J. Bangladesh Acad. Sci. 47(2); 215-222: December 2023 DOI:https://doi.org/10.3329/jbas.v47i2.66977

Journal of Bangladesh Academy of Sciences

Journal homepage: http://www.bas.org.bd/publications/jbas.html

Research Article

Stereoselectivity of thiazolidine, malonamides and bicyclic tetramates with isopropyl NH and SH protecting group

Halima Bagum* and Mark G. Moloney[1]

Department of Chemistry, University of Barishal, Bangladesh

ARTICLE INFO

Article History

Received: 18 June 2023
Revised: 14 September 2023
Accepted: 17 October 2023

Keywords: Tetramate, Cyclization, Heterocycle, Stereoselectivity

ABSTRACT

The stereochemistry of the routes to two different bicyclic tetramates are reported which enables to synthesize highly functionalized systems. An analysis of the structure shows that the tetramates permit ready incorporation of three to five functionality at different positions. This work demonstrates that novel bicyclic tetramates can be synthesized via stereoselective cyclization. The resulting heterocycles were studied with the help of NMR techniques.

Introduction

The tetramate moiety occurs in a diverse range of natural products which demonstrate a wide range of biological activity (Petermichl and Schobert, 2017; Schobert and Schlenk, 2008). Bicyclic tetramates, which may exhibit biological activity, are accessible by stereoselective Dieckmann ring closure reaction. We have shown this cyclization (Scheme 1) to get **4** and utilization of the cyclized product **4** to synthesize a library of compounds for a number of systems (Andrews et al., 1998; Bagum et al., 2019a, 2019b, 2020; Saney et al., 2023).

Alternative C7-methyl tetramate **8** was developed following the methodology reported by Andrews and co-workers (Andrews et al., 1994). The thiazolidine **2** was *N*-acylated by ethyl α-methylmalonyl chloride **6** and pyridine to afford *cis*-2,5 malonamide **7** (Scheme 2). The *trans*-2,5 malonamide was also formed as a minor product but only *cis*-2,5 malonamide **7** was isolated. Dieckmann cyclization at basic condition furnished in C7-methyl tetramates **8** and **9** which were inseparable at this stage. The structures of these novel compounds were determined by NMR and MS analysis. Previous works (Anwar et al., 2010; Bagum et al., 2019a, 2020; Saney et al., 2023) on this field has extensive examples with different NH and SH protecting groups including *t*-Bu and aryl systems. Herein, we have examined thiazolidine, malonamides and bicyclic tetramates with isopropyl NH and SH protecting group.

Of interest we studied the products of cyclization pathways (Scheme 1 and 2) by using spectroscopic techniques and herein we report the results of that exploration.

Materials and Methods

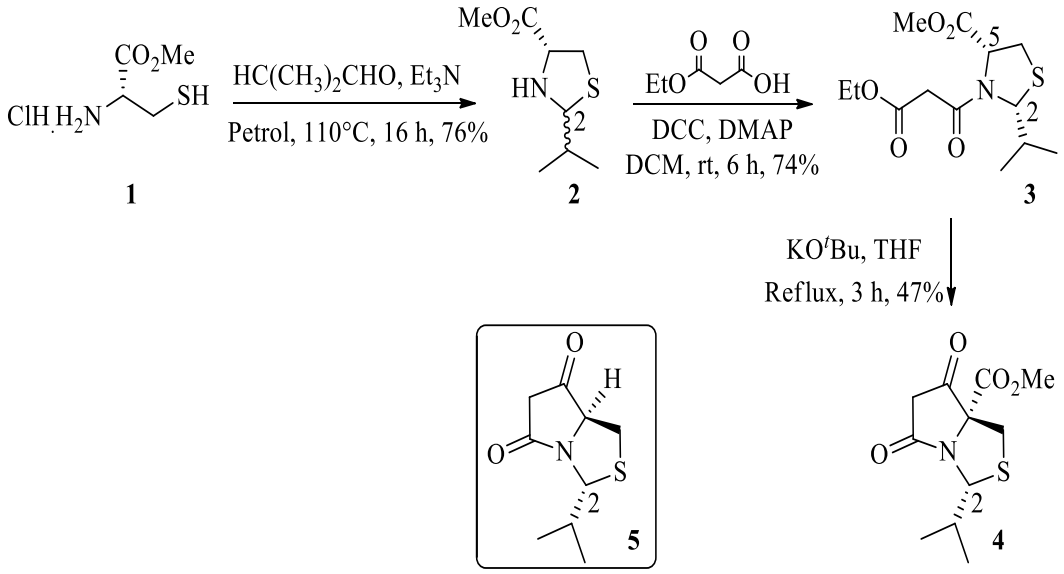
Starting materials were obtained from Sigma Aldrich, Apollo Scientific, Alfa Aesar, Fluorochem or Acros Organics. Reactions were carried out in oven-dried glassware and under an inert medium of nitrogen. Minutes (min), hours (h) and days (d) were used to record reaction times. Light petroleum ether of boiling point 40-60℃ was used, without further purification, as purchased from the commercial suppliers. Solvents were evaporated under reduced pressure at 40 ℃. Büchi R-210 and RE 111 rotary evaporator, attached to

