Hydroxy-L-prolines as asymmetric catalysts for aldol, Michael addition and Mannich reactions

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DOI: http://dx.doi.org/10.3998/ark.5550190.0013.609

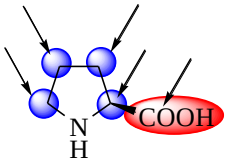
Abstract

The hydroxyprolines (Hyps) **2-6** are tested as organocatalysts for aldol, Michael additions, and Mannich reactions. The results are compared with the well-known analogous L-proline (**1**).The effect of the additional hydroxyl group and chiral center was investigated in the three types of reactions. Catalyst **2** shows an enhancement in the stereoselectivity of the aldol reaction, while **3** in Michael addition and **5** in Mannich reaction give the best results. Derivatives of hydroxyprolines show diversity in the catalytic behavior like **6**.

Keywords: Hydroxyprolines, organocatalysis, chemoenzymatic synthesis, amino acids

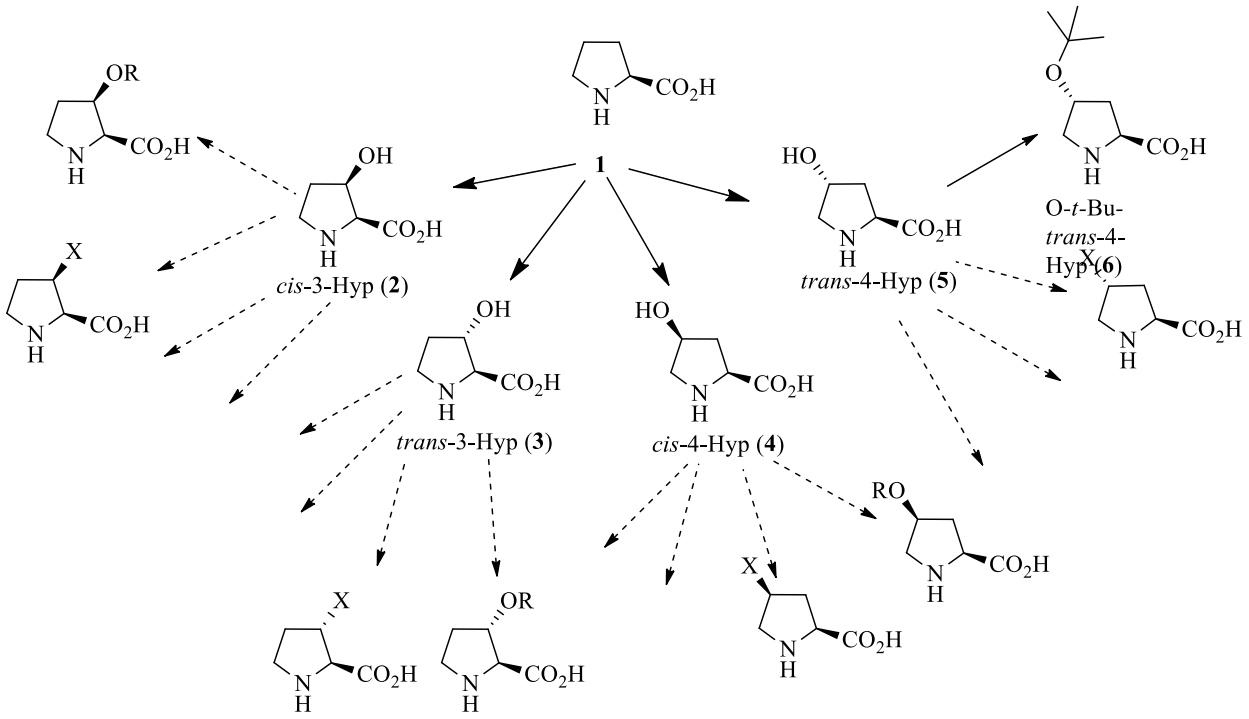
Introduction

L-Proline (**1**) is one of the most well-known organocatalysts.[1] It has been used over a wide range of organic synthesis reactions to obtain enantiomerically or diastereomerically highly enriched asymmetric products.[2-4] It is used as an asymmetric catalyst for the synthesis of β-hydroxy ketones via aldol additions,[5-11] Michael addition reactions,[12-15] and β-amino ketones via Mannich reactions.[16,17] The importance of L-proline (**1**) – more than all other amino acids as catalyst – derives from the fact that it is the only secondary proteinogenic amino acid, and it has a special rigidity which could control the stereochemistry through the formed imine/enamine intermediate.[16-20] Moreover, L-proline is a natural amino acid, and it is available in very pure form and is inexpensive. Modification and derivatization[21-25] of L-proline (**1**) have been the target of many groups working to improve the efficiency of its catalytic behavior. The carboxylic acid moiety[26-29] as well as the ring C-atoms have been the targets of most modifications.



Transformation of the carboxylic acid moiety (red) into an amide or peptide bond was the main idea to obtain more efficient and selective catalysts for the aldol addition.[26-32] The effect of chiral centers on the amide group was also studied. High activity and enantioselectivity were observed for prolinamide derivatives with chiral auxiliaries.[23,33-36] Another thought was to exchange the carboxylate group with other functional groups. An improvement in the activity and stereoselectivity was observed in many cases.[21,22,37-39] The main C-skeleton modifications divide into two main themes: insertion of a heteroatom in the ring, such as sulfur,[9,19] or replacement of C-hydrogen with another group at one or more of the ring positions (blue).[19,40-42]

