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3,4-Dihydroxypyrrolidines via Modified Tandem Aza-Payne/Hydroamination Pathway

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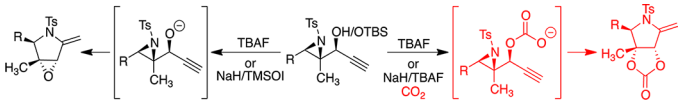
ABSTRACT



The outcome of a tandem aza-Payne/hydroamination reaction is modified via the use of a latent nucleophile. The latter initially serves as an electrophile to intercept the aziridine alkoxide and afterward turns into a nucleophile thereby performing the aziridine ring opening, out competing the intramolecular aza-Payne pathway. Subsequent hydroamination in the same pot provides *N*-Ts enamide carbonates, which can be easily converted into biologically significant 3,4-dihydroxylactams.

Polyhydroxylated alkaloids constitute the skeletal framework of several important iminosugars and a number of natural products.[1] They mimic the structures of monosaccharides, and their exceptional biological activity as glycosidase inhibitors makes them one of the most attractive classes of carbohydrate mimics reported so far.[2]

Motivated by both their biological significance and our synthetic interest, we have focused on the diastereoselective assembly and functionalization of heterocycles that possess the latter structural motif.[3] A tandem aza-Payne/hydroamination methodology was recently reported that yields densely decorated pyrrolidines.[3b] The protocol involves the deprotonation of a stereodefined aziridine alcohol **1a** (*syn*-aziridinols are obtained efficiently and in high stereoselectivity)[4] followed by an aza-Payne rearrangement of the resulting alkoxide intermediate **2a** yielding an epoxy *N*-Ts amide intermediate **3a** (Figure 1a). The latter readily undergoes a 5-*exo*-*dig* ring closure to yield the tetrasubstituted pyrrolidine **4a**.[3b] Synthetic elaborations on the latter toward complex and advanced level intermediates are currently underway. Nonetheless, our interest in further exploiting the aza-Payne/hydroamination pathway in a manner to increase diversity in structure, particularly in light of our interest to gain access to polyhydroxylated motifs, led us to explore the reaction manifold.[1,5]

We began our investigation with a plan of intercepting the aza-Payne intermediate **2a** with a latent nucleophile to alter the outcome of the subsequent hydroamination reaction. Aziridine ring opening with a modified nucleophile would then lead to enamide compounds embellished with functionalities of different natures. Figure 1a illustrates our proposal that relies on the use of CO_2 as a latent nucleophile. We anticipated that CO_2 would initially serve as an electrophile to affect the carboxylation of the alkoxide intermediate, thereby introducing instead a carbonate nucleophile to carry out the aziridine ring opening. Ensuing 5-*exo*-ring closure would then deliver the functionalized enamide carbonate product containing the masked dihydroxylated unit **6a**.[6]

The aza-Payne process is an efficient intramolecular pathway and therefore makes the attempt to interject an

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external electrophile a challenging task.[7] Two points were critical in our assessment that led us to believe a longer-lived alkoxide species could participate in an intermolecular pathway prior to intramolecular ring opening of the aziridine. First, evidence for an altered pathway that did not immediately participate in an aza-Payne rearrangement of alkoxide **2a** came from a desilylation experiment (Figure 1b). The TBS ether **7a** participated in a semi-Pinacol rearrangement[8] affording an unexpected aldehyde product **8a**; the transformation entails migration of an alkyl group and insinuates the higher stability of the alkoxide **2a** generated under the specific reaction conditions. Second, a handful of reports have shown the feasibility of 2,3-epoxy-1-ols to trap CO_2 in the form of a carbonate,[6] which further proceed to open the epoxide in a Payne-like reaction.

