Pergamon

Tetrahedron Letters 39 (1998) 2203–2206

TETRAHEDRON LETTERS

Rationalising Diastereoselection in the Dynamic Kinetic Resolution of α-Haloacyl Imidazolidinones

Stephen Caddick,*[a] Kerry Jenkins,[a] Nigel Treweeke,[a] Sara X. Candeias,[b] Carlos A. M. Afonso.[b]

[a]Centre for Biomolecular Design and Drug Development, The Chemistry Laboratory, University of Sussex, Brighton BN1 9QJ, U.K.

[b]Dept. de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2825 Monte da Caparica, Portugal.

Received 15 December 1997; revised 12 January 1998; accepted 16 January 1998

Abstract: A crossover from S_N2 to general base catalysed nucleophilic substitution can account for the dichotomous diastereoselectivity observed in DKR reactions of α-haloacyl imidazolidinones. Aprotic nucleophiles (Nu^-) react preferentially with the 5*S**,2'*R** diastereomer *via* an S_N2 mechanism. Conversely, amines (R_2NH) generally react preferentially with the 5*S**,2'*S** diastereomer. General base catalysis *via* a bifurcated hydrogen bonded assembly accounts for this anomalous stereoselectivity.

Dynamic resolution has gained popularity in recent years as a useful strategy for asymmetric synthesis.[1] A number of recent studies have focused on the dynamic kinetic resolution (DKR) of α-halo substituted carbonyl compounds.[2] Unusual diastereoselection has been observed in systems where chiral imidazolidinones have been used as an auxiliary.[2a-e] These substrates exhibit dichotomous stereoselective behaviour towards nucleophilic substitutions in DKR reactions. Herein we disclose new DKR results which have enabled us to devise a new model that rationalises the stereochemical outcome of these reactions. The ability to be able to predict the stereochemical course of an asymmetric transformation is an essential pre-requisite for its general synthetic utility.

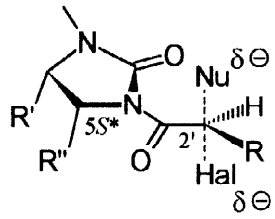


Fig.1. Transition State Assembly for Path A (5*S**, 2'*R** Diastereomer)

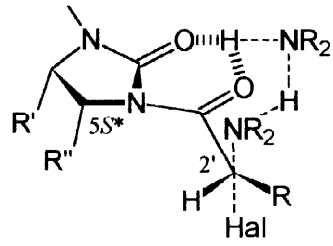
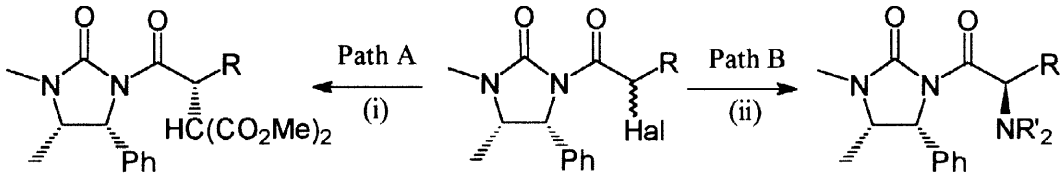


Fig. 2. Transition State Assembly for Path B (5*S**, 2'*S** Diastereomer)

The transition state assembly depicted in figure 1 accounts for the kinetic preference of ionic nucleophiles such as malonic ester enolates and phthalimide salts for the 5*S**, 2'*R** diastereomers.[2c,d] It is also consistent with some of our amine DKR's conducted in media of high ionic strength (*vide infra*). However it does not account for the majority of cases in which amines preferentially react with the 5*S**, 2'*S** diastereomer, often with excellent selectivity. The transition state assembly depicted in figure 2, involving a bifurcated hydrogen bond, can be used to rationalise these results. The conformation of the acyl side chain is reversed as compared with the assembly in figure 1. The sense of stereoselectivity is therefore reversed. A transition state of this type might

0040-4039/98/$19.00
PII: S0040-4039(98)00175-0

provide a viable reaction pathway as one could envisage a general base catalysed mechanism. The bifurcated amine acts as a general base assisting a second molecule of amine in the nucleophilic displacement. A mechanism of this type is favourable due to the avoidance of large charge localisations in the transition state. There is some literature precedent for non-S_N2 mechanisms in the reaction of amines with α-halo carbonyl compounds.[3] The results of the DKR reactions (scheme 1) with various nucleophiles are highlighted in table 1. All of the results are consistent with the proposed mechanistic interpretation for diastereoselection.



6a-c **1a-c, 2a** **3a-c, 4a-c, 5a-c**

1, Hal = Br; **2**, Hal = I
a, R = Me; **b**, R = Et; **c**, R = *n*-Bu

3, $NR'_2 = Nc(CH_2)_4$
4, $NR'_2 = Nc(CH_2)_5$
5, $NR'_2 = NHCH_2Ph$

(i) $NaCH(CO_2Me)_2$, *n*-Bu_4NX; (ii) R'_2NH, *n*-Bu_4NX, Et_3N (1.2 eq.)

