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Baylis-Hillman Reaction of *N*-Trityl Aziridine-2-(*S*)-Carboxaldehyde

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Abstract:

N-Trityl aziridine-2-(*S*)-carboxaldehyde **1** undergoes a facile Baylis-Hillman reaction with a variety of activated vinyl compounds in the presence of a catalytic amount of DABCO to furnish the corresponding adducts **2** in good yields. Unexpectedly, acetylation of the adduct **2a** derived from methyl acrylate takes place using Ac_2O/py with concomitant allylic transposition. The predominant *Z*-isomer **4** gives a SN2 type displacement of the acetate with various nucleophiles in contrast to reported SN2' type displacement in similar systems.

In recent years, there has been a significant interest in the synthesis and reactions of chiral aziridines because of their versatility in asymmetric synthesis of biologically important molecules.[1-3] The strain in the three-membered ring system is the driving force for its facile ring-opening reactions.[4] During the course of our work on the synthesis and exploration of chiral aziridine derivatives,[5-7] we observed that *N*-trityl aziridine-2-(*S*)-carboxaldehyde **1** is remarkably stable, both chemically and configurationally. Herein, we report the Baylis-Hillman reaction of **1** and the synthetic elaboration of its methyl acrylate adduct **2a**.

The tertiary amine catalysed coupling of an activated vinyl system with an electrophile (usually an aldehyde) is commonly termed the Baylis-Hillman (B.-H.) reaction.[8-11] Though the reaction is operationally simple and often high yielding, it suffers from low reaction rates as it takes several days and even weeks for completion. However, the presence of three functionalities; the hydroxyl group, the double bond and the olefin activating group makes the B.-H. adduct a very attractive building block for further synthetic studies.

There are only a few reports of attempts to carry out asymmetric B.-H. reactions using either chiral acrylates,[12-15] chiral aldehydes[16-20] or chiral catalysts[21] but so far with limited success. Drewes *et al.*[16] reported that B.-H. reactions of a protected cyclic β-hydroxy-α-amino aldehyde (the Garner aldehyde) with methyl acrylate in the presence of DABCO yielded the *optically inactive* adduct after 7 days (75%) due to *racemisation* of the aldehyde by DABCO.

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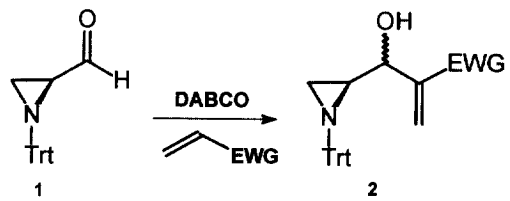
Since racemisation of the aldehyde **1**, a synthetic equivalent of L-serinal, is not easy due to the large inversion barrier for racemisation of the three membered ring,[22] it was of interest to use it as the electrophile in B.-H. reaction. Compound **1** {$[\alpha]_D^{22}$ -66^0 (c 1.1, $CHCl_3$)} was prepared in high yield from *N*-trityl aziridine-2-(*S*)-carboxylic methyl ester on a multigram scale following a literature procedure.[23] In a typical experiment, a mixture of aldehyde **1**, methyl acrylate (1.5 equiv.) and DABCO (0.15 equiv.) were allowed to react at room temperature until **1** had been consumed (8 d). The excess methyl acrylate was removed on a rotavap and the residue was chromatographed (SiO_2) to yield **2a** (82%) as a 1:1 mixture of *syn* and *anti*-diastereomers (measured by the ^{1}H NMR shift of the methine proton C<u>H</u>-OH).[1] The *anti*-diastereomer was separated by careful column chromatography and crystallised from methanol {$[\alpha]_D^{22}$ -19.8^0 (c 1.06, $CHCl_3$)}. The structure of the *anti*-adduct was unequivocally established by X-ray crystallography.



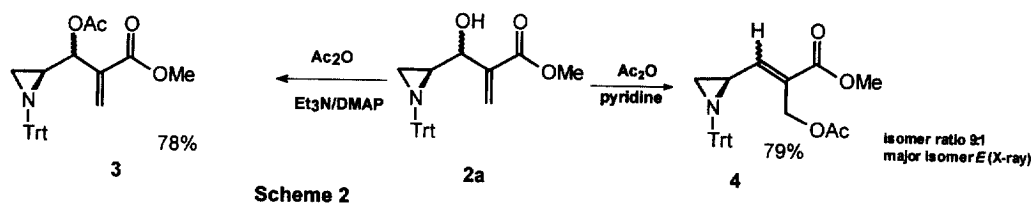
1 2

	EWG	yield (%)[a]	syn/anti[b]	time (days)
a	CO_2Me	82	1:1	8
b	CO_2Et	81	1:1	8
c	CN	83	2:1	3
d	C(O)Me	57	2:3	10
e	SO_2Ph	28	3:4	45

[a] after column chromatography; [b] the ratio of the *syn/anti* diastereomers was determined by the ^{1}HNMR shift of methine protons <u>H</u>-C-OH; the methine proton of the *syn*-isomers were always at higher field than those of the *anti*-isomers.[1]

