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# A synthesis of aziridines from α-iodoenones

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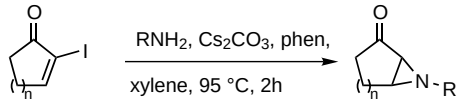
**Abstract**—Aziridines were prepared from α-iodocycloenones in very good yield, by a Michael addition/cyclisation (Gabriel–Cromwell) process employing a slight excess of primary amine and $Cs_2CO_3$ as base at 95°C. Using chiral amines it was possible to prepare optically pure aziridines. The same method was also efficient for the synthesis of aziridines from acyclic α-halounsaturated compounds. 2-Oxoazabicycles reacted with several nucleophiles to afford α-heteroatom substituted cyclic enones in excellent yield. © 2002 Elsevier Science Ltd. All rights reserved.

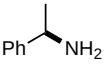
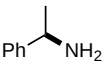
Aziridines display great potential and versatility as chiral substrates, auxiliaries, reagents and ligands in stereoselective synthesis.[1] Several natural molecules possessing an aziridine ring have been found which exhibit potent biological activity.[2] One of the most convenient methods for the formation of aziridines is exemplified by their direct construction from α,β-dibromo acyclic esters and ketones simply by reaction with an excess of a suitable primary amine (Gabriel–Cromwell reaction).[3] The excess of amine employed has the triple role of eliminating HBr, to form an α-bromoenone, performing conjugated addition, and deprotonating the cyclised product to afford the aziridine. To our knowledge this procedure has not been employed for cyclic substrates other than lactones[4] and lactams.[5] We have no reference to this reaction using α-haloenones within carbocyclic systems. Previous studies[6] indicate that the cyclisation step requires the leaving group to be *trans* to the adjacent amino group, and thus the reprotonation of the enolate to form an α-halo-β-aminoketone is fundamental. This requires that the equilibrium between the starting compound and the amine addition intermediate is favourable and that conditions do not exist for the overall reverse reaction.

α-Iodocycloenones are readily prepared from the corresponding cycloenone,[7] and have played an important part as intermediates in stereoselective synthesis.[8] Thus, we anticipated that they could be employed as substrates for aziridination, and the presence of an adjacent asymmetric centre could induce stereoselectivity during the process. The bicyclic products would be of value in organic synthesis, due to the ability of aziridines to undergo highly regio- and stereoselective ring opening reactions, and to induce stereoselectivity in subsequent reactions at adjacent functional groups.

**Table 1.**




**1-3** **4-13**

| n | Amine | Products | Yield % |
|---|---|---|---|
| 1 | $BnNH_2$ | **4** R=Bn | 92 |
| 1 | $CH_2{=}CHCH_2NH_2$ | **5** R=allyl | 94 |
| 1 |  | **6** and **7** R=(R)-MeBn 2 diastereoisomers d.r.=1:1 | 91 |
| 2 | $BnNH_2$ | **8** R=Bn | 88 |
| 2 | $CH_2{=}CHCH_2NH_2$ | **9** R=allyl | 96 |
| 2 |  | **10** and **11** R=(R)-MeBn 2 diastereoisomers d.r.=1:1 | 89 |
| 3 | $BnNH_2$ | **12** R=Bn | 92 |
| 3 | $CH_2{=}CHCH_2NH_2$ | **13** R=allyl | 87 |

Phen = 1,10-phenantroline (1 eq)

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Attempts to carry out the aziridination reaction on α-iodocycloenones using an excess of benzylamine under standard Gabriel–Cromwell conditions resulted in the recovery of starting material. It appeared that the failure of these compounds to undergo aziridination was due to the rapid collapse of the intermediate enolate, to reform the starting material, before any cyclisation to the aziridine could occur. We anticipated that the addition of an inorganic base would absorb irreversibly any acid formed and perhaps reprotonation of the enolate would occur *cis* to the amino group via a 1,3-proton transfer. This would set the system up for ring closure.

On adding cesium carbonate[9] to a mixture of benzylamine (1.5 equiv.) and α-iodocycloalkenone at 95°C in xylene, the reaction proceeded in good yield to afford the corresponding aziridine. The addition of the bidentate ligand 1,10-phenanthroline to this mixture increased the reaction rate and the yield (Table 1 exemplified in Table 2), perhaps by serving as a ligand for $Cs^+$ ions. In fact, this reaction was very clean and the product only needed to be filtered through a pad of silica gel to be purified.

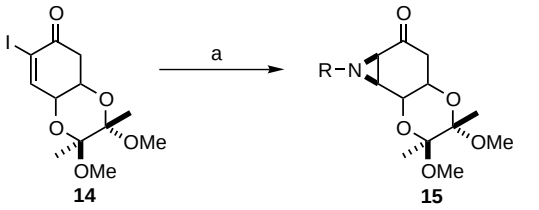
For all three substrates, α-iodocyclopentenone **1**, α-iodocyclohexenone **2** and α-iodocycloheptenone **3**, the yields of the respective aziridines were very good. When (*R*)-methylbenzylamine was the reagent, the two diastereoisomeric pairs, **6** and **7**, **10** and **11** (Table 1), were easily chromatographically separated and each compound obtained optically pure. Surprisingly no diastereomer preference was observed.