*Corresponding author: <halimaju35@gmail.com>

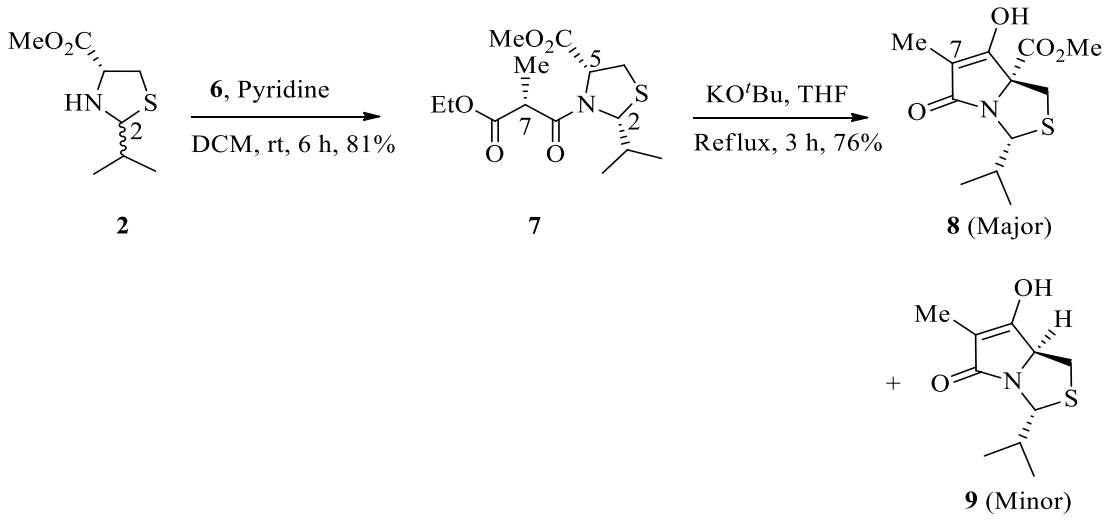
[1]*Department of Chemistry, University of Oxford, United Kingdom*

a Vacuubrand CVC2 pump and pressure control system, were used to evaporate solvents.

Merck aluminium foil backed sheets precoated with 0.2 mm Kielselgel 60 F_{254} was used to perform Analytical thin-layer chromatography (TLC). Kielselgel 60 silica gel (230-400 mesh particle size) was used to accomplish flash column chromatography. The eluents are identified clearly for each column.



Scheme 1. Synthesis of tetramate 4.



Scheme 2. Synthesis of C7-Me Tetramate 8 with isopropyl NH and SH-protecting group.

Bruker DPX200 (200 MHz), AVF400 (400 MHz), AVG400 (400 MHz), AVH400 (400 MHz), AVB500 (500 MHz), AVC500 (500 MHz) and AVX500 (500 MHz) were used to record NMR spectra by the internal assistance at the Chemistry Research Laboratory, Department of Chemistry, University of Oxford. Confirmation of stereochemistry was made using NOESY. In the circumstances where products subsist as a mixture of diastereomers, rotamers or tautomers, ^{1}H NMR spectrum was used to calculate the ratio of the mixtures.

Synthesis of Methyl Ester Hydrochloride 1 (Chaudhari and Bari,2015)*: General Method A*

To stirring anhydrous MeOH (2 M) at 0°C, $SOCl_2$ (1.5 eq) was added dropwise. L-cysteine (1 eq) was added portion-wise. The mixture was warmed up to 40°C and stirred at this temperature for 3 h. Then the solvent was evaporated under reduced pressure to produce the ester hydrogen chloride of the L-cysteine **1**.

