Efficient base catalyzed alkylation reactions with aziridine electrophiles†

Thomas A. Moss,[a] Aurelie Alba,[a] David Hepworth[b] and Darren J. Dixon*[a]

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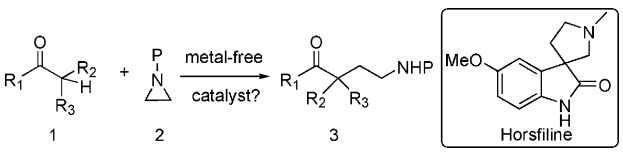
***N*-Mesitylene sulfonyl and *N*-tosyl aziridines have been identified as effective electrophiles in alkylation reactions of carbon acids catalyzed by the organic phosphorine base BEMP; yields of up to 99% for a range of pro-nucleophiles under mild reaction conditions are reported.**

Compounds containing the ethylene amino group attached to a stereogenic quaternary carbon ($R^1R^2R^3CCH_2CH_2N$) are widespread amongst natural products such as those belonging to the indole alkaloid family, of which horsfiline is representative. The impressive bioactivities of many of these compounds encouraged us to investigate a synthetic strategy that was simple in concept but broad in applicability. Our plan, outlined in Scheme 1, required a base-catalyzed addition of a suitably protected form of aziridine **2** to various methine pro-nucleophiles **1**. This alkylation reaction would allow direct access to the desired product **3** in one step from simple starting materials.

N-Substituted aziridines are mildly electrophilic reagents previously employed for the homologation of a range of carbon and heteroatom nucleophiles.[1] Their ready preparation from inexpensive commercial materials[2] and ease of handling makes them attractive in synthetic strategies.[3]

Owing to their moderate reactivity and their ability to readily polymerize, most efforts with carbon-centred nucleophiles have concentrated on the use of stoichiometric quantities of reactive metal enolates or organometallic reagents, and little attention has been devoted to facilitating the reaction under mild and catalytic conditions.[4–6] Furthermore, to the best of our knowledge there have been no reports of aziridine ring opening,[7] enantioselective[8] or otherwise, with carbon acids under *base-catalyzed* conditions.

To be catalytic in base and synthetically useful, the balance of pK_a values and the reactivity of the aziridine electrophile is critical; following alkylation of carbanion **4** with aziridine **2**, the adduct **5** must be sufficiently basic to deprotonate another molecule of pro-nucleophile **1** and thus complete the catalytic cycle (Scheme 2). As the same adduct is also nucleophilic at nitrogen, the equilibrium must be weighted towards **4** to suppress polymerization of the aziridine. By careful choice of pro-nucleophile, aziridine protecting group and base catalyst,

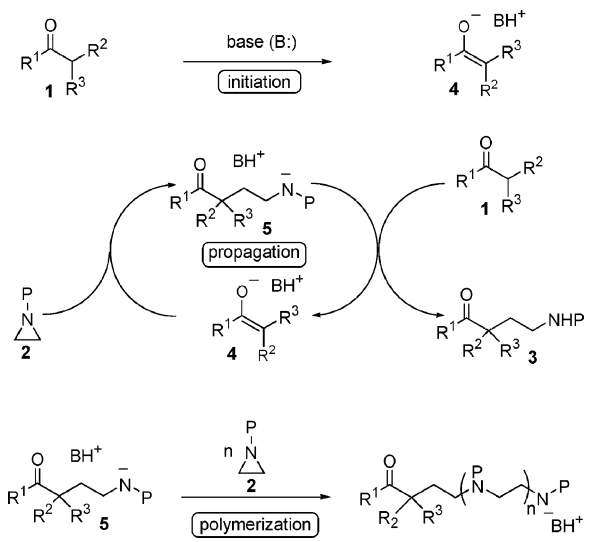


Scheme 1 Concept of a catalyzed aziridine alkylation reaction.

we reasoned that a *base-catalyzed* aziridine alkylation reaction would be possible. Herein we present our findings.

Preliminary studies using a range of *N*-sulfonyl aziridines (**2a–f**) with ethyl phenylcyanoacetate **1a** as a representative pro-nucleophile were performed to assess the viability of the concept.

