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Nickel–palladium-catalyzed hydroamination/cyclization of sulfur-substituted 1,6-diynes with secondary amines

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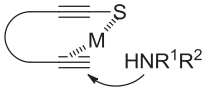
ABSTRACT

Hydroamination/cyclizations of sulfur-substituted 1,6-diynes catalyzed by nickel or nickel–palladium in DMSO were examined. Pyrroles **2a**–**l** and furans **5a**–**i** bearing various secondary amines were obtained in high yields. The organosulfanylmethyl group on pyrroles was easily oxidized with ceric ammonium nitrate to produce the pyrrolecarboxaldehyde and corresponding acetal.

1. Introduction

Hydroamination (HA) of alkynes, defined as a simple and atom-economical process leading to enamines and imines, has been usually applied to the intramolecular cyclizations for the syntheses of a wide variety of nitrogen containing heterocycles such as pyrrolidines, pyrazoles, indoles, isoindoles, and imidazoles scaffolds.[1] Recently, considerable attention has been paid to HA-triggered cyclizations of alkynes for the synthesis of heterocyclic skeletons of greater structural complexity in a variety of biologically active natural products.[2] General and convenient methods for HA/cyclization processes consist of two common important strategies: i, activation of alkynes using transition metals[3–13] as well as lanthanides;[14–16] ii, nucleophilic attack of the intramolecular nitrogen atom, where, the possibility of successful construction of heterocycles is attributed to the nucleophilicity of nitrogen. Recently we investigated metal-free and metal-catalyzed cyclizations of sulfanyl 1,6-diynes triggered by some useful functionalization. Our concept is one of the useful approaches for the synthesis of heterocycles from 1,6-diynes bearing organosulfur substituents, which could activate their alkynes by their strong electron-donating effect. We previously reported that the alkoxylation- and aryloxylation-triggered cyclizations of oxygen-tethered 1,6-diynes afforded alkoxymethyl- and aryloxymethyl-furans and anti-cancer tanshinone derivatives.[17] Furthermore, the organosulfur functional group on the 1,6-diynes could be coordinated with some transition metals.[18] Therefore, the transition metal-catalyzed functionalization-cyclizations of the sulfanyl 1,6-diynes are expected to proceed with high regioselectivities. During the course of our study on the functionalization-cyclizations, we explored the HA-triggered cyclizations of 1,6-diynes, as shown in Fig. 1. To date, the only example of amine functionalization-cyclizations of 1,6-diynes is cobalt-mediated reactions using carboxamides,[19] which have very low nucleophilicities. However, the development the clinical drugs requires the preparation of heterocycles bearing a wide variety of highly nucleophilic amines, rather than amides (Fig. 2). A metal-free or metal-catalyzed amine functionalization-cyclization of 1,6-diynes leading to the amine-functionalized heterocycles will be an important tool in drug-discovery processes.

Here we report the first catalytic HA/cyclization of 1,6-diynes leading to functionalized heterocycles as shown in Eq. 1. Furthermore, we demonstrate that the organosulfanylmethyl group on the



Amine functionalization-cyclizations (This work)

Fig. 1. Intermolecular hydroaminations/cyclizations.

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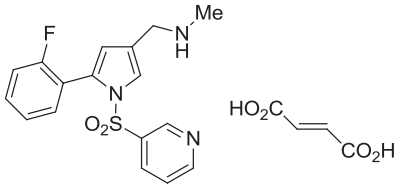
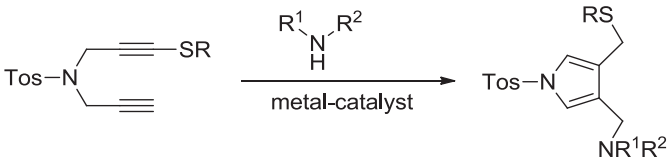


Fig. 2. Representative aminomethylpyrrole, TAK-438.

heterocycles is successively transformed to the formyl group, which is potentially useful for further transformations.