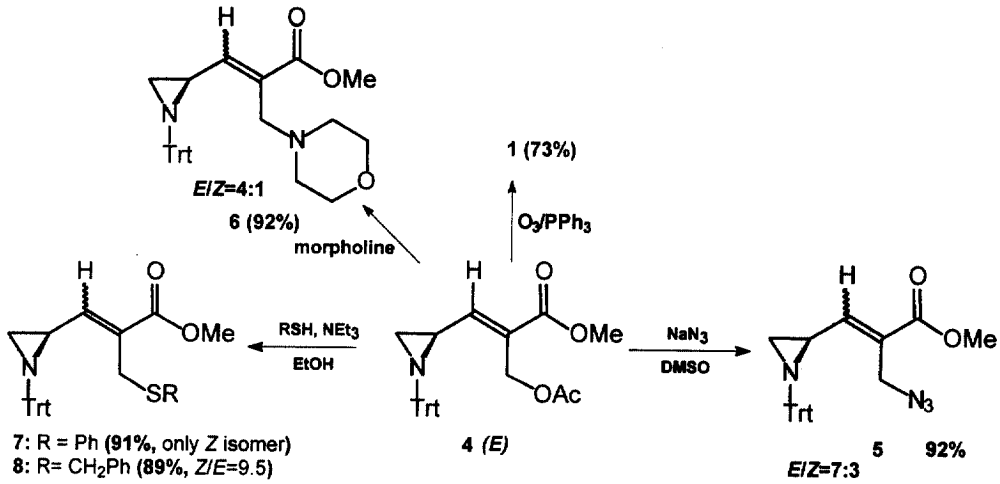
Scheme 1

The scope of this reaction was exemplified further by using several other activated vinyl compounds *viz.* ethyl acrylate, acrylonitrile, methyl vinyl ketone and phenyl vinyl sulphone The products **2b-e** were isolated in good yield except for the adduct **2e** of phenyl vinyl sulphone (see Table in Scheme 1).



Scheme 2

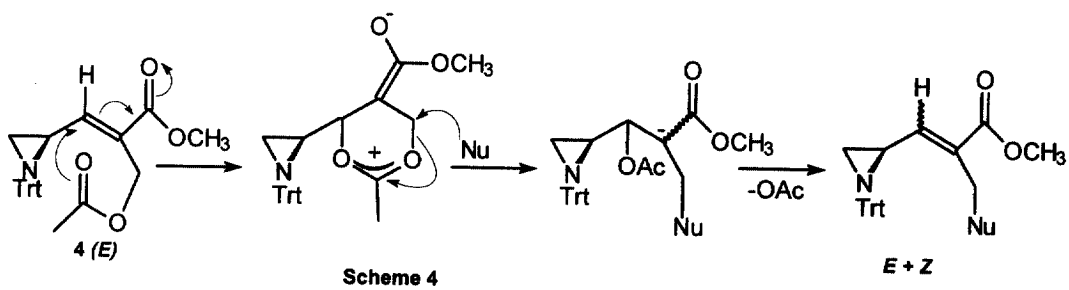
The synthetic utility of the chiral B.-H. adducts was investigated next. Acetylation of **2a** with Ac_2O/Et_3N yielded the acetate **3** in good yield (Scheme 2). In contrast, acetylation of **2a** with Ac_2O/pyridine at room temperature for 24 hours resulted in the rearranged acetate **4** with the *E*-isomer as the major product (*E*/*Z* = 9:1, Scheme 2). The *E*-isomer was purified by crystallization {$[\alpha]_D^{22}$ -94.9^0 (c 1.11, $CHCl_3$)} and the structure was confirmed by NMR and X-ray crystallography.



Scheme 3

Apparently a S_N2' substitution of the allylic acetate **3** by the acetoxy group (produced in the reaction medium during acetylation) takes place to furnish the thermodynamically more stable trisubstituted alkene **4**. This was substantiated by the isolation of a mixture of **3** and **4** on quenching the reaction after 14 h. Incidently, there is no precedent of this type of allylic transposition in an aliphatic system. Ozonolysis of **4** (*E/Z* mixture) proceeded smoothly to yield **1** (73%) with no change of its optical rotation ($[\alpha]_D^{22}$ -66° (c 1.1, $CHCl_3$). This suggests that little or no racemisation of **1** has occurred during the long exposure to DABCO.

The alkene moiety in **4** is expected to be highly reactive because of its conjugation with the carbomethoxy group and the acetoxy group in the allylic position. The reactivity of **4** was studied with various nucleophiles. Treatment of **4** *(E)* with NaN_3 in DMSO yielded the apparent S_N2 product **5** as the sole regioisomer. Remarkably, this compound **5** was a mixture of *E* and *Z*-isomers, which is not in line with a direct S_N2 displacement. Similarly, apparent S_N2 substitution of the allylic acetate **4** *(E)* was accomplished with morpholine to give **6** and with thiols, *viz.* thiophenol and benzylmercaptan to furnish **7** and **8**, respectively (Scheme 3).