The results of the preliminary studies are presented in Table 1. After a base screen, the organic phosphorine base 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) was identified as the most effective, catalyzing the alkylation of **1a** with *N*-tosyl aziridine **2a** to afford **3a** in a 93% yield, with a reaction time of 19 h at room temperature (entry 2). The high yield and relatively short reaction time was attributed to the strong basic nature (pK_a = 27.5) and low nucleophilicity of BEMP. *N*-Nosyl aziridine **2d** was completely insoluble in THF at room temperature and no reaction was observed whilst *N*-phosphoryl aziridine **2e** was soluble but unreactive under our conditions. Interestingly, when *N*-2-(trifluoromethane)benzenesulfonyl aziridine **2f** was used as the electrophile under base-catalyzed conditions, only

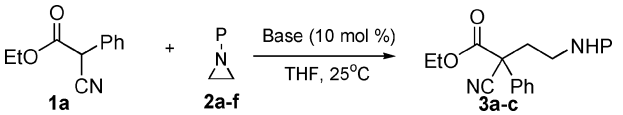


Scheme 2 Initiation, propagation and polymerization pathways in the base-catalyzed alkylation of carbon acids with aziridine electrophiles.

[a] *School of Chemistry, The University of Manchester, Oxford Road, Manchester, UK M13 9PL. E-mail: Darren.Dixon@man.ac.uk; Fax: +44 (0)161 2754939; Tel: +44 (0)161 2751426*
[b] *Pfizer Global Research & Development, Ramsgate Road, Sandwich Kent, UK CT13 9NJ*

† Electronic supplementary information (ESI) available: Experimental procedures, and spectral data for compounds **2b**, **2f**, **3a–p**, **6**, **7** and **8a–b**. See DOI: 10.1039/b802447b

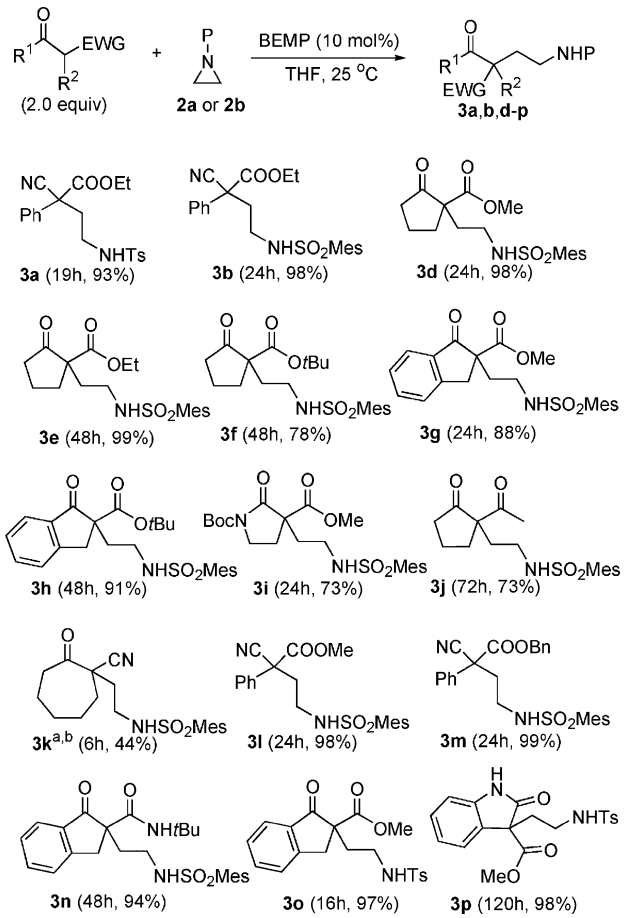
Table 1 Preliminary studies into the base-catalyzed alkylation of ethyl phenylcyanoacetate **1a** with aziridine electrophiles



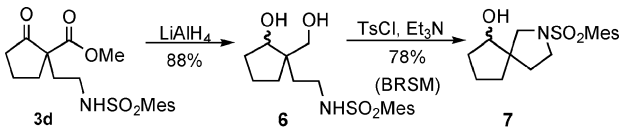
Entry	P	Base	Time/h	Product	Yield (%)
1	Tosyl (**2a**)	DABCO	72	**3a**	69
2	Tosyl (**2a**)	BEMP	19	**3a**	93
3	SO_2Mes (**2b**)	BEMP	24	**3b**	99
4	Cbz (**2c**)	BEMP	672	**3c**	83
5	*p*-Nosyl (**2d**)	DABCO	1	—	0[ab]
6	$PO(OEt)_2$ (**2e**)	BEMP	168	—	0[b]
7	*o*-$CF_3C_6H_4SO_2$ (**2f**)	BEMP	1	—	0[c]

[a] Aziridine was insoluble in THF at 25 °C. [b] No reaction occurred. [c] Polymeric products were obtained.

