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# Synthesis of 2,5-Disubstituted 6-Azaindoles from Substituted Aziridines via Intramolecular Cyclization

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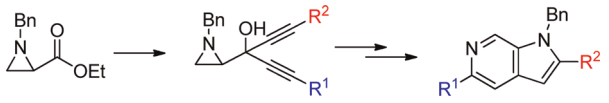
## ABSTRACT




**A new and efficient preparation of pharmacologically and biologically important 2,5-disubstituted 6-azaindoles was achieved from cyclizations of aziridin-2-yl dipropargylic alcohols as adducts of two propargyl groups to ethyl 1-benzylaziridine-2-carboxylate. The sequential cyclizations include pyrrole formation and a novel base-catalyzed intramolecular acetylenic Schmidt reaction.**

Azaindole structural units are found in natural marine products, and the importance of their derivatives is reflected in biologically active compounds as indole isosteres.[1] Several strategies for azaindole synthesis have been reported by Reissert, Batcho-Leimgrube, Hemetsberger-Knitel, and Bartoli.[2] However, these methods need improvement in terms of long reaction times, harsh reaction conditions, and low yields. Yet, recently better preparatory methods have come to light such as the Aza-Fischer reaction;[2] transition metal catalyzed cyclizations[4] using Pd, Ru, Zr, Ti, and Cu; and a dilithiation pathway.[5] However, previous synthetic methods cannot provide functionalized 6-azaindoles in high yields.

Compounds containing 6-azaindole show pharmacological activity[1,6] as HIV-1 inhibitors and have a characteristic photophysical property.[7] The synthetic routes for these compounds are limited. Most azaindole syntheses start from substituted pyridines to form a pyrrole unit.[3−5,8] Here, we would like to propose a new efficient synthetic route for the 2,5-substituted 6-azaindoles using an intramolecular pyrrole formation followed by a pyridine ring formation *via* an intramolecular azide cyclization reaction into the acetylenic unit.

We recently reported an efficient synthesis of 1,2,3,5-substituted pyrroles from *N*-benzylaziridine-2-carboxylate (**1**),[9] which is a readily available starting material. The ester **1** was reacted with 2 equiv of various lithium acetylides to

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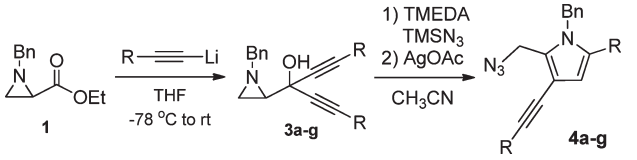
provide the corresponding dipropargylic alcohols **3** in high yields. This time we were able to prepare 1,2,3,5-substituted pyrroles which have a 2-azidomethyl substituent and various acetylenic substituents at the C-3 position *via* regioselective aziridine ring opening[10] by $TMSN_3$, followed by silver ion catalyzed intramolecular cyclization (Scheme 1 and Table 1).

**Table 1.** Preparation of Substituted Pyrrole **4**




| entry | R | yield of **3** (%) | yield of **4** (%) |
|---|---|---|---|
| 1 | phenyl | **3a**, 98 | **4a**, 92[a] |
| 2 | 4-methoxyphenyl | **3b**, 84 | **4b**, 89[a] |
| 3 | 2-tolyl | **3c** 85 | **4c**, 92[a] |
| 4 | 4-fluorophenyl | **3d**, 94 | **4d**, 95[a] |
| 5 | pyridin-2-yl | **3e**, 91 | **4e**, 80[b] |
| 6 | 6-methoxynaphthalen-2-yl | **3f**, 91 | **4f**, 91[a] |
| 7 | phenanthren-9-yl | **3g**, 76 | –[c] |

[a] The reaction was carried out in $CH_3CN$ . [b] The reaction was carried out in DCM . [c] The reaction was carried out in DCM/$CH_3CN$. Not isolated.

With the 2-azidomethyl-substituted pyrroles, we carried out intramolecular acetylenic Schmidt reactions[11] for the synthesis of azaindoles in various reaction conditions. Unlike usual indolization reactions in the presence of a pyrrole ring, pyrrole-fused pyridine cyclization methods to provide azaindoles are rare[12] and introducing various substituents in the azaindole ring is another challenging task.

