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ARTICLE

Silver(I)-catalyzed sequential hydroamination and Prins type cyclization for the synthesis of fused benzo-δ-sultams

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An intramolecular annulation strategy has been developed for the synthesis of tetrahydrobenzo[*e*]pyrano[4,3-*c*][1,2]thiazine derivatives by means of coupling of aldehydes with 2-(4-hydroxybut-1-yn-1-yl)-*N*-arylsulfonamides using a catalytic amount of silver hexafluoroantimonate in toluene at 80 °C. This is the first report on the synthesis of fused benzo-δ-sultam derivatives through C-N, C-O, and C-C bond formations. The reaction proceeds through a cascade of hydroamination and Prins type cyclization.

Introduction

Benzosultams are important targets for drug discovery because of their potent biological activities.[1] In particular, 1,2-benzothiazine-1,1-dioxides are the most important class of non-steroidal anti-inflammatory drugs (NSAIDs) available in the market (Figure 1).[2] They behaves as calpain I inhibitors[3] and HIV inhibitors[4] and also used for the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis (Figure 1).[5] Consequently, several methods have been developed for the synthesis of benzosultam derivatives[6] through a transition metal catalysis.[7-11] Recently, silver(I) catalysts[12] have been successfully utilized for the annulation of alkynes to construct aromatic and heteroaromatic ring systems. Indeed, Ag(I) salts are highly efficient in the activation of alkynes and also act as Lewis acids to facilitate C-C and C-N bond formations.[13] Among them, $AgSbF_6$ is the most preferred catalyst for alkyne annulations.[14] However, there are no reports on the synthesis of dihydropyran fused benzo-δ-sultam derivatives.

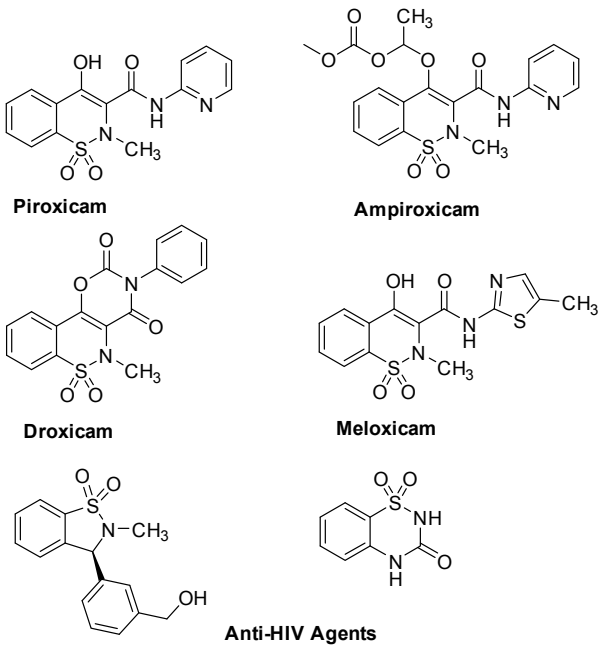

Figure 1. Biologically active benzosultams

Results and discussion

Following our interest on Prins type cyclizations,[15] we herein report a novel strategy for the synthesis of benzo-δ-sultams through a cascade of sulfonamide-alkynol-aldehyde cyclization. Based

[a,a]*Centre for Semiochemicals,* [b]*Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007 India. E-mail: basireddy@iict.res.in;* [1]*H and* [13]*C NMR spectra of products. See DOI: 10.1039/x0xx00000xAddress here.*

