Reactions of Azidoacetate Enolates with Aromatic Aldehydes: Preparation of N-BOC 3-Arylserines

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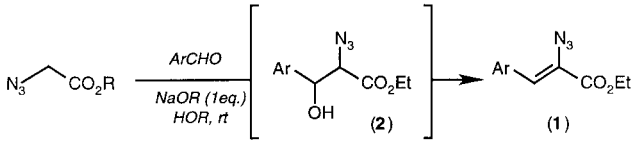
Abstract: Azidoacetates undergo aldol-like reaction with aromaticaldehydes in the presence of sub-stoichiometric amounts of NaOEt. Theproduct azido alcohols (**2a**)-(**2q**) may be directly converted to *N*-BOC phenyl serine analogues

Keywords: aminoacids, arylserines

As part of a program of research concerning incorporation of non-proteinogenic aminoacids into polypeptides, we required a new entry to a range of 2-amino-3-hydroxyesters.[1] We thought that such compounds would be available from the corresponding azidoalcohols, and that if such compounds could be prepared *via* an aldol-like reaction, this would represent a useful addition to the armoury of synthetic chemistry. We here report the preliminary results wehave obtained from study of such reactions.

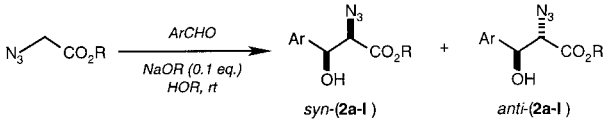


Scheme 1

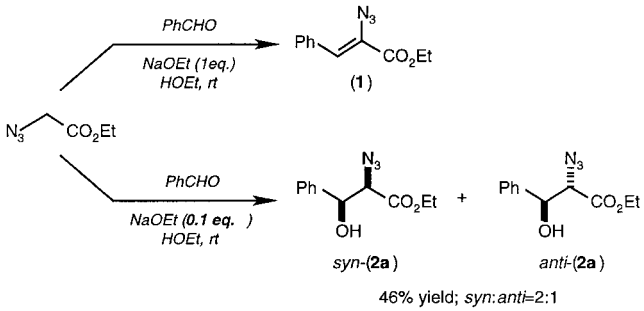
The reaction of aryl aldehydes with ethylazidoacetate is well-known to give good yields of 2-azidocinnamates (**1**), through the intermediacy of hydroxyazide (**2**) (Scheme 1), the reaction forming the basis of the Hemetsberger-Knittelsynthesis of indoles.[2] Very littlework has been reported concerning the interception of the reaction to allow isolation of these hydroxyazides,[3] and our synthetic studies commenced here. Thus, reaction of benzaldehyde with ethylazidoacetate in the presence of one equivalent of sodium ethoxide in ethanol at room temperature overnight gave, as expected, a good yield of azidocinnamate (**1a**). We then repeated the reaction at low temperature, this time using a hindered base (LDA) and an aprotic solvent (THF): we isolated only starting materials from the reaction. Using a variety of strong bases, a similar lack of success was observed. When the original, protic reaction was repeated using a sub-stoichiometric amountof base (0.1eq.), rather than a full equivalent, no azidocinnamate was observed and hydroxyazide (**2a**) was isolated as the only product of the reaction, in 46% yield (Scheme2). This observation is at odds with that previously described, which concluded that azidoalcohols could only be obtained from such reactions when reaction temperatures were considerably lower than ambient (*ca*. -40°C).[3] Thus, (**2a**) was obtained as a 2:1 mixture of diastereoisomers, in favour of the *syn*-isomer (as judged from analysis of ^{1}H nmr data);[4] the isomers were not separable using standard column chromatography.