The hydroxyprolines **2-5** and some of their derivatives like **6** are supposed to be very valuable L-proline derivatives. Hydroxprolines **2-5** are prepared from L-proline via enzymatic hydroxylation reactions. These hydroxylations were carried out by Hüttel and Klein,[43,44] and were performed at gram scales. The *trans*-4-isomers and some derivatives have been known for a long time and tested as catalysts for aldol additions and other reactions.[9,19,45] Very few studies are reported on *cis*-isomers. Several studies were conducted on a Zn-proline complex as an asymmetric catalyst.[46-48] The hydroxyprolines **2-5** and the *tert*-butyl ether **6** are the targets of this study. The results of all hydroxyprolines and their derivatives are compared with L-proline (**1**) under the same conditions. Three asymmetric reactions are studied: aldol addition reactions, Mannich reactions, and the Michael addition reactions. Here, enzymatic[43] or microbial[49-51] access of all regio- and stereoisomeric hydroxyprolines is combined with a thorough investigation of the influence on stereoselectivity in asymmetric catalysis.



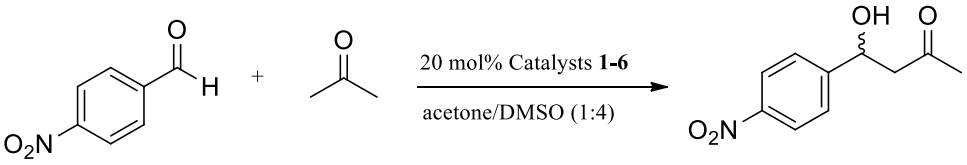
Scheme 1. Hydroxyprolines and some proposed derivatives.

Recently, Müller *et al*. published results of aldol reactions using a Zn-complex of some chorismate metabolites such as *trans*-2,3-CHA and *trans*-3,4-CHA which showed high enantioselectivity in the aldol addition.[52,53] Hüttel *et al*. studied the influence of hydroxyproline derivatives and some other non-proteinogenic amino acids on the aldol addition and on Michael and Mannich reactions.

Results and Discussion

Aldol reaction

A summary of the results of the reaction of 4-nitrobenzaldehyde with acetone is given in Table 1 using the hydroxyprolines **2**-**5** and ether **6** as catalysts. As mentioned above, the *trans*-isomers have been tested as organocatalysts, but the *cis*-isomers are rarely cited in the literature. To make a complete study, it is better to test all hydroxyprolines **2**-**5** under the same conditions.



