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Proline imidazolidinones and enamines in Hajos–Wiechert and Wieland–Miescher ketone synthesis

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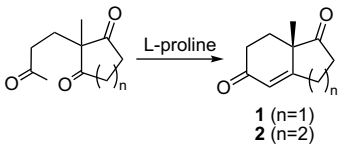
ABSTRACT

Readily available aromatic prolinamides obtained from the acid chloride of proline hydrochloride and anilines induce large enantiomeric excesses in intramolecular aldol condensations. Imidazolidinones derived from the reaction of the catalyst and enamines have been found as intermediates in these reactions.

1. Introduction

Since its discovery nearly 40 years ago,[1] the proline-catalyzed intramolecular aldol reaction has been applied to several substrates and building blocks such as the Hajos–Wiechert (Parrish) ketone (**1**) and the Wieland–Miescher ketone (**2**) (Scheme 1). These compounds present interesting industrial applications.[2]



Scheme 1. Proline-catalyzed intramolecular aldol cyclization.

While proline is a good catalyst for the enantioselective synthesis of the Hajos–Wiechert ketone **1**, the results are poor in the six-membered ring closure of the Wieland–Miescher compound.[3]

The mechanisms of proline catalysis are still a matter of discussion[4] and four different ones have been proposed. A reasonable mechanism that accounts for the observed enantioselectivity is the one proposed by Houk and List,[5] in which an intermediate enamine attacks the carbonyl group assisted by the proline carboxylic acid. If this is the case, proline might not be an ideal catalyst for the following reasons:

- Protonation of the reactive intermediate always takes place from the *syn* carboxylic acid, while *anti* carboxylic acids are more stable.[6]
- Proline shows a zwitterionic structure and is sparingly soluble in apolar organic solvents. A higher solubility would be desirable.
- Nucleophilic attack from the proline nitrogen is necessary to generate the enamine intermediate, but the concentration of the basic amine is very low due to the high acidity of the proline carboxylic acid.

An alternative strategy to overcome these drawbacks is to use proline derivatives that exhibit better solubility and the appropriate acidity. In fact, proline amides have already shown promising results in these cyclizations and intermolecular aldol condensations.[7]

To study the effect of the NH acidity several proline amides were prepared starting from the acid chloride of L-proline hydrochloride and substituted anilines as shown in Table 1.

2. Results and discussion

We evaluated the catalytic properties of these prolinamides (**4**–**8**) in the Hajos–Parrish reaction and compared them with the

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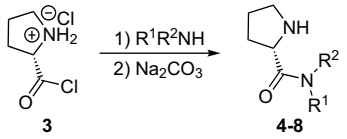
Table 1
Structure of L-prolinamides **4**–**8**



Prolinamide	R^1	R^2
4	4-Methylphenyl	H
5	4-Nitrophenyl	H
6	3,5-Bis(trifluoromethyl)phenyl	H
7	3,5-Bis(methoxycarbonyl)phenyl	H
8	Phenyl	Me

catalytic activity of L-proline butyl ester (**9**) and that of L-proline itself (**10**). The results are summarized in Table 2.

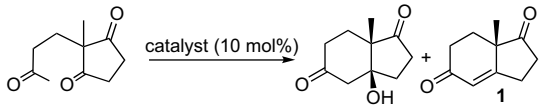
As shown in Table 2, rate acceleration and improvement in enantioselectivity were observed when using more acidic prolinamides. Thus, a comparison between catalyst **7** with the 3,5-bis(methoxycarbonyl)phenyl group and catalyst **4** with a 4-methylphenyl unit revealed the more acidic prolinamide **7** as a more active (rate acceleration of more than twofold) and more selective (98 vs 91% ee) catalyst (entries 1 and 4). These results were consistent with the Houk and List[5] enamine mechanism for the intramolecular aldol reaction (Scheme 2).

Additionally, the dehydration step seemed to be related to the NH acidity of prolinamides (Scheme 3). While the previously mentioned toluidine catalyst **4** yielded mainly the aldol-type product (58%, entry 1) the isophthalic acid derivative **7** afforded the highest amount of the α,β-unsaturated ketone (40%, entry 4) among all the prolinamides studied.

To gain further insight into the reaction mechanism, we explored alternative catalyst modifications, preparing the tertiary prolinamide **8** and the proline butyl ester **9**. These compounds lack the amide NH, involved in the intramolecular hydrogen bonds depicted in Schemes 2 and 3. This NH proved to be essential for high enantiomeric induction since catalysis with **8** or **9** (entries 5 and 6) afforded low enantioselectivities (ee <24%).

