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Divergent synthesis of withasomnines via synthesis of 4-hydroxy-1*H*-pyrazoles and Claisen rearrangement of their 4-*O*-allylethers

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ABSTRACT

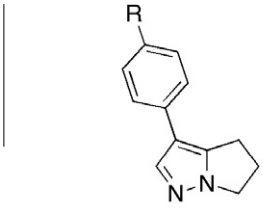
4-Hydroxypyrazoles were synthesized by the alkaline hydrolysis of the Baeyer–Villiger oxidation products of 4-formylpyrazoles. This new synthesis of 4-hydroxypyrazoles was applied to the divergent synthesis of withasomnine alkaloids in a unique strategy, for which the key steps included the regioselective Claisen rearrangement of their 4-*O*-allyl-4-hydroxy-1*H*-pyrazoles and a Suzuki coupling of 4-trifluoromethanesulfonyloxy-1*H*-pyrazoles and arylboronic acids.

Withasomnine (**1**) was originally isolated in 1966 from the root bark of *Withania somnifera* (*Solanaceae*), which is distributed around India and Africa (Fig. 1).[1] Withasomnine **1** exhibited a depression of the CNS and circulatory systems, a mild analgesic effect, and the inhibition of TBL_4, COX-1 and COX-2.[2] There have been several reports of the synthesis of **1**.[3] Recently, Harrity et al. reported the divergent synthesis of **1**–**3** via a key step involving sydnone-alkynylboronate cycloaddition.[3f]

Pyrazoles are important heterocyclic compounds that take part in various kinds of bioactivities.[4] The synthesis of substituted or functionalized pyrazoles has been studied extensively. However, most pyrazoles are made up of a pyrazole ring from the condensation of 1,3-diketones and hydrazines and/or the 2+3 cycloaddition. The synthetic challenge of the direct functionalization of pyrazoles has been scarcely reported. Our interest is the direct functionalization of pyrazoles at C-4, since the novel binuclear platinum complex bearing C-4 alkylpyrazoles as ligands has exhibited an enhanced anticancer activity against cisplatin-resistant human cancer cell lines.[5] We have reported the cross coupling reaction of halopyrazoles to produce 4-arylpyrazoles, 4-vinylpyrazoles and 2*H*-indazoles.[6] The study of 4-substituted pyrazoles heightened our interest in the synthesis of 4-hydroxypyrazoles. Almost no report exists on the synthesis of 4-hydroxypyrazoles despite its importance and interesting bioactivities such as the inhibition of several kinds of CYP-enzymes and the induction of CYP2E1. Therefore, the establishment of a synthetic method to produce 4-hydroxypyrazole would be significant to synthetic organic chemistry.

In the course of continuous study into the total synthesis of small, natural products and their analogues,[7] our group began work on the divergent synthesis of withasomnines **1**–**3**. Herein is a description of that study based on the synthesis of 4-hydroxypyrazoles following the Claisen rearrangement of 4-*O*-allyl ether.

1-Substituted-4-iodopyrazoles **6** prepared from pyrazole (**4**) via 4-iodopyrazole (**5**), as with previous work,[6a,d] were reacted with isopropylmagnesium chloride for halogen-metal exchange (Scheme 1). After 1 h, *N*,*N*-dimethylformamide (DMF) was added to the reaction mixture as a formylating reagent to afford 4-formylpyrazoles **7**. Baeyer–Villiger oxidation of **7b** with 30% aqueous hydrogen peroxide using catalytic 2-trifluoromethansulfonylben-



1: R = H withasomnine
2: R = OH 4'-hydroxywithasomnine
3: R = OMe 4'-methoxywithasomnine

Figure 1. Withasomnines.

