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# UNUSUAL N-ACYLATION OF GLYCINE SCHIFF BASES. A SIMPLE APPROACH TO 3,3-DIPHENYLAZIRIDINE-2-CARBOXYLATES+

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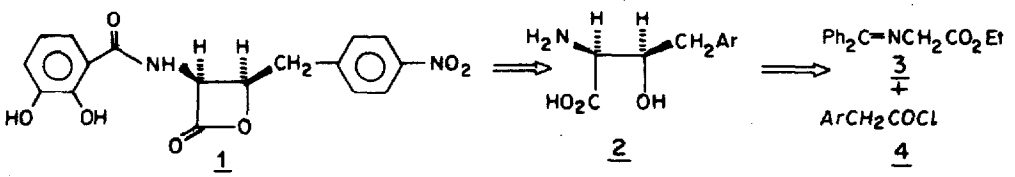
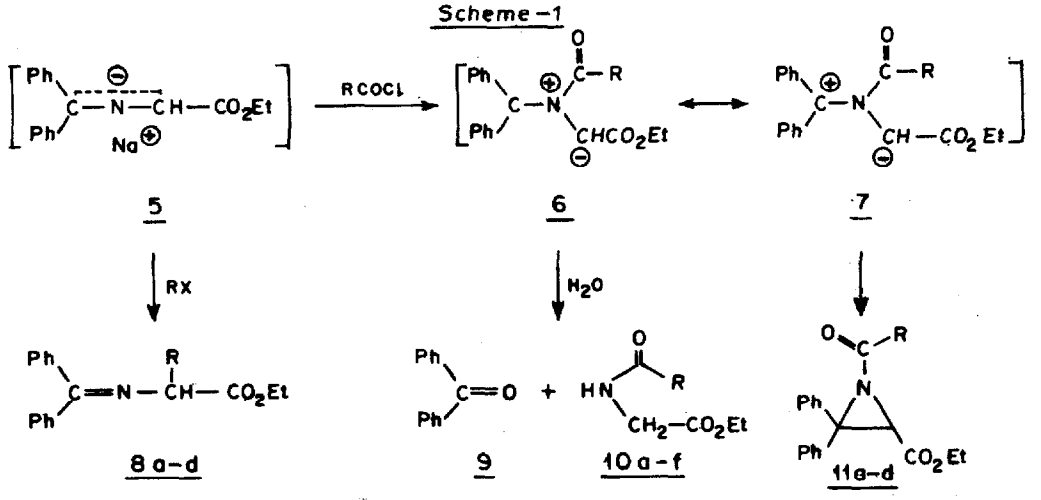
**Abstract:** Treatment of azaallyl anions, generated from glycine Schiff bases, with Ar-acyl halides furnishes N-acylaziridines *via* intramolecular cyclization.

The recent report of a broad-spectrum β-lactone antibiotic, obafluorin **1**[1] with 'unprecedented' biological activity has prompted us to devise a synthetic strategy *via* α-amino-β-hydroxy acids **2**. Based on a precedent,[2] it was presumed that acylation of the glycine Schiff base derivative **3** with an appropriate acid chloride **4** would be possible



under basic conditions. The choice of protecting the $NH_2$ group as a Schiff base instead of the dibenzyl derivative is based on its ready availability[3] and selective deprotection in the presence of a $NO_2$ group. However, treatment of the azaallyl anion **5**, generated from **3**, with acid chlorides led to unexpected products (Scheme-1) contrary to a literature report.[4] This communication describes the generality of unusual N-acylations and reports a convenient method for the synthesis of N-acylated aziridines.[5] The relative importance of steric and electronic factors, in the intramolecular cyclization of **7** to the aziridine **11** is delineated.

Scheme-1



Treatment of glycine Schiff base ethyl ester **3**[3] with sodium hydride in THF followed by the addition of phenylacetyl chloride gave the aziridine **11a** (entry 1, Table)[6-8] in 75% yield. The structure of the new aziridine was established on the basis of relevant spectral data,[7] including a characteristic aziridine proton signal (1H, s) at δ5.40 in $^{1}$H NMR and carbon signals at δ66.17 (C-2,d) and 73.61 (C-3, s) in the $^{13}$C NMR spectra. Aziridine formation probably arises *via* N-acylation followed by intramolecular cyclization of **7** as shown in Scheme 1. The potential of azomethine ylides **7** as synthons to aziridines **11** has not been fully utilized, though their generation from imines of α-amino acid esters and aziridines has been reported.[9,10]