Synthesis of Thiazolidine Compound 2 (Andrews et al., 1998; Seebach and Aebi, 1984)*: General Method B*

L-Cysteine methyl ester hydrogen chloride **1** (1.0 eq) was added in petroleum ether (50-100 mL). Then triethylamine (1.5 eq) and 2-methylpropanal (1.2 eq) were added. The reaction mixture was refluxed with continuous removal of water using a Dean-Stark apparatus for 18 h. The white precipitate was then filtered and washed with Et_2O. The combined filtrates were concentrated under reduced pressure to result the thiazolidine **2**.

N-Acylation of Thiazolidine 2 (Andrews et al., 1998)*: General Method C*

To a solution of thiazolidine **2** (1.0 eq) in anhydrous DCM, 4- dimethylaminopyridine (0.05 eq) and N,N'-dicyclohexylcarbodiimide (1.05 eq) were added. The mixture was cooled to 0°C followed by the addition of ethyl hydrogen malonate (1.05 eq). At 0°C, the reaction mixture was stirred for 30 minutes and at room temperature, the mixture was stirred for 5-6 h. A white precipitate was resulted, which was filtered and washed with dichloromethane. The combined filtrates were concentrated *in vacuo* and purified by flash column chromatography to furnish the expected products, *N*-acyl thiazolidines **3, 7**.

Dieckmann Cyclization (Andrews et al., 1998)*: General Method D*

Potassium *tert*-butoxide (1.05 eq) was added to a solution of *N*-acyl thiazolidine **3** or **7** (1.0 eq) in anhydrous tetrahydrofuran (THF). The reaction mixture was refluxed for 3 h. The mixture was separated between diethylether (Et_2O) and water. The aqueous phase was acidified with 2 M HCl and extracted with ethylacetate (EtOAc). 1 M aqueous solution of NaH_2PO_4 and brine was used to wash the organic layer. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce the methyl ester tetramic acids **4** or **8**.

Results and Discussion

Products of cyclization pathways

The following thiazolidine, malonamide and bicyclic tetramate derivatives (Fig. 1) were obtained from the cyclization pathways using isopropyl NH and SH protecting group. The stereochemistry of the thiazolidine **2**, malonamides **3, 7**, and tetramates **4, 8** were assigned by NOE analysis (Fig. 2).

C2 Epimerisation and Rotameric Behaviour of Malonamide 3: Rationalisation.

A mixture of two different species, even after careful column chromatography, was apparent in the ^{1}H NMR spectra of malonamide **3**. These mixtures could have been rotamers due to the presence of the *N*-protecting group or an inseparable mixture of diastereomers (Fig. 3).

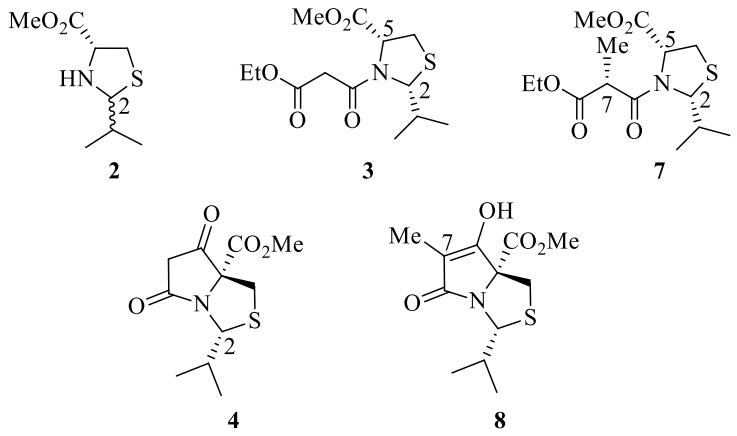


Fig 1. Products of cyclization pathways.