7 **8** **9**

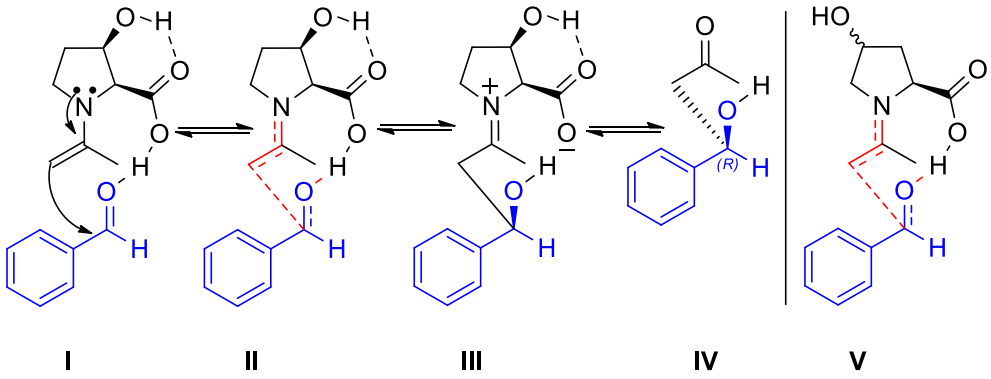
Table 1. Summary of the results of aldol-addition reaction

Entry	Catalyst	Aldol addition reaction		
		Time of reaction (h)	Conversion (%)	*ee* (%) / *Isomer*
1	**1**	24	100	65 / (*R*)-**9**
2	**2**	18	91	74 / (*R*)-**9**
3	**3**	20	75	39 / (*R*)-**9**
4	**4**	20	86	55 / (*R*)-**9**
5	**5**	18	100	57 / (*R*)-**9**
6	**6**	18	89	69 / (*R*)-**9**

All results are compared with the naturally L-proline (**1**). It is obvious from the results that the *cis*-3-hydroxyproline (**2**) gave the best outcome of about 91% conversion and 74% *ee*, while L-proline (**1**) showed a quantitative conversion and 65% *ee*. It seems that the hydroxyl group in the *cis*-isomer **2** affects the transition state via intramolecular hydrogen bonding and assists the attack from one side which enhances the *ee* (Scheme 1, **I**-**IV**). The yield and the *ee* of the *trans*-3-Hyp (**3**) are significantly less under the same conditions. The inversion of stereocenter at position 3 diminishes the stereoselectivity of the aldol addition reaction. The intermolecular

hydrogen bond made by the hydroxy group at position 3 of *trans*-isomer (**3**) could be the reason for this decrease in the enantioselectivity.

In the case of the 4-Hyp, both *cis*-isomer (**4**) and *trans*-isomer (**5**) gave a very good yield and almost similar enantioselectivities, (*ee* of about 55-57%). As the hydroxyl group is located further away from the carboxylic acid group, this could result in weakening of H-bonding in both



Scheme 2. Description of imine/enamine intermediate of the aldol mechamism.

cases by preventing the intramolecular interaction between the hydroxy and the carboxylic acid groups (Scheme 2, **V**). Intermolecular hydrogen bonding is suggested. This led to a decrease in the stereoselectivity by about 10-20% compared with L-proline (**1**) (65% *ee*) and *cis*-3-hydroxyproline (**2**) (74% *ee*).

Some calculations were carried out using the ChemDraw program. They showed an indication of the effect of the intramolecular hydrogen-bonding in both cases of 3-*cis*- (**2**) and 4-*cis*-Hyp (**4**), while the hydroxy groups in both cases of **3** and **5** have no intramolecular interaction (Figure 1)

