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N-Amino-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide in reaction of oxidative aminoaziridination

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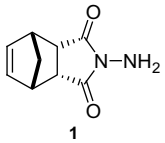
ABSTRACT

The ability of easily accessible *N*-amino-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide to undergo oxidative addition to double bonds of alkenes has been explored. The compound is active toward alkenes with electron-withdrawing groups, aryl- and alkyl-substituted alkenes, providing access to stable derivatives of *N*-aminoaziridine. Yields varied from 20% to 70%. No products of self-aminoaziridination were isolated.

Presently, there are a limited number of *N*-aminoheterocycles known to be capable of oxidative addition to carbon–carbon double bonds. 1-Aminoquinolin-2(1*H*)-one,[1a,b] 3-amino-1,3-benzoxazol-2(3*H*)-one,[1a,c] 3,5-disubstituted 4-amino-1,2,4(4*H*)-triazoles,[1d–f] 1-amino-2,5-diphenylpyrrole,[1d] diethyl 1-amino-2,5-dimethylpyrrole-3,4-dicarboxylate,[1d] and some other *N*-aminoheterocycles have all been found reactive toward alkenes, but in practice only *N*-aminophthalimide[1a,2a–d] and 3-aminoquinazolin-4(3*H*)-ones[1a,2e–g] were applied in the synthesis of *N*-aminoaziridines. The ability of alicyclic *N*-aminoimides to participate in oxidative aminoaziridination is clearly underreported.[1g] In particular, it is not known whether *N*-aminoimides containing an olefinic double bond can react intermolecularly with alkenes. Readily available *N*-amino-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic (endic) acid imide (EnN–NH_2, **1**) seems to be an appropriate test compound of this type:



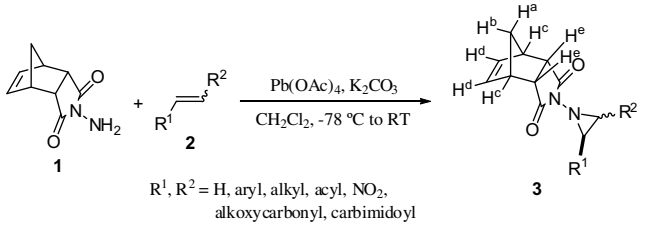
1

The synthesis of **1** was first reported in 1965 by Furdik.[3a] In 2005, Kas'yan et al. published the full analytical data on **1** and discussed some of its reactions.[3b] However, its oxidation in the presence of electron-rich compounds has not been investigated.

Herein, we present our study of oxidative addition of **1** to substituted alkenes. While several oxidizing systems were found practical for this reaction ((diacetoxyiodo)benzene,[2g,4a–c] dimethyldioxirane–iodobenzene,[2g] *m*-chloroperoxybenzoic acid (*m*CPBA)–aryl iodide,[4d] potassium superoxide,[4e] electrochemical oxidation[4f,g]), lead(IV) acetate was the oxidant of choice in our work due to its lower cost and ease of removal in the course of isolation of the products.

As the substrates, we have chosen a series of alkenes with aryl and alkyl substituents at the double bond, with either electron-donating or electron-withdrawing groups, including several cyclic compounds. All reactions were carried out with 1 equiv of lead(IV) acetate in dichloromethane solution at −78 °C for 30 min, warmed up to room temperature, and stirred for additional 10 min.[5] In contrast with *N*-aminophthalimide, we were able to take advantage of good solubility of **1** in dichloromethane and were adding the solutions of the oxidizing agent and the *N*-aminoheterocycle simultaneously to the reaction mixture. The excess of anhydrous potassium carbonate was used as a base (Scheme 1).

Most of the substrates were converted into the corresponding aminoaziridines in moderate yields (20–70%, Table 1). Despite the fact that **1** possesses the norbornene type double bond, which is generally considered more reactive than the unstrained cis-double bond, the product of intermolecular self-aziridination was never isolated from the reaction mixture. The slow addition of the *N*-aminoheterocycle may have helped to maintain the



1 **2** **3**

Scheme 1. Oxidative aminoaziridination of alkenes with EnN–NH_2/$Pb(OAc)_4$ system.

