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The first intermolecular interrupted imino-Nazarov reaction: expeditious access to carbocyclic nucleoside analogues[†]

Ronny William, Wei Lin Leng, Siming Wang and Xue-Wei Liu*

The analogous imino-variant of the Nazarov reaction suffers from unfavorable energetics associated with the ring closure process, thereby limiting the utility of this class of reactions. In this report, the realization of the first intermolecular interrupted imino-Nazarov reaction utilizing silvlated pyrimidine derivatives as nucleophilic trapping partners culminated in an expedient synthetic route to carbocyclic nucleoside analogues. The potential application of silvlated nucleobases to intercept the oxyallyl cation in other variants of the Nazarov reaction provides vast opportunities to develop new strategies for the formation of carbocyclic nucleoside analogues.

Carbocyclic nucleosides represent an emerging class of privileged therapeutic compounds which exhibit interesting biological properties.^{1,2} Substitution of endocyclic oxygen by a methylene unit in a carbocyclic nucleoside derivative imparts greater stability in the C–N pseudoglycosidic bond towards both chemical and enzymatic processes as compared to the parent nucleoside counterpart.² Some examples of naturally-occurring and synthetic carbocyclic nucleosides with potent pharmacological activity, such as aristeromycin,³ neplanocin A,⁴ carbovir⁵ and abacavir,⁶ are depicted in Fig. 1.

Nazarov cyclization involving 4π electrocyclic ring closure of the pentadienyl cation has long been regarded as a versatile method to construct five-membered carbocycles which are ubiquitous in nature.⁷ In the classical Nazarov reaction, a variety of nucleophiles have been utilized to ingeniously intercept the cyclopentenyl cation formed following cyclization in inter- or intramolecular fashion, allowing rapid access to more elaborate cyclopentanoid compounds.⁸ The imino variant of the Nazarov reaction⁹ and the related intercepted process,^{9f} in contrast, have not been exploited to a great extent due to unfavourable energetics of the ring closure reaction.¹⁰

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Our previous success in the development of efficient domino processes involving intramolecular imino-Nazarov cyclization of the 1-aminopentadienyl cation prompted us to explore the fundamentally similar intermolecular capture of the transient oxyallyl cation intermediate.⁹ In particular, we became interested in the prospect of employing a silylated nucleobase as the intermolecular trapping partner to render formation of the nucleobase-containing cyclopentanone, which can be potentially transformed into carbocyclic nucleoside analogues (Scheme 1). It is notable that nitrogen nucleophiles have not been widely used in interrupted Nazarov reactions, presumably



Fig. 1 Biologically active carbocyclic nucleoside analogues.

[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/c5sc03559g



Scheme 1 N-nucleophiles in interrupted Nazarov reactions.

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371. E-mail: xuewei@ntu.edu.sg

a consequence of the incompatibility of basic nitrogen-based nucleophiles with a highly acidic promoter, which is often necessary to effect cyclization. Tius reported a silica gel-/florisilpromoted amine intercepted Nazarov reaction,11 whereas West utilized organoazides as viable N-nucleophiles to trap the oxyallyl cation¹² (Scheme 1). The present work described herein represents the first example in which a silvlated nucleobase serves as an effective trapping agent for the oxyallyl cation in Nazarov-type cyclization.

Our initial efforts focused on the treatment of 4,6-dimethoxyhexa-2,4-dienal 1a, N-benzyl-4-methoxyaniline 2a and O,O'-bis(trimethylsilyl)thymine 3a in the presence of a Lewis acid catalyst. The requisite 4,6-dimethoxyhexa-2,4-dienal 1a could be obtained readily from 3,4,5-tri-O-methyl-D-glucal as an inseparable mixture of 2Z, 4Z and 2Z, 4E isomers in a 5 : 4 ratio, as described previously.^{9h} We began our investigation with SnCl₄ as the choice of Lewis acid catalyst as it is commonly used to activate silvlated nucleobases in the Vorbrüggen method for preparation of nucleosides.¹³ To our delight, when the reaction was carried out in the presence of 30 mol% of SnCl₄ in acetonitrile at 25 °C, dienal 1a was fully consumed within an hour. Instead of the expected cyclopentanone product, however, the corresponding highly functionalized cyclic enol ether 4a was isolated in 63% yield (Table 1, entry 1). Structural elucidation and stereochemical determination of compound 4a was accomplished based on extensive 2D NMR (COSY and NOESY) studies. On the basis of the NOESY experiment, the absence of an observed correlation between protons at C-4 and C-5 indicates a trans configuration between the substituents. Additionally, a strong correlation between the protons of benzylic methylene and the proton at C-3 suggests that nucleophilic