The asymmetric enone **14**, when treated under the above conditions, afforded excellent yields of only one diastereoisomer to which we have tentatively assigned the configuration depicted in structure **15**. The effect of changing the reaction conditions for this transformation was also obvious from the results depicted in Table 2. Similar selectivities have been obtained during nucleophilic epoxidation of this compound.

In order to demonstrate that these reaction conditions could equally be applied to the aziridination of acyclic esters, aziridination was performed on esters **16**, **17**, **18** (mixture), and **19** (Scheme 1). All the reactions gave good to excellent yields, comparable with those already reported.[3,10] The aziridines **26**–**29** derived from cinnamate **19** appear not to have been previously reported.

Exploratory studies on the reduction of 2-oxoazabicycloalkanes with borohydride were carried out. Diastereoisomers **6** and **7** and compounds **4** and **12** were reduced by $NaBH_4$ with very high stereoselectivity with all affording only one diastereoisomer of the respective alcohol. The alcohols derived from reduction of **6** and **7** were optically pure. Two diastereoisomeric alcohols were formed from the reduction of 2-oxoazabicycloheptane **8**, d.r. = 2.8:1. The configuration of these alcohols is not obvious from the spectroscopic data available although we suspect that the OH is *cis* with

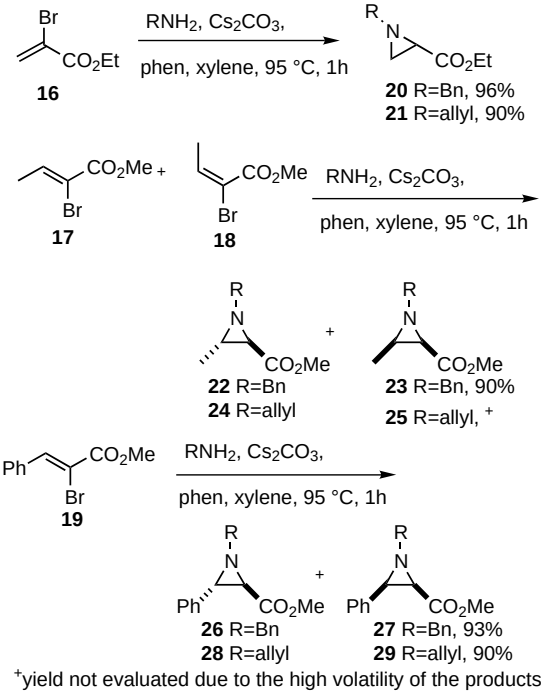
**Table 2.**




**14** **15**

a) Reaction conditions

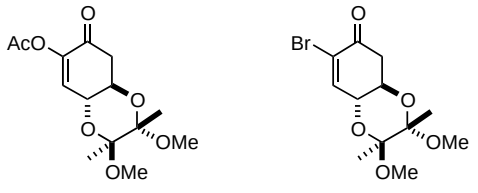
| Amine | $Cs_2CO_3$ | Phen | Product | Yield % |
|---|---|---|---|---|
| $BnNH_2$ | No | No | **14** | |
| " | Yes | " | **15** R=Bn | 80 |
| " | " | Yes | **15** R=Bn | 94 |
| $CH_2=CHCH_2NH_2$ | " | " | **15** R=allyl | 90 |
| $Me_3CNH_2$ | " | " | **15** R=$CMe_3$ | 95 |
| $BnONH_2$ | " | " | **15** R=OBn | 88 |




**16**
**20** R=Bn, 96%
**21** R=allyl, 90%
**17** **18**
**22** R=Bn
**24** R=allyl
**23** R=Bn, 90%
**25** R=allyl, +
**19**
**26** R=Bn
**28** R=allyl
**27** R=Bn, 93%
**29** R=allyl, 90%

+yield not evaluated due to the high volatility of the products

**Scheme 1.**




**30** **31**

**Figure 1.**

respect to the aziridine ring in the major product. More results on this study will be forthcoming.

Preliminary studies on the acid-catalysed aziridine ring opening reactions of the azabicycloalkane **15** (R = Bn) with AcOH and $MgBr_2$ afforded the α-acetoxy and α-bromoenones **30** (94%) and **31**[11] (89%), respectively

(Fig. 1). This indicated that these aziridines were regioselectively opened and that the amine function was then lost to produce a new enone. This is the reverse equivalent to the aziridine formation reaction. Normally, ring opening produces vicinally bifunctional compounds. Further studies are required in order to determine the scope of this reaction.