Scheme 1

Excellent yields and levels of stereoselectivity can be achieved (e.g. entries 8-14). In cases where selectivity is modest the methodology can still be preparatively useful as the diastereomeric nature of the products usually enables efficient separation by chromatography or crystallisation. It is apparent that stereoselectivity is very dependant on both substrate and nucleophile and is also significantly influenced by epimerising agent and salts. Some notable observations are as follows:

i) Selectivity tends to increase with chain length (**1c** > **1b** > **1a**) which probably reflects a steric requirement in the transition state. This trend would be consistent with *transoid vs. cisoid* R group conformations in our proposed transition state assemblies (*vide supra*).

ii) The use of an excess of tetra-*n*-butylammonium halide often erodes selectivity of amine DKR's. In some instances the sense of diastereocontrol reverses (entry 21). The use of an excess of *n*-Bu_4NNO_3 (16.0 eq.) with catalytic *n*-Bu_4NI (0.2 eq.) confirmed that the reversal was not halide dependant (entries 22-24) which implies a secondary salt effect as opposed to some feature specific to the epimerisation catalyst. The high ionic strength of these reaction media increases the stability of an S_N2 transition state. Selectivity drops as the S_N2 component increases and ultimately selectivity may reverse.

iii) The use of *n*-Bu_4NI in place of *n*-Bu_4NBr generally improved selectivity with amine nucleophile DKR's (entries 2 *vs.* 1, 4 *vs.* 3 & 6 *vs.* 5) whilst the best results with sodium dimethylmalonate (SDM) as the nucleophile were obtained using *n*-Bu_4NBr (entries 17 *vs.* 18 & 19 *vs.* 20). Use of *n*-Bu_4NI generates the 2'-iodo analogues *in-situ* which may account for the enhanced stereoselectivity with amines. Indeed, the use of the stoichiometric 2'-iodo substrate, **2a**, led to higher diastereoselectivities (entries 7, 8, 9 *cf.* 1- 6). In the SDM cases, where the reactions proceed more rapidly, generation of the more reactive 2'-iodo compounds may compromise the efficiency of the DKR process if the rate of alkylation becomes comparable to the rate of epimerisation of the substrate. The use of high dilution, slow addition of nucleophile and excess *n*-Bu_4NBr gave moderate selectivity in this asymmetric carbon-carbon bond forming reaction (entry 16).

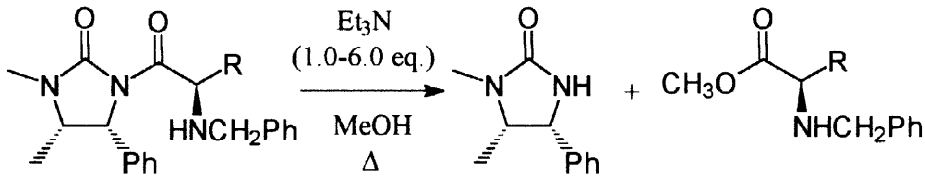
Entry	S.M.	Nucleophile (eq.)[a]	n-Bu_4NX X (eq.)[b]	Temp.[c]	Time	Product[d]	Yield %	d.c. %[e]
1	1a	Pyr	Br	rt	62 hrs	3a	62	24
2	1a	Pyr	I	rt	46 hrs	3a	100	42
3	1a	Pip	Br	rt	91 hrs	4a	88	57
4	1a	Pip	I	rt	91 hrs	4a	93	72
5	1a	BA	Br	rt	77 hrs	5a	87	58
6	1a	BA	I	rt	48 hrs	5a	100	74
7	2a	Pyr	I	rt	69 hrs	3a	79	68
8	2a	Pip	I	rt	50 hrs	4a	91	81
9	2a	BA	I	rt	51 hrs	5a	96	79
10	1b	Pyr	I	Δ	48 hrs	3b	87	90
11	1b	Pip	I	Δ	43 hrs	4b	100	94
12	1b	BA	I	Δ	43 hrs	5b	97	80
13	1c	Pyr	I	Δ	6 d	3c	99	100
14	1c	Pip	I	Δ	50 hrs	4c	94	100
15	1c	BA	I	Δ	72 hrs	5c	72	82
16[f]	1a	SDM (1.20)	Br (2.0)	rt	6 d	6a	62	54-60
17	1b	SDM (2.75)	Br	Δ	48 hrs	6b	90	35
18	1b	SDM (2.75)	I	Δ	48 hrs	6b	94	14
19	1c	SDM (2.75)	Br	Δ	26 hrs	6c	83	52
20	1c	SDM (2.75)	I	Δ	26 hrs	6c	99	31
21[g]	1a	Pyr	Br (5.0)	rt	44 hrs	S-3a	64	-28
22	1a	Pyr	I , NO_3	rt	24 hrs	S-3a	64	-22
23	1b	Pyr	I ,NO_3	Δ	47 hrs	S-3b	91	-13
24	1c	Pyr	I , NO_3	Δ	23 hrs	S-3c	80	-13