Table 1	Optimization of reaction conditions ^a
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attack of silylated thymine occurs trans to the amino group at C-
4. As compound 4a retained the enol ether functionality,
possibly allowing introduction of an electrophile at the
$\boldsymbol{\alpha}$ carbon, we decided to pursue formation of this type of
carbocyclic nucleoside.14

Encouraged by this satisfactory initial result, we directed our attention to the investigation of a series of Lewis acids including TiCl₄, Cu(OTf)₂, FeBr₃, InBr₃ and In(OTf)₃ in acetonitrile as the solvent. Although all tested Lewis acids were able to promote the desired intermolecular interrupted imino-Nazarov reaction, InBr₃ emerged as the best catalyst, affording 4a in 93% yield diastereoselectively (Table 1, entries 2-6). The reaction gave a lower yield when carried out in CH₂Cl₂ or THF (79% and 65% respectively), whereas no desired product 4a was observed in DMF (Table 1, entries 7-9). An attempt to perform the present domino reaction using a lower loading of InBr₃ (20 mol%) led to a diminished vield of 4a (Table 1, entry 10).

With the optimal conditions in hand, we set out to demonstrate the general utility of this transformation by varying the silvlated pyrimidine derivatives employed to furnish a library of carbocyclic nucleoside analogues 4b-4k (Scheme 2). Simple unsubstituted silvlated uracil furnished the cyclopentenol scaffold bearing a natural uracil group at C-3 4b in 91% yield. In general, substitution at the 5-position of silvlated pyrimidine nucleophiles is tolerated in the present intermolecular interrupted imino-Nazarov reaction. Electron-withdrawing halogen substituents did not significantly influence the reactivity of silvlated pyrimidine in trapping the oxyallyl cation, affording the desired product 4d-4g in yields ranging from 87-91%. When silvlated uracil derivatives with strongly electron-withdrawing groups such as -CF₃ and -NO₂ at the 5-position were used, the efficiency of the trapping process diminished slightly, giving 79% and 81% yield of 4h and 4i, respectively. Finally, modified uracil derivatives with more distinct variation in the

MeO MeO	CHO PMP M ^{Bn} + H Ha 2a	Me N 3a N OTMS catalyst solvent 25°C, 1h	MeO MeO MeO 5 0 NBn Bn 4a
Entry	Catalyst	Solvent	Yield ^b (%)
1	SnCl_4	CH ₃ CN	63
2	$TiCl_4$	CH_3CN	57
3	$Cu(OTf)_2$	CH_3CN	52
4	FeBr ₃	CH_3CN	58
5	InBr ₃	CH_3CN	93
6	$In(OTf)_3$	CH_3CN	71
7	InBr ₃	CH_2Cl_2	79
8	InBr ₃	THF	65
9	InBr ₃	DMF	—
10 ^c	InBr	CH ₂ CN	61

 a Unless otherwise noted, reactions were performed using dienal 1a (0.1 mmol, 1 equiv.), aniline 2a (0.1 mmol, 1 equiv.) and silylated thymine 3a (0.2 mmol, 2 equiv.) with 30 mol% of catalyst in 1 mL of solvent. ^b NMR yield determined by ¹H NMR analysis of the crude reaction against CH₂Br₂ as an internal standard. ^c Reaction was carried out in the presence of 20 mol% of $InBr_3$. PMP = *p*-methoxyphenyl.



Scheme 2 Scope of silvlated uracil derivatives.

core skeleton, including silylated 2-thiouracil and 5-azauracil, successfully participate in the reactions to provide **4j** and **4k** in good yields.