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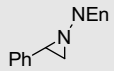
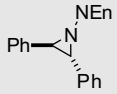
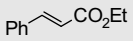
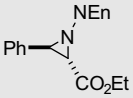
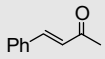
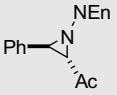
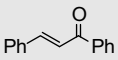
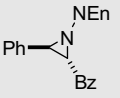
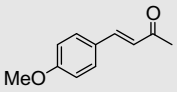
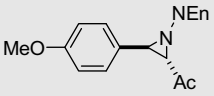
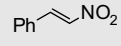
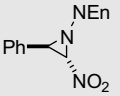
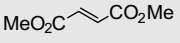
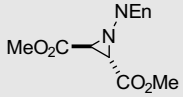
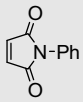
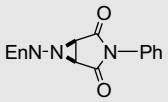
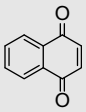
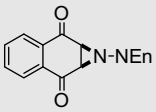
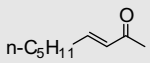
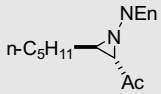
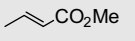
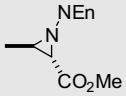
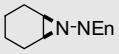
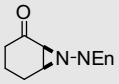
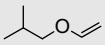
Table 1
Oxidative aminoaziridination of alkenes with EtN–NH_2

Entry	Alkene		Aziridine		Yield (%)
1	**2a**		**3a**		37
2	**2b**		**3b**		40
3	**2c**		**3c**		30
4	**2d**		**3d**		48
5	**2e**		**3e**		70
6	**2f**		**3f**		63
7	**2g**		**3g**		50
8	**2h**		**3h**		41
9	**2i**		**3i**		48
10	**2j**		**3j**		47
11	**2k**		**3k**		40
12	**2l**		**3l**		56
13	**2m**		**3m**		60
14	**2n**		**3n**		20
15	**2o**		–		–
16	**2p**		–		–

adequately low concentration of the intermediary *N*-aminonitrene or its synthetic equivalent. Importantly, the increasing concentration of the target aminoaziridine over the course of reaction did not seem to result in formation of its adduct with the second molecule of the reactive species to a significant extent.

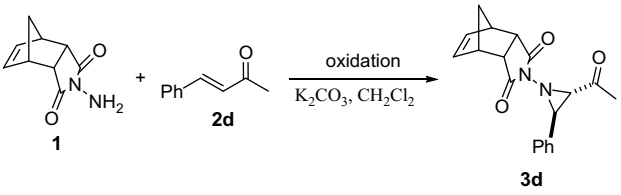
A brief screening of other available oxidants in the reaction of oxidative aminoaziridination with **1** has also been performed (Table 2).

While (diacetoxyiodo)benzene[4a] (entry 2) gave slightly better results than lead(IV) acetate, no product was isolated from the reaction with (dichloroiodo)benzene (entry 3). Common electrophilic halogenating agents (NBS, NCS, trichloroisocyanuric acid—entries 5, 6, and 7) failed to provide preparatively significant yields of the target adduct **3d**; however, in the reaction with *tert*-butyl hypochlorite under identical conditions the product was formed in 37% yield (entry 8). Activated MnO_2 (entries 9), known to efficiently oxidize hydrazones to diazo compounds,[6] was found ineffective in this reaction. Noticeably, aryl iodide mediated oxidation with *m*CPBA (entry 4), previously reported as high-yielding for aminoaziridination with *N*-aminophthalimide,[4d] failed to give **3d** despite our multiple attempts under various conditions, most likely due to side reactions involving the olefinic double bond of **1**.

A considerable barrier of the endocyclic nitrogen atom inversion in *N*-aminoaziridines usually makes it possible for the two invertomers to co-exist on the NMR time scale. However, most of the products showed only one set of signals in ^{1}H NMR spectra, which indicated that one of the invertomers strongly prevailed. This may be due to relative bulkiness of the *endo*-bicyclo-[2.2.1]hept-5-ene-2,3-dicarboximide fragment, which rests preferably in *anti* position to the larger substituent in the aziridine ring. For molecules **3b** and **3h** with axial symmetry of the aziridine fragment, the nitrogen inversion is a degenerate process. However, the slower rate of inversion in these cases causes nonequivalence of the *syn*-and *anti*-substituents (as related to the –NEn substituent) at the carbon atoms of the aziridine ring. Significant broadening of the NMR signals in some of the aziridines **3** can be caused either by 'borderline' values of the inversion rate or by hindered rotation around N–N bond.

According to its NMR data, compound **3g** exists in $CDCl_3$ at 20 °C as two rota- or invertomers in 1:0.55 ratio. The chemical shifts of the aziridine ring protons are found to be close to those in the adduct of β-nitrostyrene and *N*-aminophthalimide.[7a] In the ^{13}C NMR

Table 2
Oxidative aminoaziridination of 4-phenyl-3-butene-2-one **2d** with various oxidizing agents[a]



Entry	Oxidizing agent	Yield of **3d** (%)
1	$Pb(OAc)_4$ (1 equiv)[b]	48
2	$PhI(OAc)_2$ (1 equiv)[c]	55
3	$PhICl_2$ (1 equiv)	–
4	*m*CPBA (1.5 equiv) + 4-iodoanisole (1 equiv)	–
5	NBS (1 equiv)	8
6	NCS (1 equiv)	19
7	Trichloroisocyanuric acid (0.5 equiv)	5.5
8	*t*-BuOCl (1 equiv)	37
9	MnO_2 (4 equiv)[d]	–