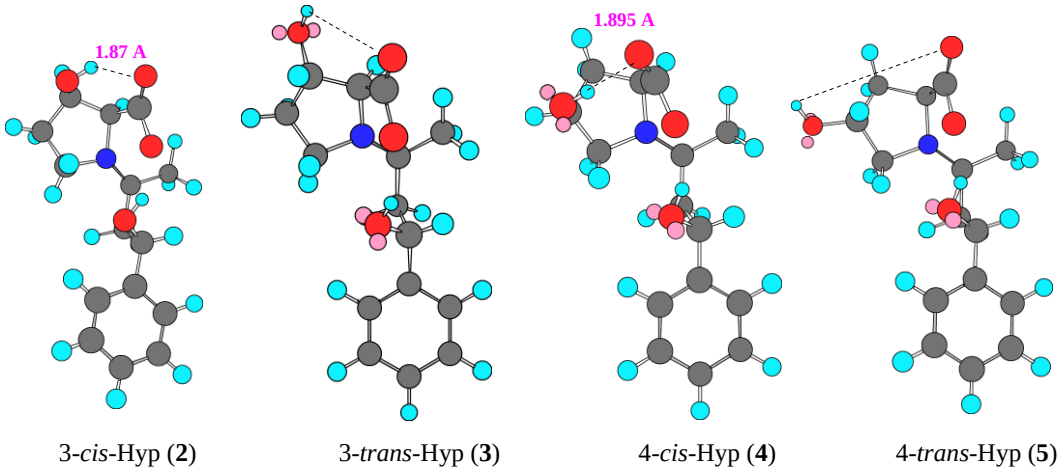
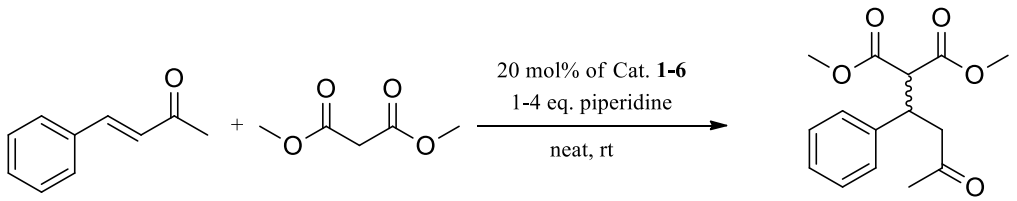


Figure 1. The close contact between the hydroxyl and the carboxylic acid groups in Hyps.

The hydroxyl group in the *trans*-4-Hyp (**5**) is substituted with a bulky *tert*-butyl-group in compound **6**. That results in the enhancement of the *ee* of compound **9**. Ether **6** almost shows the same selectivity (*ee* = 69%, coversion of 89%) as that for L-proline (**1**) (*ee* = 65%, conversion of 100%) and lower conversion. The termination of intermolecular hydrogen bonding is suggested to be responsible for this result. Catalyst **6** behaves as if it were L-proline (**1**). Also, the *tert*-butyl group partially blocks one side and assists the attack to come from the other side.

Michael addition



10 **11** **12**

Table 2. Summary of the results of Michael addition reaction

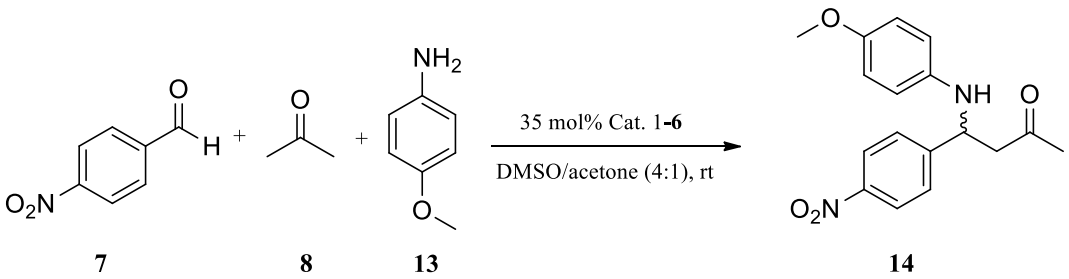
Entry	Catalyst	Michael addition reaction		
		Time of reaction (day)	Conversion (%)	*ee* (%)
1	**1**	2	100	25
2	**2**	2	93	<5
3	**3**	2	100	27
4	**4**	2	92	<5
5	**5**	3	84	<5
6	**6**	2	100	19