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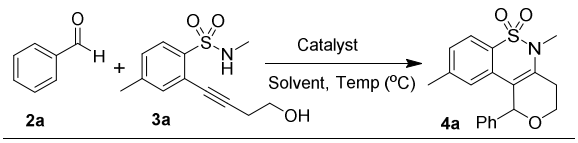
on our previous work on sequential alkyne annulation and Prins cyclization using Au(I) catalysis[15d,e] we attempted the coupling of benzaldehyde (**2a**) with alkynol (**3a**) using 5 mol% Ph_3PAuCl or IPrAuCl in dichloroethane (Table 1, entries a, b). But none of them gave the desired product **4a** either at room temperature or under reflux conditions. The reaction was then performed using 5 mol% $AgSbF_6$ in dichloroethane. To our delight, the product **4a** was isolated in 65% yield (Table 1, entry c). To improve the yield, the reaction was further carried out in toluene (Table 1, entry d). Interestingly, **4a** was obtained in 91% yield under above reaction conditions. To know the efficacy of other silver catalysts, the reaction was performed using AgOTf and $AgBF_4$ (Table 1, entries e and f). But the product **4a** was obtained in low yields. Therefore, the reaction was further carried out with different Lewis acids such as TMSOTf, $BF_3.OEt_2$, $FeCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, and $InCl_3$ (Table 1, entries e, f, g, h, i, j, k, and l). To our surprise, no desired product was obtained with TMSOTf or $BF_3.OEt_2$ or $FeCl_3$. Other Lewis acids like $In(OTf)_3$, $Sc(OTf)_3$ and $InCl_3$ gave the product in low yields (Table 1, entries j, k, and l). However, Bronsted acids such as *p*-TSA, camphorsulfonic acid and TFA failed to give the desired product (Table 1, entries m, n, and o). To know the effect of solvent, the reaction was carried out in various solvents such as DCE, toluene, DCM and acetonitrile. Among them, toluene was found to be the most preferable in terms of yields (Table 1).

Table 1. Screening the reaction conditions



2a 3a 4a

Entry	Catalyst[a]	Temp (°C)	Solvent	Yield (%)[b]
a	IPrAuCl	80	DCE	NR
b	PPh_3AuCl	80	DCE	NR
c	$AgSbF_6$	80	DCE	65
d	$AgSbF_6$	80	Toluene	91
e	$AgBF_4$	80	Toluene	25
f	AgOTf	80	Toluene	20
g	TMSOTf	40	DCM	NR
h	$BF_3.OEt_2$	40	DCM	NR
i	$FeCl_3$	40	DCM	NR
j	$In(OTf)_3$	80	DCE	10
k	$Sc(OTf)_3$	80	CH_3CN	15
l	$InCl_3$	80	DCE	10
m	TFA	80	DCE	NR
n	*p*-TSA	80	Toluene	NR
o	CSA	80	Toluene	NR

[a]All reactions were performed using **2** (1 mmol), **3** (1 mmol), catalyst (5 mol%) in solvent (3 mL) under N_2 for 6h. [b]Yield refers to pure products. NR refers to no reaction.

Inspired by above results, we extended this process to various aldehydes such as aromatic, aliphatic and heteroaromatic and the results are presented in Table 2.

