Organocatalysis

Dihydroxyacetone in Amino Acid Catalyzed Mannich-Type Reactions**

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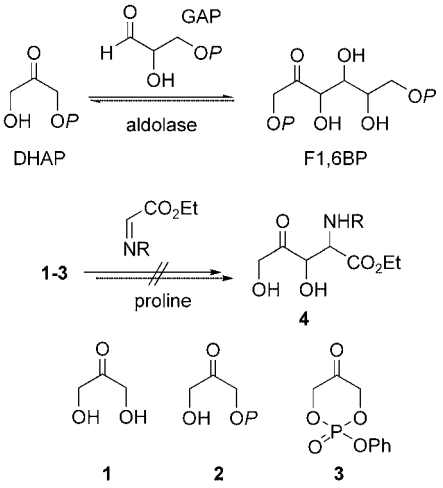
After lying in obscurity for more than 40 years, proline-catalyzed carbonyl reactions have been studied intensively in recent years.[1] Although Martens and co-workers pointed out the enormous potential of these reactions in a Review in 1982, they did not attract significant interest until the studies of List, Barbas, MacMillan, Jørgensen, and others were published.[2] Proline-catalyzed reactions could possibly explain the origin of prebiotic aldol and Mannich products and thus the stereoselective synthesis of carbohydrates. During glycolysis and gluconeogenesis, an aldolase-catalyzed aldol reaction of two C_3 building blocks, 3-glyceraldehyde phosphate (GAP), and dihydroxyacetone phosphate (DHAP) takes place (Scheme 1).[3]



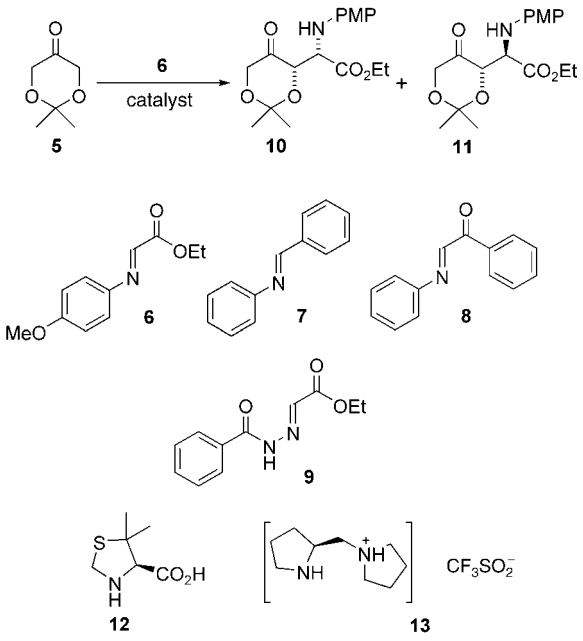
Scheme 1. Dihydroxyacetone and phosphorylated derivatives in aldol and Mannich reactions.

Despite the enormous number of publications dealing with organocatalytic carbonyl reactions, only a few examples can be found in which dihydroxyacetone (DHA, **1**) was used as the C_3 methylene compound in aldol reactions towards carbohydrate precursors.[4,5] Mannich and Mannich-type reactions of DHA are, to the best of our knowledge, unknown.[6] These reactions would offer a very simple approach to azasugar and aminosugar derivatives, which are of considerable biological interest owing to their glycosidase-inhibiting and aminoglycoside-mimicking properties.[7] As a multistep sequence is generally required in the synthesis of these compounds, a simple approach is highly desirable.

Herein we report the use of protected dihydroxyacetone and various imines in Mannich reactions. In this context, we present 2,2,2-trifluoroethanol (TFE) as a highly suitable solvent and describe the application of microwave irradiation to accelerate organocatalytic reactions.[8]

In contrast to hydroxyacetone no reaction could be observed with DHA (**1**) under the conditions provided by List and by Cordova and co-workers (L-proline (30 mol%), DMSO, room temperature).[9] Therefore, we used phosphate-protected dihydroxyacetone derivatives **2** and **3** in preliminary reactions.[10] Unfortunately, no reaction occurred between imine **6** and the methylene compound (Schemes 1 and 2).[11] Subsequently, we used the acetonide **5** of dihydroxyacetone which can easily be synthesized in large amounts in two steps. Acetonide **5** was previous employed in diastereo- and enantioselective aldol reactions as a DHA equivalent.[12] Besides the distinct reactivity, we assumed that a very compact, bicyclic transition state would result with this cyclic ketone, thus leading to high diastereoselectivities.