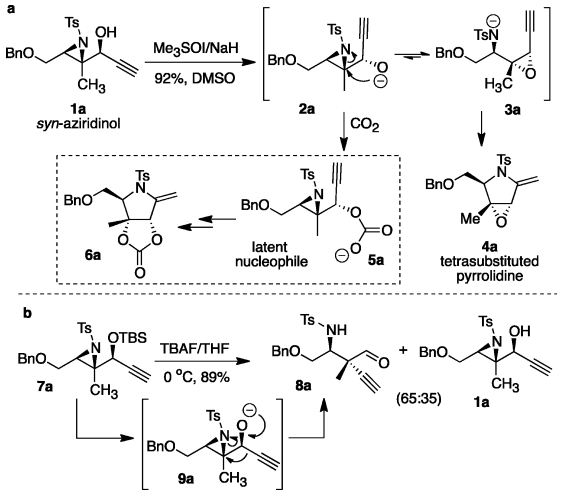
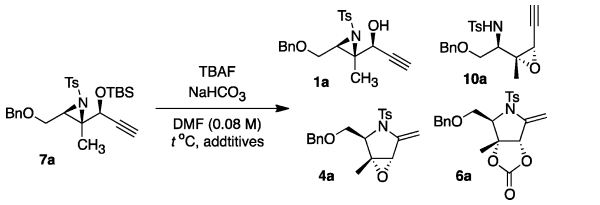


Figure 1. (a) Tandem aza-Payne/hydroamination yields tetrasubstituted pyrrolidines. Dashed box: Trapping a latent nucleophile such as CO_2 by the alkoxide intermediate. (b) The alkoxide intermediate leads to a semi-Pinacol rearranged aldehyde product without any evidence of an aza-Payne rearranged process under the reaction conditions.

Having witnessed the ability of the alkoxide **2a** to circumvent aza-Payne, we subjected TBS ether **7a** under similar reaction conditions in the presence of an excess of $NaHCO_3$ as a source of CO_2 dissolved in a polar solvent. The reaction in DMF at 0 °C for 2 h led to a mixture of four products (Table 1). As anticipated, the desilylated product **1a** was observed. Along with that, the aza-Payne rearrangement led to significant amounts of **10a**, and the previously reported pyrrolidine **4a**. Nonetheless, a substantial amount of the enamide carbonate **6a** was isolated, suggesting that the alkoxide intermediate must have trapped a molecule of CO_2, which subsequently initiated a downstream hydroamination to yield the stated molecule. Table 1 demonstrates various conditions that were examined to optimize the reaction in order to maximize the production of the desired carbonate compound. Warming the reaction to rt led to the first significant improvement (entry 2) by completely eliminating compounds **1a** and **10a**. Inclusion of molecular sieves furnished the enamide epoxide **4a** only, suggesting that the presence of water is necessary to carry the reaction toward the desired molecule (entry 4).

The source of CO_2 is critical as can be seen from the comparison of entries 2 with 7−10. The best results were obtained with bubbling CO_2 in the presense of $NaHCO_3$. Curiously, the greater amount of TBAF was also necessary to yield the desired product **6a**, exclusively (entry 10). Scheme 1 illustrates the scope of 2,2,3-trisubstituted aziridine alcohols that successfully participated in the modified tandem aza-Payne/hydroamination reaction, utilizing the optimized conditions, yielding the desired enamine carbonate products **6a**−**c**. The crystal structure of **6c** provided unequivocal determination of stereochemistry and, in conjunction with NMR, was used for assignment of **6a** and **6b** through analogy (see Supporting Information (SI)).

Table 1. Optimization of Reaction Conditions for the Synthesis of *N*-Ts Enamide Carbonate **6a**



entry	TBAF (equiv)	$NaHCO_3$ (equiv)	time (h)	*t* (°C)	additives	ratios (**1a/10a/4a/6a**)
1	5	10	2	0	–	18/22/26/34
2	5	10	6	0→rt	–	0/0/20/80
3	2.5	10	12	0→rt	–	0/0/38/62
4	5[a]	10	12	0→rt	4 Å MS	0/0/100/0
5	2	20	8	−10→rt	–	0/0/18/82
6	2	20	12[b]	−30→60	–	0/0/30/70
7[c]	2	20	6	0→rt	$CsCO_3$	0/0/62/38
8[e]	2	20	5	0→rt	$CsCO_3$	0/0/90/10
9	2	20	5	0→rt	CO_2	0/0/5/95[d]
10	11	20	8	0→rt	CO_2	0/0/0/100

[a] TBAF was stirred over 4 Å MS for 1 h before it was added to the reaction. [b] Polar and unidentified impurities were observed, as analyzed by NMR of crude mixture, at elevated temperature. [c] TBAF was added at 0 °C, and then reaction was warmed to rt followed by sonication. [d] Only 38% conversion was observed by NMR analysis of crude reaction mixture. [e] Products **4a** and **6a** in separate experiments, when subjected to the reaction conditions, did not interconvert.

