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Hydroamination of olefin in a special conjugated spiroketal enol ether system, diastereoselective synthesis of amino-containing tonghaosu analogs

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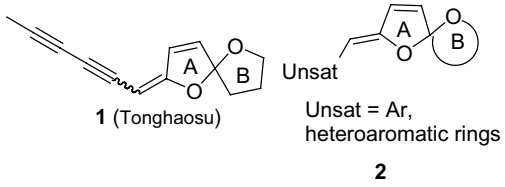
Abstract—Lithium amide reacted with spiroketal enol ether characterized tonghaosu analog at −78 °C to give the only hydroamination product **4** in a highly regio- and diastereoselective manner. At a higher temperature, −40 °C, the presence of free amine was critical for the hydroamination to take place; otherwise, rearrangement of tonghaosu analog to 2,3-dihydrofuran derivative like **6** was the only reaction.

Tonghaosu, 2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.4]-non-3-ene (**1**), is an antifeedant component of a vegetable called tonghao (*Chrysanthemum segetum* L. or *C. Coronarium* L.) in China and was also found in other plants of the tribe *Athemdeae*.[1,2] The first synthesis of tonghaosu was reported in early 1960s by Bohlmann group, though in quite low overall yield.[3] Recently, we have developed a general and concise synthetic methodology for tonghaosu and its spiroketal enol ether characterized analogs. A variety of tonghaosu analogs (**2**) with varied unsaturated groups and B-rings (Scheme 1) have been prepared in our laboratory,[4–6] and most of them showed antifeeding activity comparable to that of tonghaosu. This method provides an easy access to tonghaosu as well as its analogs for molecular diversity.



Scheme 1. Tonghaosu and its analogs.

Amines and their derivatives are of great importance in many fields of chemistry, especially in pharmaceuticals and agrochemicals. Olefins hydroamination is one of the most atom economic ways to prepare these compounds. Hydroamination may take place under a variety of catalytic reaction conditions including basic, acidic; in the presence of lanthanoid complexes, transition metals or rhodium catalysts.[7] Among them the base-catalyzed hydroamination of simple olefins often requires harsh conditions, such as high temperature and high pressure. Nevertheless the addition of amines to olefins with adjacent electron-withdrawing groups proceeds very readily, especially the conjugated addition of chiral lithium amide to α,β-unsaturated ester, which can proceed in high yield and stereoselectivity.[8] However, to the best of our knowledge, no hydroamination of α,β-unsaturated acetal has been reported. Therefore the hydroamination of 2,4-dienyl spiroketal containing tonghaosu analogs would not only be interesting from the point of view of chemistry, but it also gives amino-containing tonghaosu analogs, which would be useful candidates in searching for more efficient insect antifeedant or other agrochemicals. Herein, we would like to report the highly regio- and diastereoselective hydroamination of tonghaosu analogs.

The reaction of tonghaosu analogs **3** with lithium amide generated in situ from amine and *n*-butyllithium proceeded readily at −78 °C. The regioselectivity was excellent with amine attacking exclusively on C4 of

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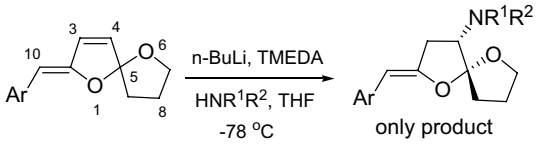
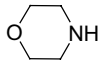
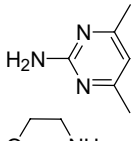
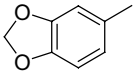
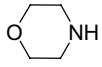
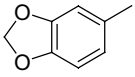
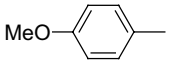
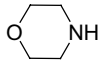
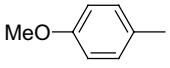
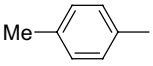
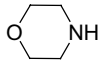
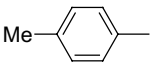
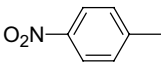
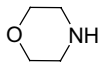
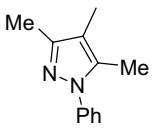
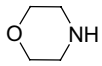
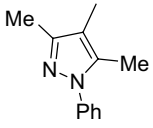
tonghaosu analogs.[9] Furthermore only one diastereomer compound **4** with amino group *cis* to O6 was obtained. The results are summarized in Table 1. As can be seen, lithium amide from secondary amines, such as morpholine, pyrrolidine, and piperidine, all afforded the products in good yields, while primary amine, such as *n*-butylamine (entry 2) gave much lower yield, and aromatic amines (entries 3 and 4) did not react with tonghaosu analog at all even the reaction mixture was warmed up to room temperature. The relative configuration of compound **4a** was unambiguously determined by the X-ray crystallography (Fig. 1) with the amino group *cis* to O6. The excellent regioselectivity and diastereoselectivity were presumably resulted from the chelating effect of lithium amide with O6, which directed the attack of amine at C4 from the same face as O6 (Scheme 3). These results indicated that the hydroamination of 2,4-dienyl spiroketal containing tonghaosu analogs was somewhat different from the Michael addition of lithium amide to an α,β-unsaturated ester,