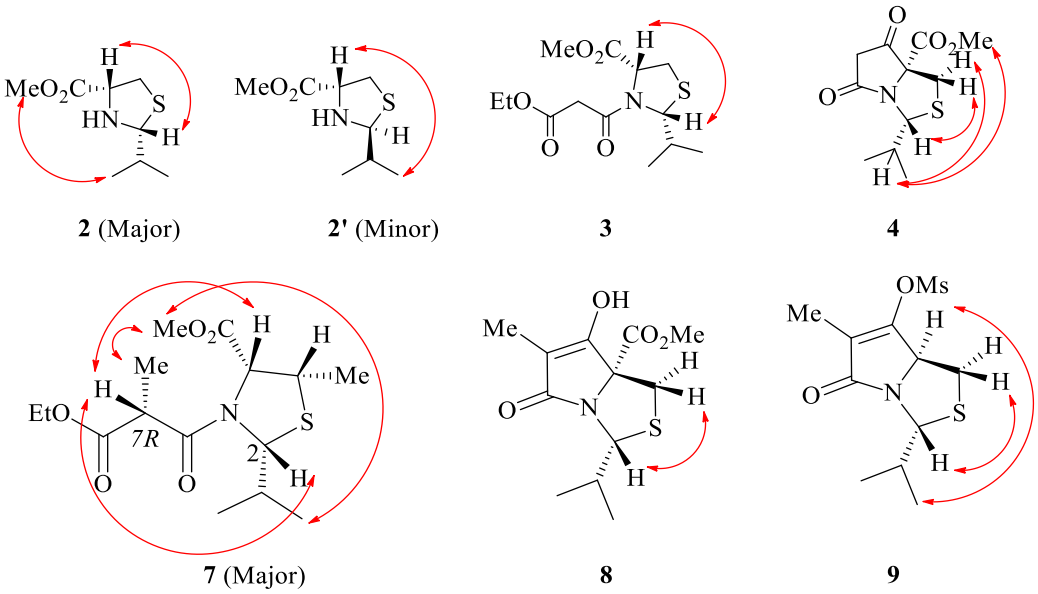


Fig. 2. Nuclear Overhauser Effect (NOE) analysis of thiazolidine 2, malonamides 3,7, and tetramates 4,8.

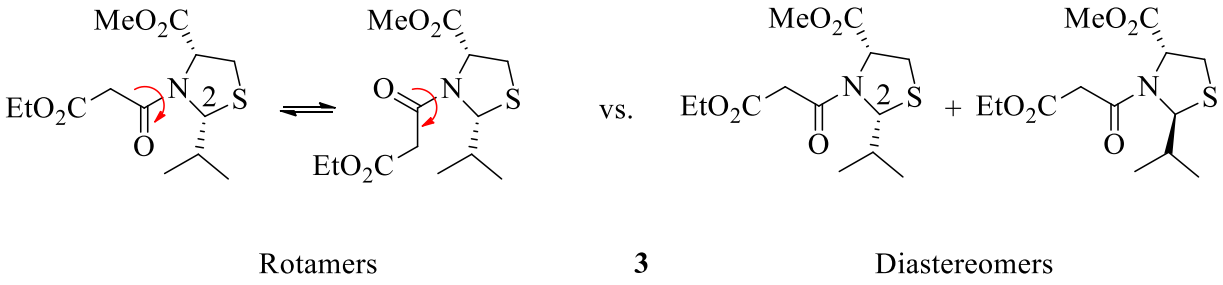
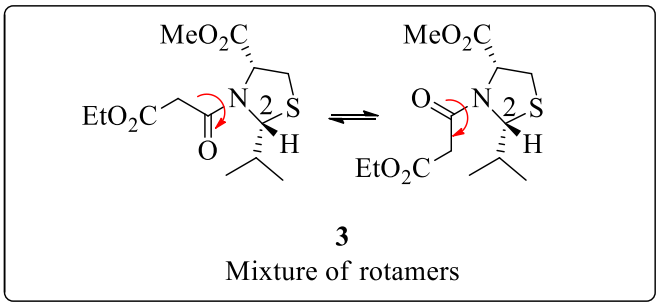


Fig. 3. Structure of rotamers and diastereomers for malonamide 3.

The rate of rotameric exchange is fast and can be examined by using variable temperature (VT) ^{1}H NMR, 1D selective chemical exchange NMR experiment or 2D gradient NOE experiment. In the VT NMR experiment, ^{1}H signals from rotameric species would coalesce. On the other hand, proton signals for the rotameric species would exhibit similar behaviour in a 1D gradient NMR experiment or exchange peaks would appear in 2D gradient NOE experiment.