Hydroxyprolines **1**-**6** were studied in a Michael addition reaction (Table 2). In general, it seems that the presence of the hydroxy group does affect the enantiomeric excess (*ee*). In most cases, an *ee* of < 5% was observed. In the case of *trans*-3-Hyp (**3**) as catalyst, the *ee* was similar to that observed for L-proline (**1**) itself. It is proposed that the hydroxy group attached to the proline ring disturbs the hydrogen bonding in the imine/enamine intermediate. This results in decreased enantioselectivity. In the case of catalyst **6**, substitution of the hydroxyl group by *tert*-butoxy group enhances the conversion as well as the enantioselectivity of the Michael reaction.

Mannich reaction

L-Proline (**1**) and hydroxyprolines **2-6** were studied as catalysts in the Mannich reaction of 4-nitrobenzaldehyde **7**, acetone **8**, and aniline **13** with conversions in the range 75-95%. Therefore, they almost have the same effect on the yield. However, a dramatic effect is seen on

enantioselectivity. Both *cis*- and *trans*-3-Hyps (**2** and **3** respectively) showed a decrease in the *ee* in comparison with L-proline (**1**). The presence of the hydroxyl group adjacent to the carboxyl group inhibits the selectivity of the reaction because of the strong intramolecular hydrogen bonding (Table 3).



7 **8** **13** **14**

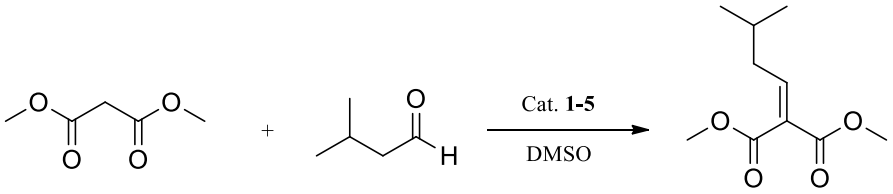
Table 3. Summary of the results of Mannich reaction

Entry	Catalyst	Michael addition reaction		
		Time of reaction (day)	Conversion (%)	*ee* (%)
1	**1**	2	88	54
2	**2**	2	87	20
3	**3**	2	79	42
4	**4**	2	77	61
5	**5**	2	95	75
6	**6**	2	94	27

Whereas in the case of the *cis*- and *trans*-4-Hyps (**4** and **5** respectively), the *ee* is enhanced in comparison with the result of L-proline (**1**). As the distance between carboxyl group and hydroxyl group increases, the intramolecular forces decrease and the selectivity of Mannich reaction increases. In the Hyp-derivative **6**, the substitution of hydroxyl with *t*-butoxy group showed no effect on the conversion and had a strong effect on the stereoselectivity in comparison with its precursor **5** (Table 3)

Knoevenagel reaction

Compounds **1-6** were also tested as catalysts for the Knoevenagel reaction of dimethyl malonate (**15**) and 3-methylbutyraldehyde (**16**). Excellent yields of product dimethyl 2-(3-methylbutylidene)malonate (**17**) were obtained for all catalysts **1-6**. The yields were of 85-95%.



15 **16** **17**

Scheme 3

Conclusions

Hydroxyprolines **2** and **4** are available on a gram scale via chemoenzymatic synthesis while **3**, **5** and **6** are commercially available. Each of these showed variable behaviors as organo-catalysts in aldol addition, Michael, and Mannich reactions. Study of the derivative **6** indicates the diversity in the behavior of each hydroxyproline and its possible derivatives. The substitution of the hydroxy group with another group (X = halogen, OR and NH_2,….. etc.) will generate diverse organo-catalysts with different selectivities and efficiencies toward the three reactions and other organo-synthetic reactions.

