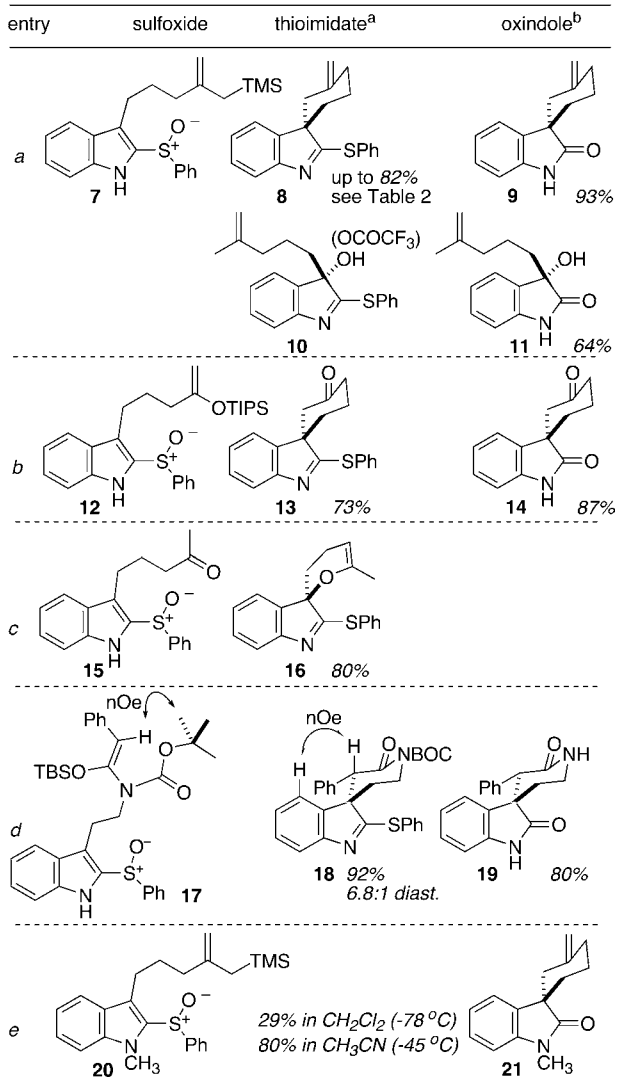
(1) (a) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397−4408. (b) Somei, M.; Noguchi, K.; Yamagami, R.; Kawada, Y.; Yamada, K.; Yamada, F. *Heterocycles* **2000**, *53*, 7−10. (c) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 4685−4693. (d) Irikawa, H.; Mutoh, S.; Uehara, M.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3031−3033. (e) Güller, Borschberg, H.-J. *Helv. Chim. Acta* **1993**, *76*, 1847−1862.

(2) (a) Moiseen, A. M.; Dragan, V. A.; Veselovskii, V. V. *Russ. Chem. Rev.* **1991**, *60*, 643−657. (b) de Lucchi, O.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1991; Vol. 40, pp 157−405. (c) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353−1377.

(3) Leading references to additive and vinylogous Pummerer reactions can be found in: (a) Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256−4268. (b) Shibata, N.; Fujimori, C.; Fujita, S.; Kita, Y. *Chem. Pharm. Bull.* **1996**, *44*, 892−894. (c) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566−5572.

Table 1. Examples of 3,3-Disubstituted Oxindole Synthesis via Extended Pummerer Reaction of 2-(Phenylsulfinyl)indoles



[a] Conditions: **7**, see Table 2; **12**, **15**, **17**, Tf_2O, 2,6-lutidine CH_2Cl_2, −75 °C; **20**, Tf_2O, 2,6-lutidine, indicated solvent/temperature. [b] Conditions: **9**, CAN, H_2O; **10**, **13**, **18**, $HgCl_2$, H_2O.

with (additive), nucleophilic attack. In either circumstance, the transposition of "oxidation" results in electrophilic activation at C(3) (cf. **1** → **2** or **3**). This electrophilicity can be quenched through internal trapping by a pendant nucleophilic atom to provide a thioimidate product **5** en route to the ultimate spirocyclic oxindole product **6**. Nucleophilic addition at other accessible and conceivably electrophilic sites in **2** or **3** such as C(2) or C(4) is likely to be dissuaded by the loss of aromaticity upon bond formation. In this way, the regiochemistry of nucleophile addition is assured.

