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Direct Aza-Darzens Aziridination of *N*-Tosylimines with 2-Bromomalonates for the Synthesis of Highly Functionalized Donor-Acceptor Aziridines

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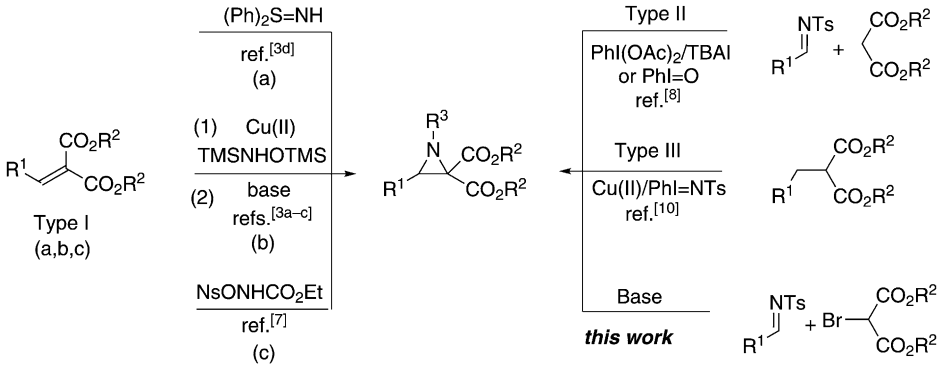
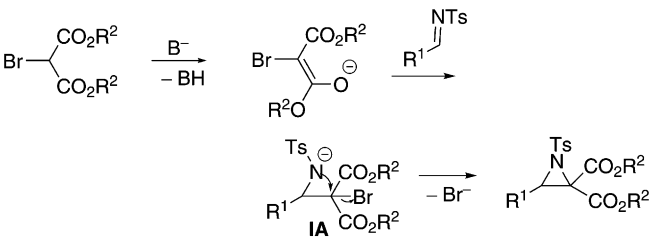
Abstract: An approach to highly functionalized donor-acceptor aziridines by the aziridination of *N*-tosylimines and 2-bromomalonates in the presence of sodium hydride under mild conditions has been developed. The high-yielding reaction has a relatively broad scope and can be easily scaled up to the gram level.

Keywords: aziridination; 2-bromomalonates; donor-acceptor aziridines; sodium hydride; *N*-tosylimines

Aziridines are highly useful synthetic intermediates in organic synthesis and structural units of many biologically natural products and drugs.[1] Various synthetic methods, including Wenker synthesis,[2a,b] aza-Darzens reaction,[2c–g] Corey–Chaykovsky aziridination,[2h,i] reactions of α-halo ketimines with nucleophiles,[2j–l] or the direct aziridination of olefins[2m,n] have been largely reported. So far, a vast and diverse family of aziridines has been synthesized by these protocols, among which, aziridine-2,2-diesters are special members as one kind of donor-acceptor aziridine. These highly functionalized three-membered nitrogen heterocyclic molecules are of particular significance, not only because of the pronounced biological activities as inhibitors,[3] but also for their wide applications in organic synthesis. Since Huisgen's[4j] pioneering work, aziridine-2,2-diesters have been largely utilized as precursors of azomethine ylide (AMYs) intermediates by thermal or photolytic aziridine ring-opening.[4] Recently, Carrie,[5a] Johnson,[5b] Engle[5c] and our group[5d–g] achieved the Lewis acid-catalyzed C–C bond heterolysis, leading to AMYs, and providing general and direct access to five-membered heterocycles, such as 1,3-oxazolidines,[5e] 1,3-imidazolidines,[5g] pyrroles[5a,d] and pyrrolines[5f]. However, in contrast with the extensive studies on the synthesis of aziridine 2-monocarboxylate,[6] the preparation of aziridine 2,2-dicarboxylates is not always straightforward.[3d,7–9] Typical synthetic methods are illustrated in Scheme 1, including: (a) Michael-type addition of diphenylsulfi-



Scheme 1. Approaches to aziridine-2,2-dicarboxylates.

