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# N-Acyl Aziridines - C-Acylating Agents for the Preparation of Polyketides

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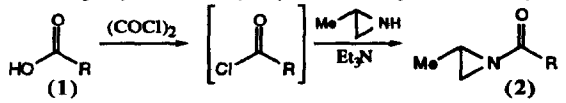
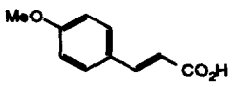
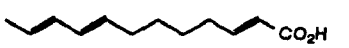
*Abstract: A one-pot synthesis of N-acylaziridines from carboxylic acids has been developed, and their reaction with dianions derived from β-ketoesters studied. The aziridines were found to be efficient C-acylating agents, giving polyketide-like products in good overall yields.*

As part of a recent study into the ring opening of aziridines with functionalized carbon nucleophiles we had cause to study the effect of N-substitution on the reaction course. This lead to the observation that the reaction of a N-benzoylaziridine with the dianion derived from methyl acetoacetate led to highly efficient C-benzoylation of the β-ketoester moiety[1,2]. Since the product of this reaction possesses the 1,3,5-tricarbonyl array common to polyketide systems we decided to investigate the generality of this process and now present the preliminary results of this study. In order to initiate this study we required an efficient route to the preparation of N-acylaziridines. These systems have previously been prepared in good yield by the reaction of an acid chloride with an aziridine under a variety of conditions[2]. Since, in many cases the acid chlorides themselves were generated from the corresponding carboxylic acids we decided to develop a one-pot procedure for the conversion of carboxylic acid (**1**) into N-acyl aziridine (**2**)[3]. We found that this could readily be achieved by sequential treatment with oxalyl chloride, followed by evaporation of the volatile components and addition of base and the aziridine (table 1). The overall yields for this transformation were comparable with those we obtained starting from the purified acid chloride and so this represents an effective procedure for the preparation of these systems.

**Table 1** - *One-pot formation of acylaziridines from carboxylic acids*[4]




| Entry | Acid | Yield of (2) | Entry | Acid | Yield of (2) |
|---|---|---|---|---|---|
| a | $PhCO_2H$ | 86% | f |  | 75%[a] |
| b |  | 92% | g |  | 72% |
| c | $t\text{-}BuCO_2H$ | 87% | h |  | 64%[b] |
| d |  | 75% | | | |
| e |  | 76% | | | |

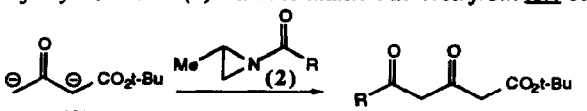
a - the acylation step was carried out in petroleum ether - dichloromethane (1:1).
b - the acylation step was carried out in dichloromethane, yield quoted is for the bis-aziridine product.

As can be seen from the table, alkyl, aryl, and α,β-unsaturated acids can all be used in this process with the corresponding acylaziridine being isolated in good yields. We also examined the reaction of a dicarboxylic acid (entry h) which was smoothly converted into the corresponding bis-acylaziridine (**2h**). In general petroleum ether was the preferred reaction solvent for the acylation step[2], although in some cases

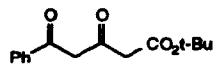
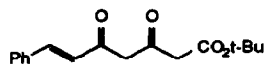
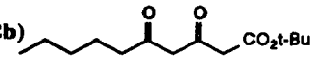
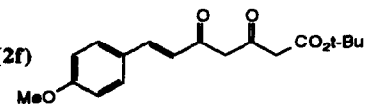
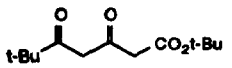
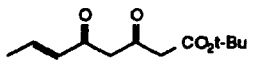
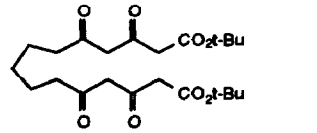
dichloromethane (entry h) and petroleum ether - dichloromethane (entry f) were required because of insolubility of the acid chloride intermediates.

With the acylaziridines readily available we next turned our attention to their reaction with the dianion (3) derived from *tert*-butyl acetoacetate. All the acylaziridines investigated gave clean C-4 acylation of the dianion (table 2). In no cases could we identify any O-acylated material or evidence of reaction at C-2[5], and the mass balance could usually be accounted for by the isolation of unreacted β-ketoester.

**Table 2** - *Reaction of acylaziridines (2) with the dianion derived from tert-butyl acetoacetate*[6]




(3) (4)

| Aziridine | Product | Yield | Aziridine | Product | Yield |
|---|---|---|---|---|---|
| (2a) |  | 96% | (2e) |  | 58% |
| (2b) |  | 98% | (2f) |  | 53% |
| (2c) |  | 93% | | | |
| (2d) |  | 60% | (2h) |  | 78% |

As can be seen from the above table excellent yields are obtained with simple alkyl- and aryl-acylaziridines and the reaction is relatively insensitive to steric bulk in the acyl-group. But perhaps most notable is the observation that reasonable yields are also obtained with α,β-unsaturated acyl-units. C-Acylation of such dianions with these systems is a notoriously difficult operation due to competing Michael-addition processes[7].

**Acknowledgements:** We would like to thank Mrs. R. Howard for mass spectra and Dr. M. Stuckey for nmr spectra.

**References and Notes:**

1. Lygo, B. *Synlett*, **1993**, 764.
2. For the use of acylaziridines as acylating agents for other nucleophiles, see: Wattanasin, S; Kathawala, F.G. *Tetrahedron Lett.*, **1984**, *25*, 811 and references therein.
3. 2-Methylaziridine was used in these studies as it is commercially available.
4. *Typical Procedure*: A mixture of the carboxylic acid (6.24mmol) and freshly-distilled oxalyl chloride (3ml) was stirred overnight at room temperature under argon. The volatile reaction components were then removed *in vacuo*, and dry petroleum ether (20ml) added. The resulting solution was cooled to -10°C with stirring under argon, and then triethylamine (6.85mmol) added, followed by 2-methylaziridine (6.24mmol). The mixture was stirred at -10°C for 30min, then diluted with diethyl ether (20ml), and filtered through Celite®. The resulting clear solution was concentrated on a rotary evaporator (bath temp. ≤30°C) and the residue purified by chromatography on silica gel.
5. Monoanions derived from β-ketoesters have been reported to ring open acylaziridines on prolonged reaction times, see: Stamm, H; Budny, J. *J. Chem. Res. (S)*, **1983**, 54.
6. *Typical Procedure*: *tert*-Butyl acetoacetate (96μl, 0.58mmol) was added dropwise to a stirred suspension of sodium hydride (25mg of a 60% dispersion in oil, washed twice with dry petroleum ether, *ca.* 0.63mmol), in dry tetrahydrofuran (5ml) at room temperature under argon. The mixture was stirred at room temperature for 15min., then cooled to 0°C and n-butyl lithium (433μl, of a 1.46M solution in hexanes, 0.63mmol) was added dropwise. After the addition was complete, the solution was stirred at 0°C for 5min, then a solution of the acylaziridine (0.58mmol) in dry tetrahydrofuran (0.5ml) was added. The resulting solution was stirred at 0°C for 1h, then 2M hydrochloric acid (5ml) added. The mixture was extracted with ethyl acetate (3x10ml) and the combined extracts washed with brine (5ml). The ethyl acetate solution was dried over sodium sulfate, and then concentrated on a rotary evaporator. The residue was then purified by chromatography on silica gel.
7. See; Hanamoto, T; Hiyama, T. *Tetrahedron Lett.*, **1988**, *29*, 6467 and references therein.

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