When (**2a**) was resubjected to the dipolar, aprotic reaction conditions previously examined, (LHMDS base, THF solvent,-78°C), retro-aldol reaction occurred and only ethyl azidoacetate andbenzaldehyde were isolated from the re-

Table 1 Preparation of 2-Azido-3-Hydroxyesters via Azidoaldol reaction



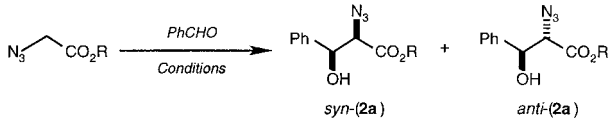
Ar	R	Yield	Compound	*syn*:*anti*
Ph	Et[3]	32	**2a**	2.5:1
2-Cl-C_6H_4	Et[3]	69	**2b**	2.5:1
2,6-Cl_2-C_6H_3	Et	48	**2c**	1:1
4-F-C_6H_4	Et	52	**2d**	1.8:1
2-Br-C_6H_4	Et	55	**2e**	2.8:1
3-Br-C_6H_4	Et	54	**2f**	2.0:1
Ph	Bu^t	56	**2g**	2.5:1
2-Cl-C_6H_4	Bu^t	64	**2h**	3.0:1
2,6-Cl_2-C_6H_3	Bu^t	57	**2i**	1:1
2-F-C_6H_4	Bu^t	39	**2j**	2.6:1
4-F-C_6H_4	Bu^t	50	**2k**	2.4:1
2-Br-C_6H_4	Bu^t	53	**2l**	3.3:1
3-Br-C_6H_4	Bu^t	39	**2m**	2.7:1
4-Br-C_6H_4	Bu^t	36	**2n**	2.2:1
2-naphthyl	Bu^t	9	**2o**	2.6:1
2-MeO-C_6H_4	Bu^t	25	**2p**	4.8:1
4-MeO-C_6H_4	Bu^t	13	**2q**	1.8:1



Scheme 2

action, thereby giving a clue as to the reason for poor reaction under those conditions. Using five other aromatic aldehydes, the 'azidoaldol' reaction proved to be a general one (Table 1),[5] although in all cases, the diastereoselectivity of the reaction was mediocre (3.3:1-1:1, always in favour of *syn*-isomers) even when a bulkier ester group was employed. The greatest selectivity was observed inthe reaction of t-butyl azidoacetate and *ortho*-anisaldehyde. Table 2 shows the variation of yield and diastereoselectivityof the reaction with change in the base employed. Note that, in all the reactions examples, the use of strong bases under aprotic conditions led topoor yields of hydroxy azides, although in some cases the diastereoselectivity was improved. Some of these hydroxyazides were then converted to the corresponding N-BOC arylserines, in acceptable yields (Table 3).[6] Separation of the *anti*- and *syn*-isomers could not be accomplished using usual flash chromatographic techniques.

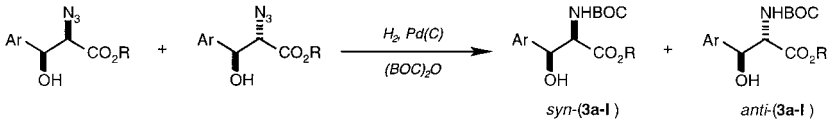
Table 2 Effect of base on Azidoaldolreaction



Conditions	R	Yield/%	*syn:anti*
NaOEt, EtOH, rt	Et	46	2.5:1
NaO^{t}Bu, ^{t}BuOH, rt	Bu^t	56	2.5:1
LiHMDS, THF, -78ûC, 10 h	Et	12	1.5:1
LiHMDS, THF, 0ûC, 10 h	Et	10	2.3:1
LiHMDS (2eq.), THF, -78ûC to rt, 48 h	^{t}Bu	20	4.4:1
LiHMDS (2eq.), THF, -78ûC to rt, 72 h	Et	15	4.3:1
NaHMDS, THF, -78ûC to rt, 18 h	Et	27	3.4:1
KHMDS, THF, 0ûC, 10 h	Et	22	2.1:1
LiH, EtOH (R=Et), rt 18 h	Et	33	1.8:1
LDA, THF, -78ûC, 15 min then rt 10 h	Et	0	-
LDA, THF, -78ûC, 15 min then rt 72 h	Et	0	-

Thus, we have shown that aldol-like reactions of azidoacetates havepotential in synthesis; the optimization and augmentation of thepreliminary results presented above is a focus of our present research.