Table 1. Hydroamination of **3** with amines at −78 °C



3 **4**

Entry	Tonghaosu analog	Ar	R^1R^2NH	Products	Yield (%)
1	**3a**	Ph		**4a**	94
2	**3a**	Ph	NH_2Bu	**4b**	41
3	**3a**	Ph	$PhNH_2$	NR	
4	**3a**	Ph		NR	
5	**3b**			**4c**	87
6	**3b**			**4d**	82
7	**3c**			**4e**	83
8	**3c**			**4f**	80
9	**3d**			**4g**	90
10	**3d**			**4h**	70
11	**3e**			**4i**	44
12	**3f**			**4j**	87
13	**3f**			**4k**	71

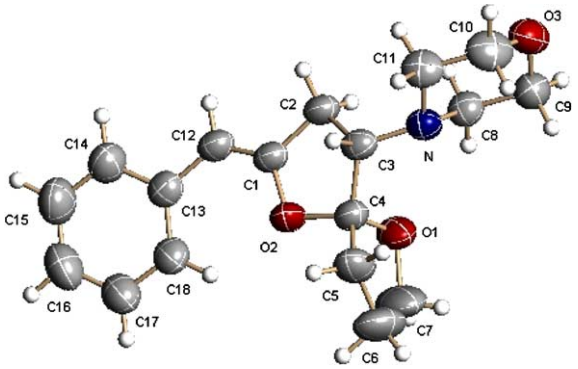


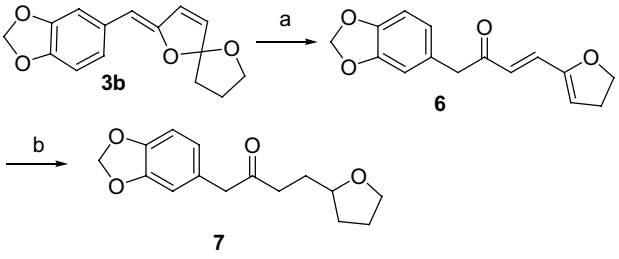
Figure 1. X-ray crystal structure of compound **4a**.[11]

where β addition would take place.[10] In addition, no hydroamination took place, if free amines instead of lithium amides were used as the nucleophiles.

Regioselectivity of the hydroamination here was found to be dependent on reaction temperature. When the addition reaction of amine to tonghaosu analog took place at higher temperature −40 °C, two products, **4** and **5**, were isolated in a ratio of ~12:1 favoring compound **4** (Table 2). The determination of compound **5** as a regioisomer of **4** relied mainly on ^{1}H NMR spectroscopic data. The chemical shift of H10 in compound **5** was ca. 5.9, while that of H10 in compound **4** was ca. 5.2, the chemical shift of H10 in **5** appearing at much lower field might be attributed to electrostatic repulsion from neighboring amino group. The relative configuration of compound **5** was tentatively assigned as depicted, where amino group was located at the same face as O6.

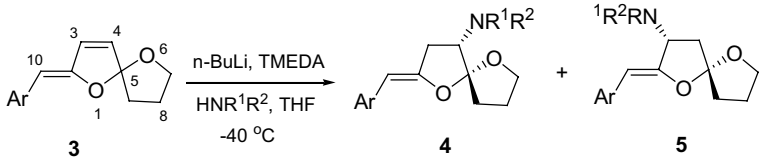
In contrast to the hydroamination at −78 °C where the absence of free amine in reaction mixture had no effect on the reaction, more amounts of amine than *n*-butyllithium was necessary for the reaction at −40 °C to proceed in the desired direction. For instance, after treatment of morpholine with 1 equiv of *n*-butyllithium, there should be no free morpholine in the reaction mixture. The resulting lithium amide then reacted with tonghaosu analog **3b** at −40 °C to give compound **6** instead of the hydroamination products **4c** and **5c** (Scheme 2). In addition, treatment of **3b** with LDA (lithium diisopropylamide) also gave compound **6**. Compound **6** and its derivative **7** were identified by 1D, 2D NMR, HREIMS, EIMS, and IR data.

