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One-Pot Synthesis of Highly Substituted 4-Acetonylindoles via Sequential Dearomatization and Silver-Catalyzed Domino Reaction

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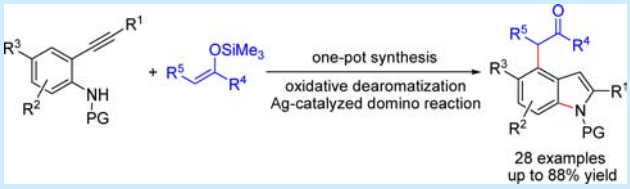
Supporting Information

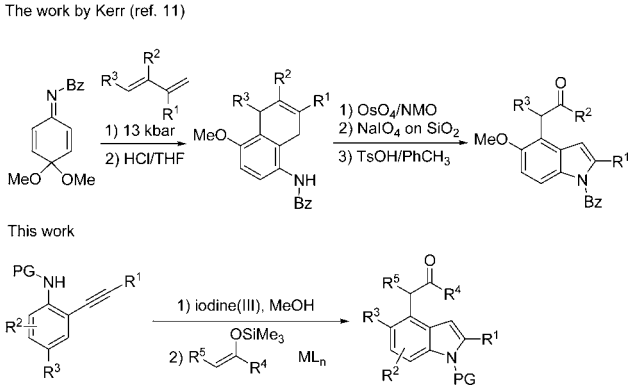
ABSTRACT: Synthetically useful 4-acetonylindoles have been conveniently prepared from 2-alkynylanilines and silyl enol ethers using a dearomatization strategy. The two-step/one-pot protocol involves an iodosylbenzene-mediated oxidative dearomatization and a silver-catalyzed domino reaction.



4-Substituted indoles constitute a valuable class of compounds because of their wide range of biological activities.[1] 4-Acetonylindoles have found widespread use in the synthesis of natural products containing a 4-substituted indole core, such as dragmacidins D and E,[2] welwitindolinones,[3] and ergot alkaloids.[4] Accordingly, a variety of strategies have been developed to prepare these synthetically useful intermediates. Traditionally, 4-acetonylindoles are synthesized from 5-halo-4-oxo-4,5,6,7-tetrahydroindoles and the dianion of acetoacetic esters via 1,2-addition, dehydration, and dehydrohalogenation.[5] The difficulty of this three-step synthesis has limited the application of this method. 4-Halo-substituted indoles are alternative precursors to prepare 4-acetonylindoles. Besides palladium-catalyzed enolate arylation,[6] 4-halo-substituted indoles can be converted to lead(IV) 4-indolyl triacetates to react with α-ketoester to form 4-acetonylindoles.[7] However, the direct electrophilic halogenation of the C-4 position of indoles is not preferred. The preparation of 4-halo-substituted indoles requires multistep synthesis. Additionally, Witkop photocyclization,[8] Rh-catalyzed C−H insertion by α-diazo ketone,[9] and the addition of enolates onto an *in situ* generated indolyne species[10] have also been developed to construct 4-acetonylindoles, but these reactions only proceed in an intramolecular way.

Recently, the Kerr group reported an elegant method for synthesizing 4-acetonylindoles that relied on the [4 + 2] cycloaddition of quinone imine ketals (QIK) and subsequent oxidative olefin cleavage and cyclization (Scheme 1).[11] Although a multistep process is required, the success of this tactic leads us to speculate that 4-acetonylindoles might be prepared from simple aniline derivatives using a dearomatization strategy.[12] Herein, we wish to present our success in this regard. Highly substituted 4-acetonylindoles are rapidly constructed from 2-alkynylanilines and silyl enol ethers (Scheme 1). Our strategy involves a hypervalent iodine-mediated oxidation to break the aromaticity of 2-alkynylanilines,[13] a Michael-type addition with silyl enol ethers to install the acetony group, and a tandem cyclization/aromatization to build the indole ring.