Table 2. Scope of the reaction with different aldehydes

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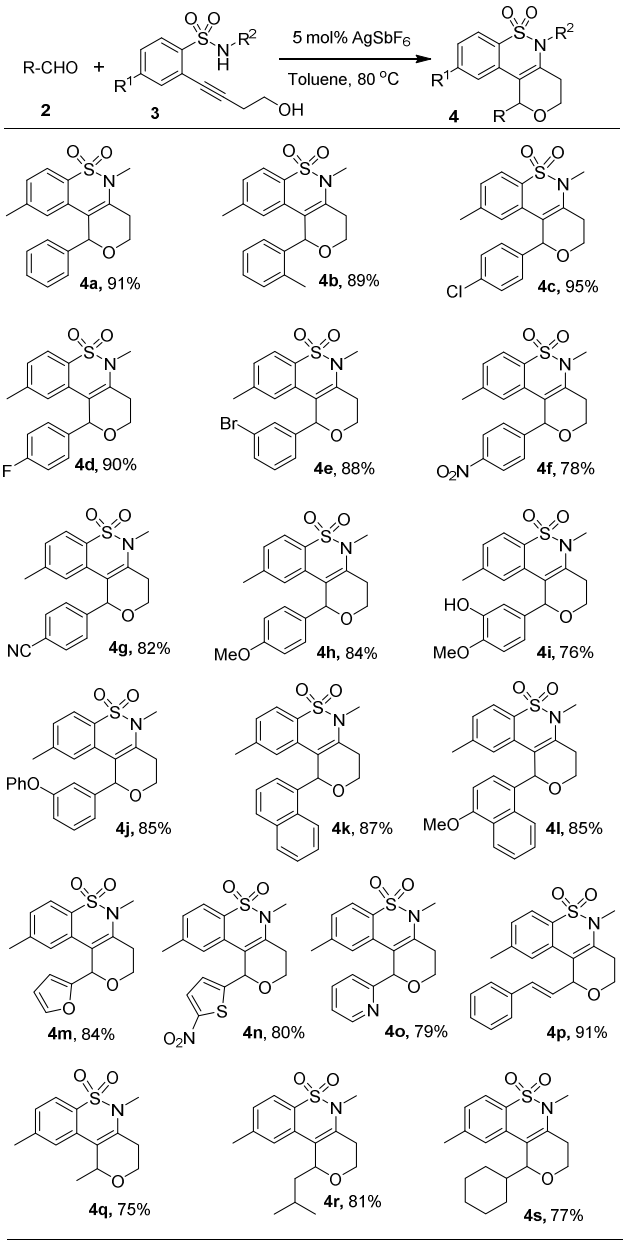

[a]Yield refers to pure products after column chromatography.
[b]Reaction was complete in 6h

However, the substituent present on aromatic ring had shown some effect on the conversion. In contrast, halo substituted aryl aldehydes gave the products in excellent yields (Table 2, entries c-e). However, *para*-substituted chloro and fluoro aryl aldehydes gave the products in higher yields compared to *meta*-substituted bromo aldehyde (Table 2, entries e). However, *ortho*-tolualdehyde gave the product in low yield (Table 2, entries b) compared to *para*- and *meta*-substituted tolualdehyde (Table 3, entries t and z). Furthermore, aryl aldehydes bearing electron withdrawing substituents like nitro- and cyano groups afforded the products in low yields (Table 2, entries f and g) compared to unsubstituted aldehyde and aryl aldehydes having electron donating groups (Table 2, entries a, h, i and j). The steric effect was observed in the case of *ortho*-substituted aromatic aldehyde and naphthaldehyde (Table 2, entries b, k, and l). Furthermore, heteroaromatic aldehydes such as furfural, 5-nitrofurfural, 2-formylpyridine also gave the corresponding products in reasonably good yields ranging from 84, 80 to 79% respectively (Table 2, entries m, n, and o). Remarkably, an acid sensitive α,ß-unsaturated aldehyde also afforded the product in excellent yield (Table 2, entry p). However, aliphatic aldehydes such as acetaldehyde, isovaleraldehyde, cyclohexanecarboxaldehyde (Table 2, entries q, r, and s) and *n*-hexanal (Table 3, entry x) gave the products in lower yields compared to aromatic counter parts.

The scope of the reaction was further extended to substituted sulfonamides and the results are presented in Table 3. The effect of substituent on the *N*-atom of sulfonamide was examined using ethyl and benzyl groups (Table 3, entries t, u, v, w and x). Both *N*-ethyl and *N*-benzyl substituted sulfonamides gave the products in excellent yields with aromatic aldehydes (Table 3, entries t, u, v and w). Furthermore, phenyl substituted sulfonamides also afforded the products in high yields ((Table 3, entries y, and z). The reaction was also quite successful with 2-naphthyl substituted sulfonamide (Table 3, entry aa).