In the first experiment it could be shown that the desired products **10** (*syn*) und **11** (*anti*) were formed by using protected DHA **5** and imine **6** in the presence of racemic proline (30 mol%) (Scheme 2; Table 1, entry 1 (91:9 d.r.)). Further experiments with L-proline led to identical diastereomeric ratios; the enantioselectivity (82% *ee*) was satisfying.[13] Whereas solvents such as acetonitrile, toluene, and ionic liquids (Table 1, entries 4–6) did not result in notable improvements in stereoselectivites, very polar solvents such as formamide and TFE led to excellent diastereo- and enantioselectivities (Table 1, entries 7, 8). The use of TFE



Scheme 2. Catalyzed Mannich reactions. The reaction conditions are given in Table 1; PMP = *p*-methoxyphenyl.

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Table 1: Results of the Mannich reaction with **5** and **6** (see Scheme 2).

Entry	Catalyst	Conc. [mol%]	Solvent[a]	*t* [h]	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	D,L-proline	30	DMSO	20	RT	46	91:9	–
2	L-proline	30	DMSO	20	RT	37	91:9	82
3	L-proline	30	H_2O	96	RT	34	93:7	34
4	L-proline	30	acetonitrile	40	RT	52	93:7	80
5	L-proline	30	toluene	40	RT	52	92:8	42
6	L-proline	30	$BMIMBF_4$	40	RT	39	89:11	n.d.
7	L-proline	30	formamide	20	RT	54	95:5	96
8	L-proline	30	TFE	20	RT	72	97:3	99
9	L-proline	30	TFE/H_2O (95:5)	20	RT	76	95:5	96
10	L-proline	30	TFE/H_2O (90:10)	20	RT	76	95:5	95
11	L-proline	20	TFE	20	RT	68	96:4	99
12	L-proline	10	TFE	20	RT	75	95:5	95
13	L-proline	5	TFE	20	RT	70	93:7	91
14	L-proline	30	TFE	20	0	44	97:3	97
15	L-proline	30	TFE	20	−20	36	96:4	97
16	DMTC (**12**)	30	TFE	40	RT	28	86:14	n.d.
17	diamine (**13**)	30	TFE			no reaction		

[a] $BMIMBF_4$ = 1-butyl-3-methylimidazolium tetrafluoroborate; TFE = 2,2,2-trifluoroethanol. [b] Yields of isolated products. [c] d.r. determined by GC–MS. [d] *ee* determined by HPLC (Chiralcel OD-H); n.d.: not determined.

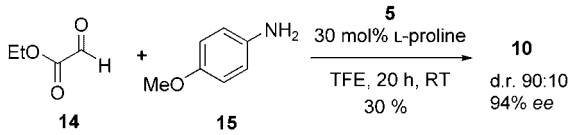
allowed the isolation of the product in 72% yield with reproducible diastereoselectivity (97:3 d.r.) and enantioselectivity (99% *ee*). A slight decrease in the selectivities (95:5 d.r. and 96/95% *ee* (Table 1, entries 9, 10) was observed in TFE/H_2O solvent mixtures (95:5; 90:10). To decrease the amount of proline, we ran further experiments in TFE with decreasing concentrations of catalyst (Table 1, entries 11–13). We proved that the amount of catalyst could be decreased significantly. Only at 5 mol% of L-proline did the stereoselectivity decrease quite drastically. Temperature effects were not observed (Table 1, entries 14, 15).

Other proline-derived catalysts proved to be unsuitable. L-5,5-Dimethylthiazolidine-4-carboxylic acid (DMTC; **12**) resulted in poor selectivities. No reaction occurred in the presence of (*S*)-1-(2-pyrrolidinylmethyl)pyrroline triflate (**13**) (Table 1, entries 16, 17). Disappointingly, imines **7** and **8** and hydrazone **9**[14] did not react with **5**.