Scheme 1. Synthesis of 4-Acetonylindoles from Aniline Derivatives



2-Alkynylaniline **1** was conveniently prepared from *p*-toluidine via an iodination and a Sonogashira coupling with phenylacetylene. Many hypervalent iodine compounds could mediate the oxidative dearomatization of compound **1**, but most of the reactions produced acidic metabolites, which are harmful to subsequent reaction with silyl enol ethers. Iodosylbenzene proved to be the best oxidant for this one-pot synthesis. To avoid the decomposition of silyl enol ethers, methanol was removed under a pressure-reducing condition before adding silyl enol ethers. The catalytic activities of a variety of metal salts in the formation of 4-acetonylindole **3** were evaluated (Table 1, entries 1−10). When Bi(III), In(III), Zn(II), Cu(II), Au(III), Pd(II), or Pt(II) salt was used, the reaction gave rise to a 4-methoxy-substituted indole as the major product. When AuCl or AgOTf was used, the desired 4-acetonylindole **3** was isolated in 43% or 50% yield, respectively.

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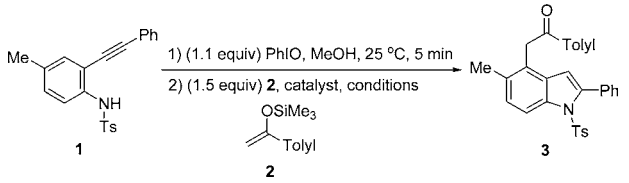
Table 1. Evaluation of Catalysts and Conditions



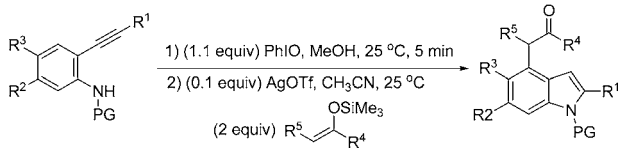
entry	catalyst (equiv)	conditions	3 (%)[a]
1	$Bi(OTf)_3$ (0.1)	THF, 25 °C, 3 h	0
2	$In(OTf)_3$ (0.1)	THF, 25 °C, 3 h	0
3	$Zn(OTf)_2$ (0.1)	THF, 25 °C, 3 h	0
4	$Cu(OTf)_2$ (0.1)	THF, 25 °C, 3 h	<5
5	$CuCl_2$ (0.1)	THF, 25 °C, 3 h	7
6	$AuCl_3$ (0.1)	THF, 25 °C, 3 h	27
7	AuCl (0.1)	THF, 25 °C, 3 h	43
8	$PdCl_2$ (0.1)	THF, 25 °C, 3 h	<5
9	$PtCl_2$ (0.1)	THF, 25 °C, 3 h	<5
10	AgOTf (0.1)	THF, 25 °C, 3 h	50
11	AgOTf (0.1)	DCM, 25 °C, 3 h	32
12	AgOTf (0.1)	toluene, 25 °C, 3 h	61
13	AgOTf (0.1)	dioxane, 25 °C, 3 h	45
14	AgOTf (0.1)	CH_3CN, 25 °C, 3 h	65
15[b]	AgOTf (0.1)	CH_3CN, 25 °C, 3 h	73
16[c]	AgOTf (0.1)	CH_3CN, 25 °C, 3 h	72
17	AgOTf (0.2)	CH_3CN, 25 °C, 2 h	63
18	AgOTf (0.05)	CH_3CN, 25 °C, 5 h	65
19	AgOTf (0.1)	CH_3CN, 0 °C, 8 h	55
20	AgOTf (0.1)	CH_3CN, reflux, 1 h	51

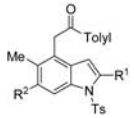
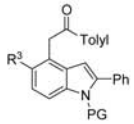
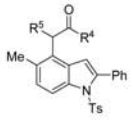
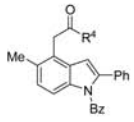
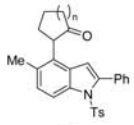
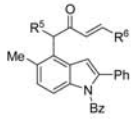
[a]Reported yields are of the isolated products. [b]Two equivalents of compound **2** was used. [c]Three equivalents of compound **2** was used.

