Intermolecular Alkyl Radical Addition to Methyl 2-(2,6-Dichlorophenyl)-2*H*-azirine-3-carboxylate

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Abstract: The 2*H*-azirine **1** acts as an effective radical acceptor for secondary and tertiary alkyl iodides mediated by triethylborane. The addition proceeds with high regio- and diastereo-selectivity.

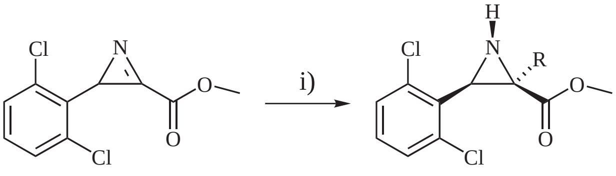
Key words, 2*H*-azirine, intermolecular radical addition, triethylborane

When compared with other functional groups, free radical additions to C=N have received much less attention. In recent years, however, much work has been carried out on intramolecular (cyclisation) radical addition to imines, oxime ethers and hydrazones.[1] More recently, intermolecular radical additions to C=N bond have become an established and powerful method for the formation of C–C bonds,[1,2] and studies have been made in order to bring about the addition in a stereocontrolled manner.[3]

It has been shown that 2*H*-azirine-3-carboxylates are particularly good electrophiles, in reactions with a variety of electron rich dienes and nucleophiles,[4] as a consequence of the conjugative effect of the ring strain and extra activation by the ester group. From a side and fortuitous (single) reaction with tetrahydrofuranyl radical, it was postulated that azirines could be susceptible to radical addition.[4c]

These facts provided the basis for the exploration of the potential of 2*H*-azirine-3-carboxylates to act as intermolecular radical acceptors.

In our preliminary experiments, we submitted the azirine **1** to classical peroxide and tin hydride/AIBN conditions (Table 1, entries 1, 2). Although the disappearance of the azirine could be observed, the reaction product consisted of a complex mixture from which no pure compound could be obtained. It has been demonstrated that intermolecular radical reactions can be efficiently carried out under tin or peroxide free conditions.[5] The initial sets of experiments with triethylborane did not produce better results, only polymer like material being recovered from the reaction (entries 3, 4). However at –40 °C, the azirine was smoothly and cleanly converted to the correspondent aziridine in moderate to good yields (entries 5–8). A strongly activating Lewis acid was not needed, evidently due to the high reactivity of the azirine **1** rather than the role of triethylborane, (acting as radical initiator and terminator but also as Lewis acid).[1a,2h,5] The reaction, with these iodides, proceeded with a high degree of selectivity. Neither ethylated by-products could be detected (Scheme 1) when alkyl iodides different from ethyl iodide were used, nor *N*-ethylated or bis *C*- and *N*-ethylated products, as it has been established with other imines.[2c,2h,2i,2k] These results are, to some extent, in good agreement with the nucleophilicity (and/or) stability of the radical involved.



1

2

a : R = Et (71%)
b : R= *i*-Pr (82%)
c : R= *t*-Bu (89%)
d : R= Cyclohexyl (79%

Scheme 1 i) Et_3B, RI, CH_2Cl_2, –40 °C, 30 min.

These reactions proceeded with a high degree of stereoselectivity; only one single diastereoisomer could be detected as a consequence of the addition, which is controlled by the position of the aryl group and occurs from the less hindered face of the azirine ring. An X-ray single crystal structure of azirine **2b** is shown in Figure 1.[6]

Having these results in hand, we then tried to apply the same conditions of intermolecular radical addition to other iodides (Table 1, entries 9–19; Scheme 2). With 4-chloroiodobenzene, cleanly, aziridine **2a** was the only reaction product, in 53% yield (entry 9). Similarly, with (2-iodoethyl)benzene, *n*-hexyl, *n*-octyl and allyliodide, the aziridine **2a**[8] was isolated (in these cases the reaction was not so clean and other complicated mixtures were also isolated from the reaction, entries 10–13 and 16).

