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Novel aziridination of α-halo ketones: an efficient nucleophile-induced cyclization of phosphoramidates to functionalized aziridines

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Abstract

A novel and efficient aziridination of α-halo ketones is reported. The reaction of α-halo ketones with diethyl *N*-arylphosphoramidates affords diethyl *N*-aryl-*N*-(2-oxoalkyl)phosphoramidates which undergo reductive (H^--induced) cyclization with sodium borohydride followed by sodium hydride to give 1,2-disubstituted and 1,2,3-trisubstituted aziridines. The cyclization induced by NCS^- or PhS^- affords substituted aziridines functionalized at C-2. The reactions give excellent yields and are highly diastereoselective in favour of *cis* aziridines.

Keywords: Aziridines; α-Halo ketones; Phosphoramidates; Nucleophile-induced; Reduction; Cyclization reactions

Owing to the inherent strain in small ring heterocycles, they are useful as feedstocks in organic synthesis to provide functionalized carbon chains. Aziridines have been synthetic targets as well as building blocks in synthesis since Gabriel's 1888 discovery of the smallest nitrogen-containing heterocycle.[1–3] In terms of synthetic transformations, the utility of aziridines derives from their selective ring-opening reactions,[4,5] which often form the basis for more complex target syntheses.[6,7] Yudin and co-workers have demonstrated a number of connections between aziridines and the products of their ring-opening.[8]

Antibiotic, anticancer and antitumour activities of aziridine-containing natural products, such as azinomycins,[9–11] mitomycins,[12,13] FR-900482, FR-66979 and related compounds,[14] are of significant interest. Of these, azinomycins possess a broad spectrum of activity against cancers, including tumours, and mitomycin C has been in clinical use since the 1960s for the treatment of a wide range of tumours. FR-900482 and FR-66979 are structurally related to mitomycins and show similar anticancer activity. The activity of all these compounds lies in the role of aziridines as powerful alkylating agents.[15] Furthermore, several synthetic aziridines have also been reported to exhibit useful biological properties such as irreversible inhibition of glutamate racemase,[16] and diaminopimelic acid epimerase (DAP),[17] and high level cytotoxicity against melanoma cell lines.[18]

Numerous methods are available for differently substituted aziridines, which include aziridination of olefins,[19–21] carbene and ylide addition to imines,[22–24] and cyclization of β-amino alcohols,[25,26] α-halo imines,[27] β-amino halides,[25,26] and β-azido alcohols.[25,26,28] Very recently, an excellent review by De Kimpe and co-workers covered the synthesis and reactivity of *C*-heteroatom-substituted aziridines,[29] which also includes *C*-sulfur-substituted aziridines similar to those reported in the present Letter. α-Halo imines are important intermediates in aziridine synthesis, which involves a two-step process starting from α-halo ketones or aldehydes.

In continuation of our efforts to develop new one-pot cyclization processes,[30] we report herein a two-step synthetic protocol for the synthesis of aziridines starting from

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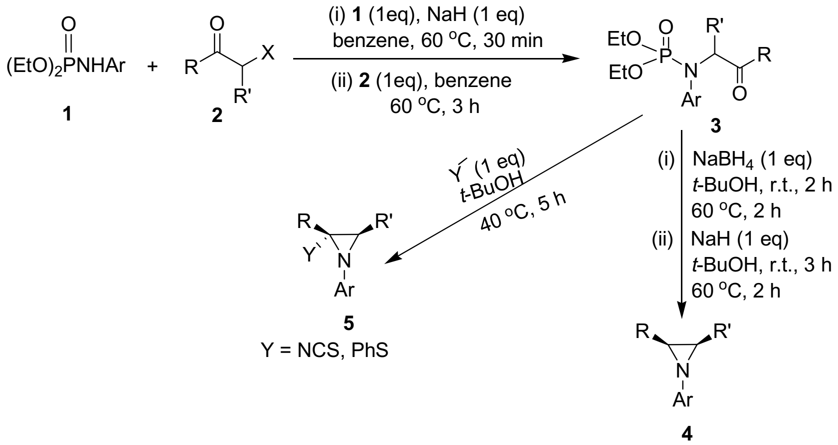