Having established the scope of silylated pyrimidine, we then directed our attention to examine the applicability of this reaction to a number of secondary anilines (Scheme 3). Various substituents including methyl, allyl, propargyl and 4-methoxybenzyl groups on the aniline nitrogen were well-tolerated, allowing formation of the carbocyclic nucleoside-like compounds **41–40**. A more electron-deficient aniline with a –Cl group at the *para* position of the aniline ring resulted in a moderate yield of 56% of the intercepted product **4p**.

Subsequently, we proceeded to perform the reaction starting with different dienals which can similarly be derived from the corresponding glycals (Scheme 4). During the preparation of benzyl- and MOM-protected dienal 1b and 1c, as well as dienal 1d derived from L-rhamnal, we found that the geometrical isomers (2Z, 4Z and 2Z, 4E) turn out to be separable, in contrast to the methyl protected counterpart 1a. The reactions with these dienals were thus carried out using the pure Z-isomers instead of a mixture of isomers. When the benzyl protected dienal 1b was subjected to the same reaction conditions, the interruption of the imino-Nazarov reaction proceeded smoothly to give an excellent yield of 4q (Scheme 4). In the case of the more labile methoxymethyl protected dienal 1c, the reaction still led to the formation of 4r, albeit in a much lower yield of 52%, along with a substantial amount of 4-aminocyclopentenone (Scheme 4).15 It is notable that the presence of alkoxy (-OMe/-OBn) or methoxymethyl (-OMOM) groups is imperative for the success of this transformation, due to stabilization of the allyl cation intermediate.

To test our hypothesis that isomerization occurs prior to cyclization, we treated the 4Z isomer **1b** and 4E isomer **1b'** separately with aniline **2a** and silylated thymine **3a** under the same reaction conditions (Scheme 5). As expected, both isomers led to the formation of the same diastereomeric product **4q**,



Scheme 3 Scope of secondary anilines.





indicating that the initial cyclization provided only the *trans* oxyallyl cation intermediate, a consequence of alkene isomerization.¹⁶

It is noteworthy that, in all cases, the reactions exhibited excellent diastereoselectivity with regard to the nucleophilic addition of silylated pyrimidine to the oxyallyl cation species. To confirm that the diastereofacial selectivity arises due to steric hindrance, a simple theoretical DFT calculation for the possible trajectory of addition to the oxyallyl cation was conducted (see Fig. S1 in ESI[†]). The results of our theoretical studies correlate well with the experimental observation of complete diastereoselectivity.

Besides silvlated pyrimidine, trimethylsilyl azide proved to be a competent nucleophile in trapping the oxyallyl cation, giving adduct 6 as the only diastereomer in which the azido group was incorporated into the cyclopentanoid framework. The instability of compound 6 in silica gel prevented us from isolating it in its pure form. The ESI mass spectrum of the crude product with molecular ion at m/z (M⁺ + H) coupled with its ¹H NMR analysis provided strong evidence for the formation of 6. Sequential hydrogenation on Pd/C in methanol resulted in the reduction of azide and alkene, along with removal of the benzyl group, rendering conversion of compound 6 to diaminocyclopentane 7 with an overall yield of 84% for 2 steps (Scheme 6). The structure and stereochemical assignment were determined based on a combination of 1D and 2D (COSY and NOESY) NMR studies. To date, there is only a single documented example of azidation of the oxyallyl cation, reported by West, using Me₂AlN₃ as the azide source.^{8e}



Scheme 5 Stereoconvergence cyclization of 1b and 1b'. Reaction conditions: (a) 30 mol% $InBr_3$, CH_3CN , 25 °C. Yield of 4q: 91% from 1b and 85% from 1b'.



Scheme 6 One-pot azide trapping/hydrogenation.

Conclusions

In conclusion, we have developed the first examples of intermolecular interrupted imino-Nazarov reactions using silylated pyrimidine to provide convenient access to carbocyclic nucleoside analogues. The novel utility of using a silylated nucleobase as the nucleophilic trapping partner to intercept the fleeting oxyallyl cation from the imino-Nazarov reaction can potentially be extended to other variants of the Nazarov reaction.

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