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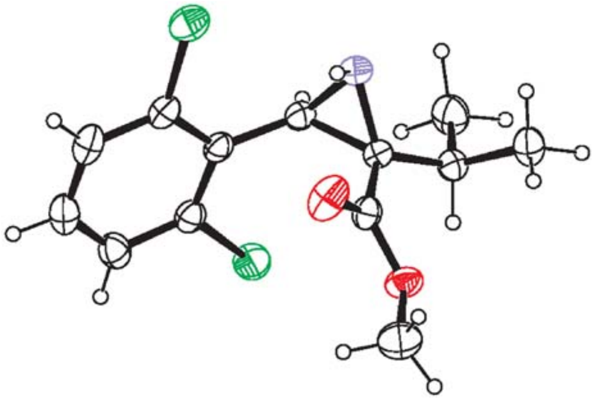
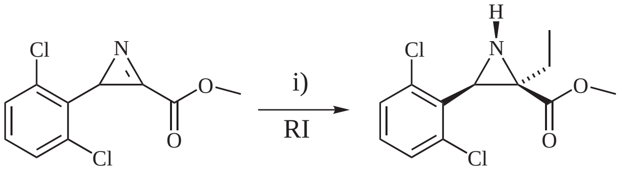


Figure 1 X-Ray crystal structure of aziridine **2b**.



1

R = 4-chlorobenzene (53%)[2a]
= CH_2CH_2Ph (45%)
= n-C_6H_{13} (38%)
= n-C_8H_{17} (7%)
= allyl (-)

Scheme 2 i) Et_3B, CH_2Cl_2, –40 °C.

Table 1 Radical Additions to Azirine **1**

Entry	Radical Initiator	Temperature	Solvent	Substrate	Product	Yield (%)
1	Benzoyl Peroxide	Reflux	THF	EtI	a)	
2	AIBN/ nBu_3SnH	Reflux	THF	EtI	a)	
3	Et_3B	Ambient	CH_2Cl_2	EtI	b)	
4	Et_3B	–5–0 °C	CH_2Cl_2	EtI	b)	
5	Et_3B	–40 °C	CH_2Cl_2	EtI	**2a**	71
6	Et_3B	–40 °C	CH_2Cl_2	*i*-PrI	**2b**	82
7	Et_3B	–40 °C	CH_2Cl_2	*t*-BuI	**2c**	89
8	Et_3B	–40 °C	CH_2Cl_2	Iodocyclohexane	**2d**	79
9	Et_3B	–40 °C	CH_2Cl_2	4-Chloroiodobenzene	**2a**	53
10	Et_3B	–40 °C	CH_2Cl_2	(2-Iodoethyl) benzene	**2a**	45
11	Et_3B	–40 °C	CH_2Cl_2	1-Iodooctane	**2a**	7
12	Et_3B	–40 °C	CH_2Cl_2	1-Iodohexane	**2a**	38
13	Et_3B	–40 °C	CH_2Cl_2	Allyl iodide[c)]	**2a**	d)
14	Et_3B	r.t.	CH_2Cl_2	Allyl iodide	b)	
15	Et_3B	–5 °C	CH_2Cl_2	Allyl iodide	b)	
16	Et_3B	–20 °C	CH_2Cl_2	Allyl iodide[e)]	**2a**	d)
17	Et_3B	–40 °C	CH_2Cl_2	$MeOCH_2I$	b)	
18	Et_3B	–70 °C	CH_2Cl_2	$MeOCH_2I$	b)	
19	Et_3B	–100 °C	CH_2Cl_2	$MeOCH_2I$	b)	
20	Et_3B	–40ºC	CH_2Cl_2	None	d)	
21	Et_3B/ nBu_3SnH	–40 °C	CH_2Cl_2	EtI	**2a**	37
22	Et_3B	–40 °C	Toluene	Iodocyclohexane	**2d**	45
23	$ZnEt_2$	–40 °C	CH_2Cl_2	*i*-PrI	–	
24	$ZnMe_2$	–40 °C	CH_2Cl_2	*i*-PrI	–	