One disadvantage of many proline-catalyzed reactions is the long reaction time. We therefore tried to accelerate the reaction under the action of microwaves. The results of the microwave-assisted organocatalytic Mannich reactions are listed in Table 2. Consistent with the previously observed results, TFE was once again the solvent of choice. After only 10 min **10** was obtained in 72% yield with high diastereo- (90:10 d.r.) and enantioselectivities (95% *ee*). A decrease in the irradiating power led to a lower yield, although the selectivities remained the same. The use of DMSO or formamide as solvent led to a significant decrease in the yield and diastereoselectivity.[15]

The Mannich-type reaction could also be carried out as a three-component process (Scheme 3). The reaction of glyoxylate **14**, *p*-anisidine (**15**), and **5** yielded **10** in 30% yield with selectivities comparable with those of the two-component reaction.

The relative configuration of all the products was determined by NMR spectroscopy. The *syn* conformation of the main diastereomer can be concluded based on the ^3J coupling constant (CHO-CHN) of 2.3 Hz and on NOE interactions.[16] This is consistent with results from other Mannich-type reactions. Therefore, it is possible to assume the same transition state proposed by Cordova.[6]



Scheme 3. Three-component reaction to **10**.

In conclusion nitrogen-containing carbohydrate derivatives were obtained with very good stereoselectivities from DHA derivatives. Furthermore it is possible to improve existing protocols (shorter reaction times, less catalyst) by using 2,2,2-trifluoroethanol as solvent and microwave-assisted procedure.[17]

Table 2: Results of the microwave-assisted Mannich reaction of **5** and **6** in the presence of L-proline (30 mol%).[a]

Solvent	*t* [min]	*E* [W][b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
TFE	5	300	63	89:11	94
TFE	10	300	72	90:10	94
TFE	10	100	64	90:10	95
DMSO	10	300	18	92:8	n.d.
formamide	5	300	40	83:17	n.d.
formamide	10	300	38	80:20	n.d.

[a] All reactions were carried out in sealed 10-mL tubes. [b] Maximal irradiated power. [c] Yields of isolated products. [d] Determined by GC–MS. [e] Determined by HPLC (Chiralcel OD-H).

Experimental Section

Solvent (1 mL) and L-proline (35 mg, 0.3 mmol) were stirred at room temperature for 3 min, before **5** (130 mg, 1.0 mmol) was added. After 15 min **6** (207 mg, 1.0 mmol) was added. The reaction mixture was stirred for 20 h. A saturated solution of NH_4Cl (1.0 mL) was added, and the mixture was extracted with ethyl acetate (2 × 15 mL). The combined organic extracts were dried with Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography through silica gel (petroleum ether/ethyl acetate 3:1) to give the product **10** as an oil. R_f = 0.8 (petroleum ether/ethyl acetate 3:2); HPLC (Daicel Chiralcel OD-H, hexane/2-propanol 90:10, 1.0 mL min^{-1}, λ = 254 nm); $[\alpha]_D^{20} = -107.0$ (c = 0.2, ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.24 (t, ^3J = 7.1 Hz, 3H; Me), 1.44 (s, 3H; Me), 1.49 (s, 3H; Me), 3.73 (s, 3H; Me), 4.02 (d, ^2J = 16.5 Hz, 1H; CH*H*, 5-H), 4.13 (dq, J = 7.1, 10.8 Hz, 1H; O*CH*$_2$CH$_3$), 4.24 (dq, J = 7.1, 10.8 Hz, 1H; O*CH*$_2$CH$_3$), 4.30 (dd, J_1 = 1.6 Hz, J = 16.5 Hz, 1H; CH*H*, 5-H), 4.59 (d, J = 2,3 Hz, 1H; 2-H), 4.74 (dd, J = 1.6, 2.3 Hz, 1H; 3-H), 6.7–6.8 ppm (m, 4H; Ar-H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.2 (q), 23.3 (q), 24.2 (q), 55.5 (q), 58.8 (d), 61.5 (t), 67.0 (t), 76.4

(d), 100.7 (s), 114.5 (d, 2C), 116.8 (d, 2C), 140.7 (s), 153.3 (s), 171.1 (s), 206.0 ppm (s); HRMS [M+Na^+]: 337.1423 (calcd), 337.1427 (found).

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