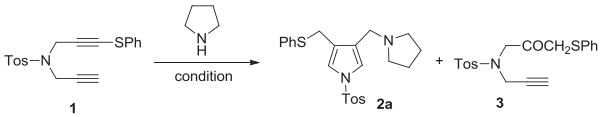
2. Results and discussion

First, we screened the suitable reaction condition for HA/cyclization of a simple *N*-tosyl 1,6-diyne **1**, which were simply prepared by Mitsunobu reaction from *N*-tosylpropyne and phenylsulfanylpropargyl alcohol, using pyrrolidine. We attempted the metal-free amination/cyclization of **1**; however, the reaction did not proceed. According to our alkynylation condition of 1,6-diynes, we examined the Cu(I)-catalyzed reactions and obtained the 4-pyrrolidinylmethylpyrrole **2a** in low yields (entry 1). Next, we performed the copper-catalyzed amination/cyclizations under the similar conditions. The results were not satisfied (entries 2 and 3), however, we continued to perform the HA/cyclizations catalyzed by transition metals such as palladium, nickel, and other lanthanides. Lanthanide metals were not effective. Nickel and palladium dramatically improved the yields of **2a** (entries 4 and 5), however, ynone **3** was obtained as a side product.

We attempted the palladium-catalyzed HA/cyclizations in the presence of some ligands and bases, however, the yields of the products did not dramatically change (entries 5 and 6). Then, we next performed the nickel-catalyzed amination/cyclizations as shown in entries 7–22. The inert ligands like chloride, triflate and diphenylphophinoethane (dppe), diethyl dithiocarbamate (dedt) were not effective (entries 7–9, 12). The reaction of **1** in DMSO/H_2O gave rise to increasing the yield of **3** (entry 10). The molecular sieves (MS) were not effective for the formation of **2a** (entry 11). The reaction using Ni(0), nickelocene, of which reactions would usually provide the nickellacycle intermediates, also afforded the pyrrolidinylmethyl **2a** in moderate yield (entry 13). DBU also accelerated the HA/cyclization reaction at room temperature (entry 14). Bis(hexafluoroacetylacetonato)nickel mono hydrate in DMSO was found to give superior results by comparing the examinations of both the solvent effects and the additives (entries 15–20). When the nickel-catalyzed HA/cyclizations were examined, the diyne **1** was not disappeared in the reaction mixture (entries 20 and 22). Since the reaction under the nickel–palladium mixed catalyst condition was complete without the formations of any side products (entry 21), we selected the suitable reaction condition (method B): Ni(hfa)$_2$ (0.1 equiv)/Pd(PPh$_3$)$_2$Cl$_2$ (0.1 equiv), DBU (1 equiv) in DMSO. We next performed amination/cyclizations using various amines. The results are shown in Table 2.

For a series of cyclic amines, two kinds of experiments were performed to investigate HA/cyclizations of 1,6-diynes **1**. The reaction with piperidine using Ni-catalyst at room temperature gave 4-(1-piperidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole **2b** in 79% yield (entry 1) (method A). The Ni/Pd-catalyzed reaction quantitatively afforded