The *cis*-2,5 malonamide **3** was found to exist as a mixture of rotamers detected by a 1D gradient selective NOE NMR experiment (Fig. 4). Selective



3
Mixture of rotamers

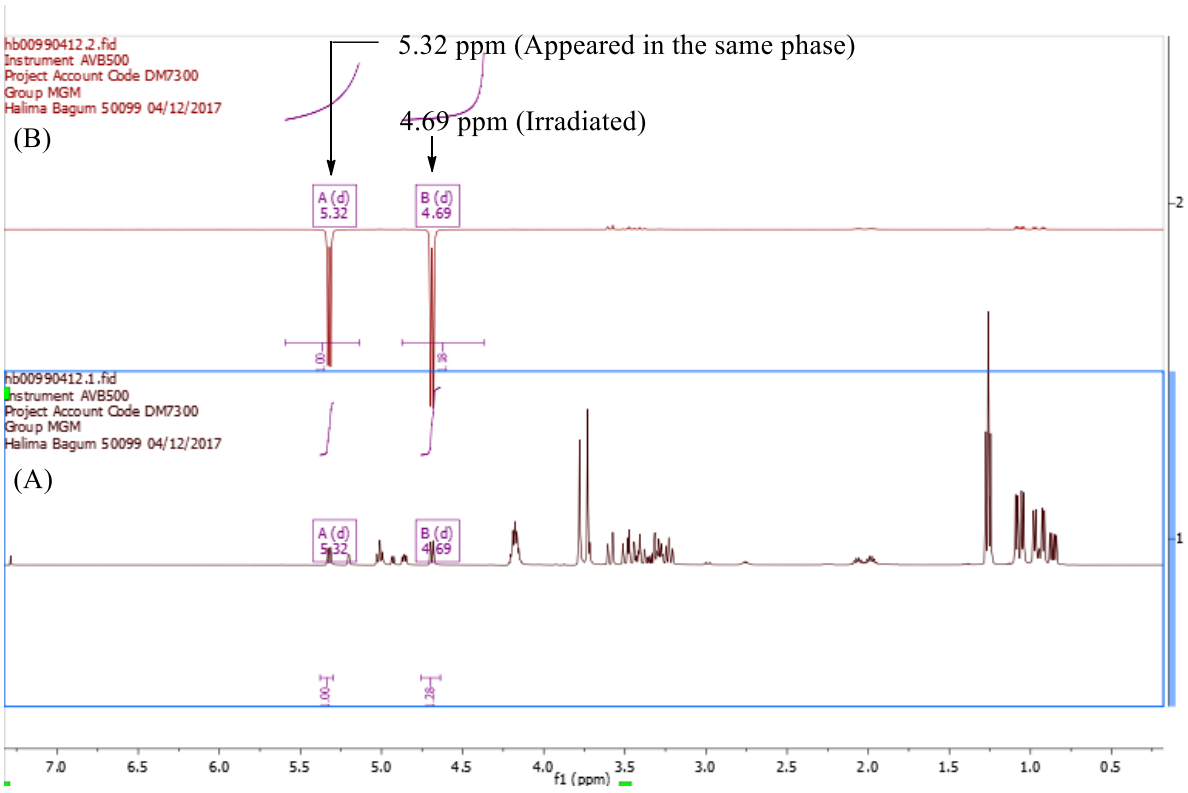


Fig. 4. (A) ^{1}H NMR of *cis*-2,5 malonamide 3; (B) 1D gradient NOE showing selective irradiation at H2.

irradiation of signal at 4.69 ppm in 1D gradient NOE experiment provided a spectrum (B) with two negative signals at 4.69 ppm and 5.32 ppm. This experiment revealed the rotameric exchange in *cis*-2,5 malonamide **3**.

Following the remarkable success in the synthesis of bicyclic teramate motif **4,** easy and cost efficient access to tetramate derivative, it was of interest to investigate the preparation and reactions of C7-methyl bicyclic tetramate with an isopropyl NH and SH-protecting group. This would permit access to 3, 4-substituted tetramate, pyrrolinone and pyrroglutaminol derivatives.