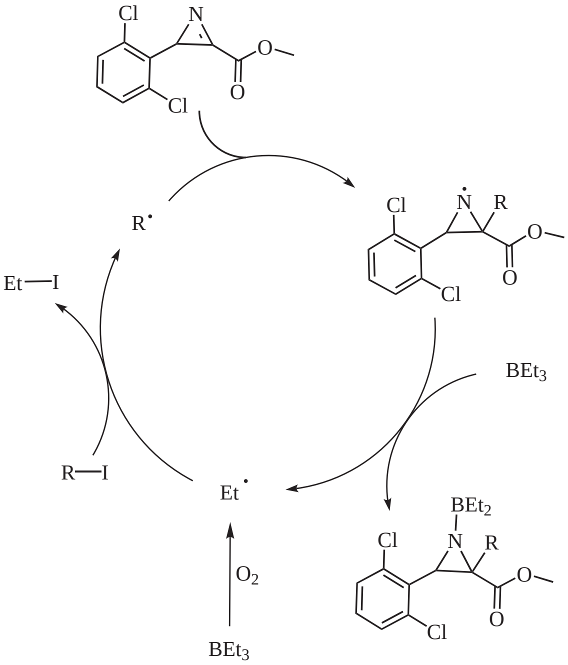
[a] Complex mixture without isolable product.
[b] Polymer like product.
[c] 3 h Reaction.
[d] Complex mixture from which **2a** was isolated in very low yield.
[e] Reaction time: 1.5 h.

These results where rather surprising and puzzling, because they not only contrast with the good results previously described (entries 5–8) but also with the results obtained in the absence of any alkyl iodide (entry 20). Iodomethyl methyl ether and allyl iodide constituted particular cases. Even at much lower temperatures, the reaction with iodomethyl methyl ether was very fast, but the product consisted of polymer like material (entries 17–19). On the other hand, with allyl iodide the reaction at lower temperatures was slow and poor (entries 13 and 16) and at higher temperatures only polymer like material was isolated (entries 14, 15).

Under the conditions that we have investigated, the efficiency of the intermolecular radical addition to the azirine **1** increases in the order primary < secondary < tertiary alkyl iodide, which is usual for cyclic chain reactions, where the radical formation, its addition and the trapping of the adduct radical governs the chain.[9] The rate of abstraction of iodine atoms versus addition at the π-bond by ethyl radicals (the chain carriers, Scheme 3), will govern the process and the efficiency of the desired reaction. In the cases where the abstraction is not fast enough (the use of lower temperatures, compelled by the high reactivity of the azirine, may slow down the process[2c] even more), the formation of the ethyl aziridine will be prevalent. Presumably, this is what happens with *n*-hexyl, *n*-octyl, phenethyl and chlorophenyl iodides. With allyl iodide, possibly, the low reactivity of its corresponding radical towards the π-bond is the main factor associated to the results obtained.

We also briefly explored some variables such as solvent and radical initiator. The addition to the reaction mixture of 1 equivalent *n*-Bu_3SnH (entry 21), or the use of toluene as solvent (entry 22) did not bring advantages. The use of diethyl[2h] or dimethyl zinc,[7] which have been successfully applied to intermolecular radical additions to imines, proved to be a complete failure as only degradation products were identified (entries 23, 24).

In summary, we have found that intermolecular radical addition of secondary and tertiary alkyl radicals to methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate proceeded in good yields and with high regio- and diastereoselectivity. When the conjugation of high reactivity of azirine and radical (e.g. methoxymethyl) is observed the reaction is (under the conditions used) incontrollable. For iodides where the rate of iodine atom transfer is not so fast, a proper balance must be reached in order to avoid polymerization (high reactivity of azirine) or the ethyl addition from Et$_3$B. The scope (generality) of the intermolecular radical additions as well the reactivity of other activated and unactivated 2*H*-azirines are under investigation.