Product	R	R'	Ar	Y	Yield (%)*	Product	R	R'	Ar	Y	Yield (%)*
3a	Ph	H	Ph	—	89	**4d**	Ph	H	$4\text{-FC}_6\text{H}_4$	—	82
3b	Ph	H	$4\text{-FC}_6\text{H}_4$	—	88	**4e**	$4\text{-ClC}_6\text{H}_4$	H	Ph	—	81
3c	Ph	Me	Ph	—	78	**4f**	$4\text{-ClC}_6\text{H}_4$	H	$4\text{-FC}_6\text{H}_4$		83
3d	Ph	Me	$4\text{-FC}_6\text{H}_4$	—	81	**5a**	Me	Me	Ph	NCS	78
3e	$4\text{-ClC}_6\text{H}_4$	H	Ph	—	84	**5b**	Me	Me	$4\text{-FC}_6\text{H}_4$	NCS	84
3f	$4\text{-ClC}_6\text{H}_4$	H	$4\text{-FC}_6\text{H}_4$	—	91	**5c**	$4\text{-ClC}_6\text{H}_4$	H	Ph	NCS	88
3g	Me	Me	Ph	—	85	**5d**	$4\text{-ClC}_6\text{H}_4$	H	$4\text{-FC}_6\text{H}_4$	NCS	89
3h	Me	Me	$4\text{-FC}_6\text{H}_4$	—	83	**5e**	Me	Me	Ph	PhS	79
4a	Ph	Me	Ph	—	79	**5f**	Me	Me	$4\text{-FC}_6\text{H}_4$	PhS	81
4b	Ph	Me	$4\text{-FC}_6\text{H}_4$	—	77	**5g**	$4\text{-ClC}_6\text{H}_4$	H	Ph	PhS	85
4c	Ph	H	Ph	—	80	**5h**	$4\text{-ClC}_6\text{H}_4$	H	$4\text{-FC}_6\text{H}_4$	PhS	88

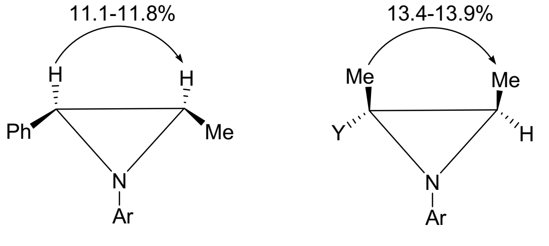
* Yields of isolated and purified products.

Scheme 1. Synthesis of aziridines **4** and **5** from α-halo ketones **2**.

α-halo ketones. The synthesis involves a novel one-pot nucleophile-induced intramolecular cyclization of α-halo ketone-derived phosphoramidates **3** to yield aziridines **4** and **5** (Scheme 1). Thus, treatment of diethyl *N*-aryl-phosphoramidates **1** with sodium hydride in benzene followed by α-halo ketones **2** afforded diethyl *N*-aryl-*N*-(2-oxoalkyl)phosphoramidates **3**[31] in 78–91% yields. Conventional reduction of phosphoramidates **3** with sodium borohydride afforded the corresponding alcohols in addition to a small amount of aziridines **4**. Thus, phosphoramidates **3** were reduced with sodium borohydride in *t*-butanol followed by treatment with sodium hydride in the same vessel to produce the corresponding aziridines **4**[32] in 77–83% yields (Scheme 1). Furthermore, phosphoramidates **3**, on reaction with potassium thiocyanate, or sodium thiophenolate in *t*-butanol afforded functionalized aziridines **5**[33] in 78–89% yields (Scheme 1). The synthesis of a few aziridines similar to **5** has been previously reported from 1,3-diphenyl-2-chloroaziridines via displacement of the chloride ion by hydride or thiolates,[29,34,35] however, the present method provides a direct access to this class of aziridines.

The nucleophile-induced cyclization of (2-oxoalkyl)-phosphoramidates **3** to aziridines **4** and **5** was highly diastereoselective in favour of the cis isomers. Diastereomeric ratios in the crude isolates were checked by ^{1}H NMR to note any alteration of these ratios during subsequent purification. The crude isolates of **4a**, **4b**, **5a**, **5b**, **5e** and **5f** were found to be diastereomeric mixtures containing 94–97% of the cis isomer. Strong NOEs were observed between 2-H/3-H and 2-Me/3-Me of these aziridines, which conclusively demonstrate their cis stereochemistry (Fig. 1). The cis stereochemistry of aziridines **4** was also supported by comparison of the *J* values of 2-H and 3-H with those reported in the literature.[27g]

The formation of aziridines **4** is best explained through intramolecular attack of the alkoxide ion **7** on the phosphorus atom (Scheme 2). This assumption is supported by the exclusive formation of aziridines **4** on addition of a base, such as sodium hydride, to facilitate alkoxide ion formation. On the other hand, aziridines **5** are formed by



4a, Ar = Ph
4b, Ar = $4\text{-FC}_6\text{H}_4$

5a, Ar = Ph; Y = NCS
5b, Ar = $4\text{-FC}_6\text{H}_4$; Y = NCS
5e, Ar = Ph; Y = PhS
5f, Ar = $4\text{-FC}_6\text{H}_4$; Y = PhS

Fig. 1. NOE experiments on aziridines **4** and **5**.