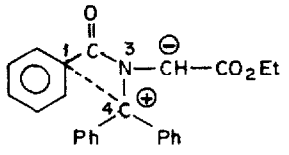
In order to determine the generality of this unusual cyclization and to derive the probable mechanism, we examined the reaction with different electrophiles (Table). Arylacetyl chlorides (entries 2&3) with electron-withdrawing (Nitro) and electron-donating (Methoxy) groups in the phenyl ring also gave aziridines **11b** and **11c** in good yields with no substituent effects. However, the reaction of phenoxyacetyl chloride (entry 4) formed N-acylglycinate **10a** and aziridine **11d** in 1:1 ratios, probably *via* competing hydrolysis[11] or cyclization of the intermediate **6**, **7**. Although the distribution of products **10a** and **11d** was surprising, it gave some hints about the role of the ring size in the transition state, for cyclization.

Winstein and Heck[12] have proposed intermediates similar to **$Ar_1$-4**, **$Ar_1$-5** and **$Ar_1$-6** in their solvolysis studies and found the rate sequence (4 << 5 >> 6) and ratios (**$Ar_1$-5:$Ar_1$-6** = 100:1) which indicated maximum neighbouring group participation in the **$Ar_1$-5** transition state. As these transition states differ only in the ring size, we were curious whether such differences could lead to different reaction pathways.[13] Indeed, when the transition

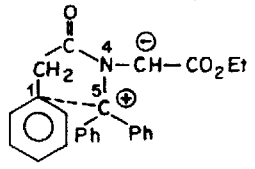
**Table**

| Entry | Electrophile | Substituent R | Product[7] | mp(°C) | Yield (%)[8] |
|---|---|---|---|---|---|
| 1 | RCOCl type | $C_6H_5$-$CH_2$- | **11a** | 105 | 75 |
| 2 | " | 4-$O_2N$-$C_6H_4$-$CH_2$- | **11b** | 136 | 74 |
| 3 | " | 3,4-$(MeO)_2$-$C_6H_3$-$CH_2$- | **11c** | 134 | 79 |
| 4 | " | $C_6H_5$-O-$CH_2$- | **11d** | 78-79 | 50 |
| | | | **10a** | 55-56 | 47 |
| 5 | " | $C_6H_5$- | **10b** | 60 | 81 |
| 6 | " | 4-$O_2N$-$C_6H_4$- | **10c** | 147-48 | 94 |
| 7 | " | $C_6H_5CH_2CH_2$- | **10d** | | 72 |
| 8 | " | $CH_3CH_2$- | **10e** | 50-51 | 83 |
| 9 | " | Cyclo-$C_6H_{11}$-$CH_2$- | **10f** | 94-95 | 69 |
| 10 | R-Br type | $CH_3CH_2$- | **8a** | | 66 |
| 11 | " | $C_6H_5CH_2$- | **8b** | 102 | 82 |
| 12 | " | 4-$O_2N$-$C_6H_4$-$CH_2$- | **8c** | 105 | 84 |
| 13 | R-Cl type | $CH_3$-O-$CH_2$- | **8d** | | 84 |

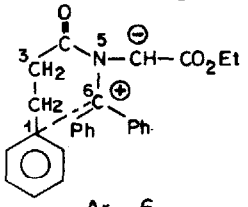
state was shortened ($Ar_1$-4 type, entries 5 & 6) or enlarged ($Ar_1$-6 type, entry 7) the intramolecular cyclization leading to aziridine became an inefficient pathway and quantitative yields of N-acylglycinates **10b-d** were obtained. These results together with a recent report[14] substantiate the importance of $Ar_1$-5 transition state in cyclization.



$Ar_1 - 4$



$Ar_1 - 5$



$Ar_1 - 6$

Deyrup *et al*[15] have reported the importance of steric factors in related intramolecular cyclizations. However, the formation of N-acylglycinates **10e** and **10f** in reactions with propanoyl and cyclohexylacetyl chlorides (entries 8&9) respectively indicates that the steric bulk at the acyl group had little effect in intramolecular cyclization.

In continuation, the reaction of **5** was studied with different electrophiles, eg. R Br and R Cl type (entries 10-13) under identical experimental conditions and invariably C-alkyl products[4] were obtained. Although the exclusive formation of N-acyl products is unusual, the hard and soft acids and bases (HSAB)[16] concept does explain the regioselective formation of N-acylated and C-alkylated products from the ambident azaallyl anion **5**.