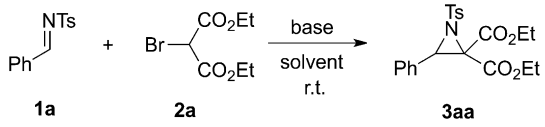


Scheme 2. Proposed mechanism for the formation of aziridine-2,2-dicarboxylates.

mide,[3d] hydroxylamino derivatives,[3a–c] or nosyloxy carbamates[7] to the electron-deficient alkenes to produce the desired aziridines (Type I); (b) aziridination of *N*-tosylimines with activated methylene compounds induced by $PhI(OAc)_2$/TBAB[8a] or PhI=O[8b] under mild conditions (Type II); (c) Cu(II)-catalyzed formal aziridination of 2-alkyl-substituted 1,3-dicarbonyl compounds with PhI=NTs.[9] (Type III). Type I reactions (a, b, c) suffer from several drawbacks, such as the not commercial availability of starting material for reactions (b) and (c), the limited reaction scope for reactions of type (a), or the use of transition metals in reactions (b). The second and third classes of transformations are generally more efficient in terms of the high yield of the products and broad reaction scope. However,, an excess of the high-cost hypervalent iodine reagents (2–3 equiv,) is required and an equivalent amount of by-product iodobenzene is generated, which makes the work-up step quite hard on a large scale.[8,9] Considering the significance of the aziridine-2,2-diesters in organic synthesis and pharmaceuticals, the facile and practical preparation of 2,2-difunctionalized aziridines from readily available materials without the use of transition metals and high-cost reagents is still highly desirable. Herein, in this context we describe an efficient direct aza-Darzens aziridination of *N*-tosylimines with 2-functionalized malonates under mild conditions, providing a facile and practical route to synthetic useful aziridinyl diesters.

During the course of our studies on the cycloaddition reactions of donor-acceptor aziridines *via* C–C bond cleavage,[5d–g] we became interested in developing a novel and easy access to this class of aziridines, if applicable, which would in turn enhance the synthetic value of the aziridine-2,2-diesters, especially in the synthesis of N-heterocycles. Scheme 2 shows a mechanism for our proposed annulation reaction. Nucleophilic addition of enolate, generated from the activated methylene compound under basic conditions, to the *N*-tosylimine gives the intermediate **IA**, which undergoes subsequent intramolecular nucleophilic substitution to afford the donor-acceptor aziridines.

Table 1. Screening of the reaction conditions.[a]



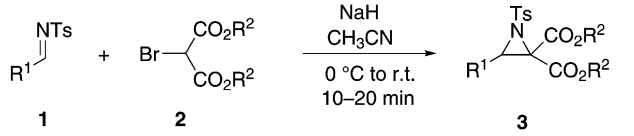
Entry	Base	Solvent	Time [h]	Yield [%][c]
1	*t*-BuOK	CH_3CN	0.5	83
2	Cs_2CO_3	CH_3CN	2.5	74
3[b]	K_2CO_3	CH_3CN	3.5	69
4[b]	K_2CO_3	acetone	4	73
5	NaOH	CH_3CN	4	81
6	KOH	CH_3CN	4	86
7[b]	KOH	CH_3CN	4	85
8	DBU	CH_3CN	8	70
9	NaH	CH_3CN	0.16	92
10	NaH	THF	0.16	91

[a] *Reaction conditions:* **1a** (0.5 mmol), **2a** (1.1 equiv.), and base (1.1 equiv.) in 5 mL of solvent at room temperature.
[b] 2 equiv of base was used.
[c] Isolated yield.

We began our investigation with *N*-tosylimine **1a**, which was readily prepared from the condensation of *p*-toluenesulfonamide with benzaldehyde,[10] and the inexpensive diethyl 2-bromomalonate **2a** as model substrates. As illustrated in Table 1, treatment of **1a** and **2a** (1.1 equiv.) with *t*-BuOK (1.1 equiv.) in acetonitrile provided aziridine **3aa** in 83% yield (Table 1, entry 1). Other selected representative bases including Cs_2CO_3, K_2CO_3, NaOH, or DBU were tested to optimize the reaction conditions. Notably, relatively lower product yields (69–81%) were afforded with relatively longer reaction times (2.5–8 h), probably due to the weak alkalinity of the bases. (Table 1, entries 2-5 and 8) A slight increase in yield was observed when KOH was employed as the base, and a higher KOH loading (2 equiv.) only gave a 1% decrease in product yield (Table 1, entries 6 and 7). To our delight, the reaction worked very well in CH_3CN at room temperature by using NaH (1.1 equiv.) as the base, which provided the aziridine **3aa** in 92% isolated yield (Table 1, entry 9). Replacement of CH_3CN by THF as the solvent failed to improve the yield (Table 1, entry 10).