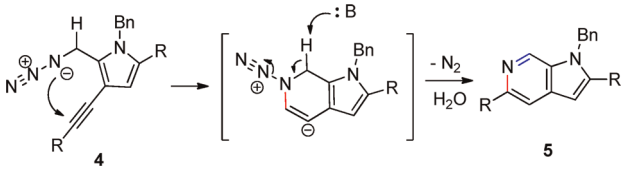
In the reactions of modified intramolecular azido, cyclization provides 6-azaindoles in high yield without using metal catalysts (Table 2).[13] When the reaction was carried out without a base in DMSO and toluene, we could not obtain any product (entries 1 and 3). But in DMF we obtained the expected 6-azaindole in 18% yield (entry 2). However, when we added a hydroxide base (KOH), the cyclization reaction proceeded smoothly to provide the corresponding azaindole (entries 4 and 5). After nitrogen cyclization to the acetylenic unit, the deprotonation followed by $N_2$ elimination seemed to be the driving force to form 2,5-substituted 6-azaindoles in both DMSO (49%) and DMF (87%).

**Table 2.** Formation of 2,5-Diphenyl-6-azaindole


| entry | base (equiv) | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | – | toluene | 140 | 48 | failed |
| 2 | – | DMF | 140 | 8 | 18 |
| 3 | – | DMSO | 140 | 12 | failed |
| 4 | KOH (5) | DMSO | 140 | 18 | 49 |
| 5 | KOH (5) | DMF | 140 | 6 | 87 |

The mechanism of this modified intramolecular azido cyclization of 2-azidomethyl-substituted pyrroles **4** with a hydroxide base to form 6-azaindoles **5** is proposed with the intramolecular base-catalyzed Schmidt cyclization shown in Scheme 1. The anionic nitrogen of the azide attacks the acetylene to form a six-membered ring, and then deprotonation of the benzylic proton by the hydroxide base releases nitrogen gas to promote aromatization. As far as we know, this is the first example of 6-endo intramolecular acetylenic Schmidt cyclization that is free from any metal catalyst.[14]

**Scheme 1.** Proposed Mechanism of 6-Azaindoles Formation




This synthetic method was used to introduce various substituents on the 2- and 5-positions of 6-azaindoles. The cyclization reactions provided 6-azaindoles with diverse aryl groups bearing electron donors, electron acceptors, and bulky substituents. In all cases, intramolecular cyclization was succeeded to provide 6-azaindoles **5a**–**5g** in high yields of 74–87% (Table 3).

We also prepared 6-azaindoles which have different substituents on the 2- and 5-positions from heterosubstituted bispropargylic alcohols **3h**, **3i**, and **3j** synthesized by two successive alkylation processes using different acetylene reagents.

Low temperature alkynylations provided the corresponding ketones **2** in good yields. Subsequent addition of one more alkyne afforded tertiary bispropargylic alcohols **3h**, **3i**, and **3j** with two different substituents $R^1$ and $R^2$ (Table 4).

When pyrrole cyclization was carried out with the tertiary alcohols containing two different acetylenic

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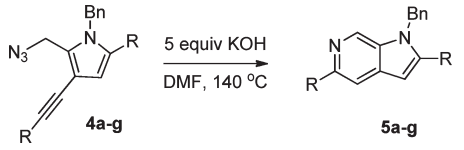
(14) The intramolecular acetylenic Schmidt cyclization was first reported in ref 11, which was a gold(II)-catalyzed 5-*exo* process.

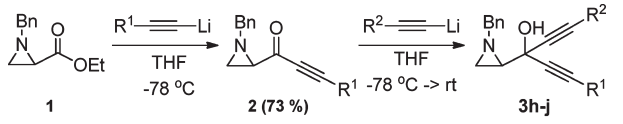
**Table 3.** Preparation of 2,5-Disubstituted 6-Azaindoles (**5**) from Pyrroles (**4**)




| entry | R | yield of **5** (%) |
|---|---|---|
| 1 | phenyl | **5a**, 87 |
| 2 | 4-methoxyphenyl | **5b**, 84 |
| 3 | 2-tolyl | **5c**, 74 |
| 4 | 4-fluorophenyl | **5d**, 84 |
| 5 | pyridin-2-yl | **5e**, 75 |
| 6 | 6-methoxynaphthalen-2yl | **5f**, 78 |
| 7 | phenanthren-9-yl | **5g**, 76[a] |

[a] Three-step yield.