Amine DKR's carried out at 0.1M with respect to S.M. (unless otherwise stated) in THF. Sodium dimethyl malonate (SDM) DKR's carried out by addition of SDM (0.70M in THF unless otherwise stated) to solution of S.M. (0.1M in THF).

a) 1.5 eq. nucleophile used unless indicated in parentheses. Pyr = pyrrolidine; Pip = piperidine; BA = benzylamine; SDM = sodium dimethyl malonate. b) 0.2 eq. n-Bu_4NI/n-Bu_4NBr used unless otherwise stated in parentheses; 16.0 eq. n-Bu_4NNO_3 used in entries 22 - 24. c) r.t. = ambient temperature (20 - 30°C); Δ = reflux temperature. d) Products have the 2'*R* stereochemistry (as depicted) unless otherwise stated. e) d.e. values determined by ^1H NMR signal integrations except entries 19 and 20 which were isolated. Minus (-) prefix denotes opposite sense of stereoselectivity to that depicted in the scheme 1. f) SDM (0.034M in THF) added over 28 hrs to S.M. (0.1M in THF). g) 0.05M with respect to S.M.

Table 1

During the course of our study we developed a remarkably mild methanolysis protocol. *N*-Acyl imidazolidinones undergo facile trans-acyl cleavage with triethylamine in methanol. This is exemplified with some of the products from amine DKR (scheme 2).



2'*R*-**5a-c** 7 2*R*-**8a** (R = Me), 74%
2*R*-**8b** (R = Et), 84%
2*R*-**8c** (R = *n*-Bu), 62%

Scheme 2

An activated hydrogen bonded complex could account for this unusually facile methanolysis reaction. Hydrogen bonding between the substrate and methanol should render the C=O group more electrophilic. Additionally, such an interaction would increase the acidity of the methanolic proton - especially if a bifurcated hydrogen bond were involved. In the presence of a suitable base, such as triethylamine, this complex may be activated sufficiently to undergo methanolysis.

In summary the transition state assemblies proposed in this paper are consistent with the current experimental data. The development of a device to assist in the prediction of the stereochemical outcome of such DKR reactions is an essential prerequisite for the development of a useful synthetic methodology. The examples presented in this paper demonstrate that DKR can be a useful method for the synthesis of α-substituted carboxylic acid derivatives. Moreover, the ease of removal of the ephedrine derived auxiliary, 7, makes it an attractive candidate for use in these reactions. We are currently exploring further synthetic and mechanistic aspects of both the DKR and methanolysis methodologies.

Acknowledgements.

We thank the University of Sussex, Subprograma Ciência e Tecnologia do 2° Quadro Comunitário de Apoio (PRAXIS/PCEX/C/QUI/53/96 and PRAXIS XXI/BD/4024/94) and the British Council/JNICT Protocol 97/98 for financial support for this research. We also thank Zeneca for additional financial support. We gratefully acknowledge the contributions of the EPSRC mass spectrometry service, Swansea (UK), Dr. A. Abdul-Sada, Dr. P. B. Hitchcock and Dr. A. G. Avent (Sussex). We also thank Dr. R. M. Topping (Sussex) for stimulating discussion.

REFERENCES AND NOTES

1. a) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.*, **1996**, 447-456; b) Ward, R. S. *Tetrahedron: Asymmetry*, **1995**, *6*, 1475-1490; c) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 36-56.
2. a) Caddick, S.; Jenkins, K. *Tetrahedron Lett.*, **1996**, *37*, 1301-1304; b) Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K. *J. Org. Chem.*, **1995**, *60*, 6776-6784; c) Kubo, A.; Kudota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.*, **1997**, *62*, 5830-5837; d) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *Tetrahedron Lett.*, **1995**, *37*, 4957-4960; e) O'Meara, J. A.; Jung, M.; Durst, T. *Tetrahedron Lett.*, **1995**, *36*, 2559-2562; corrigendum, *ibid.*, 5056; f) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry*, **1995**, *6*, 469-498; g) Devine, P. N.; Dolling, U. H.; Heid, R. M.; Tschaen, D. M. *Tetrahedron Lett.*, **1995**, *37*, 2683-2686; h) Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron: Asymmetry*, **1997**, *38*, 1877-1894.
3. a) Ross, S. D.; Finkelstein, M.; Peterson, R. C. *J. Am. Chem. Soc.*, **1958**, *90*, 6411-6415; b) Taylor, P. J. *J. Chem. Soc. (B)*, **1957**, 904-908; c) Pearson, R. G.; Langer, S. H.; Williams, F. V.; McGuire, W. J. *J. Am. Chem. Soc.*, **1952**, *74*, 5130-5132.