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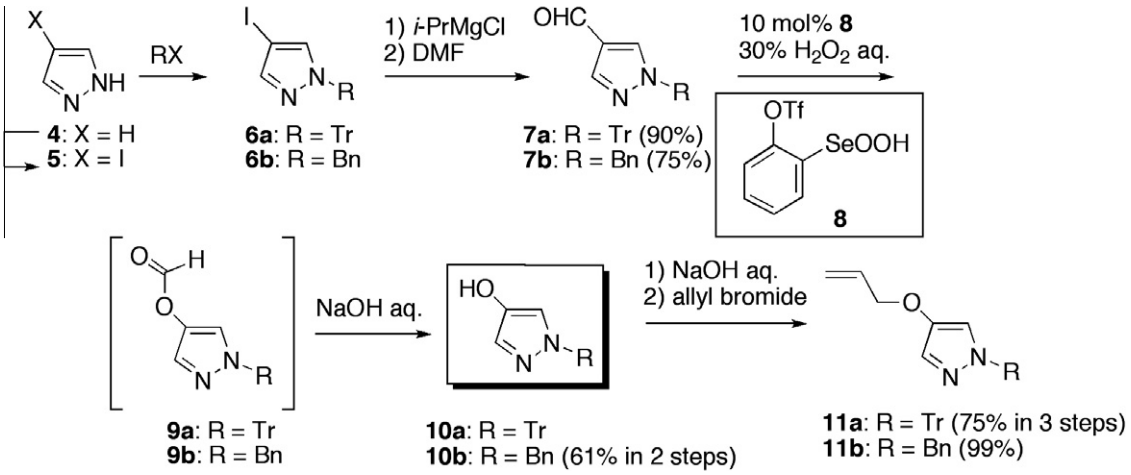
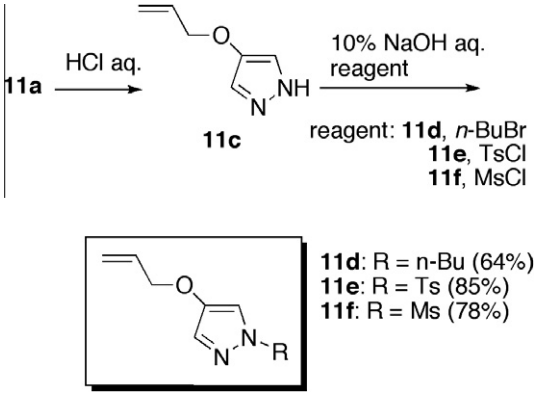


Scheme 1. The synthesis of 4-hydroxy-1-substitutedpyrazoles **10** and allyl ether **11.**

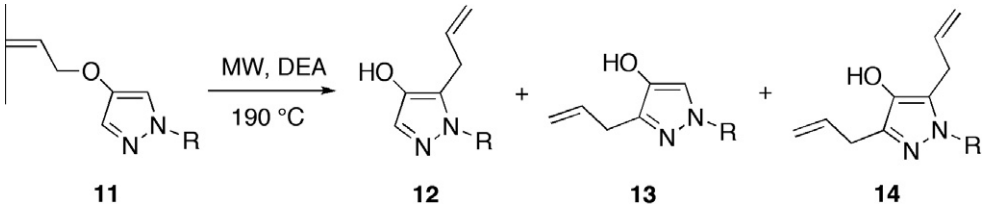
zeneseleninic acid (**8**), which was developed in previous work,[8] gave a reaction mixture containing formates **9**. The following alkaline hydrolysis of the mixture with aqueous NaOH under reflux afforded the desired 4-hydroxypyrazoles **10b** in a 61% yield in two steps. The resulting **10b** was reacted with allyl bromide to give allyl ether **11b** in a 99% yield. Similarly, **7a** was applied to the one-pot sequence oxidation-hydrolysis-*O*-allylation to give allyl ether **11a** via **9a** and **10a** in a 75% yield in three steps. At this point, more analogues, **11d**–**f**, were also prepared from **11a** via deprotected **11c** shown in Scheme 2, using for examination of regioselectivity in the following Claisen rearrangement.