A screening of solvents for the AgOTf-catalyzed reaction revealed that acetonitrile was the best reaction media (Table 1, entries 10−14). The best ratio of 2-alkynylaniline, silyl enol ether, and catalyst was 1:2:0.1, increasing the yield to 73% (Table 1, entry 15).

With the optimized conditions established, the two-step/one-pot synthesis of 4-acetonylindoles was investigated, and the results are presented in Table 2. A range of 2-alkynylanilines bearing different substitutions were suitable substrates. The structure of compound **10** was confirmed by its single-crystal diffraction analysis (Figure 1).[14] The protecting group of 2-alkynylanilines played a significant role in the formation of 4-acetonylindoles. For example, when the *para* substitution of 2-alkynylaniline was a *n*-butyl group, the reaction of the *N*-Ts-protected substrate gave rise to the 4-methoxy-substituted indole as product. When the *N*-Bz-protected substrate was used instead, the desired 4-acetonylindole was formed in 54% yield (Table 2, entries 11 and 12). When the *para* substitution was a phenyl group, the reaction was complex. For a series of silyl enol ethers derived from aryl methyl (ethyl) ketones, the reactions proceeded smoothly (Table 2, entries 15−22). The yield was diminished when the enol silane bearing *ortho* substitution was employed. For silyl enol ethers derived from cyclic ketones, cyclopentanone-derived enol silane was a suitable reaction partner (Table 2, entry 23). It is noteworthy that when Danishefsky's diene was used, the reaction produced 4-acetonylindole **27**, and no Diels−Alder cycloaddition product was isolated (Table 2, entry 25). With respect to other (silyloxy)dienes, reactions of dienes bearing an electron-donating group gave rise to products in higher yields compared

Table 2. Two-Step/One-Pot Synthesis of 4-Acetonylindoles



entry	product		yield (%)[a]
1		**3**: R^1 = Ph, R^2 = H	73
2		**4**: R^1 = H, R^2 = H	80
3		**5**: R^1 = 4-MeC_6H_4, R^2 = H	74
4		**6**: R^1 = 4-$MeOC_6H_4$, R^2 = H	81
5		**7**: R^1 = TMS, R^2 = H	80
6		**8**: R^1 = *n*-Bu, R^2 = H	78
7		**9**: R^1 = *t*-Bu, R^2 = H	82
8		**10**: R^1 = cyclopropyl, R^2 = H	81
9		**11**: R^1 = Ph, R^2 = Me	75
10		**12**: R^3 = OMe, PG = Ts	77
11		**13**: R^3 = *n*-Bu, PG = Ts	0
12		**14**: R^3 = *n*-Bu, PG = Bz	54
13		**15**: R^3 = Me, PG = Bz	78
14		**16**: R^3 = Ph, PG = Bz	0
15		**17**: R^4 = Ph, R^5 = H	53
16		**18**: R^4 = 4-$MeOC_6H_4$, R^5 = H	74
17		**19**: R^4 = 4-BrC_6H_4, R^5 = H	64
18		**20**: R^4 = 4-$MeOC_6H_4$, R^5 = Me	63
19		**21**: R^4 = 3-MeC_6H_4	72
20		**22**: R^4 = 2-MeC_6H_4	64
21		**23**: R^4 = 3-$MeOC_6H_4$	69
22		**24**: R^4 = 3-BrC_6H_4	60
23		**25**: n = 1	61
24		**26**: n = 2	0
25		**27**: R^5 = H, R^6 = OMe	81
26		**28**: R^5 = H, R^6 = Ph	88
27		**29**: R^5 = H, R^6 = 4-$MeOC_6H_4$	79
28		**30**: R^5 = H, R^6 = 4-MeC_6H_4	77
29		**31**: R^5 = H, R^6 = 4-ClC_6H_4	52
30		**32**: R^5 = H, R^6 = 4-BrC_6H_4	53
31		**33**: R^5 = Me, R^6 = 4-$MeOC_6H_4$	73

[a]Reported yields are of the isolated products.

with those bearing an electron-withdrawing group (Table 2, entries 26−31).