Table 3. Scope of the reaction with different sulfonamides

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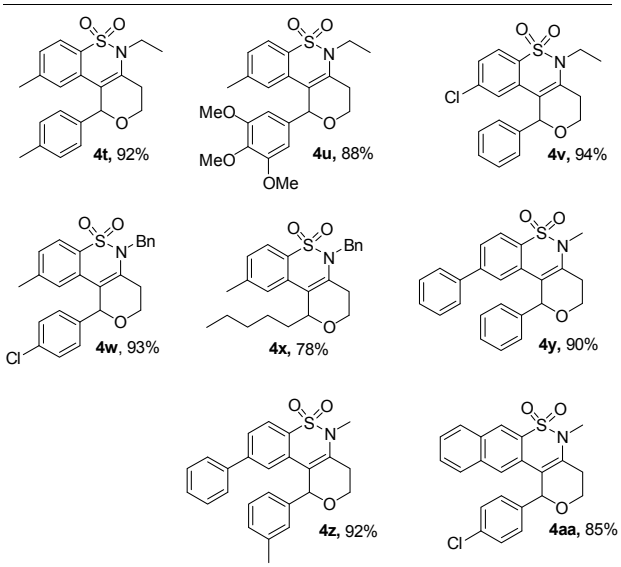


[a]Yield refers to pure products after column chromatography.
[b]Reaction was complete in 6h

The structure of **4d** was established by a single crystal X-ray crystallography (Figure 2).[16]

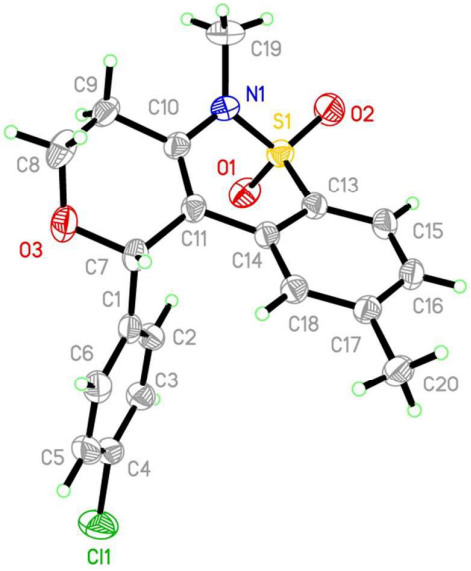
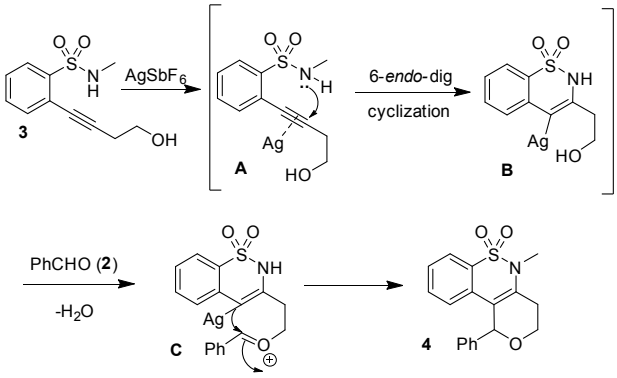


Figure 2. ORTEP diagram of **4d**

A plausible reaction mechanism is illustrated in Scheme 1. The reaction is expected to proceed by the coordination of cationic Ag(I) species with alkyne generating a Ag-π complex **A.**[15d,e] An intramolecular hydroamination of **A** led to the formation of intermediate **B**. A simultaneous reaction of the pendent alcohol with aldehyde generates the oxo-carbenium ion **C**, which is trapped intramolecularly by a silver vinylidene species resulting in the formation of the desired product **4** with a regeneration of the Ag catalyst (Scheme 1).



Scheme 1. A plausible reaction pathway

Conclusions

In summary, we have developed a novel strategy for the synthesis of fused benzo-δ-sultam derivatives through a series of C-N, C-O, and C-C bond formations catalyzed by Ag(I) catalyst. This method is applicable to a wide range of substrates with high functional group tolerance. This is the first report on the synthesis of fused benzo-δ-sultams by means of hydroamination triggered Prins type cyclization.

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Supporting Information

Experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectrum of products can be found, in the online version, at http://dx.doi.org/

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16. CCDC 1834668 for compound **4d** contains supplementary Crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html

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