***Stereochemistry of Intermediate* 7**

The *cis*-2,5 malonamide **7** was obtained as a mixture of C7 epimers with *7R* as a major one and 1D gradient NMR spectropscopy revealed the presence of rotameric exchange (Fig. 5). The stereochemistry of the major malonamide analogue **7** was assigned confidently by NOE analysis (Fig. 2). Nuclear Overhouser Effect (NOE) analysis was used to determine the stereochemistry of the major tetramic acid **8**, whereas the stereochemistry of minor one was assigned by NOE analysis of mesylate derivative **9.**

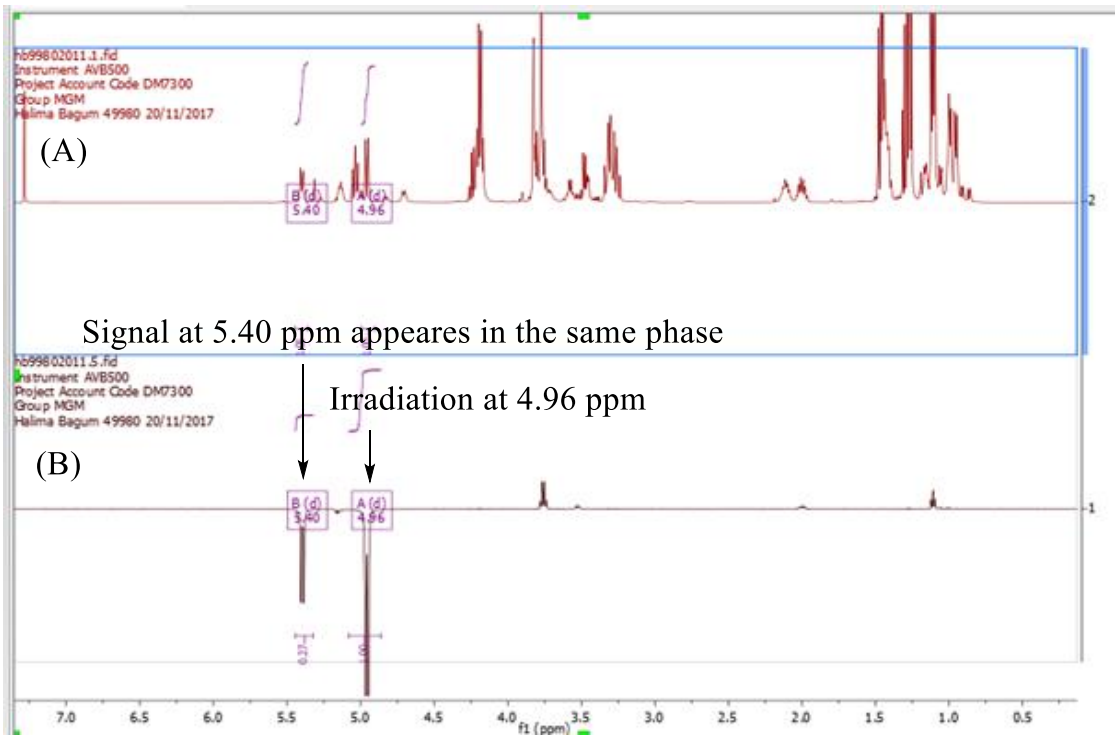
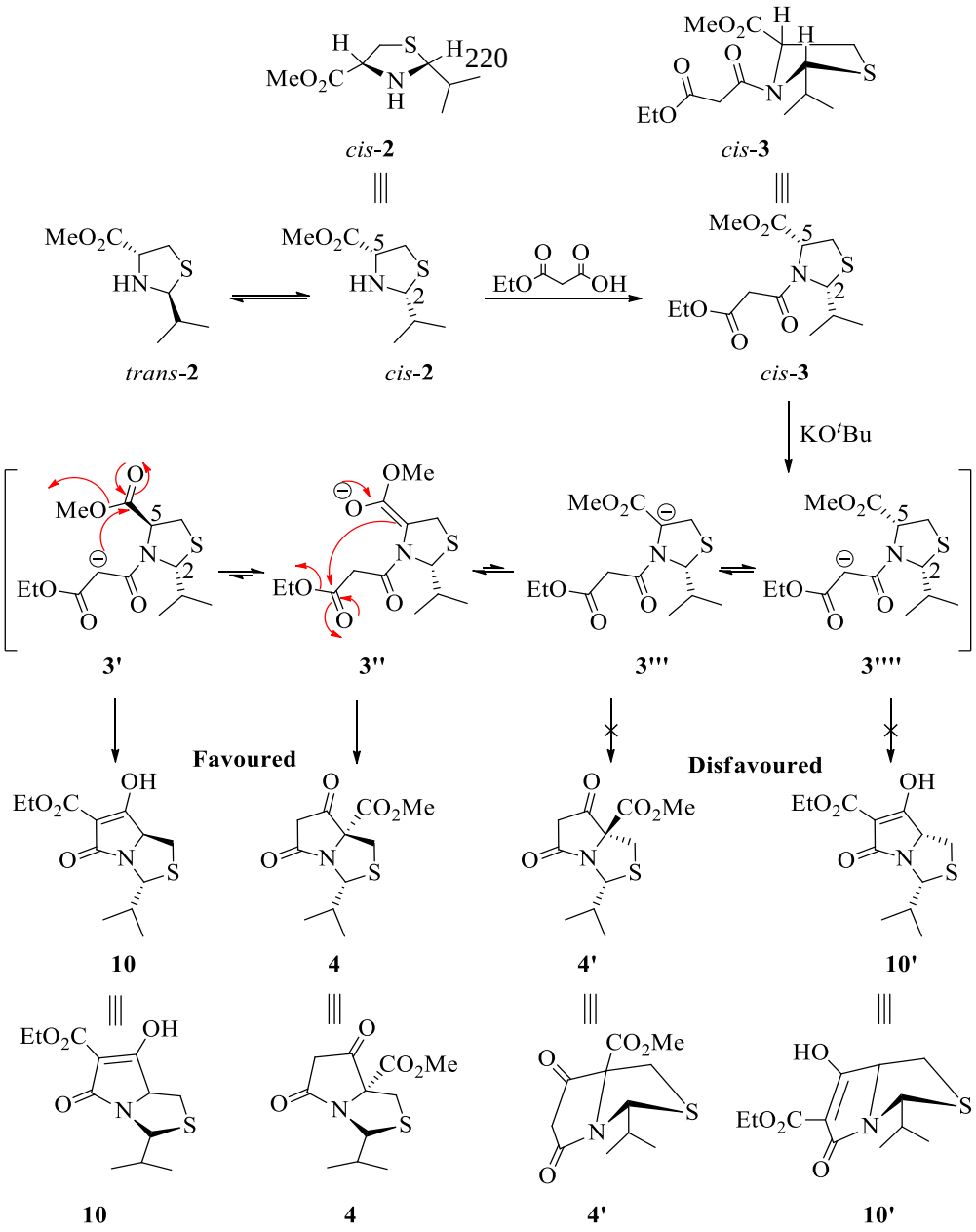