A plausible reaction pathway for this two-step/one-pot synthesis is shown in Scheme 2. Iodosylbenzene mediates oxidative dearomatization of *para*-substituted 2-alkynylaniline in methanol to form 2-alkynylcyclohexadienimine. AgOTf functions as a π acid to induce heterocyclization of 2-alkynylcyclohexadienimine. The formed pyrrole-like intermedi-

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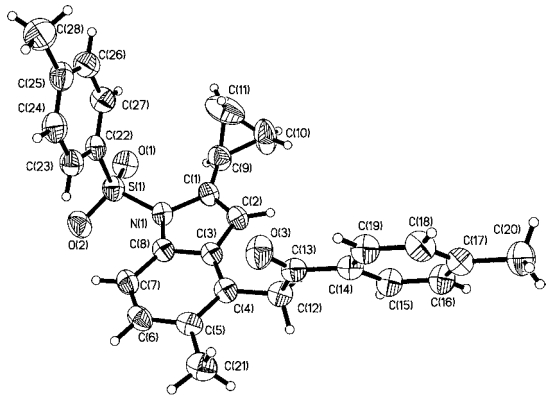
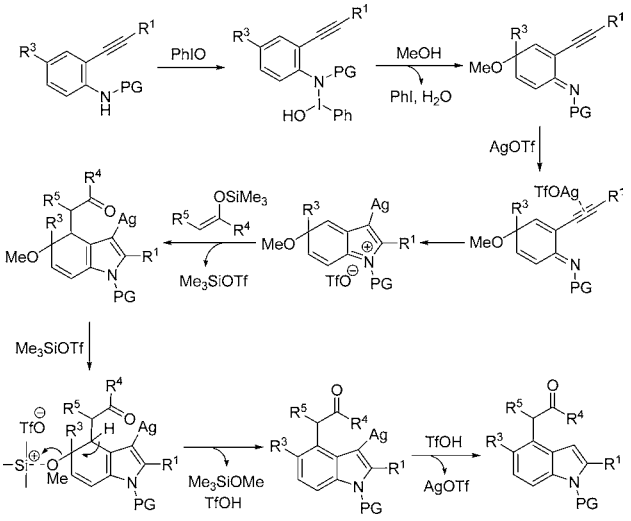


Figure 1. X-ray diffraction structure of compound **10**.

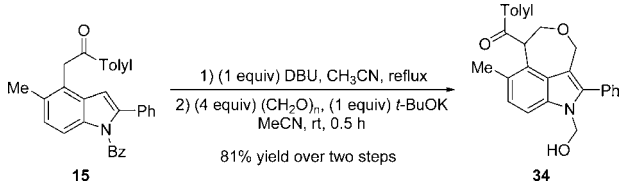
Scheme 2. Plausible Reaction Pathway



ate is ready to undergo a Mukaiyama−Michael addition with silyl enol ethers. The *in situ* generated Me_3SiOTf promotes aromatization. Subsequent protonation of the carbon−silver bond by TfOH affords 4-acetonylindole and regenerates the catalyst AgOTf.

Compound **15** could be easily converted to a 3,4-fused tricyclic indole[15] **34** via a deprotection and a condensation with paraformaldehyde (Scheme 3).

Scheme 3. Conversion of 4-Acetonylindole to Oxepino[3,4,5-*cd*]indole Derivative



In conclusion, we have developed a dearomatization strategy for synthesis of highly substituted 4-acetonylindoles. The process involves an oxidative dearomatization of 2-alkynylanilines followed by a silver-catalyzed domino reaction with silyl enol ethers. The application of this method to the synthesis of natural products is currently underway in our laboratory, and these results will be forthcoming.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of ^1H NMR and ^{13}C NMR of new compounds, and crystallographic data of compound **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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