**Table 4.** Preparation of Bispropargylic Alcohols




$R^1$ = 3,5-difluorophenyl, $R^2$ = aryl

| entry | $R^2$ | yield of **3** (%) |
|---|---|---|
| 1 | 4-(dimethylamino)phenyl | **3h**, 75 |
| 2 | 4-methoxyphenyl | **3i**, 84 |
| 3 | 4-tolyl | **3j**, 88 |

substituents, the regioselectivity of the cyclization was controlled by the electronic character of the alkynic bond. It was observed that only one pyrrole product **4 hα** was obtained when we had a strongly electron-donating 4--(dimethylamino)phenyl substituent and a strongly electron-withdrawing 3,5-difluorophenyl (Table 5, entry 1). However, as the difference between EDG and EWG became smaller, i.e. from 4-(dimethylamino)phenyl to 4-methoxyphenyl and 4-tolyl, the regioselectivity between α and *β* in the cyclization became poorer, i.e. 83:17 and 77:23 (Table 5). Regioselectivity of the pyrrole formation was controlled by the electronic character of the triple bond. A silver cation activates the comparably electron-rich acetylene between two substituents. As a consequence the pyrrole formation proceeds regioselectively toward the triple bond containing an electron-donating substituent.

The structure of the 6-azaindole **5h** was confirmed by NOE experiments (Figure 1). These data confirm the structure of the 6-azaindole **5h** and also show that intramolecular pyrrole cyclization occurred selectively to more electron-rich acetylenic systems.

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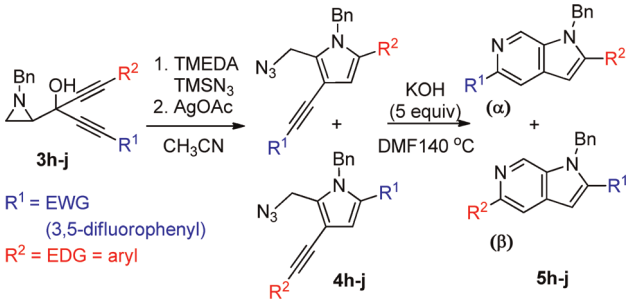
**Table 5.** Regioselective Formation of Pyrroles **4** and 6-Azaindoles **5** from Aziridin-2-yl Bispropargylic Alcohols **3**




| entry | $R^2$ | yield of **4** (%) | yield of **5** (%) | α/*β* |
|---|---|---|---|---|
| 1 | 4-(dimethylamino)phenyl | **4h**, 84 | **5h**, 70 | 100:0 |
| 2 | 4-methoxyphenyl | **4i**, 84 | **5i**, 71 | 83:17 |
| 3 | 4-tolyl | **4j**, 82 | **5j**, 79 | 77:23 |

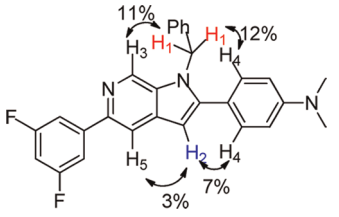
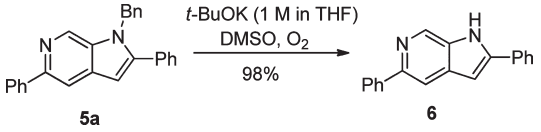



**Figure 1.** NOE interaction of 6-azaindole **5h**.

**Scheme 2.** Cleavage of the *N*-Benzyl Substituent




The *N*-benzyl group originating from aziridine was easily removed with *t*-BuOK to provide 6-azaindole **6**, which has a free pyrrole unit in high yield (Scheme 2).[15]

In conclusion, 2,5-disubstituted 6-azaindoles were efficiently synthesized in high yields by an intramolecular azido cyclization reaction to the acetylenic group of azidomethyl substituted pyrroles which were prepared from substituted aziridines.

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**Supporting Information Available.** Experimental details and copies of $^1$H and $^{13}$C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.