Table 3 Preparation of N-BOC-Arylserines



Ar	R	Yield	Product	*syn:anti*
Ph	Et	32	**3a**	2.5:1
2-Cl-C_6H_4	Et	61	**3b**	2.5:1
2,6-Cl_2-C_6H_3	Et	49	**3c**	1:1
4-F-C_6H_4	Et	61	**3d**	1.8:1
3-Br-C_6H_4	Et	57	**3f**	2.0:1
Ph	Bu^t	32	**3g**	2.5:1
2-Cl-C_6H_4	Bu^t	74	**3h**	3.0:1
2,6-Cl_2-C_6H_3	Bu^t	65	**3i**	1:1
4-F-C_6H_4	Bu^t	42	**3j**	2.4:1
3-Br-C_6H_4	Bu^t	45	**3l**	2.7:1

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References and Notes

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(5) The experimental procedure for the preparation of ethyl 2-azido-3-hydroxy-3-(2-chlorophenyl)propanoate (2a) is representative:sodium (10.9 mg, 0.47 mmol, 0.1 eq) was added to dry ethanol (6 mL), followed sequentially by ethyl azidoacetate (0.550 g, 4.26 mmol, 1 eq) and benzaldehyde (0.458 g, 4.32 mmol, 1 eq) and the reaction was stirred overnight. after which time 2M HCl (5 mL) was added. The solution was extracted with ethyl acetate (2 x10 mL) and the combined extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product as a yellow oil. After column chromatography, acolourless oil (0.46 g, 46%) was obtained; R_f 0.13(petrol:ether (7:1)); ν_{max} (neat) / cm^{-1} 3481, 2984, 2114, 1734; d_H (400 MHz, $CDCl_3$) 1.24 (3H, m), 3.98 & 4.09(total 1H, 2 x d, J 4.6 & 6.9), 4.24 (2H, m), 4.99 & 5.15 (total 1H, 2 x d,J 6.9 & 4.6), 7.35 (5H, m); d_C (100 MHz, $CDCl_3$) 13.9, 62.1, 66.7, 67.6, 74.0, 74.4, 139.1, 128.8, 126.4, 126.2, 168.5;$^m/_z$ (CI) (%) 51.03 (6), 79.05 (44), 107.04 (100),163.08 (28), 253.10 (14) $[M^+ + NH_4^+]C_{11}H_{13}N_3O_3$ requires 253.1301; found 253.1310. When *tert*-butyl esters were employed, distilled *tert*-butanol replacedethanol in the above procedure.

(6) The experimental procedure for the preparation ofethyl 2-(N-BOC)-3-hydroxy-3-(2-chlorophenyl)propanoate (**3b**) isrepresentative: palladium on carbon (0.052 g, 0.1 eq) was stirred in ethylacetate (4 mL) under a hydrogen atmosphere until hydrogen uptake ceased. Ethyl 2-azido-3-hydroxy-3-(2-chlorophenyl)propanoate (0.500 g, 1.86 mmol) anddi-*tert*-butyl dicarbonate (0.618 g, 2.83 mmol, 1.5 eq) were then added simultaneously, as a solution in ethyl acetate (1 mL). To the reaction wasthen added Celite and the mixture was filtered through a Celite pad; this pad was then washed with ethyl acetate and the filtrate concentrated *in vacuo*, to yield the crude product as an oil, which was purified by column chromatography, to give (**3b**) as a colourless oil(0.393 g, 61%); R_f 0.43 (Petrol:ether (2:3)); ν_{max} (neat) / cm^{-1} 3441, 2981, 2935, 1730, 1716; d_H (400MHz, $CDCl_3$) 1.00-1.44 (3H, br. m), 4.17 (2H, m), 4.63 (1H, d, J 9.5), 5.22 (1H, s),5.34 (1H, d, J 9.5), 5.51-5.56 (1H, br. m), 7.13-7.46; d_C (100 MHz, $CDCl_3$) 14.0, 14.4, 27.6, 28.3, 57.3, 58.2 (CNH), 61.9, 62.0, 71.0, 71.8, 85.5, 126.3, 126.8, 127.2, 128.1, 128.3,128.4, 128.5, 128.6, 129.1, 129.3, 129.4, 129.5, 132.0, 132.3, 137.5,137.8, 155.8, 156.0, 170.4, 171.1; $^m/_z$ (CI) (%) 57.05 (26), 104.02 (59), 147.04 (100), 169.99 (9), 210.09 (20),243.94 (65), 288.02 (32), 344.13 (3) $[M+H^+]$ $C_{16}H_{22}ClNO_5$ requires 344.1265; found 344.1278. It should be noted that, especially for (**3g-3l**), many of the ^1H nmr resonances were broadened by the presence of different rotameric forms.

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