Scheme 3 Plausible mechanism for the alkyl addition to **1**.[10]

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(8) **Typical Procedure:** A solution of triethylborane (15% in hexane) (0.4 mL, 6.12 mmol) was added to a mixture of methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate (0.3g, 1.23 mmol) and the alkyl iodide (12.4 mmol) in CH_2Cl_2 (20 mL) at –40 °C. The reaction was maintained at this temperature for 30 min and the mixture was then washed with a 10% aq solution of $NaHCO_3$ the organic layer dried (Na_2SO_4) and evaporated. Flash chromatography (hexanes/EtOAc: 80/20) afforded the product.
With iodoethane: Methyl 3-(2,6-dichlorophenyl)-2-ethylaziridine-2-carboxylate **2a**, 0.24 g (71%), mp 53.0–54.5 °C (from toluene/CH_2Cl_2). (Found: C, 52.28; H, 4,92; N, 5,07. $C_{12}H_{13}Cl_2NO_2$ requires C, 52.57; H, 4.78; N, 5.11%). IR ν_{max} = 1724, 1433, 1207, 777 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.11 (3 H, t, *J* = 7.5 Hz), 1.52–1.64 (1 H, m, CH_3HCH), 2.41–2.53 (2 H, m, CH_3HCH and NH, integration became one after D_2O shake), 3.12 (1 H, br s, H-3, turns into a sharp singlet after D_2O shake), 3.57 (3 H, s,) 7.12–7.17 (1 H, m), 7.27–7.29 (2 H, m). MS (CI): *m*/*z* (%) = 274 (100), 276 (66), 278 (12) [(M + H)$^+$].
With 2-iodopropane: Methyl 3-(2,6-dichlorophenyl)-2-(1-methylethyl) aziridine-2-carboxylate **2b**, 0.29 g (82%); mp 81.7–82.9 (from hexanes/EtOAc). (Found: C, 53.96; H, 5.47; N, 5.03; $C_{13}H_{15}Cl_2NO_2$ requires C, 54.18; H, 5.25; N, 4.86%). IR ν_{max} = 3209, 2968, 1724, 1433, 1207, 775 cm^{-1}. ^{1}H NMR (300 Mz): δ = 1.2 (9 H, s), 2.66 (1 H, br d, *J* = 7.3 Hz, aziridine NH), 3.28 (1 H, br d, *J* = 7.1 Hz, H-3), 3.47 (3 H, s) 7.10–7.16 (1 H, m), 7.25–7.28 (2 H, m). MS (CI): *m*/*z* (%) = 288 (100), 290 (66), 292 (12) [(M + H)$^+$].

With 2-iodo-2-methylpropane: Methyl 3-(2,6-dichlorophenyl)-2-(1,1-dimethylethyl)aziridine-2-carboxy-late **2c** (0.33 g, 89%), as a low melting point solid. IR ν_{max} = 3406, 2959, 1714, 1431, 1242, 774 cm^{-1}. ^1H NMR (300 Mz): δ = 1.2 (9 H, s), 2.66 (1 H, bd, *J* = 7.3 Hz, aziridine NH), 3.28 (1 H, bd, *J* = 7.1 Hz, H-3), 3.47 (3 H, s) 7.10–7.16 (1 H, m), 7.25–7.28 (2 H, m).

With iodocyclohexane: Methyl 3-(2,6-dichlorophenyl)-2-cyclohexylaziridine-2-carboxylate **2d**, (0.32 g, 79%), mp 105.6–107.2 °C (from toluene/CH_2Cl_2), IR ν_{max} = 3209, 2967, 1724, 1433, 1207, 775 cm^{-1}. ^1H NMR (300 Mz): δ = 1.08–1.9 (10 H, multiplet), 2.29 (1 H, br t, *J* = 4.2 Hz), 2.54 (1 H, br s, NH), 3.28 (1 H, br s), 7.10–7.16 (1 H, m), 7.26–7.29 (2 H, m).

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