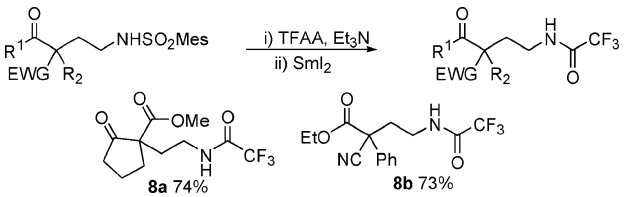
polymerization products were rapidly formed (entry 7). This can be rationalized from the various reaction pathways presented in Scheme 2. If the adduct **5** resulting from ring opening of the aziridine is relatively stable, as one could envisage by virtue of the *ortho* placement of an electron-withdrawing trifluoromethyl group, proton transfer from the parent acid



Scheme 3 BEMP catalyzed alkylation reactions with *N*-sulfonyl aziridines **2a** and **2b**. [a]Reaction performed at 65 °C. [b]23% *O*-Alkylated product was also isolated.



Scheme 4 Spirocyclization of **3d**.



Scheme 5 One pot activation–cleavage of the *N*-SO_2Mes group.

1 will effectively stall, and the dominant reaction pathway will be polymerization of the aziridine. Successful alkylation was observed with carbamate-protected aziridines (entry 4), however the reaction was prohibitively slow. That no significant polymerization of the aziridine was observed in this reaction despite the long reaction time suggests proton transfer in the catalytic cycle was fast, the sluggish reaction being a result of weaker inductive activation of the aziridine when compared to its sulfonyl analogues. A further enhancement in reaction efficiency was noted when *N*-mesitylsulfonyl aziridine **2b** was employed (entry 3). Overall, the optimal conditions employed 2 equivalents of pro-nucleophile **1a** to 1 equivalent of **2b** with 10 mol% BEMP in THF at 25 °C.

With the optimal conditions established, the scope of the alkylation reaction was surveyed by probing changes to the pro-nucleophile (Scheme 3). A range of carbonyl compounds, including esters, lactams, acetates, and nitriles, in addition to cyanoacetates, amides and oxindoles, were screened. Yields ranged from 73–99% with the exception of entry **3k** where appreciable oxygen alkylation was also observed; the total yield for alkylation (C and O) was 67%. At 25 °C in THF reaction times typically ranged from 24–48 h. 2-Acetyl cyclopentanone was less reactive than its ester analogues, presumably reflecting the enhanced stability of the enolate.

With the scope of the reaction established, the synthetic utility of the alkylation adducts was investigated in the preparation of azaspirocycles. Adduct **3d** was synthesized on a gram scale with no reduction in chemical yield. Reduction of the β-keto ester adduct **3d** furnished the di-alcohol **6** as 2 diastereoisomers (5 : 2 ratio) in an 88% overall yield. This could be further elaborated into the *N*-protected spiro adduct **7** (dr = 2 : 1) by a one-pot tosylation–cyclization reaction (Scheme 4).

Finally, for this method to be synthetically useful, the robust sulfonyl protecting group has to be removed under non-destructive conditions. Of the methods reported in the literature[9] we found that the trifluoroacetamide exchange protocol of Moussa and Romo to be the most effective. Thus, subjection of the selected adducts **3b** and **3d** to a one-pot activation–cleavage reaction using TFAA and SmI_2,[10] resulted in smooth exchange of the sulfonamide protecting group to the readily manipulated trifluoroacetamide[11] in good yield (Scheme 5).

In conclusion, we have presented the first base-catalyzed ring opening alkylation of a range of pro-nucleophiles with *N*-sulfonyl aziridines under mild reaction conditions. Removal of the *N*-sulfonyl group under non-destructive conditions has also been demonstrated. Work to further expand the nucleophile and electrophile range, and to develop an enantioselective variant of this methodology is currently underway and will be reported in due course.

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