Scheme 4

Tentatively, this result may be explained by invoking an initial formation of an ionic intermediate which is then followed by the reaction with the nucleophile as indicated in Scheme 4. Therefore, the configuration of the olefinic bond will not be controlled thus giving a mixture of *E* and *Z*-isomers.

In summary, we have demonstrated that *N*-trityl aziridine-2-(*S*)-carboxaldehyde **1** undergoes a facile Baylis-Hillman reaction with various activated olefins in good yields without racemisation during the long exposure to DABCO. Acetylation of one of the adducts **2a** led to the formation of the allylic transposed acetate **4** with *E* selectivity which is the first report of its kind. Nucleophilic substitution of this allylic acetate **4** with various nucleophiles took place in an S_N2 fashion instead of a reported S_N2' type displacement in a similar system. Further elaboration of **4** to some useful chiral molecules is currently under investigation.

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References:

1. Hwang, G.-II.; Chung, J.-H.; Lee, W.K.; *J. Org. Chem.*, **1996**, *61*, 6183-6188.
2. Ohno, H.; Mimura, N.; Otaka, A.; Tamamura, H.; Fujii, N., Ibuka, T.; *Tetrahedron*, **1997**, *53*, 12933-12946.
3. Tamamura, H.; Yamashita, M.; Muramatsu, H.; Ohno, H.; Ibuka, T.; Otaka, A.; Fujii, N.; *J. Chem. Soc., Chem. Commun.*, **1997**, 2327-2328.
4. Tanner, D.; *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 599-619.
5. Legters, J.; Willems, J.G.H.; Thijs, L.; Zwanenburg, B.; Recl. *Trav. Chim. Pays- Bas*, **1992**, *111*, 59-68.
6. Willems, J.G.H.; Dommerholt, F.J.; Hammink, J.B.; Vaarhorst, A.M.; Thijs, L.; Zwanenburg, B.; *Tetrahedron Lett.*, **1995**, *36*, 603-606. Willems, J.G.H.; Hersmis, M.C.; Gelder, R.D.; Smits, J.M.M.; Hammink, J.B.; Dommerholt, F.J.; Thijs, L.; Zwanenburg, B.; *J. Chem. Soc., Perkin Trans. 1*, **1997**, 963-967.
7. Thijs, L.; Porskamp, J.J.M.; van Loon, A.A.W.M.; Derks, M.P.W.; Feenstra, R.W.; Legters, J.; Zwanenburg, B.; *Tetrahedron*, **1990**, *46*, 2611-2622.
8. Ciganek, E.; *Org. React.*, **1997**, *51*, 201-350.
9. Basavaiah, D.; Rao, P.D.; Suguna Hyma, R.; *Tetrahedron*, **1996**, *52*, 8001-8062 and references cited therein.
10. Drewes, S.E.; Roos, G.H.P.; *Tetrahedron*, **1988**, *44*, 4653-4670.
11. Hoffman, H.M.R.; Rabe, J.; *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 94-108.
12. Basavaiah, D.; Gowriswari, V.V.L.; Sarma, P.K.S.; Rao, P.D.; *Tetrahedron Lett.*, **1990**, *31*, 1621-1624.
13. Gilbert, A.; Heritage, T.W.; Isaacs, N.S.; *Tetrahedron: Asymmetry*, **1991**, *2*, 969-972.
14. Khan, A.A.; Emslie, N.D.; Drewes, S.E.; Field, J.S.; Ramesar, N.; *Chem. Ber.*, **1993**, *126*, 1477-1480.
15. Drewes, S.E.; Emslie, N.D.; Karodia, N.; Khan, A.A.; *Chem. Ber.*, **1990**, *123*, 1447-1448.
16. Drewes, S.E.; Khan, A.A.; Rowland, K.; *Synth. Commun.*, **1993**, *23*, 183-188.
17. Drewes, S.E.; Manickum, T.; Roos, G.H.P.; *Synth. Commun.*, **1988**, *18*, 1065-1070.
18. Drewes, S.E.; Njamela, O.L.; Roos, G.H.P.; *Chem. Ber.*, **1990**, *123*, 2455-2456.
19. Manickum, T.; Roos, G.; *Synth. Commun.*, **1991**, *21*, 2269-2274.
20. Manickum, T.; Roos, G. H.P.; *S. Afr. J. Chem.*, **1994**, *47*, 1-16 .
21. Oishi, T.; Oguri, H.; Hirama, M.; *Tetrahedron: Asymmetry*, **1995**, *6*, 1241-1244.
22. Haner, R.; Olano, B.; Seebach, D.; *Helv. Chim. Acta.*, **1987**, *70*, 1676-1693.
23. Utsunomiya, I.; Fuji, M.; Sato, T.; Natsume, M.; *Chem. Pharm. Bull.*, **1993**, *41*, 854-860.