Fig. 5. (A) ^{1}H NMR of *cis*-2,5 malonamide 218b; (B) 1D gradient NOE showing selective irradiation at H2

Regioselectivity and Diastereoselectivity in Dieckmann Cyclization

Andrews and co-workers (Andrews et al., 1994, 1998) have reported a comprehensive study on the regioselectivity, diastereoselectivity and enantioselectivity of the Dieckmann ring closure of *N*-acyl oxazolidines. Similarly, the regioselectivity, diastereoselectivity and enantioselectivity of the Dieckmann ring closure of *N*-acyl thiazolidine can be described (Scheme 3). The steric bulk from the isopropyl group plays a vital role in the observed regioselectivity and diastereoselectivity in Dieckmann cyclization.



Scheme 3. Mechanism and possible outcomes for the Dieckmann cyclization.

Deprotonation of *cis*-**3** results in four possibilities for cyclization among which only two are favoured as the bulky isopropyl group is placed on the less obstructed *exo*-face of the bicyclic ring system and consequently, the major product comes from the more stable enolate **3’’**. The other two structures, **3’’’** and **3’’’’**, set the isopropyl group in the more obstructed *endo*-face of the bicyclic ring system and thereby cannot be formed. Jeong *et al.*(Jeong et al., 2011) have examined the chemoselectivity in Dieckmann cyclisation. Seebach’s substrate-controlling protocol ‘Self Regeneration of Stereocentres’(Seebach et al., 1996; Seebach and Aebi, 1984) allows this route to avoid racemization in the formation of chiral tetramates **4** and **10**. The optical purity of products for *O*-system was also

examined by Andrews (Andrews et al., 1998). These results clearly demonstrate that this three-step route to tetramate proceeds with regio- and chemoselectivity and develops tetramates **4** of excellent enantiomeric purity.