The perceived mechanism for the transformation would suggest no need for requisite silyl protected alcohol as the starting material. As such, we next explored the use of unprotected aziridine alcohols **1b**−**1d** as starting material for the conversion into the enamide carbonate products. Surprisingly, our first attempt met with failure and led to the isolation of the unreacted aziridine alcohol under

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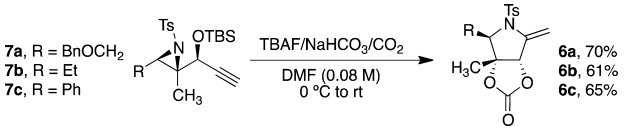
conditions that otherwise should have delivered the product (Table 2, entry 1).

Scheme 1. Synthesis of *N*-Ts Enamide Carbonates from Silyl Aziridine Alcohols



Inclusion of $NaHCO_3$ made no change, neither did the use of trimethylsulfoxonium iodide, the preferred proton source for the hydroamination step, as was reported previously (Table 2, entries 2−4).[3b] Solubility of the sodium alkoxide was also probed via changing the solvent and also the use of TBAI as a phase transfer catalyst, but those also did not resolve the issue. To our surprise, addition of TBAF did yield the desired enamine carbonate **6b** as the sole isolable product (entry 5). As evident from entries 6 and 7, the same was true with different substrates, thus illustrating the importance of TBAF in promoting the reaction. The latter data suggest the fortuitous nature of our initial reaction conditions, in which TBAF was used to promote the desilylation of the TBS-protected alcohol. Nonetheless, it seems that the presence of TBAF is required for further reactivity after the alkoxide is revealed. This was further probed by running the reaction under identical conditions with the exception of substituting TBAF with CsF, CsI/TBAF, and CsF/TBAI. In all cases, starting material was recovered quantitatively.

A few reports might suggest the role of fluoride in the generation of a fluorocarbonate species (fluoride reacting with CO_2).[9] Based on DFT analysis (SI), this fluorocarbonate is an incongruous candidate as a potential electrophile in comparison to CO_2. This insinuates its role in increasing the soluble CO_2 concentration, and as a result of its reversible nature, it promotes the carboxylation reaction. This is also in agreement with our initial observation that an increased equivalence of TBAF was necessary to achieve full conversion to the product (Table 1, entry 10). Interestingly, the use of TBAOMe, which can also lead to the production of methoxycarbonate *in situ*, and thus higher solubility of CO_2, did lead to the isolation of product **6c** in a shorter reaction time (Table 2, entry 8).

Scheme 2 provides anecdotal evidence for the need of TBAF as a necessary reagent in promoting the carboxylation of the intermediate alkoxide (transformation of **2a** to **5a** in Figure 1). Primary alcohol **11** successfully traps CO_2 and, via the aza-Payne like ring opening of the adjacent aziridine, yields **13** with or without TBAF (condition B and A, respectively, Scheme 2). It should be noted that the reaction was completed in a slightly faster time course in the presence of TBAF. The secondary alcohol **12** reacted only in the presence of TBAF as an additive (condition B) to furnish the CO_2 trapped aza-Payne-like product **14** in high yield. This clearly suggests the crucial role of TBAF in enabling

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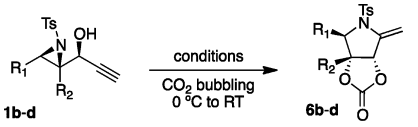
Table 2. Reaction Conditions for Aziridine Alcohols

