



S0040-4039(96)00405-4

Study of the Reactivity profile of Glycine Schiff's bases with Dipolarophiles: Application towards a concise synthesis of CCG-II

Subhash. P. Chavan*, M. S. Venkatraman, Anil. K. Sharma and Amar Gopal Chittiboyina

Division Of Organic Chemistry: Technology
National Chemical Laboratory, Pune 411008, India

Abstract: The reactivity profile of glycine Schiff's bases with crotonate and bromocrotonate has been shown to take a different course depending on the choice substituent on the imine. Application of the above study for the mild and concise synthesis of CCG-II has been achieved.

Copyright © 1996 Published by Elsevier Science Ltd

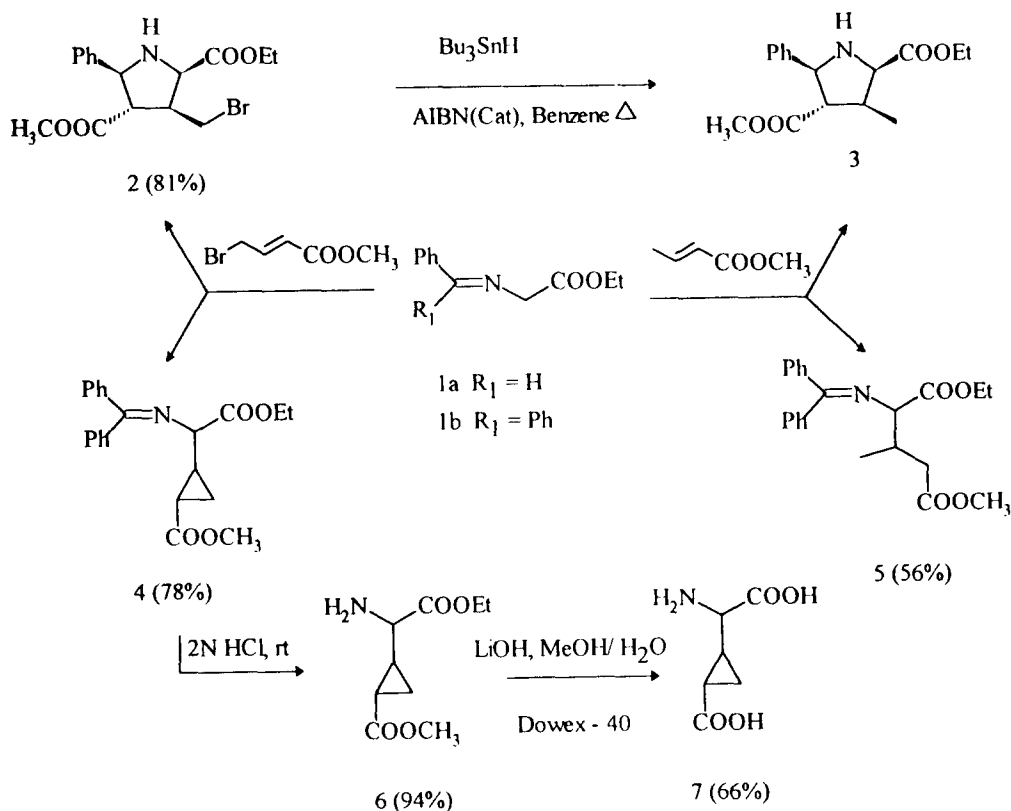
In connection with our synthetic study on Camptothecin, we needed to alkylate Schiff's base of glycine **1b** with methyl bromo crotonate under mild conditions. In a recent study benzaldehyde Schiff's base of glycine ester has been shown to undergo 1,3-dipolar cycloaddition with methylcrotonate under mild conditions ($\text{LiBr}/\text{Et}_3\text{N}$).¹ Under more forcing/drastring conditions Schiff's bases of glycine ester derived from camphor have been shown to undergo diastereoselective Michael addition.²

When **1a** was treated with methyl 4-bromocrotonate employing $\text{LiBr}/\text{Et}_3\text{N}$, 1,3-dipolar cycloadduct **2** was obtained in 81% yield. The structure **2** was established by reduction of the halide by Bu_3SnH in refluxing benzene in the presence of AIBN as the initiator to obtain **3**. Structure of **3** was further confirmed by independent synthesis. **3** was also obtained by reaction of **1a** with methyl crotonate following Yoshioka conditions.¹

However, when methyl 4-bromocrotonate was subjected to reaction with **1b** using $\text{LiBr}/\text{Et}_3\text{N}$, 1,3-dipolar cycloaddition was not observed, instead a product corresponding to cyclopropane **4** was obtained in 78% yield. Formation of **4** implies that the Michael addition is favoured over 1,3-dipolar cycloaddition. To test this hypothesis, we subjected **1b** to reaction with methylcrotonate under identical conditions. Here formation of **5** corresponding to Michael reaction was observed in 56% yield based on ^1H NMR spectral analysis.

From the above results it is obvious that a subtle change in the choice of the carbonyl functionality for the formation of Schiff's base derived from glycine and its further reaction has a pronounced effect on the reaction pathway. It is envisaged that the presence of the extra phenyl group in **1b** exerts a steric effect thus preventing the further addition leading to the 1,3-dipolar cycloaddition product. In the presence of a good leaving group such as bromine in bromocrotonate, the anion generated after initial Michael reaction can be trapped efficiently to furnish the cyclopropane ring.

CCG-II **7**, a novel neuroactive glutamic acid derivative isolated from *Aesculus parviflora* and *Bli-gira spalda* has attracted the attention of synthetic chemists owing to its biological activity and has been



Scheme 1

synthesised in a variety of ways.³ Herein we report a concise, mild and efficient synthesis of CCG-II 7. Compound 4, which was easily obtained under mild conditions was subjected to hydrolysis to furnish the amino ester 6 in 94% yield. Saponification of 6 using LiOH furnished the cyclopropane amino acid 7 (CCG-II), after passing it through Dowex-40 ion exchange resin in 66% yield. The amino acid thus obtained had identical spectral data in all respects with the literature reported values.^{3c}

Thus, in conclusion we have demonstrated that by the proper choice of substituent on the glycine Schiff's base one can fine tune the reaction pathway to proceed in a Michael or 1,3-dipolar manner. This observation has been applied towards an efficient synthesis of CCG-II.

Acknowledgements: M.S. Venkatraman and Anil. K. Sharma thank CSIR New Delhi, India for the award of fellowship. We are thankful to Dr T. Ravindranathan for his constant support and encouragement.

References:

1. Tsuge, O.; Yoshiyoka, M. *J. Org. Chem.* **1988**, 53, 1384.
2. Kanemasa, N.; Ohfuné, Y. *Chemistry Lett.* **1991**, 1301.
3. a) Kurokawa, N.; Ohfuné, Y. *Tetrahedron Lett.* **1985**, 20, 83. b) Yamanoi, K.; Ohfuné, Y. *Tetrahedron Lett.* **1988**, 29, 1181. c) Shinamoto, K.; Ohfuné, Y. *Tetrahedron Lett.* **1989**, 30, 3803. d) Yamaguchi, M.; Torisu, K.; Minami, T. *Chemistry Lett.* **1990**, 377.

(Received in UK 22 January 1996; revised 26 February 1996; accepted 1 March 1996)