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Reagent-Controlled Oxidative Aromatization in Iodocyclization: Switchable Access to Dihydropyrazoles and Pyrazoles

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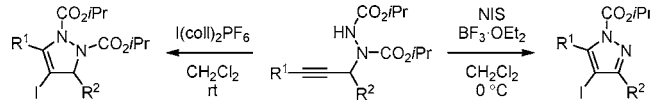
ABSTRACT



Switchable access to dihydropyrazoles and pyrazoles has been developed from common hydrazides by reagent-controlled iodocyclization. Controlling the oxidative aromatization in iodocyclization for heterocycles is reported for the first time, and this methodology maximally utilizes the dual nature of iodine.

Pyrazoles and its derivatives have been recongnized as an important framework in pharmaceutical science.[1] For example, Rimonabant (Acomplia) works as CB1 cannabinoid receptor antagonist for the treatment of obesity.[1a] Celecoxib (Celebrex) is used as an anti-inflammatory as a COX-2 inhibitor.[1b] Certain pyrazole derivatives possess antitumor[1c] and antiviral activities.[1d] Due to the attractive medicinal properties of the pyrazole skeleton, various efficient approaches have been developed for the preparation of these compounds.[2]

Iodocyclization is one of the most attractive methods for the construction of functionalized molecular architecture because this reaction can create not only ring skeletons but can also introduce the iodo functionality for further transformations. In addition, iodinating reagents are relatively inexpensive and are ideal for achieving environmentally friendly reactions.[3,4] During our iodocyclization project,[5] we thought of the iodocyclization of propargylic hydrazide **1a** for the synthesis of dihydropyrazole **2a** (Table 1) since there have been no reports for the iodocyclization of hydrazide as

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a nitrogen nucleophile toward alkynes.[6] In addition, propargylic hydrazide **1** could be easily prepared in only one step by the Mitsunobu reaction of diisopropyl azodicarboxylate with propargylic alcohol or *N*-alkylation of hydrazide with corresponding bromide (Scheme 1).[7]

Scheme 1. Preparation of the Precursors in Iodocyclization

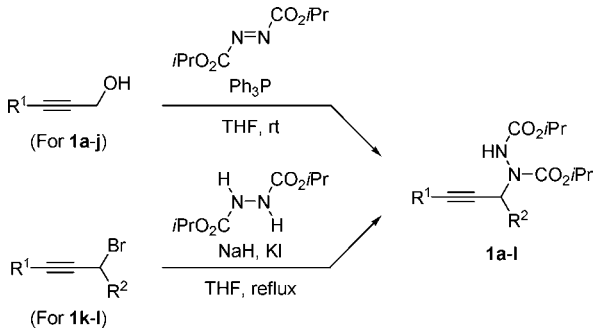
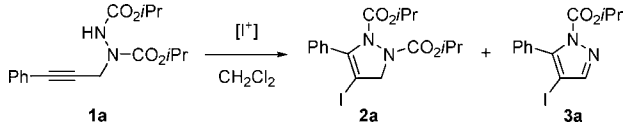


Table 1. Optimization for the Iodocyclization of **1a**[a]

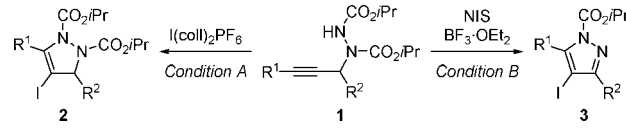


entry	$[I^+]$ (equiv)	additive	temp (°C)	time (min)	**2a** (%)	**3a** (%)
1	$I(coll)_2PF_6$ (2)	$BF_3{\cdot}OEt_2$	rt	30	17	44
2	**$I(coll)_2PF_6$ (2)**	**none**	**rt**	**30**	**85**	**0**
3	$I(coll)_2PF_6$ (1.5)	none	rt	20	82	0
4	NIS (2.5)	none	0	180	19	7
5	NIS (2.5)	$BF_3{\cdot}OEt_2$	0	30	0	72
6	**NIS (3)**	**$BF_3{\cdot}OEt_2$**	**0**	**10**	**0**	**84**
7	ICl (2.5)	$NaHCO_3$	rt	30	8	48

[a] Reaction was performed in CH_2Cl_2 (0.1 M) under Ar atmosphere. [b] Equivalent of additive is the same as that of $[I^+]$. [c] Isolated yield after purification by column chromatography.