Previously, regioselectivity of the Claisen rearrangement on 3-substituted-5-hydroxypyrazoles was reported by Hori[9] and Hwang,[10] independently. But in this case, 4-allyloxypyrazoles **11** had two possibilities for a regioselective Claisen rearrangement. It seemed efficient to control regioselectivity in the Claisen rearrangement of **11** depending on the protective group at the 1-position (N1) of pyrazole. The results of a Claisen rearrangement of various 4-allyloxypyrazoles **11** under microwave irradiation are summarized in Table 1. All entries exhibited a high preference toward the C5-allylated product **12** contrary to our prediction. It was interesting that only in the case of **11b** was a small amount of 3,5-diallyl-1-benzyl-5-hydroxypyrazole (**14**) obtained along with the major product **12b**. The structures of all rearranged products **12**–**14** were determined by NOESY analysis.



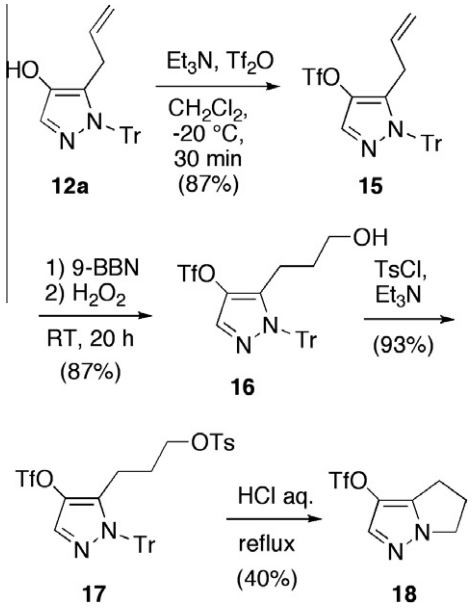
Scheme 2. The synthesis of various 4-allyloxy-1-substituted pyrazoles.

Table 1
Claisen rearrangement of 4-allyoxypyrazoles **11**[a]

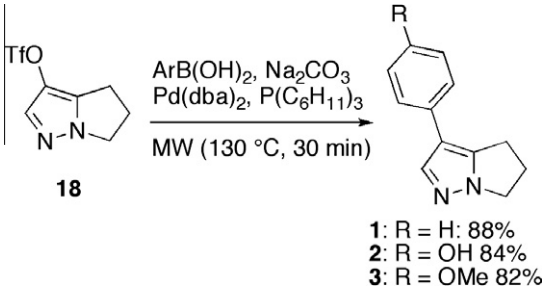


Entry	R	Time (min)	Yield[c] (%)		
			12	**13**	**14**
1	Tr (**11a**)	60	61	3	0
2	Tr (**11a**)	60	59	3	0
3[b]	Bn (**11b**)	30	92	0	2
4	*n*-Bu (**11d**)	60	84	2	0
5	Ts (**11e**)	30	65	20	0
6	Ms (**11f**)	60	68	Trace	0

[a] MW irradiation took place under a sealed vessel.
[B] With conventional heating.
[C] Isolated yield, MW: microwave, DEA: diethylaniline, **a** = Tr, **b** = Bn, **c** = H, **d** = *n*-Bu, **e** = Ts, **f** = Ms.



Scheme 3. Cyclization to **18** from the Claisen rearrangement products **12a.**



Scheme 4. Divergent synthesis of **1**–**3.**

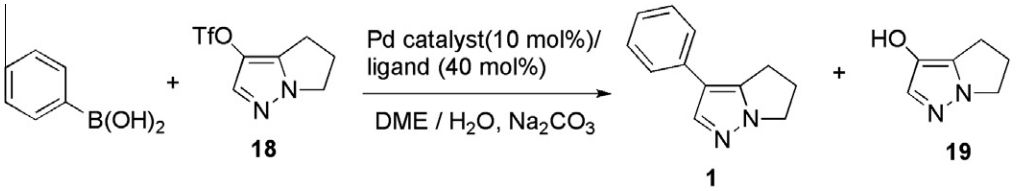
It seems that the C4–C5 bond of **11** has a double bond character. Therefore, the rearrangement took place regioselectively to produce **12**. However, the minor rearrangement products, 3-allyl-4-hydroxypyrazoles **13** might be afforded when **11** have an electron-withdrawing group such as the tosyl group (**11e**) at N1. Because the C3–C4 bond of **11e** has more double bond character than that of **11a** and **b**. Therefore, **13e** is obtained from the rearrangement of **11e** in 20% yield (Table 1, entry 5).