Experimental Section

General. All reagents used were of analytical grade. Solvents were dried by standard methods if necessary. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merck). Detection was accomplished by UV light (λ=254 nm). Preparative column chromatography was carried out on silica gel 60 (Merck, 40 - 63 μm). ^{1}H-NMR spectra were recorded on an AMX400 (Bruker BioSpin, Germany). $CDCl_3$ (δ=7.26 ppm), HDO (δ=4.81 ppm) and DMSO (δ=2.50 ppm) were used as internal standards. ^{13}C-NMR spectra were calibrated with $^{13}CDCl_3$ (δ=77.00 ppm) and DMSO (δ=39.43 ppm) as internal standard. *Ee* was determined by chiral phase HPLC (Chiralpak AS-H, Daicel). In the aldol reaction, the eluent was *n*-hexane/isopropanol (70:30), UV 254 nm, flow rate 0.7 mL/min. *R*-isomer, t_R = 13.6 min and *S*-isomer, t_R = 17.3 min. and 25 °C. In the Michael addition reaction, the eluent was *n*-hexane/isopropanol (85:15), UV 254 nm, flow rate 0.7 mL/min. isomer 1, t_R = 12.1 min and isomer 2, t_R = 14.5 min. 25 °C. In the Mannich reaction, the eluent was *n*-hexane/isopropanol (90:10), UV 254 nm, flow rate 1.0 mL/min. isomer 1, t_R = 30.7 min and isomer 2, t_R = 33.5 min. 25 °C.

Aldol reaction

Product (9). *p*-Nitrobenzaldehyde (**7**) (151 mg, 1.0 mmol) was dissolved in 2 mL acetone (**8**). A solution of 23 mg (0.2 mmol) of **1** in 10 mL DMSO was added and the mixture stirred overnight

at rt. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organic layer (the product **9**) was dried over anhydrous Na_2SO_4. ^{1}H NMR (400 MHz, 298 K, ppm, in $CDCl_3$): δ= 8.21 (d, *J* = 8.8 Hz, 2H, H-arom), 7.54 (d, *J* = 8.6 Hz. 2H, H-arom), 5.26 (dt, *J* = 3.7 Hz, *J* = 7.6 Hz, 1H, C*H*-O), 3.58 (d, *J* = 3.3 Hz, 1H, CO-C*H*H), 2.85 (dd, *J* = 3.4 Hz, *J* = 6.1 Hz, 1H, CO-CH*H*) , 2.22 (s, 3H, CO-CH_3), 1.59 (bs, 1H, O*H*). ^{13}C NMR (101 MHz, 298 K, ppm, in $CDCl_3$): δ= 208.47 (C=O), 149.94 (C-arom), 147.26 (C-arom), 126.37 (2 x C-arom), 123.72 (2 x C-arom), 68.86 (C-O), 51.46 (CO-*C*H_2), 30.68 (CO-*C*H_3).

Michael addition

Product (12). Compound **10** (117 mg, 0.8 mmol) was added to 2 eq. of dimethyl malonate (**11**) (211 mg, 1.6 mmol, 183 μL) and mixed. Piperidine (2 eq., 1.6 mmol, 136 mg, 158 μL) was added to the mixture and stirred at rt for 10 min. 5.0 mg (0.04 mmol) of Cat. **1** were added. The reaction mixture was stirred to completion and diluted with ethyl acetate. It was washed twice with water. The organic layer (the product **12**) was dried over anhydrous Na_2SO_4. The reaction was repeated with the same molar ratio using catalysts **2**-**6**. ^{1}H NMR (400 MHz, 298 K, ppm, in $CDCl_3$): δ = 7.22-7.09 (m, 5H, H-arom), 3.89 (ddd, *J* = 5.6 Hz, *J* = 8.4 Hz, *J* = 9.6 Hz, 1H, CH_2-C*H*), 3.65 (s, 3H, O-CH_3), 3.63 (s, 3H, O-CH_3), 3.48 (m, 1H, CO-C*H*-CO), 3.29 (m, 1H, CO-C*H*H), 2.87 (dd, *J* = 5.3 Hz, *J* = 6.9 Hz, 1H, CO-C*H*H), 1.94 (s, 3H, CO-CH_3). ^{13}C NMR (101 MHz, 298 K, ppm, in $CDCl_3$): δ= 205.58 (C=O), 168.24 (C=O), 167.96 (C=O), 167.72 (C-arom), 163.75 (C-arom), 140.10 (C-arom), 128.22 (C-arom), 127.68 (C-arom), 126.95 (C-arom), 56.80 (O-*C*H_3), 52.04 (O-*C*H_3), 46.81(CO-*C*H-CO), 40.13(CO-*C*H_2), 29.99 (*C*H-CH_2), 24.04 (CO-*C*H_3).

