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

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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.

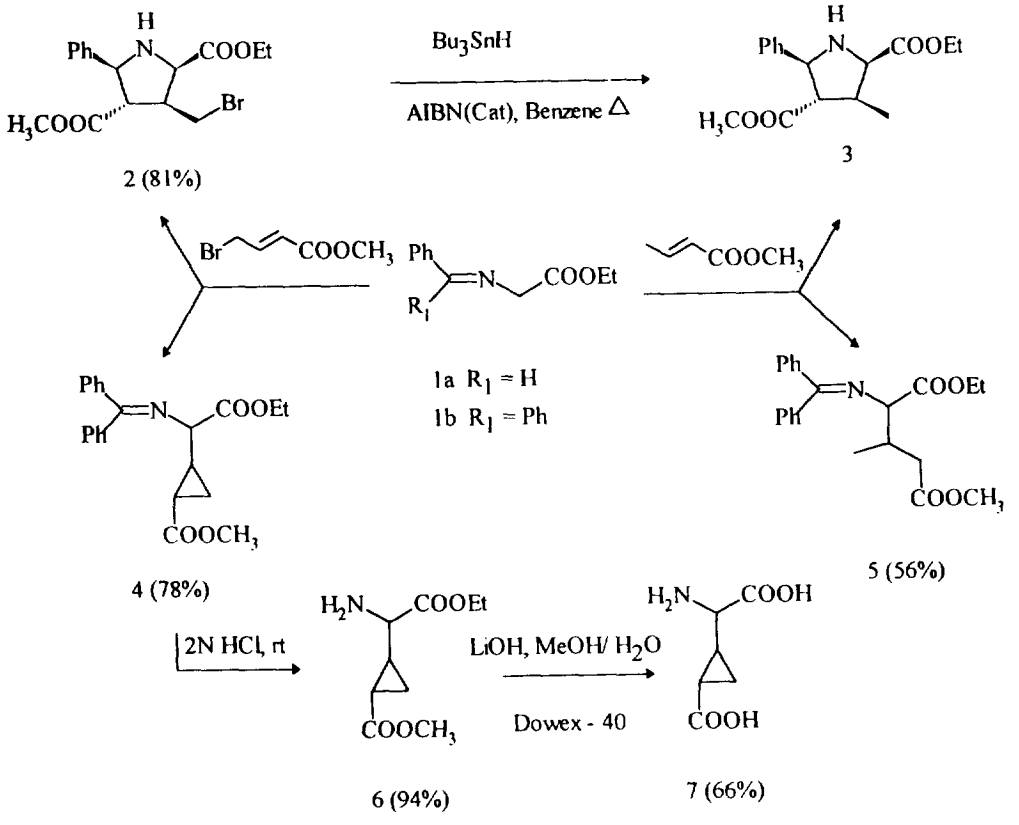
In connection with our synthetic study on Camptothecin, we needed to alkylate Schiff's base of glycine **1b** with methyl bromo crotonate under mild conditions. In a recent study benzaldehyde Schiff's base of glycine ester has been shown to undergo 1,3-dipolar cycloaddition with methylcrotonate under mild conditions ($LiBr/Et_3N$).[1] Under more forcing/drastic 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 $LiBr/Et_3N$, 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 $LiBr/Et_3N$, 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 *Bliglira 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.

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