[a] All reactions were performed for 16 h at rt in CH_2Cl_2 in the presence of K_2CO_3 (3 equiv), unless noted otherwise.
[b] −78 °C, 30 min, then rt, 10 min.
[c] Running this reaction for 4 h gave similar yield.
[d] No K_2CO_3 added.

spectrum, the chemical shift of $CHNO_2$ carbon (70.15 ppm for major and 73.68 ppm for minor isomer) is in good agreement with the data for other nitro-substituted aziridines.[7b] Furthermore, a cross-peak was observed in gHMQC experiment between the signals at 6.72 ppm (^{1}H) and 70.15 ppm (^{13}C).

The difference between the cis- (7.7 Hz), trans- (6.1 Hz), and *gem*- (2.3 Hz) spin–spin coupling constants in the three-membered ring can be seen distinctly in the spectrum of the styrene adduct **3a**. Comparing these values with the data for other *N*-aminoaziridines, we have determined relative configurations of the substituents in aziridine ring for the majority of the products. In analogy with epoxidation, the oxidative aminoaziridination with **1** proceeded with retention of the configuration of alkene, which was also reported for other *N*-aminoheterocycles.[2g,4b,c]

In the ^{1}H NMR spectrum of the compound **1**, the H^c and H^e protons appear in the form of broad singlets with no spin–spin interaction typical for *endo*-derivatives of norbornane and norbornene. Therefore, we found it necessary to confirm the *endo*-configuration of **1** by NOESY experiment, where the cross-peak is present only between the protons H^e (δ = 2.23 ppm) and the upfield CH_2 proton H^a (δ = 1.52 ppm), which further supported our assignment of the signals in its ^{1}H NMR spectrum.

The ^{1}H NMR spectra of the tricyclic fragments of **3** differ from the spectrum of the starting hydrazide **1**: in most cases, spin–spin interaction between H^c and H^e of **3** can be observed (J = 4.4–4.8 Hz). Another notable feature of the aziridines **3** (except for symmetrical **3i**, **3j**, and **3m**) is the chirality of the aziridine fragment that causes the diastereotopicity of atoms and groups in the tricyclic moiety, complicating their ^{1}H and ^{13}C NMR spectra. For this reason, H^c, H^d, and H^e atoms (as well as the corresponding carbon atoms) of several aziridines formed from prochiral alkenes are nonequivalent. However, the degree of nonequivalence can vary from case to case. For instance, in the spectrum of the *trans*-stilbene adduct **3b** there is a single broad H^c signal, while the spectrum of fumarate derivative **3h** shows two distinct peaks for these protons. In sterically congested aziridine **3b**, additional complication of the NMR spectra is caused by hindered rotation around the N–N bond.

The aminoaziridines formed from alkenes with electron-donating substituents are generally known to be unstable.[1a] The structures of their decomposition products depend on the nature of the substituents in alkene. In our attempt to react **1** with isobutyl vinyl ether **2o** the corresponding aziridine could not be isolated. However, the signals of both alkene and bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide fragments were present in the ^{1}H NMR spectrum of the impure product of the reaction. This allowed us to suggest that the addition to the double bond did take place in this case, but was immediately followed by the aziridine ring opening.[1g,4b,8] The product of this reaction was found too unstable for purification and further analysis.

The adduct with 3,3-dimethylbut-1-ene **2p** was not stable at room temperature and underwent spontaneous decomposition with evolution of gas during evaporation of its dichloromethane solution. All other aminoaziridines were stable in pure state under standard conditions.

Acknowledgments

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Supplementary data

Supplementary data (mp, HRMS, elemental analysis data, ^{1}H and ^{13}C NMR spectra for compounds **3a**–**n**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.046.

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5. *Typical experimental procedure:* 3.1 g (22.5 mmol) of anhydrous K_2CO_3 was added to the stirred solution of 1–3 equiv of alkene in 10 mL of dry CH_2Cl_2. Reaction mixture was cooled down to −78 °C, and the solutions of 2.49 g (5.6 mmol) of $Pb(OAc)_4$ in 10 mL of dry CH_2Cl_2 and 1 g (5.6 mmol) of **1** in 10 mL of dry CH_2Cl_2 were added simultaneously dropwise to the reaction mixture over 10 min. The mixture was stirred at −78 °C for 30 min and then warmed to room temperature and stirred for 10 min. The resulting solution was filtered through a short plug of silica gel, solvent was removed on rotary evaporator without heating and the residue was triturated with 15 mL of diethyl ether. If no crystallization occurred, the crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 1:1). Recrystallization of the product from methanol was necessary in some cases.
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