The aziridination method described afforded very good yields of easily purified products using only a slight excess of amine. High stereoselectivity was observed with a chiral substrate. Oxoazabicycloalkanes were available by this method and not by the classical Gabriel–Cromwell procedure. Using a chiral amine it was possible to produce chiral, easily separable aziridines from achiral iodocycloenones. This method was also applicable to acyclic substrates, producing the same products in similar or higher yields than those previously described in the literature. The scope of this reaction appears to be large both for the enone and amine. These previously unknown 2-oxoazabicycloalkanes undergo novel aziridine ring-opening reactions which are under study.

## Acknowledgements

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9. All reagents were dried carefully before use. Potassium carbonate could be used instead of cesium carbonate in some cases.
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11. All compounds afforded spectral data consistent with the structure proposed. NMR data for representative compounds (assignments for $^{13}C$ spectra supported by DEPT experiments): **Compound 4**: $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 212.0 (C=O); 138.1 (quaternary Ar); 128.4, 127.6, 127.2 (Ar); 61.4 ($\underline{C}H_2Ph$); 46.9, 46.1 (C-2, C-3); 32.8, 24.0 (C-4, C-5). **Compound 5**: $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 212.0 (C=O); 134.2 ($CH_2\underline{C}H{=}CH_2$); 116.9 ($CH_2CH{=}\underline{C}H_2$); 60.3 ($\underline{C}H_2CH{=}CH_2$); 46.8, 45.9 (C-2, C-3); 32.8, 24.0 (C-4, C-5). **Compound 8**: $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 207.6 (C=O); 138.4 (quaternary Ar); 128.4, 127.5, 127.2 (Ar); 63.3 ($\underline{C}H_2Ph$); 46.3, 43.8 (C-2, C-3); 37.0 (C-6); 23.2, 18.8 (C-4, C-5). **Compound 9**: $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 207.5 (C=O); 134.5 ($CH_2\underline{C}H{=}CH_2$); 116.6 ($CH_2CH{=}\underline{C}H_2$); 62.1 ($\underline{C}H_2CH{=}CH_2$); 46.0, 43.6 (C-2, C-3); 36.9 (C-6); 23.2, 18.8 (C-4, C-5). **Compound 12**: $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 212.1 (C=O); 138.6 (quaternary Ar); 128.4, 127.5, 127.1 (Ar); 64.0 ($\underline{C}H_2Ph$); 51.0, 44.8 (C-2, C-3); 41.0 (C-7); 28.3, 24.1, 23.6 (C-4, C-5, C-6). **Compound 13**: $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 212.1 (C=O); 134.7 ($CH_2\underline{C}H{=}CH_2$); 116.2 ($CH_2CH{=}\underline{C}H_2$); 62.6 ($\underline{C}H_2CH{=}CH_2$); 50.8, 44.5 (C-2, C-3); 41.0 (C-7); 28.4, 24.0, 23.5 (C-4, C-5, C-6). **Compound 30**: $^{1}H$ NMR ($CDCl_3$), 300 MHz: $\delta$ 6.50 (1H, s, H-3); 4.64 (1H, d, $J=8.9$ Hz, H-4); 4.17–4.08 (1H, ddd, $J=13.5$ Hz, $J=8.9$ Hz, $J=4.8$ Hz, H-5); 3.31 (3H, s, OMe); 3.27 (3H, s, OMe); 2.83 (1H, dd, $J=16.4$ Hz, $J=4.8$ Hz, H-6); 2.55 (1H, dd, $J=16.4$ Hz, $J=13.4$ Hz, H-6); 2.23 (3H, s, OAc); 1.36 (3H, s, Me); 1.33 (3H, s, Me). **Compound 31**: $^{1}H$ NMR ($CDCl_3$), 300 MHz: $\delta$ 7.31 (1H, d, $J=1.9$ Hz, H-3); 4.49 (1H, dd, $J=8.9$ Hz, $J=1.9$ Hz, H-4); 4.07 (1H, ddd, $J=13.8$ Hz, $J=9.1$ Hz, $J=4.8$ Hz, H-5); 3.32 (3H, s, OMe); 3.26 (3H, s, OMe); 2.95 (1H, dd, $J=16.6$ Hz, $J=4.8$ Hz, H-6); 2.60 (1H, dd, $J=16.6$ Hz, $J=13.7$ Hz, H-6); 1.36 (3H, s, Me); 1.33 (3H, s, Me). $^{13}C$ NMR ($CDCl_3$), 75 MHz: $\delta$ 188.6 (C=O); 148.7 (C-3); 124.3 (C-2); 100.9, 99.8 (2×$\underline{C}$OMe); 70.3, 67.4 (C-4, C-5); 48.3, 48.2 (2×OMe); 41.1 (C-6); 17.6, 17.5 (2×Me).