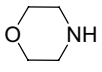
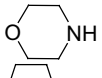
Based on the results in hand, we proposed a mechanism for the hydroamination of tonghaosu analog as shown in Scheme 3. The chelation of lithium amide with O6 of tonghaosu analog led to diastereo- and regioselective addition of amine at −78 °C to afford intermediate **I**, which after quenching with water gave compound **4** exclusively. When the reaction mixture was warmed up to −40 °C, an equilibrium between intermediate **I** and **II** occurred. The latter could be converted to compound **5** in the presence of free amine, however, if there was no excessive amine in the reaction mixture, it would be

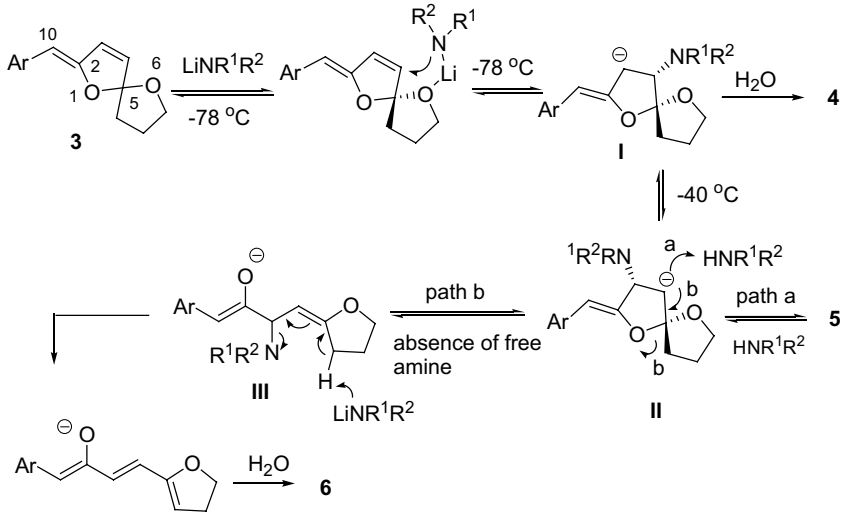


Scheme 2. Reaction of **3b** with lithium amide at −40 °C in the absence of free amine. Reagents and conditions: (a) morpholine (2 equiv), *n*-BuLi (2 equiv), TMEDA, −40 °C, 65%; (b) Pd/C, H_2, MeOH, rt, 90%.

Table 2. Hydroamination of tonghaosu analog at −40 °C in the presence of free amine



Entry	Tonghaosu analog	R^1R^2NH	Products (yield %)		Ratio **4/5**
			4	**5**	
1	**3a**		**4a** (72.4)	**5a** (5.6)	13/1
2	**3b**		**4c** (68.4)	**5c** (6.4)	11/1
3	**3b**		**4d** (63.7)	**5d** (4.3)	15/1
4	**3d**		**4h** (65.0)	**5h** (5.0)	13/1



Scheme 3. Possible mechanism for the reaction of tonghaosu analog and lithium amide.

rearranged to enolate **III** via ring opening, thus finally leading to compound **6**.

In summary, a novel addition of amine to spiroketal enol ether characterized tonghaosu analog was described. The hydroamination proceeded in a highly regio- and diastereoselective fashion at −78 °C, and the presence of free amine proved to be indispensable to the hydroamination at higher temperature. The bioassay of newly prepared amine-containing tonghaosu analogs is in progress and will be reported in due course.

Acknowledgements

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9. Typical procedure for the hydroamination (**4a**): To a mixture of morpholine (348 mg, 4 mmol) and TMEDA (1 mL) in anhydrous THF (15 mL) was added slowly 1.5 mL (2.4 mmol) of *n*-BuLi (1.6 M in hexane) at −78 °C. The mixture was stirred at the same temperature for 1 h, then a solution of **3a** (428 mg, 2 mmol) in THF (5 mL) was added slowly. After stirring at −78 °C for 10 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution, and then extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of solvent yielded a crude product, which was chromatographed to afford **4a** (566 mg, 94%) as a white solid. Mp 108–109 °C; IR (film, cm^{-1}): 2959, 2864, 2814, 2816, 1676, 1596, 1494, 1451, 761, 699; ^1H NMR (300 MHz, $CDCl_3$) 7.50 (2H, m), 7.27 (2H, m), 7.11 (1H, m), 5.22 (1H, s), 4.13 (1H, m), 4.04 (1H, m), 3.75 (4H, t, $J = 4.7$ Hz), 3.03 (2H, m), 2.78 (3H, m), 2.57 (2H, m), 2.25 (3H, m), 2.01 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 152.8, 136.5, 128.0, 124.6, 116.3, 98.4,

77.4, 77.0, 76.6, 68.6, 66.9, 66.1, 51.9, 34.8, 31.4, 30.9, 23.8; MS (m/z): 302 (15.1), 301 (100.0, M^+), 168 (45.4), 160 (19.9), 140 (18.2), 127 (30.8), 113 (19.6); Anal. calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.87; H, 7.66; N, 4.49.

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11. Crystallographic data (excluding structure factors) for the structure **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 223749. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].