A search to uncover carbon-based nucleophiles that would tolerate both sulfoxide formation and subsequent Pummerer reaction began with the allylsilane sulfoxide **7**, Table 1. Exposure of this sulfoxide to either of the two common Pummerer activators, triflic anhydride (Tf_2O) or trifluoroacetic anhydride (TFAA), in the presence of a variety of bases in moderately polar to nonpolar solvents at low

Table 2. Variation in Yield of **8** and **10** upon Attempted Pummerer-Initiated Cyclization of Indole Allylsilane Sulfoxide **7**

entry	activator	base	temp (°C)	solvent	**8**[a] (%)	**10**[a] (%)
1	TFAA	*i*-Pr_2NEt	−40	CH_2Cl_2		64
2	TFAA	DTBP[b]	−75	CH_2Cl_2		58
3	Tf_2O	*i*-Pr_2NEt	−75	toluene	<5	
4	Tf_2O	*i*-Pr_2NEt	−75	Et_2O	42	19
5	Tf_2O	*i*-Pr_2NEt	−75	CH_2Cl_2	30	
6	Tf_2O	DTBP	−75	CH_2Cl_2	56	
7	Tf_2O	2,6-lutidine	−75	CH_2Cl_2	82	

[a] Yields reported are for chromatographically pure, characterized material. [b] DTBP = 2,6-di-*tert*-butylpyridine.

temperature led to varying amounts of the desired spiromethylenecyclohexane 2-(phenylthio)indolenine **8**, Table 2. These optimization studies revealed that use of 2 equiv of Tf_2O and 3 equiv of 2,6-lutidine with 0.005 M substrate in CH_2Cl_2 at −75 °C afforded the highest yield of the desired spirocyclic product. Interestingly, use of TFAA as an activator provided only the trifluoroacetate-trapped product, isolated as the unstable alcohol **10** after SiO_2-induced trifluoroacetate hydrolysis or solvolysis upon attempted chromatographic purification (Table 2, entries 1−2). It appears that the electrophilicity at C(3) of the indole core (cf. **3**) is expressed under these conditions, but then the weak nucleophile trifluoroacetate surprisingly out-competes the pendant alkene nucleophile (allylsilane or propenyl; the timing of TMS loss is not known) for this reactive intermediate. The hydrolysis of the thioimidate function of **8** proceeded in higher yield using an oxidative protocol (CAN, H_2O)[4] rather than the standard Hg^{2+}-promoted procedure.[5] The thioimidate within **10** lacks the sensitive exocyclic alkene, and mercury-assisted hydrolysis cleanly provides the expected 3-hydroxyoxindole **11** without complication.

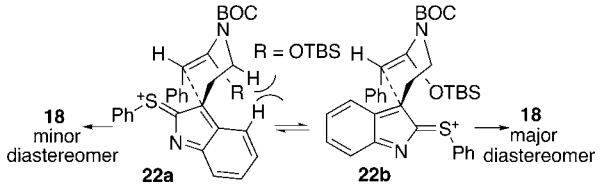
A second substrate of interest, **12**, featured a silyl enol ether nucleophilic trap (Table 1, entry b). Treatment of this species under the conditions optimized for the allylsilane analogue led to formation of the expected spirocyclohexanone product **13** in good yield. Unlike the related alkene-bearing species **8**, ketone **13** could be readily hydrolyzed with Hg^{2+} assistance to provide the oxindole product **14** in excellent yield.

A departure from C−C bond-forming nucleophiles featured ketone **15** (Table 1, entry c) as the Pummerer cyclization substrate. In this instance, cyclization at oxygen is readily accomplished, presumably via the derived enol. The O−C over C−C bond-forming selectivity observed within this putative enol-bearing Pummerer intermediate might be attributed to the facility of 6-enol-exo cyclizations over the alternative C−C bond-forming 6-enol-endo pathway.

The occurrence of several 3,3-disubstituted oxindole-derived natural products formally originating from tryptamine[6] provided the motivation to explore this Pummerer cyclization chemistry of the tryptamine derivative **17** (Table 1, entry

(4) Ho, T.-L.; Ho, H.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
(5) Satchell, D. P. N. *Chem. Soc. Rev.* **1977**, *6*, 345−371.

