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Aziridination of γ,δ-dibromoethyl-2-pentenoate with primary amines: extension of the Gabriel–Cromwell reaction ☆

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Abstract—Ethyl (*E*)-4,5-dibromo-2-pentenoate readily reacts with an assortment of primary amines in the presence of DBU to afford the corresponding conjugated aziridines in good to moderate yields. That the reaction is compatible with a nucleoside-derived amine suggests a broad scope of application.

Aziridines figure prominently in a variety of biologically active substances and more often than not are integral to the useful bioactivities of the substances which contain them. Natural and synthetic materials belonging to the FR-900482,[1–3] mitomycin,[4–6] and azinomycin[7,8] classes to name just a few, are the focus of chemists and biologists alike by virtue of complex molecular architecture and potent biological/medicinal utility. Aziridines also serve as important synthetic intermediates en route to a wide array of interesting compounds including unnatural α and β-amino acids,[9] ligands for asymmetric catalysis,[10] peptido-mimetics[11] and β-lactams.[12] The ability of aziridines to undergo highly predictable regio- and stereoselective ring opening reactions makes them powerful synthetic tools.[13]

Of several existing aziridination strategies, the Gabriel–Cromwell reaction[14] is one of the most convenient and useful. The reaction involves direct aziridination of an α,β-dibromo ester or ketone following treatment with a primary amine and a nitrogenous base, typically triethylamine. One useful feature of the Gabriel–Cromwell reaction is that the aziridination is a single convergent step resulting in a tertiary aziridine nitrogen. Many classical aziridine-forming reactions involve multiple manipulations or result in differentially masked secondary aziridines. An exception to this involves a novel electrochemical aziridination that converges primary amines and olefinic substrates.[15]

Since its inception in 1952 many variations on the Gabriel–Cromwell reaction have sought to broaden its scope. These include adaptation to solid phase,[16] development of asymmetric induction methods,[17] and the use of cyclic halides or triflates allowing access to bicyclic aziridines.[18] These efforts and many others have, however, been restricted to the use of α,β-dihalo and vinyl triflate carbonyl compounds or nitriles as the electrophilic component of such condensations. Our interests in generating aziridine modified nucleosides mandated an investigation of the Gabriel–Cromwell reaction with more elaborate dihalides.

Aziridine-containing compound **1** (Scheme 1) is intended to serve as a precursor to cofactor mimics of *S*-adenosyl-L-methionine; such 5′ aziridino adenylates are well known methyltransferase-dependent DNA alkylating agents.[19] Our interest in **1** in this capacity prompted investigation into an extended version of the Gabriel–Cromwell aziridination as a key step in the synthesis of this, and more structurally elaborate cofactor mimics. It was envisioned that a 4,5-dibromo-γ,δ-unsaturated ester would allow for aziridination at the nucleoside 5′ position while also providing an opportunity for meaningful structure elaboration of the aziridine sidechain. That dihalides such as **2** appeared to have not been utilized in aziridinations gave some cause

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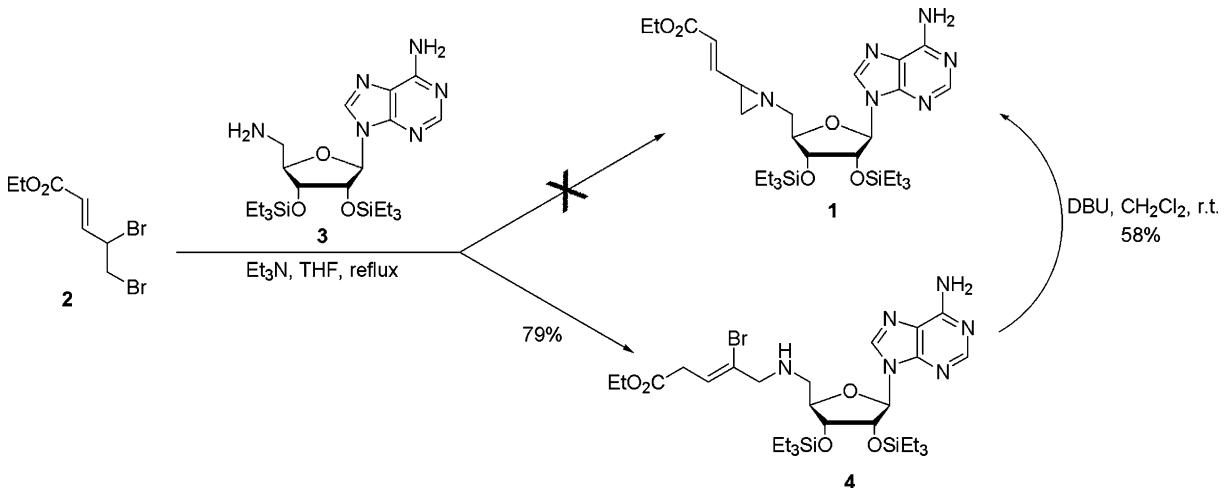


