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Synthesis of substituted 3-iodopyrroles by cycloisomerization of propargylic aziridines with iodine

Masahiro Yoshida *, Salina Easmin, Mohammad Al-Amin, Yuuki Hirai, Kozo Shishido

Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78-1 Sho-machi, Tokushima 770-8505, Japan

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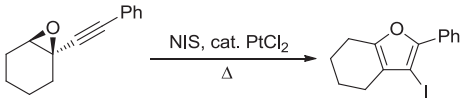
ABSTRACT

The electrophilic cyclizations of *N*-substituted propargylic aziridines are described. 3-Iodopyrroles having a variety of substituents at the 2- and 3-positions were synthesized by reacting propargylic aziridines with iodine. Whereas *N*-tosyl-substituted substrates require a platinum catalyst to promote the reaction, the iodine-promoted cycloisomerizations proceed when *N*-benzyl-substituted substrates are employed.

1. Introduction

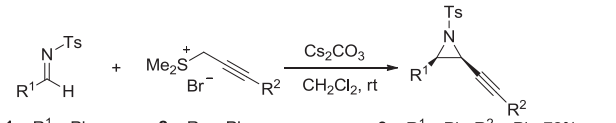
Substituted pyrroles are used extensively in heterocyclic chemistry as key structural subunits in biologically active molecules and in compounds for industrial purposes.[1] They are also widely utilized as synthetic intermediates in organic synthesis for further structural elaboration.[2] Consequently, considerable effort has been devoted to the development of an efficient methodology for the synthesis of pyrroles.[3] Transition metal-catalyzed cycloisomerization of propargylic aziridines is one such methodology, in which a variety of 2,5-disubstituted pyrroles is obtained with gold[4] or platinum[5] catalysts. During the course of our study of platinum-catalyzed cycloisomerization of propargylic oxiranes, it was found that 3-iodofurans could be synthesized in the presence of NIS as an electrophile (Scheme 1).[5,6] We anticipated that a similar reaction would proceed if propargylic aziridines were employed as the substrate. We report herein the synthesis of 3-iodopyrroles by cycloisomerization of propargylic aziridines with iodine, in which various 2,5-disubstituted 3-iodopyrroles were synthesized with high efficiency.[7]



Scheme 1. Synthesis of 3-iodofuran by cycloisomerization of propargylic oxiranes.

2. Results and discussion

N-Tosyl-substituted propargylic aziridines, the initial substrates for the cycloisomerization reaction, were easily prepared by ylide aziridination of the *N*-sulfonylimines with sulfonium propargylides (Scheme 2).[4b,8] Thus, when the imines **1a**–**f**, having a variety of substituents, were treated with the propargylic dimethylsulfonium salts **2a**–**c** and Cs_2CO_3 at rt, the corresponding *cis*-propargylic aziridines **3a**–**h** were selectively produced in moderate to good yields.



1a R^1 = Ph
1b R^1 = Cy
1c R^1 = Pr
1d R^1 = Bu
1e R^1 = ^{i}Pr
1f R^1 = 2-BrPh

2a R_2 = Ph
2b R_2 = Hex
2c R_2 = TMS

3a R^1 = Ph R^2 = Ph 72%
3b R^1 = Cy R^2 = Ph 61%
3c R^1 = Pr R^2 = Ph 53%
3d R^1 = Bu R^2 = Ph 32%
3e R^1 = ^{i}Pr R^2 = Ph 61%
3f R^1 = 2-BrPh R^2 = Ph 53%
3g R^1 = Ph R^2 = Hex 73%
3h R^1 = Ph R^2 = TMS 84%

Scheme 2. Synthesis of *N*-tosyl-substituted propargylic aziridines **3**.

The initial reactions for the synthesis of substituted pyrroles were attempted using the diphenyl-substituted propargylic aziridine **3a** (Table 1). When **3a** was subjected to the reaction with NIS and 10 mol % of $PtCl_2$ in dioxane/H_2O (2/1) at 100 °C following our procedure for the synthesis of 3-iodofuran,[5,6] only decomposition of the substrate was observed (entry 1). However, the desired 3-iodopyrrole **4a** was produced in 35% yield using iodine as the electrophile (entry 2). After experimenting with various solvents and temperatures (entries 3–8), we found that the yield of **4a** could be increased to 92% when the reaction was carried out in MeCN/H_2O (10/1) at 80 °C (entry 8).

Having identified a useful set of reaction conditions, we next conducted a study of the substrate scope (Table 2). Propargylic aziridine **3b** having a cyclohexyl group on the aziridine ring

* Corresponding author. Tel./fax: +81 88 6337294; e-mail address: yoshida@ph.tokushima-u.ac.jp (M. Yoshida).