In summary, this letter reports an efficient, synthetically useful transformation of imines **3** to aziridines **11**. The importance of $Ar_1$-5 type transitions has been emphasized in explaining apparently contradictory and incoherent experimental observations.

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NCL Communication No. 4701

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6. General Procedure: To a suspension of NaH (6.3 mmol) in dry THF (10 ml) was added a solution of ethyl N-(diphenylmethylene)glycinate (3.7 mmol) in THF (5 ml) and stirred at 0° for 0.5 h. A solution of acyl/alkyl halide (4.5 mmol) was added dropwise *via* syringe. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. After the usual work up, the products were purified by flash chromatography on silica gel using an appropriate mixture of n-hexane/ethyl acetate as eluent.

7. All new compounds were characterised by IR, $^{1}H$ NMR, $^{13}C$ NMR, mass spectrometry and satisfactory elemental analysis. Selected spectroscopic details of aziridines: **11a.** $^{1}H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 1.08 (t, 3H), 3.77, 4.00, 4.20, 4.40 (ABq, J = 16Hz, 2H), 4.00 (q, 2H), 5.40 (s, 1H), 6.76-7.44 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 300 MHz) $\delta$ 13.65 (q), 42.67(t), 61.15(t), 66.17(d), 73.61(s), 126.85, 126.94, 127.37, 127.69, 127.75, 127.79, 128.08, 128.43, 128.96, 132.72, 138.53, 140.02(s), 167.22(s), 168.42(s); IR ($CHCl_3$) 3000, 1750, 1740, 1600, 1490 $cm^{-1}$; Mass: m/e(%) 385($M^+$, 3), 194(23), 178(11), 118(65), 91(100). **11b.** $^{1}H$ NMR ($CDCl_3$, 90 MHz) $\delta$ 1.10 (t, 3H), 3.80, 4.00, 4.20, 4.40 (ABq, J = 16Hz, 2H), 4.02 (q, 2H), 5.46 (s, 1H), 6.8 - 7.44 (m, 10H), 7.20 (d, J = 8Hz, 2H), 7.88 (d, J = 8Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 300 MHz) $\delta$ 13.76 (q), 42.82(t), 61.51(t), 65.33(d), 73.70(s), 122.95, 127.75, 127.78, 127.92, 128.63, 128.76, 129.92, 137.89, 139.24, 140.48, 146.72, 167.05(s), 167.10(s); IR ($CHCl_3$) 3030, 3020, 2980, 1760, 1745, 1600, 1520, 1350, 1220, 765 $cm^{-1}$; Mass: m/e(%) 430 ($M^+$, 3), 413(1), 385(2), 343(2), 268(95), 194(100), 165(24), 91(22). **11c.** $^{1}H$ NMR ($CDCl_3$, 90MHz) $\delta$ 1.13 (t, 3H), 3.62 (s, 3H), 3.75 (s, 3H), 3.84, 4.04, 4.20, 4.40 (ABq, J = 16Hz, 2H), 4.04 (q, 2H), 5.33 (s, 1H), 6.33-7.46 (m, 13H); $^{13}C$ NMR ($CDCl_3$, 300 MHz) $\delta$ 13.51(q), 42.62(t), 55.25(d), 61.02(t), 66.24(q), 73.52(s), 110.30, 111.99, 121.73, 125.04, 126.88, 127.28, 127.59, 127.66, 127.92, 128.28, 138.54, 139.93, 147.85, 147.98(s), 167.09(s), 168.70(s); IR ($CHCl_3$) 3020, 1760, 1750, 1610, 1590, 1520 $cm^{-1}$; Mass: m/e(%) 445($M^+$, 3), 268(9), 178(100), 91(45). **11d.** $^{1}H$ NMR ($CDCl_3$, 80 MHz) $\delta$ 1.1 (t, 3H), 3.64, 3.88, 4.12, 4.35 (ABq, J = 16Hz, 2H), 3.81 (q, 2H), 5.80 (s, 1H), 6.6 - 7.3 (m, 15H); IR ($CHCl_3$) 3020, 1765, 1740, 1590, 1580 $cm^{-1}$; Mass: m/e(%) 401 ($M^+$, 1), 307(35), 268(26), 178(29), 165(25), 105(34), 91(100).

8. The unoptimised yields refer to isolated products and are calculated on the basis of recovered starting material. More than 80% of the starting material was converted into products.

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