Scheme 1. Nucleoside aziridination via isomerization of vinyl bromide **4**.

for concern. Pleasantly, these concerns were unfounded as revealed by reactions of **2** with a small array of representative amines, inclusive of 5′-amino adenylate **3**.

Dibromide **2** was synthesized from commercially available ethyl (*S*)-(*E*)-4,5-isopropylidenedioxy-2-pentenoate. It is interesting to note that this isopropylidene had been used previously by Mohr and co-workers to generate the corresponding α,β-dibromoester, from which was derived a mixture of *cis* and *trans* aziridines for the study of new oxazoline-forming reactions.[20] We found that **2** was readily generated from the corresponding diol following treatment with carbon tetrabromide and triphenylphosphine, a variation of monobromination conditions reported by Padwa and colleagues, in 70% yield.[21] Initial attempts to couple **2** with the 5′-aminoadenosine under standard Gabriel–Cromwell conditions failed to afford the desired aziridine; affording instead vinyl bromide **4** with reasonable efficiency.[22] NOESY experiments reveal spatial proximity of the vinyl proton and the amino linked allylic methylene protons consistent with *Z* olefin **4**.

It was unclear to us whether **4** was an intermediate en route to the desired product and these reaction conditions were not favorable for subsequent progression to the aziridine, or if formation of **4** is divergent from the path to aziridination. In an attempt to either prevent formation of **4** or force its conversion to **1**, THF was substituted with DMF. Disappointingly, reactions run at 90 °C or reflux in DMF for up to 2 days showed only formation of **4**, in addition to some predictable decomposition.

Confronted with **4**, we envisioned that aziridination might still be accomplished, albeit in two steps as opposed to one, via isomerization to an α,β-unsaturated ester, so as to intersect the pathway ordinarily followed in the Gabriel–Cromwell reaction. Indeed, treatment of **4** with DBU in CH_2Cl_2 afforded **1** in very respectable yield.[23]

Interestingly, model reactions run under standard Gabriel–Cromwell conditions with simplified primary amines resulted in mixtures of vinyl bromides analogous to **4**, and the desired aziridines. The fact that aziridination occurred in one step, presumably by the expected pathway, combined with the success of the DBU-mediated isomerization of **4**, suggested that reaction conditions could be found that would allow one to avoid vinyl bromide formation altogether.

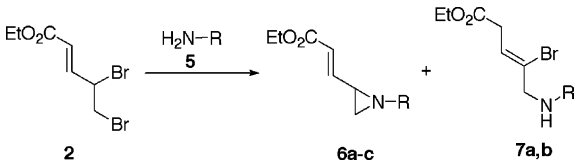
Three model amines were used to identify reaction conditions capable of effecting aziridination in one step. Benzylamine (**5a**), tetrahydrofurfurylamine (**5b**), and neopentylamine (**5c**) were reacted with **2** in THF. Optimum conditions were identified using benzylamine and tetrahydrofurfurylamine; trials were run with two different bases, triethylamine and DBU, at room temperature and reflux. The results are summarized in Table 1.

In all cases examined, the use of triethylamine led to formation of significant amounts of vinyl bromide which could not be converted to aziridine over extended periods of time. When run at room temperature, reactions failed to reach completion even after 2 days. Conversely, reactions performed at reflux reached completion within 7 h, but typically afforded lower ratios of aziridine to vinyl bromide than those conducted at ambient temperature.