Conclusion

The stereochemistry of thiazolidine **2**, malonamides **3, 7** and bicyclic lactams **4, 8**, prepared from cysteine and 2-methylpropanal, were studied extensively with the help of different NMR techniques. It has shown that the products are stereoselective and in all cases the major products are of *cis*-configuration.

Acknowledgements

I would like to express my sincere gratitude to Professor M. G. Moloney for giving me the opportunity to carry out this work in his research group. This work was conducted with the financial support of the Commonwealth Scholarship Commission in the United Kingdom and the University of Oxford, United Kingdom.

Conflict of Interest

The authors of this manuscript declare that they have no conflict of interest.

Authors Contribution

Bagum H, with the help of Moloney MG, designed the experiment. Bagum performed the experiment. Moreover, Bagum H has prepared the manuscript and Moloney MG reviewed the manuscript.

References

Andrews MD, Brewster A and Moloney MG. A concise approach to functionalised, homochiral tetramic acids. *Tetrahedron: Asymmetry*, 1994; 5(8): 1477-1478.

Andrews MD, Brewster AG, Crapnell KM., Ibbett AJ, Jones T, Moloney MG, Prout K, and Watkin D. Regioselective Dieckmann cyclisations leading to enantiopure highly functionalised tetramic acid derivatives. *J. Chem. Soc., Perkin Transactions 1*, *2*, 1998; 223-236.

Anwar M, Cowley AR and Moloney MG. Novel chiral pyrrolidinone scaffolds derived from threonine with antibacterial activity. *Tetrahedron: Asymmetry*, 2010; 21(13-14): 1758-1770.

Bagum H, Christensen KE, Genov M, Pretsch A, Pretsch D and Moloney MG. Synthetic access to 3-substituted pyroglutamic acids from tetramate derivatives of serine, threonine, allo-threonine, and cysteine. *J. Org. Chem.*, 2019a*;* 84(16): 10257-10279.

Bagum H, Christensen KE, Genov M, Pretsch A, Pretsch D and Moloney MG. Synthetic access to 3,4-disubstituted pyroglutamates from tetramate derivatives from serine, allo-threonine and cysteine. *Tetrahedron*, 2019b*;* 75(40): 130561-130581.

Bagum H, Shire BR, Christensen KE, Genov M, Pretsch A, Pretsch D, and Moloney MG. Bicyclic lactams derived from serine or cysteine and 2-methylpropanal. *Synlett*, 2020; 31(4): 378-382.

Chaudhari P and Bari S. Efficient synthesis of N-sulfonyl β -arylmethylalaninates from serine via ring opening of N-sulfonyl aziridine-2-carboxylate. *Synth. Commun.*, 2015; 45(3): 391-402.

Jeong YC, Anwar M, Nguyen TM, Tan BSW, Chai CLL and Moloney MG. Control of chemoselectivity in Dieckmann ring closures leading to tetramic acids. *Org. Biomol. Chem.*, 2011; 9(19): 6663-6669.

Petermichl M and Schobert R. 3-Acyltetramic acids: A decades-long approach to a fascinating natural product family. *Synlett*, 2017; 28(06): 654-663.

Saney L, Panduwawala T, Li X, Christensen KE, Genov M, Pretsch A, Pretsch D and Moloney MG. Synthesis of fused tetramate-oxazolidine and -imidazolidine derivatives and their antibacterial activity. *Org. Biomol. Chem.*, 2023; 21(23): 4801-4809 .

Schobert R and Schlenk A. Tetramic and tetronic acids: An update on new derivatives and biological aspects. *Bioorg. Med. Chem.*, 2008; 16(8): 4203-4221.

Seebach D and Aebi JD. α-alkylation of serine with self-reproduction of the center of chirality. *Tetrahedron Letters*, 1984; 25(24): 2545-2548.

Seebach D, Sting AR and Hoffmann M. Self-regeneration of stereocenters(SRS)—Applica-tions, Llmitations, and abandonment of a synthetic principle. *Angew. Chem. Int. Ed. Engl.*, 1996; 35(2324): 2708-2748.