First, we chose the combination of bis(2,4,6-collidine)-iodonium(I) hexafluorophosphate $[I(coll)_2PF_6]$[8] and $BF_3{\cdot}OEt_2$ as reaction conditions because this worked well in our previous studies.[5] As a result, we obtained desired product **2a** and unprecedented pyrazole **3a**, which would be formed by oxidative aromatization of **2a** (Table 1, entry 1). Iodinating reagents possess two natures: one is the ability to iodinate and the other is the ability to oxidize. Therefore, further oxidized products have sometimes been obtained during the iodocyclization process and such occasions depended on the nature of the cyclized products formed initially.[9] Nevertheless, there has been only one report of the control of such overoxidation by the conditions of iodocyclization.[10] We expected that we might achieve switchable access to dihydropyrazole **2** and pyrazole **3** from common hydrazide **1** by reagent control if the conditions

Table 2. Product Switch in Iodocyclization of **1**[a]



entry	**2** (Condition A: %)[b]	**3** (Condition B: %)[b]
1	*o*-MeO: **2b** (quant)	*o*-MeO: **3b** (99)
2	*m*-MeO: **2c** (79)	*m*-MeO: **3c** (74)
3	*p*-MeO: **2d** (78)	*p*-MeO: **3d** (quant)[c]
4	**2e** (23)	**3e** (0)
5	**2f** (88)	**3f** (91)
6	**2g** (84)	**3g** (90)
7	**2h** (83)	**3h** (87)
8	**2i** (54)	**3i** (70)[d]
9	**2j** (60)	**3j** (28)
10	**2k** (97)	**3k** (80)
11	**2l** (84)[e]	**3l** (53)[f]

[a] Condition A: $I(coll)_2PF_6$ (2 equiv), CH_2Cl_2 (0.1 M), rt, 30 min. Condition B: NIS (3 equiv), $BF_3{\cdot}OEt_2$ (3 equiv), CH_2Cl_2 (0.1 M), 0 °C, 10 min. [b] Isolated yield after purification by column chromatography. [c] Four equivalents of NIS and $BF_3{\cdot}OEt_2$ were used. [d] Two and a half equivalents of NIS and $BF_3{\cdot}OEt_2$ were used. [e] Four equivalents of $I(coll)_2PF_6$ was used. [f] Six equivalents of NIS and $BF_3{\cdot}OEt_2$ were used.

(6) Transition metal-catalyzed cyclization of hydrazides, see: (a) Yang, Q.; Jiang, X.; Ma, S. *Chem.—Eur. J.* **2007**, *13*, 9310–9316. (b) Cheng, X.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4581–4583. (c) Shu, W.; Yang, Q.; Jia, G.; Ma, S. *Tetrahedron* **2008**, *64*, 11159–11166.

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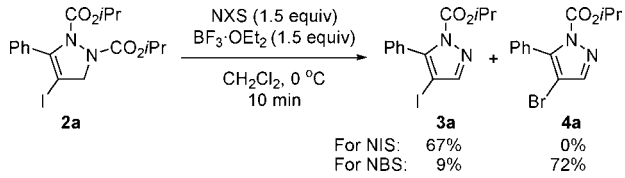
(10) During the preparation of this manuscript, the first report of controlling the oxidative aromatization for carbocycles appeared: Crone, B.; Kirsch, S. F.; Umland, K.-D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4661–4664.

were tuned.[11] To achieve our strategy, we elaborated the reaction conditions, and found that $I(coll)_2PF_6$ as the iodinating reagent at room temperature afforded dihydropyrazole **2a** in 85% yield (entry 2). In contrast, the combination of *N*-iodosuccinimide (NIS) and BF_3•OEt_2 at 0 °C gave pyrazole **3a** in 84% yield (entry 6), as the sole product.[12] In this study, other Lewis acids were not tried because BF_3•OEt_2 was the inexpensive and easy handling reagent. Among the carbamate groups, isopropyloxycarbonyl was the most suitable for both iodocyclization conditions (data was not shown).

These clear results encouraged us to examine the scope of usable substrates (Table 2). In almost cases, dihydropyrazole **2** and pyrazole **3** were selectively produced from propargylic hydrazide **1**. For the substituents on alkynes, various aryl and heteroaryl groups were successful while the *p*-nitrophenyl group was not suitable as a substrate (entries 1−7). Vinylic and alkyl substituted alkynes were also applicable under these reaction conditions and afforded the cyclized products in moderate to good yields except for **3j**, due to the unstability of formed iodonium ion (entries 8 and 9). The iodocyclizations also allowed for the presence of substitution at the propargylic position (entry 10). Furthermore, double-iodocyclizations were achieved by using twice the quantity of reagents to obtain **2l** and **3l** which contained three connected heterocycles (entry 11).

