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Tetrahedron Letters 45 (2004) 5035–5037
Tetrahedron Letters

Use of Stang's reagent, PhI(CN)OTf, to promote Pummerer-like oxidative cyclization of 2-(phenylthio)indoles

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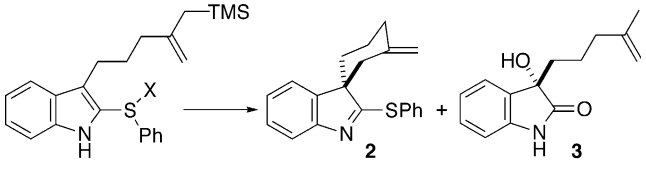
Received 21 April 2004; revised 30 April 2004; accepted 30 April 2004

Abstract—Treatment of various 2-(phenylthio)indoles, bearing nucleophilic groups tethered to C(3), with PhI(CN)OTf initiated an oxidative cyclization sequence that afforded 3,3-spirocyclic 2-(phenylthio)indolenines or oxindoles in moderate yield.

The oxidative cyclization of 2-(phenylsulfinyl)indoles bearing a nucleophile tethered to C(3) provides a range of 3,3-spirocyclic 2-(phenylthio)indolenine products as exemplified by the conversion of **1a** into **2**, Eq. 1.[1] These transformations likely proceed via a classical Pummerer-type reaction initiated by exposure of the sulfoxide to Tf_2O. Pummerer-like oxidative cyclizations with aryl *sulfide* substrates have been reported as well,[2] and a range of oxidants, including Cl_2,[2a] $ArIF_2$,[2b] and $PhI(OTFA)_2$,[2c,d] appear to find productive use in this regard. This shortcut to achieving a net Pummerer rearrangement has seen little use in synthesis, perhaps as a consequence of the relatively harsh oxidants employed, and a lack of demonstrated substrate generality. Attempts to apply either of the common hypervalent iodine oxidants $PhI(OAc)_2$ or $PhI(OTFA)_2$ to the 2-(phenylthio)indole system **1b** failed to furnish any spirocyclic product **2**, but rather returned low yields of the C(3) oxidized oxindole **3**.



(1)

However, switching to PhI(CN)OTf, a reagent introduced by Stang and Zhdankin,[3] led to a significant improvement in reaction outcome with the sulfide **1b** (Table 1). A survey of reaction parameters led to the optimized conditions described in entry 'e' of the table. Control experiments demonstrated that the thioimidate product **2** was stable to the reaction conditions, even when the hypervalent iodine oxidant was used in significant excess. The imidate resonance in **2** may diminish the reactivity of the sulfur's lone pairs in this instance. The oxidative cyclization proceeded equally well in CH_2Cl_2 and CH_3CN (0.01 M), but did not work at all in toluene. Lutidine premixed with the iodonium reagent was more advantageous than Hünig's base, and warmer temperatures led to slightly higher yields of product. Excess Stang reagent was required to consume all of the starting material (TLC), and the highest yields accompanied portionwise addition over 90 min, suggesting that unidentified processes were consuming the hypervalent iodine reagent in competition with the desired oxidative cyclization sequence. The yield of **2** was only mildly

Table 1. Optimization studies for the PhI(CN)OTf-mediated conversion of **1b** into **2**

Entry	Solvent	Temp (°C)	Base	Ratio PhI(CN)OTf to **1b**	Yield (%)
a	CH_3CN	−45	Lutidine	2.2	51
b	CH_2Cl_2	−80	Lutidine	2.5	48
c	CH_2Cl_2	0	Lutidine	2.2	61
d	CH_2Cl_2	0	iPr$_2$NEt	4.1	41
e	**CH_2Cl_2**	**0**	**Lutidine**	**4.1 (portionwise)**	**67**
f	CH_2Cl_2	20	Lutidine	2.2	61

Keywords: Pummerer; Hypervalent iodine; Oxindole.
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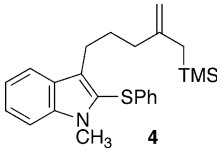
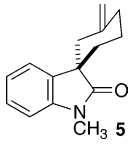
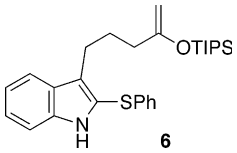
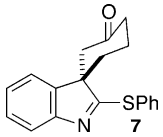
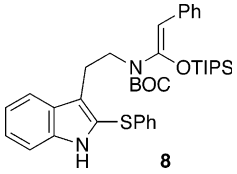
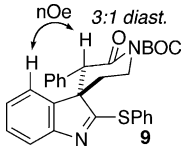
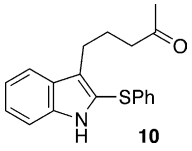
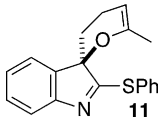
doi:10.1016/j.tetlet.2004.04.182