Mannich product

Product (**14).** Compound **7** (50 mg, 0.33 mmol) was dissolved in 2 mL of DMSO. 1.1 eq. of compound **13** (44 mg, 0.36 mmol) was added to the solution. 0.5 mL of acetone (**8**) was added to the mixture and stirred at rt for 10 min. 16.0 mg (0.12 mmol) of Cat. **1** were added. The reaction mixture was stirred to completion and diluted with ethyl acetate. The organic layer was washed twice with water. The organic layer (the product **14**) was dried over anhydrous Na_2SO_4. The reaction was repeated with catalysts **2**-**6** using the same molar ratio. ^{1}H NMR (400 MHz, 298 K, ppm, in $CDCl_3$): δ = 8.17 (d, *J* = 8.7 Hz, 2H, H-arom), 7.55 (d, *J* = 8.7 Hz, 2H, H-arom), 6.69 (d, *J* = 8.9 Hz, 2H, H-arom), 6.46 (d, *J* = 8.9 Hz, 2H, H-arom), 4.85 (t, *J* = 6.3 Hz, 1H, C*H*-NH) , 4.23 (bs, 1H, N*H*), 3.69 (s, 3H, OCH_3), 2.95 (d, *J* = 6.3 Hz, 2H, CO-CH_2), 2.15 (s, 3H, CO-CH_3). ^{13}C NMR (101 MHz, 298 K, ppm, in $CDCl_3$): δ= 206.07 (C=O), 152.74 (C-arom), 150.63 (C-arom), 147.16 (C-arom), 140.10(C-arom), 127.38 (C-arom), 124.01(2 x C-arom), 116.39 (C-arom), 115.36 (2 x C-arom), 114.77 (2 x C-arom), 55.60 (O-*C*H_3), 54.63 (N-*C*H), 50.65 (CO-*C*H_2), 30.66 (CO-*C*H_3).

Knoevenagel Reaction

Dimethyl 2-(3-methylbutylidene)malonate (17). 172 μL (1.55 mmol) of 3-methylbutyraldehyde (**16**) was dissolved in 10 mL DMSO. The addition of 23 mg (0.2 mmol) **1** was followed. After 5 min., 459 μL (4.00 mmol) dimethyl malonate (**15)** was added. The mixture was stirred overnight at rt. The reaction mixture was diluted with ethyl acetate and washed twice with water. The organic layer was dried over anhydrous Na_2SO_4. No further purification was needed. 270mg (1.35 mmol, 87%) of product dimethyl 2-(3-methylbutylidene)malonate (**17**) was isolated. The reaction was carried out with cat. **2-6** in the same molar ratio. A yield of 85-90% was obtained. ^{1}H NMR (400 MHz, 298 K, ppm, in $CDCl_3$): δ = 7.07 (t, *J* = 7.9 Hz, 1H, =C*H*), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.21 (dd, *J* = 6.9 Hz, *J* = 7.8 Hz, 2H, CH_2), 1.83 (m, 1H, C*H*(CH_3)$_2$), 0.96 (s, 3H, CH_3), 0.95 (s, 3H, CH_3).

Acknowledgements

The author would like to thank the Institute of Pharmaceutical Sciences, especially Prof. Michael Müller, Dr. Wolfgang Hüttel and Christian Klein. This research work was carried out in the laboratories of Prof. Müller. Hydroxyprolines **2** and **4** were supplied by Hüttel and Klein. the author also thanks DFG and DAAD for the financial support of his residency in Germany and Tafila Technical University (TTU) for the travel grant.

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