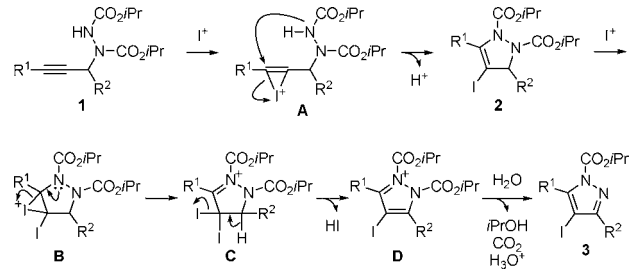
To better understand the reaction mechanism, we treated dihydropyrazole **2a** with the combined reagent NIS/BF_3•OEt_2 to give pyrazole **3a** in 67% yield (Scheme 2). The treatment of **2a** with the *N*-bromosuccinimide (NBS)/BF_3•OEt_2 combination instead of NIS afforded 4-bromopyrazole **4a** as a major product accompanied with **3a**. **4a** was individually prepared from **1a** with NBS/BF_3•OEt_2 system in 49% yield. These results indicated that pyrazole **3** was formed via electrophilic addition of halonium ion to dihydropyrazole **2**. Although **2a** was exposed to BF_3•OEt_2 alone as a control experiment, the reaction did not proceed at all.

Scheme 2. Halonium Ion-Induced Oxidative Aromatization of **2a**



On the basis of the outcomes of these reactions, we proposed a reaction mechanism for the iodocyclization

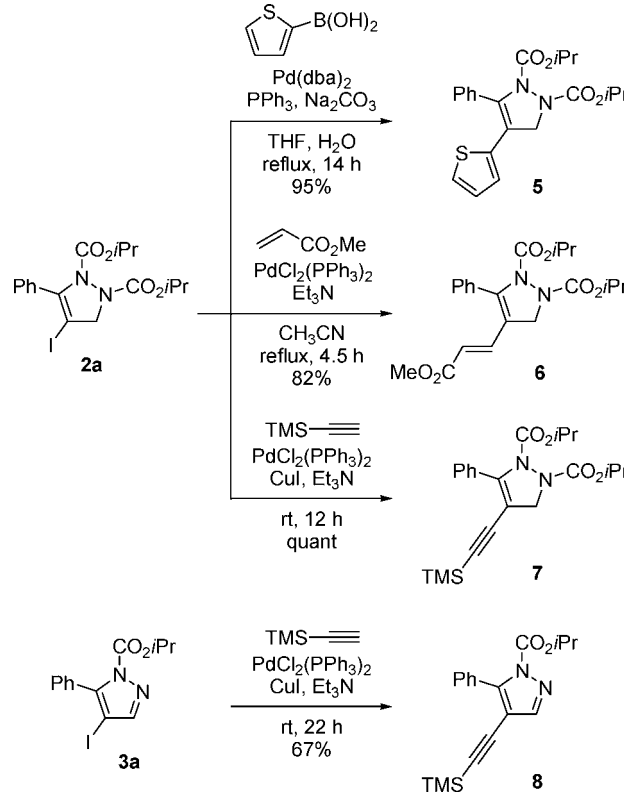
Scheme 3. Possible Reaction Mechanism



(Scheme 3). The 5-*endo* cyclization of iodonium ion **A** formed by electrophilic addition of I^+ to alkyne **1** gives dihydropyrazole **2**. When a more acidic condition, the NIS/BF_3•OEt_2 system, is employed, more reactive I^+ source might caused further iodination at an enecarbamate group to produce iodonium ion **B**. The ring-opening of **B** followed by the elimination of HI from acyl hydrazonium ion **C** affords pyrazolium ion **D**. Pyrazole **3** would be formed by hydrolysis at the less hindered carbamate group of **D**. The position of the carbamate group for **3** was unambiguously assigned by $^1H-^{15}N$ HMBC NMR spectra (see Supporting Information).

As described above, the iodo functionality can create diversity by metal-catalyzed cross-coupling. For example, we applied dihydropyrazole **2a** toward palladium-catalyzed

Scheme 4. Transformation of **2a** and **3a**



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coupling reactions such as Suzuki−Miyaura cross-coupling,[13] Heck reaction,[14] and Sonogashira cross-coupling[15] to achieve C−C bond formation in high yields (Scheme 4). In addition, pyrazole **3a** was also able to use in subsequent reaction to afford **8** in moderate yield. These results indicated that C−I bond of both **2** and **3** was available for the assembly of carbon-unit.

In summary, this work represents a switchable access to dihydropyrazoles and pyrazoles from the common hydrazides. Controlling the oxidative aromatization in iodocyclization for heterocycles is reported for the first time and this methodology maximally utilizes the dual nature of iodine. The concept of our methodology would be adaptable for other substrates. Moreover, the flexible synthetic strategy including potent functionalization may provide a powerful tool for drug discovery and other fields. Studies of the details of the mechanism and the scope of substrates are currently in progress.

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Supporting Information Available: Experimental procedures and spectroscopic data for the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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