Table 2. Survey of 2-phenylthioindole substrates subjected to PhI(CN)OTf-mediated oxidative cyclization

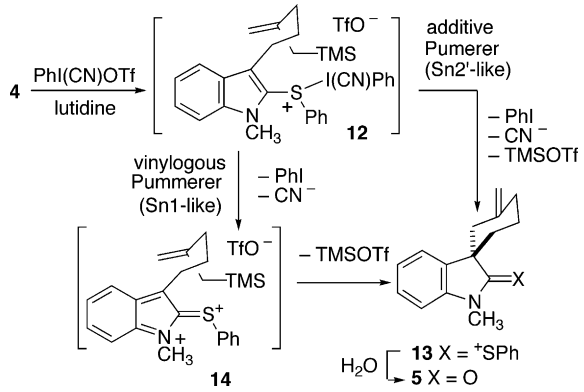
Entry	Substrate	Cond.[a]	Product[b]	Yield (%)
a		A		46
b		B		42
c		C		55
d		B		63

[a] A: 4 equiv PhI(CN)OTf, 3 equiv lutidine, CH_3CN, −40 °C; B: 1 equiv PhI(CN)OTf, 3 equiv lutidine, CH_3CN, 0 °C; C: 4 equiv PhI(CN)OTf, 3 equiv lutidine, CH_2Cl_2, −78 °C.

[b] All new compounds exhibited satisfactory spectral data (see Ref. 1, supporting information).

sensitive to concentration variance over the range 0.001 M (56%) to 0.1 M (44%).

Extension of this 2-(phenylthio)indole oxidative cyclization procedure to other substrates led to mixed but generally favorable results (Table 2). Reaction of the *N*-methyl analogue of **1b**, 2-(phenylthio)indole **4**, under the optimized conditions provided the oxindole **5** directly, entry 'a'. The yield is slightly lower than with the N–H species **1b**, perhaps reflecting the more complicated multi-step reaction course in this case. This *N*-methyl species brings into focus an interesting mechanistic question as detailed in Scheme 1. A priori, both additive and vinylogous Pummerer-like pathways can be invoked to rationalize the formation of **5**.[4] However, the vinylogous Pummerer sequence passes through a dicationic intermediate **14** whereas the additive Pummerer alternative avoids such a potentially high-energy species. At present, no basis for distinguishing between these two hypotheses for **4**, or any other substrate examined in this study, is in hand.



Scheme 1. Mechanistic speculation for the conversion of **4** into **5**.

The use of the much more nucleophilic silyl enol ether **6** (Mayr nucleophilicities:allylsilane = 1.8, silyl enol ether = 5.4)[5] raises the possibility that competitive enol ether/iodonium reaction may divert the transform. The product spirocycle **7** is formed in relatively more modest yield, but no evidence for α-keto iodonium ylide formation was detected.

An even more significant challenge can be found in substrate **8**, where the presence of the potent silyl ketene iminal nucleophile (Mayr nucleophilicities for silyl ketene acetals ≈9–10, and for enamines ≈10–11)[5] places even more stringent requirements on the selectivity of electrophile addition. Stang's reagent evidently is capable of meeting this challenge, as its apparent thiophilicity leads to appropriate Pummerer initiation and eventual formation of the spirocyclic imide product **9** in good yield.

The final substrate examined in this study has no formal alkene nucleophile at all: the simple ketone **10**. Interpretation of the mechanistic course of this reaction is clouded by uncertainty about the identity of the actual participating nucleophile. Either the carbonyl oxygen itself or the hydroxyl of a derived enol may constitute the reactive nucleophile that traps the electrophilic C(3) site of the oxidized substrate.

In summary, these examples of Pummerer-like oxidative cyclization demonstrate the feasibility of using the unconventional initiator PhI(CN)OTf with a sulfide substrate. The use of this reactive yet highly selective oxidant offers two advantages over existing indole oxidative cyclization triggers: (1) oxidative activation is confined to C(3), and (2) no potentially interfering nucleophilic counterions are introduced.

Acknowledgements

We thank the Institute of General Medical Sciences within the National Institutes of Health (GM35727) for financial support of this work.

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