Scheme 2. Postulated Origin of Diastereoselectivity with **17**



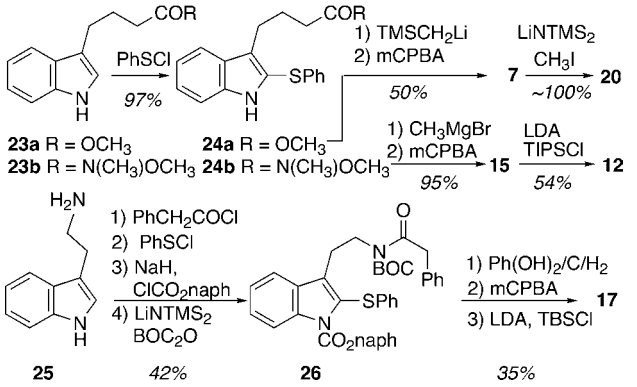
d). Triflic anhydride treatment of **17** furnished the desired cyclized material **18** in excellent yield as a mixture of diastereomers strongly favoring the equatorial-phenyl isomer shown. Resubmission of partially purified samples of either isomer to reaction conditions did not alter the diastereomer ratio. This kinetic stereochemical outcome can be rationalized by invoking differential steric interactions in the chairlike transition state models shown in Scheme 2.[7]

The successful Pummerer-initiated cyclization of the *N*-methyl indole substrate **20** (Table 1, entry e) focuses attention on the aforementioned mechanistic dichotomy between the additive and the vinylogous Pummerer pathways (cf. Scheme 1). Since the activated sulfoxide corresponding to **2** no longer has a proton to lose (NH is now NCH_3), passage through a now dicationic intermediate (cf. **3**, with N replaced by $^+NCH_3$) in the vinylogous Pummerer route might exact a substantial energetic penalty, whereas the alternative additive pathway does not engage the indole nitrogen's electrons until after C−C bond formation. There is no experimental basis for distinguishing between these proposals at present. Irrespective of the mechanistic details, the formation of the *N*-methyl oxindole product **21** directly from a C(2)-sulfur-containing starting material broadens the utility of the chemistry because a second discrete hydrolysis step is avoided.

(6) (a) Joshi, B. S.; Gundu Rao, P.; Rogers, D.; Singri, B. P.; Williams, D. J. *Ind. J. Chem.* **1984**, *23B*, 101−102. (b) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355−2358. (c) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124−7126.

(7) Similar selectivity for C(3) cyclization through an indole aryl-equatorial construct (cf. **22b**) can be cited to rationalize observations in related systems. (a) Atarabashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226−6241. (b) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785−3788.

Scheme 3. 2-(Phenylsulfinyl)indole Cyclization Substrate Syntheses



The syntheses of the 2-(phenylsulfinyl)indole substrates used in this study are detailed in Scheme 3. Notable features include (1) the formation of both the silyl enol ether unit of **12** and the silyl ketene iminal unit of **17** in the presence of the potentially interfering 2-(phenylsulfinyl)indole moiety's acidic N−H and (2) the use of the naphthylcarbamate protecting group[8] in **26** to overcome the problem of partial PhS− loss that accompanied attempted hydrogenolysis of a $-CO_2Bn$ analogue. The low yield reported for formation of silyl ketene iminal **17** was a consequence of product loss (hydrolysis) that occurred during chromatographic purification. Typically, the crude substrate **17**, which was formed in ~60% yield (^{1}H NMR assay) was used in the Pummerer sequence without further purification to furnish the thioimidate product in excellent overall yield.

Acknowledgment. We thank the NIH (GM35727) for financial support.

Supporting Information Available: Experimental procedures, spectral data (^{1}H NMR, ^{13}C NMR, IR, MS, selected combustion analyses), and copies of ^{1}H and ^{13}C NMR spectra for **7**−**9**, **11**−**16**, **18**−**21**, **24a**, **24b**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0493406

(8) Papageorgiou, E. A.; Gaunt, M. J.; Yu, J.-q.; Spencer, J. B. *Org. Lett.* **2000**, *2*, 1049−1051.