The reaction scope of this direct aziridination of *N*-tosylimines with 2-bromomalonate derivatives was further explored under the optimal conditions (Table 2). For reactions of aromatic imines **1** with diethyl 2-bromomalonate **2a**, both electron-deficient and electron-rich arylaldimines reacted well to afford the corresponding aziridines in good to high yields within 10–20 min (Table 2, entries 1–11). Some observations were particularly noteworthy: (i) generally, the aromatic *N*-tosylimines bearing electron-withdrawing groups worked better than those electron-

Table 2. Reaction scope of the aziridination of *N*-tosylimines with 2-bromomalonates.[a]



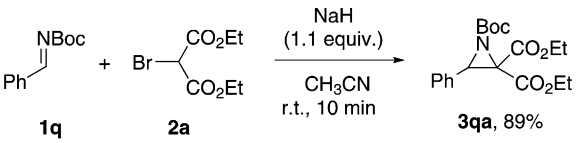
1 2 3

Entry	R^1	R^2	Yield [%][d]
1	Ph (**1a**)	Et (**2a**)	**3aa** (92)
2	*p*-FC_6H_4 (**1b**)	Et (**2a**)	**3ba** (92)
3	*p*-ClC_6H_4 (**1c**)	Et (**2a**)	**3ca** (95)
4	*p*-BrC_6H_4 (**1d**)	Et (**2a**)	**3da** (96)
5	*p*-$O_2NC_6H_4$ (**1e**)	Et (**2a**)	**3ea** (99)
6	*p*-NCC_6H_4 (**1f**)	Et (**2a**)	**3fa** (99)
7	*o*-BrC_6H_4 (**1g**)	Et (**2a**)	**3ga** (95)
8	*p*-$MeOC_6H_4$ (**1h**)	Et (**2a**)	**3ha** (51)[b]
9	*p*-MeC_6H_4 (**1i**)	Et (**2a**)	**3ia** (81)
10	*m*-MeC_6H_4 (**1j**)	Et (**2a**)	**3ja** (83)
11	1-naphthyl (**1k**)	Et (**2a**)	**3ka** (91)
12	H (**1l**)	Et (**2a**)	**3la** (82)
13	Me (**1m**)	Et (**2a**)	**3ma** (97)
14	Et (**1n**)	Et (**2a**)	**3na** (99)
15	*i*-Bu (**1o**)	Et (**2a**)	**3oa** (91)
16	Ph (**1a**)	Me (**2b**)	**3ab** (92)
17	Ph (**1a**)	*i*-Pr (**2c**)	**3ac** (95)
18	Ph (**1a**)	*t*-Bu (**2d**)	**3ad** (89)
19	Ph (**1a**)	*t*-$BuCH_2$ (**2e**)	**3ae** (99)
20	*p*-ClC_6H_4 (**1c**)	*t*-$BuCH_2$ (**2e**)	**3ce** (97)
21	*p*-BrC_6H_4 (**1d**)	*t*-$BuCH_2$ (**2e**)	**3de** (98)
22	*p*-MeC_6H_4 (**1i**)	*t*-$BuCH_2$ (**2e**)	**3ie** (95)
23	*p*-*i*-PrC_6H_4 (**1p**)	*t*-$BuCH_2$ (**2e**)	**3pe** (96)
24[c]	Ph (**1a**)	Et (**2a**)	**3aa** (86)

[a] Standard conditions: **1** (0.5 mmol), **2** (1.1 equiv.), and NaH (1.1 equiv.) in 5 mL of CH_3CN at room temperature.
[b] 82% NMR yield was detected for the crude product (CH_2Br_2 as a standard).
[c] Reaction on the gram-level scale: **1a** (20 mmol), 1.05 equiv. of **2a**, and 1.05 equiv. of NaH were used.
[d] Isolated yield.