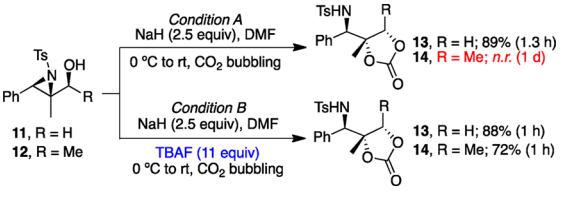


entry	R_1	R_2	substrates	conditions	products
1	Et	Me	**1b**	NaH (4 equiv), DMF, 12 h	n.r.
2	Et	Me	**1b**	NaH (2.5 equiv), $NaHCO_3$ (20 equiv), THF, 12 h	n.r.
3	Et	Me	**1b**	NaH (4 equiv), TMSOI (4 equiv), DMSO, 12 h	n.r.
4	Et	Me	**1b**	NaH (2.5 equiv), TBAI (11 equiv), $NaHCO_3$ (20 equiv), DMF, 12 h	n.r.
5	Et	Me	**1b**	NaH (2.5 equiv), TBAF (12 equiv), $NaHCO_3$ (30 equiv), DMF, 5 h	**6b**, 69%
6	Ph	Me	**1c**	NaH (2.5 equiv), TBAF (11 equiv), $NaHCO_3$ (20 equiv), DMF, 6 h	**6c**, 55%
7	Pr	H	**1d**	NaH (2.5 equiv), TBAF (11 equiv), $NaHCO_3$ (20 equiv), DMF, 4 h	**6d**, 62%
8	Ph	Me	**1c**	NaH (2.5 equiv), TBAOMe (11 equiv), $NaHCO_3$ (20 equiv), DMF, 1 h	**6c**, 55%

the participation of sluggish nucleophiles in carboxylation reactions.

Based on *ab initio* calculations at the B3LYP/6-31G* level (SI), Scheme 3 illustrates a detailed mechanistic outline proposed for the reaction that could proceed to yield either the epoxy enamine **4** (Path A) or the carbonate enamine **6** (Path B). We have assumed the irreversible nature of the first desilylation step and the protonation of the penultimate vinyl anion. With those considerations in mind, the remaining steps are assumed to be reversible and thus could siphon the reaction path toward the thermodynamically more stable *cis*-fused 5−5 ring system in comparison to the kinetically accessed *cis*-fused 3−5 ring system, given the correct conditions. Desilylation of aziridinol **7** generates the alkoxide intermediate **7.1**, which in the absence of CO_2, would exist in equilibrium with the aza-Payne intermediate **7.2**. Noticeably, the equilibrium favors species **7.2** by 25 kcal/mol where the anionic nitrogen is stabilized by an electron-withdrawing group.[7b]

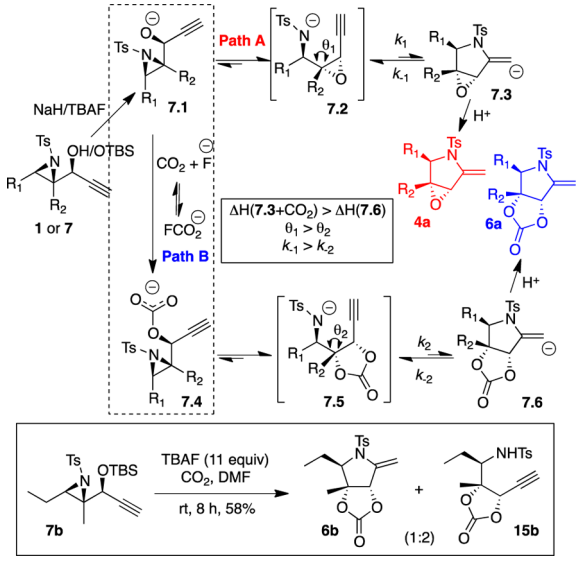
Scheme 2. Alkoxide Trap of CO_2 and Subsequent Aziridine Ring Opening



5-*Exo-dig* ring closure of **7.2** yields the vinyl anion intermediate **7.3**, which upon rapid protonation provides the epoxy *N*-Ts enamide **4a**. The rate constant k_{-1} would govern the extent of the reversibility of the *N*-Ts enamide vinyl anion back to the ring opened amide intermediate **7.2**

in the reaction (SI). On the other hand in the presence of soluble CO_2 the alkoxide intermediate **7.1** could trap the electrophile leading to the formation of the carbonate intermediate **7.4**. This seems to be further facilitated by the presence of fluoride ions, presumably increasing the solubility of dissolved CO_2 or its carbonate equivalent. The latter would execute the intramolecular aziridine ring opening to generate **7.5**, poised for a similar ring-closing event that would yield vinyl anion **7.6**.