Table 1
Screening for HA of 1,6-diyne **1** with pyrrolidine



Entry	Condition: catalyst (mol %), amine (equiv), solv, time	Yield[a] (%)	
		2a	**3**
1	CuOTf (10), DBU (1.5), DMF, rt, 0.5 h	32	0
2	CuI (3), DBU (1), DMF/H_2O, 0 °C, 1 h	19	0
3	CuBr SMe$_2$, DBU (1.5), DMSO, rt, 0.5 h	36	0
4	NiCl$_2$(PPh$_3$)$_2$ (10), DMSO, rt, 3 h	70	16
5	PdCl$_2$(PPh$_3$)$_2$ (10), DMSO, rt, 4 h	55	16
6	PdCl$_2$(PPh$_3$)$_2$ (10), DBU (1), DMSO, rt, 4 h	59	5
7	NiCl$_2$ (10), DMSO, rt, 2.5 h	64	15
8	Ni(OTf)$_2$ (10), DMSO, rt, 2 h	57	10
9	NiCl$_2$(dppe) (10), DMSO, rt, 1.5 h[b]	64	16
10	NiCl$_2$(dppe) (10), DMSO/H_2O, TBA,[c] rt, 4 h	39	19
11	NiCl$_2$(dppe) (10), MS,[d] DMSO, rt, 3.5 h	59	13
12	Ni(dedt) (10), DMSO, rt, 2 h[e]	62	15
13	Nickelocene (10), DMSO, rt, 2 h	52	23
14	NiCl$_2$(PPh$_3$)$_2$ (10), DMSO, DBU (1), rt, 1 h	88[f]	0
15	NiCl$_2$(PPh$_3$)$_2$ (10), THF, rt, 4 h	15[f]	8
16	Ni(hfa)$_2$ (10), DMSO, rt, 3.5 h[g]	78	9
17	Ni(hfa)$_2$ (10),[g] MeNO$_2$, rt, 3 h	18[f]	11
18	Ni(hfa)$_2$ (10), DMSO, rt, 1.2 h	72	13
19	Ni(hfa)$_2$ (10), DMF, rt, 2.5 h	60	19
20	Ni(hfa)$_2$ (10),[g] DBU (1), DMSO, rt, 4 h	89[f]	
21	Ni(hfa)$_2$ (10),[g] PdCl$_2$(PPh$_3$)$_2$ (10), DBU (1), DMSO, rt, 4 h	Quant.	0
22	Ni(hfa)$_2$ (10),[g] PPh$_3$ (10), DBU (1), DMSO, rt, 4 h	91[f]	

[a] Yield of isolated product.
[b] dppe: diphenylphosphinoethane.
[c] Tetrabutylammonium hydrogensulfate (0.2 equiv) was added.
[d] MS: molecular sieves.
[e] dedt: diethyl dithiocarbamate. Ni(dedt) were used as mono hydrate.
[f] The diyne **1** was recovered in 8% (entry 14), 70% (entry 16), 70% (entry 17), 4% (entry 20) and 3% (entry 22) yields.
[g] hfa: hexafluoroacetylacetone. Ni(hfa)$_2$ was used as mono hydrate.

2b (entry 2) (method B). A similar tendency was observed in the reactions with morpholine and *N*-methylpiperadine (entries 3–6). As shown in the entries 7 and 8, piperadine bearing further functionalized amines provided the aminomethylated product **2e**; however, the reaction with thiazolidine gave a ring-opening product **2f** in low yield (entry 9). Next we performed aminations using the linear amines and obtained diethylaminomethyl-, hydroxyethylmethylaminomethyl-, and 2-(*N*,*N*-dimethylamino) ethylmethylaminomethylpyrrole presented as **2g**, **2h**, and **2i**, respectively (entries 10–14). N-containing heterocycles also afforded the hetarylmethylpyrroles **2j**–**2l** in moderate-to-good yields (entries 15–20).

We also examined the HA/cyclizations of 3-aryl-4-oxahepta-1,6-diynes **4**, which were easily prepared by our usual method[20] from sulfur-substituted propargyl alcohol and prop-2-yn-1-ol, using the similar cyclic amines. The results are shown in Table 3. The cyclizations of 4-oxahepta-1,6-diynes provided 2-aryl-4-aminomethylfurans **5a**–**i** in good yields. Piperidinylmethyl-, 4-methylpiperadinylmethyl, benzimidazolylmethyl, and 3-oxo-1,4-benzthiazin-4-ylmethyl 2-arylfuran presented as **5a**–**d**, respectively, are shown in entries 1–4. 2-*p*-Bromophenyl- and *p*-chlorophenyl, and 1-naphthyl-1,6-diynes also afforded furans **4e**–**i** (entries 5–9).

Although the details of the mechanism of this HA/cyclization reaction are not completely understood, a speculative pathway is shown in Scheme 1. According to our previous reports,[17a,b] the sulfanyl 1,6-diynes isomerized to the alkyne–allene **8** or allene–allene intermediates **9** via a carbanion **7**. The nickel catalyst binds to give the sulfur-coordinated intermediate **10**, which would activate the alkyne toward intermolecular attack by the amine, and