rich ones. For instance, the 4-nitrophenyl-*N*-tosylimine (**1e**) and 4-cyanophenylimine (**1f**) both gave the desired products in nearly quantitative yield (Table 2, entries 5 and 6); (ii) aziridines bearing the electron-donating aromatic group were not stable and decomposed during the purification by column chromatography, which resulted in a relatively low isolated yield (Table 2, entries 8–10). For example, for the imine (**1h**) derived from 4-methoxybenzaldehyde, the reaction was clean as determined by the TLC analysis to give an 82% NMR yield, while only a 51% isolated yield of **3ha** can be obtained due to the easy decomposition[8a] upon work-up to give a by-product $TsNHCH(CO_2Et)_2$[5b,d] (Table 2, entry 8); (iii) when 1-naphthyl-derived imine (**1k**) was employed as the substrate, the reaction also worked very well to give the product in 91% yield (Table 2, entry 11).

We next sought to evaluate the scope of this practical methodology with respect to the *N*-tosyl-(alkyl)imines and 2-bromomalonates (Table 2, entries 12–23). The reaction behavior of *N*-tosyl-(alkyl)imines with **2a** were first tested under the standard conditions. It was pleasing to find that the expected alkyl-substituted aziridinyl-2,2-diesters could be prepared in good to excellent yields (Table 2, entries 12–15). It was noteworthy that only moderate yields can be obtained by Fan's approach.[9a]. Finally, a series of 2-bromomalonates were examined, which showed the similar reactivity as diethyl 2-bromomalonate (**2a**) (Table 2, entries 16–23). Gratifyingly, the reactions of sterically hindered *tert*-butyl and neopentyl 2-bromomalonates with imine **1a** also gave the corresponding aziridines in excellent yields within 20 min (Table 2, entries 18–23). Notably, those aziridines bearing a neopentyl ester group are much more stable than those substituted by ethyl, or methyl ester groups (Table 2, entries 19–23). To demonstrate the synthetic utility of this protocol, the reaction – scaled up to 20 mmol – was performed under the optimal conditions, which also proceeded smoothly to give 7.18 g of aziridine **3aa** in 86% yield (Table 2, entry 24). It was noteworthy that aziridine **3qa** bearing the easy removable *N*-Boc protecting group can also be prepared from the corresponding *N*-Boc-imine **1q** and **2a** by the use of this protocol [Eq. (1)].



1q 2a (1)

In summary, we have developed an efficient, convenient and practical method for the synthesis of donor-acceptor aziridines from *N*-tosyl- or *N*-Boc-imines and 2-bromomalonates in the presence of NaH. The wide substrate scope, excellent yield (up to 99%), simple operating and purification procedures, as well as the readily available and low-cost starting materials, provide a practical method for the preparation of highly synthetic important donor-acceptor aziridines. Further investigations including synthetic applications of the aziridines are underway and will be reported in due course.

Experimental Section

Typical Procedure for Aziridination of *N*-Tosylimines 1 with 2-Bromomalonates 2

In an inert atmosphere, a solution of imine **1** (0.5 mmol, 1 equiv.), 2-bromomalonate **2** (0.55 mmol, 1.1 equiv.) in

5 mL of dry CH_3CN was cooled to 0 °C, and treated with NaH (22 mg, 60% dispersion in mineral oil, 1.1 equiv.). The resultant mixture was warmed up and stirred at room temperature. After 10–20 min when the reaction was completed (determined by TLC analysis), the reaction mixture was then passed over a small plug of silica gel eluted with CH_2Cl_2 to remove the excess NaH and resulting NaBr. After evaporation under reduced pressure, usually, the crude product was of sufficient purity; it can be quickly purified by flash chromatography on 10 cm-long silica gel column (eluent, 10–30% ethyl acetate in petroleum ether) to afford the desired product **3**. The resulting compounds were confirmed by ^1H NMR and ^{13}C NMR.

Supporting Information

Experimental details and copies of $^1H/^{13}C$ NMR spectra of all new compounds are available in the Supporting Information.

Acknowledgements

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