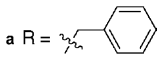
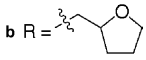
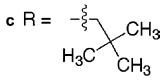
Importantly, the use of DBU instead of triethylamine makes this reaction viable. In all cases examined, the yield of aziridine either approached or exceeded 70% with no evidence of vinyl bromide formation. It is also interesting to note that refluxing conditions gave routinely higher yields and are amenable to shorter reaction times, however milder ambient conditions are clearly a viable option for sensitive substrates, still resulting in good yields.

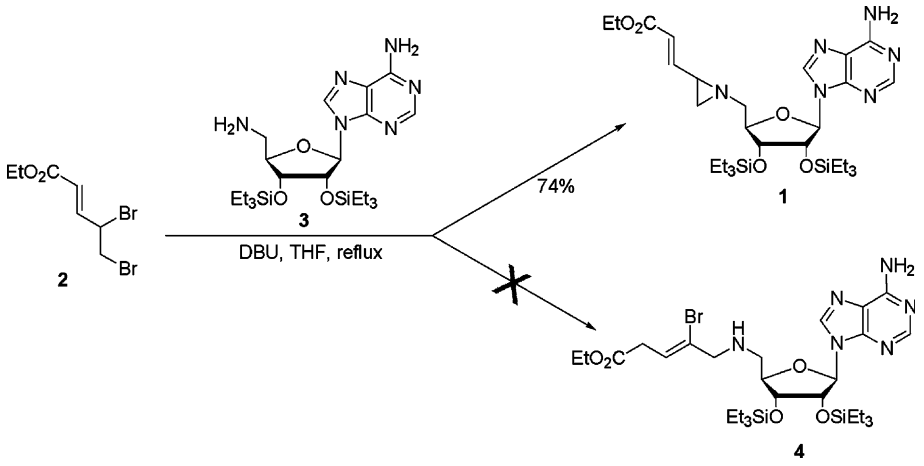
Having realized the importance of our selection of DBU for this variation of the Gabriel–Cromwell reaction, we returned our attention to nucleoside **1** (Scheme 2). Gratifyingly, 5′-aminoadenosine **3** condensed with **2** in the presence of two equivalents DBU over the course of

Table 1. Reaction of ethyl (*E*)-4,5-dibromo-2-pentenoate with model primary amines; product partitioning between aziridines and vinyl bromides



2 **6a-c** **7a,b**

	Entry	Amine	Base	*T* (°C)	**6**:**7**	Yield **6** (%)
a R = 	1	**5a**	TEA	25	1:1.9	31
	2	**5a**	TEA	67	1:2.5	24
	3	**5a**	DBU	25	n/a	68
b R = 	4	**5a**	DBU	67	n/a	75
	5	**5b**	TEA	25	1:1.6	22
	6	**5b**	TEA	67	1:1.9	30
c R = 	7	**5b**	DBU	25	n/a	63
	8	**5b**	DBU	67	n/a	80
	9	**5c**	DBU	67	n/a	74



Scheme 2. Nucleoside aziridination via extended Gabriel–Cromwell reaction.

8 h to afford **1** in yields ranging from 69% to 74%.[24] As with the simplified amines, the use of DBU completely eliminated vinyl bromide formation while affording yields very comparable to those obtained with simpler α,β-dibromoesters.[22] Not insignificantly, the use of 3 equiv of DBU allowed the reaction to reach completion after only 5 h at reflux. Just as model studies with **5a–c** demonstrated the usefulness of this new aziridination reaction with simple amines, the effective convergence of **2** with **3** demonstrates the compatibility of DBU-mediated aziridination with nucleosides and perhaps significantly more complex molecules.

This extension of the Gabriel–Cromwell reaction broadens the number of avenues by which aziridines can be constructed in a one step process. That the resulting aziridine is in conjugation with α,β-unsaturated systems suggests the possibility of significantly greater synthetic flexibility and diversification options than is ordinarily associated with aziridine-2-carboxylates resulting from classical Gabriel–Cromwell reactions. Such chemistries and the continued pursuit of cofactor mimics derived from **1** will be reported in due course.

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24. Preparation and characterization of compounds **1**, **2**, **6a**–**c**, and **7a**–**b** are available as supporting information.