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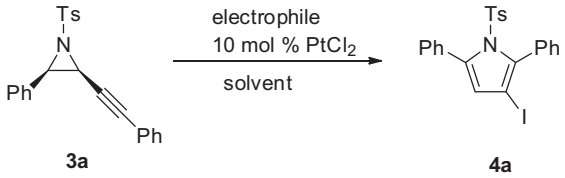
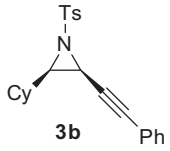
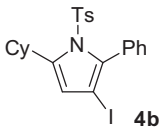
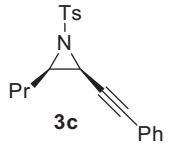
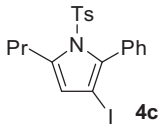
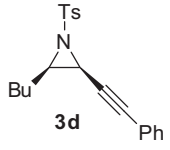
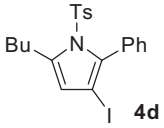
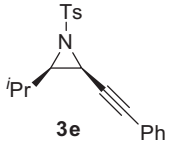
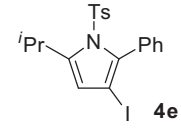
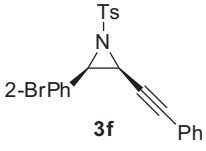
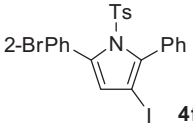
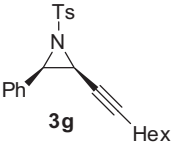
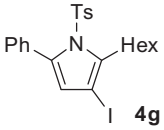
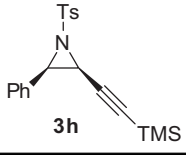
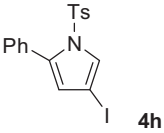
Table 1
Platinum-catalyzed iodocyclizations of **3a**



Entry	Electrophile	Solvent	Temp (°C)	Yield (%)
1	NIS	Dioxane/H_2O (2/1)	100	Decomp.
2	I_2	Dioxane/H_2O (2/1)	100	35
3	I_2	PhCN/H_2O (2/1)	100	48
4	I_2	MeCN/H_2O (2/1)	100	50
5	I_2	MeCN/H_2O (2/1)	80	55
6	I_2	MeCN/H_2O (2/1)	60	48
7	I_2	MeCN/H_2O (5/1)	80	60
8	I_2	MeCN/H_2O (10/1)	80	92

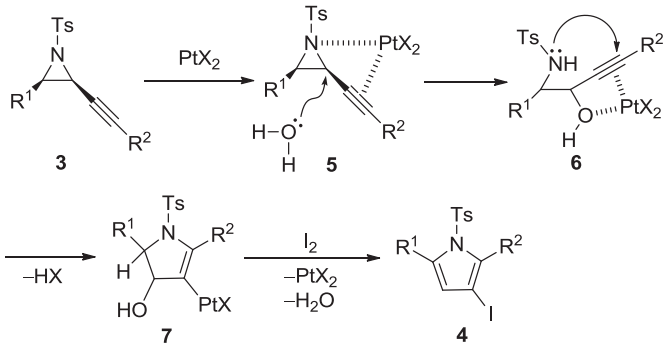
Table 2
Reactions with various propargylic aziridines **3b**–**h**[a]

Entry	Substrate	Product	Yield (%)
1			95
2			64
3			65
4			85
5			66
6			25
7			45

[a] All reactions were carried out in the presence of 2 equiv iodine and 10 mol % $PtCl_2$ MeCN/H_2O (10/1) at 80 °C for 10 min.

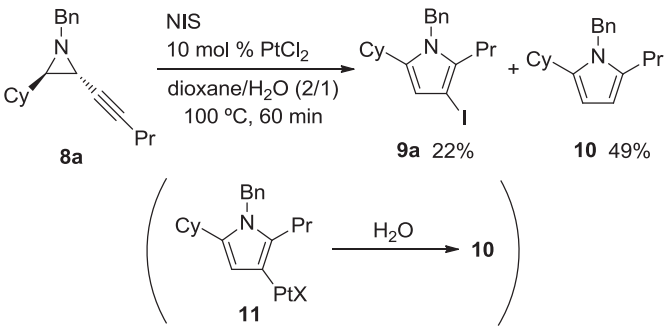
successfully reacted with iodine in the presence of the platinum catalyst to produce the 3-iodopyrrole **4b** in 95% yield (entry 1). When the reactions of the substrates **3c**, **3d**, and **3e** containing an alkyl group were carried out, the corresponding products **4c**, **4d**, and **4e** were obtained in moderate yields (entries 2–4). The reaction of **3f** having a 2-bromophenyl group also afforded the pyrrole **4f** without any problems (entry 5). The corresponding product **4g** was produced from the reaction of **3g** with a hexyl group on the alkynyl moiety; however, the yield was decreased (entry 6). When the TMS-substituted substrate **3h** was subjected to the reaction, the desilylated product **4h** was obtained in only moderate yield (entry 7).

A plausible mechanism for the platinum-catalyzed cycloisomerization of **3** is shown in Scheme 3. Recently, Pale reported results of mechanistic studies on the metal-catalyzed cycloisomerization of propargylic oxiranes to furans in the presence of alcohol, in which the epoxide ring opening product with a hydroxyl group was identified as the reaction intermediate.[9] We concluded that a similar process can be expected to occur using our aqueous reaction conditions. Thus, the platinum catalyst activates the substrate **3** by coordination to the aziridine nitrogen, which promotes the aziridine ring opening by water as shown in **5**. The resulting sulfonamide nitrogen in **6** attacks the distal position of the alkyne to form the cyclized intermediate **7**. Aromatization by elimination of water followed by iodo-demetalation with iodine produces the iodopyrrole **4**.



Scheme 3.

We next examined the reactions using *N*-benzyl-substituted propargylic aziridines.[5] In our initial attempt, we used *trans*-propargylic aziridine **8a** under platinum-catalyzed iodocyclization conditions. When **8a** was treated with 10 mol % of $PtCl_2$ and 2 equiv NIS in dioxane/H_2O (2/1) at 100 °C for 60 min, the desired 3-iodopyrrole **9a** was produced in 22% yield along with the non-iodinated pyrrole **10** as the inseparable major product[10] in 49% yield (Scheme 4). Several attempts under various platinum-catalyzed conditions resulted in similar results. For this reason, it was thought



Scheme 4.