Scheme 3. Mechanistic Rationale for the Synthesis of Enamide Epoxide and Carbonate Products



Although Path A to the epoxy enamine **4** does not depend on an intermolecular event that should hasten its production in comparison to the carbonate enamine product **6**, two points are key to understand why the equilibrium can be completely shifted toward the more stable fused ring system. First, the β-elimination of vinyl anions **7.3** and **7.6**, defined by k_{-1} and k_{-2}, respectively, would depend on the magnitude of each rate constant. As a result of the larger anticipated strain of the 5−3 fused ring system, we assume that k_{-1} is larger than k_{-2}, thus shifting the population of the reaction intermediates toward the production of the observed carbonate enamine product **6**. Second, B3LYP/6-31G*/SM8 (DMF) analysis (see SI for detailed analysis of reaction pathways) reveals that the formation of **7.4** via trapping of CO_2 by the oxyanion **7.1** is downhill by 29 kcal/mol. Furthermore, the dihedral angle θ_1, which defines the bite angle for intramolecular attack in epoxy amide **7.2**, is larger (120.0°) than θ_2 (113.3°) in the carbonate amide **7.5**. The smaller θ_2 confines a closer proximity of the reactive nitrogen anion and the acetylene carbon by 0.7 Å (Figure 2), thus leading to a more facile reaction (presumably k_2 would be larger than k_1). This geometrical disposition helps to lower the relative transition state energy barrier for the hydroamination of **7.5** as compared to that for **7.2** by 2.3 kcal/mol (see SI).

The critical element is the availability of CO_2 and its reactivity with alkoxide **7.1** since the carbonate pathway is

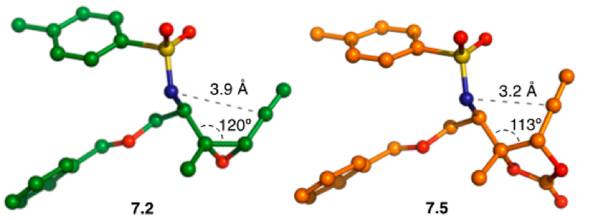
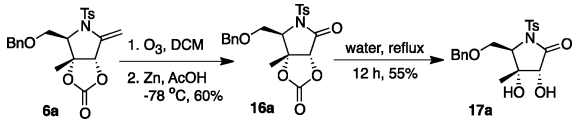


Figure 2. Geometry minimized (B3LYP/6-31G*) structures of **7.2** (green) and **7.5** (orange), indicating the closer proximity for amination of alkyne in **7.5** in comparison to **7.2**.

Scheme 4. Elaboration to 3,4-Dihydroxypyrrolidine



rate limited by its bimolecular nature. Although use of $NaHCO_3$ does provide the carbonate enamine product **6**, the reaction is marred by side products, which are generated from the second pathway. Bubbling of CO_2 greatly increases the yield of **6**. The presence of a fluoride ion is also essential to presumably increase the concentration of 'dissolved' CO_2.

Although the level of 'dissolved' CO_2 seems to have a strong influence on the fate of the reaction, the role of $NaHCO_3$ is not solely limited as a CO_2 supply reagent. Illustrated in the solid box in Scheme 3, exclusion of $NaHCO_3$ from the reaction, in the presence of saturating CO_2 and TBAF, leads to a mixture of products dominated by the nonhydroaminated compound **15b**. The same is observed if rigorously anhydrous reaction conditions are used. Presumably, this is due to the lack of a sufficient proton source in the reaction medium that would rapidly protonate intermediate **7.6**, and thus avoid the β-elimination to **7.5**.

Scheme 4 demonstrates the ease by which the carbonate enamine product can be further transformed. Reductive ozonolysis of **6a** yields lactam **16a** in a quantitative conversion. The latter can be refluxed in water for 12 h to furnish the 3,4-dihydroxylactam **17a**.

In summary, the current transformation utilizes CO_2 as a latent nucleophile, by intercepting a reactive alkoxide, to deliver a set of alternate products. The modified nucleophiles would enable access to pyrrolidines with different functionalities at the C-3 and C-4 positions.

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

The authors declare no competing financial interest.