Based on the facility of removal of the protective group on N1, **12a** was selected as a substrate for the total synthesis of withasomnines. The Claisen rearrangement product **12a** was converted into **15** in a usual way. The transformation of an allyl side chain in **15** was examined by a hydroboration–oxidation sequence with 9-BBN and gave **16** in an 87% yield. The resultant **16** was treated with *p*-toluenesulfonylchloride and triethylamine to give tosylate **17** in a 93% yield, which was then cyclized into 3-trifluoromethanesulfonyloxy-5,6-dihydro-4H-pyrroro[1,2-b]pyrazole **18** in a 40% yield under acidic reflux (Scheme 3).

The final step in this total synthesis of **1** is the Suzuki coupling between triflate **18** and phenylboronic acid. Various reaction conditions were examined and the results are summarized in Table 2. Using 1,2-dimethoxyethane (DME)–H_2O as a solvent was found to be effective, similar to Harrity's work.[3f] Reaction time was shortened to 30 min under microwave irradiation at 130 °C, as shown in the literature. The remaining two natural withasomnines **2** and **3** could also be prepared using commercially available 4-methoxyphenyl- and 4-hydroxyphenylboronic acids, respectively (Scheme 4). At this point, our divergent synthesis of natural withasomnines has been achieved.

In conclusion, 4-hydroxypyrazoles have been synthesized in a sequence of reactions: halogen-metal exchange of 4-iodopyrazoles–formylation–Baeyer–Villiger oxidation–alkaline hydrolysis. And a Claisen rearrangement of *O*-allyl-4-hydroxypyrazoles gave 5-allyl-4-hydroxypyrazoles in good yield and high regioselectively. Our divergent total synthesis of withasomnines was completed using a Suzuki coupling between a 4-triflyloxypyrazole derivative and various arylboronic acids and afforded three natural alkaloids.

Table 2
Synthesis of withasomnine **1** via Suzuki coupling of **18** and $PhB(OH)_2$



Entry	Pd catalyst/ligand	DME/H_2O	Condition	**1**(%)	**19**(%)
1	$Pd(OAc)_2/PPh_3$	1/1	Reflux, 24 h	20	77
2	$Pd(OAc)_2/PPh_3$	1/1	MW, 130 °C, 1 h	24	71
3	$Pd(OAc)_2/PPh_3$	9/1	MW, 130 °C, 1 h	29	0
4	$Pd(dba)_2/PPh_3$	9/1	MW, 130 °C, 1 h	42	0
5	$Pd(OAc)_2/PPh_3$	1/0	MW, 130 °C, 1 h	0	0
6	$Pd(OAc)_2/PPh_3$	9/1	MW, 130 °C, 1 h	31	0
7	$Pd(dba)_2/P(o\text{-}tol)_3$	9/1	MW, 130 °C, 1 h	51	0
8[a]	$Pd(dba)_2/P(C_6H_{11})_3$	9/1	MW, 130 °C, 1 h	54	0
9[b]	$Pd(dba)_2/P(C_6H_{11})_3$	9/1	MW, 130 °C, 1 h	90	0
10[b]	$Pd(dba)_2/P(C_6H_{11})_3$	9/1	MW, 130 °C, 10 min	37[c]	0
11[b]	$Pd(dba)_2/P(C_6H_{11})_3$	9/1	MW, 130 °C, 30 min	88	0

[a] Reaction in the presence of tetra-*n*-butylammonium bromide (TBAB).
[b] Reaction in the presence of trioctylmethylammonium chloride (TOMAC).
[c] Compound **18** was recovered in 55% yield.

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