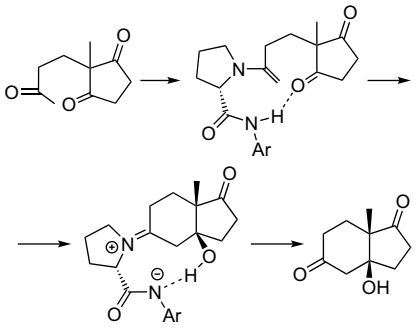
Catalysis by the 3,5-bis(trifluoromethyl)phenyl derivative **6** proved to be an unexpected challenge owing to the complexity of the ^{1}H NMR spectra. To clarify the structure of the chemical species involved in the catalytic process, we analyzed the reaction

Table 2
Results obtained in the preparation of the Hajos–Wiechert (Parrish) ketone **1** in chloroform at 20 °C at 1.0 M concentration of triketone in the presence of 10 mol% catalyst

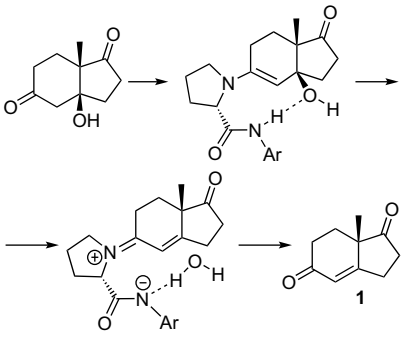


Entry	Catalyst	Conversion[a] (%)			Time (h)	ee[b] (%)
		Aldol	Ketone **1**	Total		
1	**4**	58	14	72	330	91
2	**5**	57	35	92	95	92
3	**6**	72	20	92	101	95
4	**7**	44	40	84	167	98
5	**8**	72	23	95	24	−23
6	**9**	52	46	98	18	17
7	**10**	49	42	91	316	63

[a] The yields of aldol-type and dehydrated products were determined through ^{1}H NMR integration.
[b] Enantiomeric excess of the Hajos–Wiechert ketone **1** was determined by HPLC analysis.



Scheme 2. Proposed mechanism of the catalyzed intramolecular aldol reaction by prolinamides **4**–**7** to give the aldol product.



Scheme 3. Proposed mechanism for the dehydration of the aldol catalyzed by prolinamides **4**–**7** to yield the Hajos–Wiechert ketone **1**.

mixture using ^{1}H and ^{13}C NMR working at 0 °C to prevent elimination.

After 2 h, the recorded ^{1}H NMR spectrum displayed three peaks for the quaternary methyl group protons at 1.10, 1.20, and 1.02 ppm, which were assigned to the starting material, the aldol-type product, and a new compound, respectively. The composition of the reaction mixture established by integration of the NMR signals was 12% of 2-methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione, 12% of the aldol-type product, and 76% of a new compound, **11**.

The structure of intermediate **11** (Fig. 1) was elucidated on the basis of its spectroscopic properties (NMR and MS, see Experimental section). Key data to assess this structure were the quasi-molecular ion at *m*/*z* 491 and the presence of two quaternary carbons in the ^{13}C NMR spectrum at 77.9 and 82.5 ppm, corresponding to the aminal carbon C-5 and the tertiary alcohol function C-3a, respectively.

The formation of the imidazolidinone **11** in the reaction medium was not completely unexpected. Oxazolidinones and imidazolidinethiones have already been found in the reaction of carbonyl compounds with proline and proline thioamides.[4,8] Nevertheless, in the proline-catalyzed reactions these intermediates are difficult to detect, while in the catalysis with these prolinamides the imidazolidinone is an unstable compound but can be easily studied.

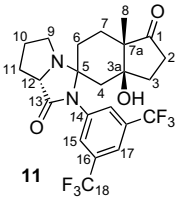
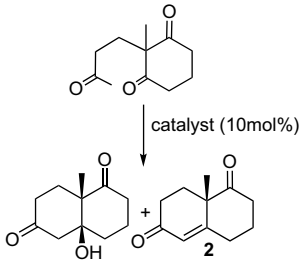


Figure 1. Proposed structure of the intermediate compound **11** in the synthesis of the Hajos–Wiechert ketone **1**, catalyzed by **6**.

Table 3
Enantiomeric excess obtained with prolinamide catalysts **4**–**8**, proline butyl ester **9**, and L-proline **10**, in the preparation of the Wieland–Miescher ketone **2** in chloroform at 20 °C at 1.0 M concentration of triketone in the presence of a 10 mol % catalyst



Entry	Catalyst	ee[a] (%)
1	**4**	94
2	**5**	87
3	**6**	96
4	**7**	92
5	**8**	−1
6	**9**	9
7	**10**	60

[a] The enantiomeric excess of the Wieland–Miescher ketone **2** was determined by HPLC analysis.

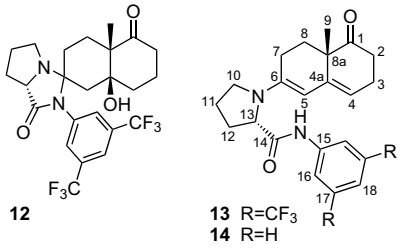


Figure 2. Intermediate compounds in the preparation of the Wieland–Miescher ketone **2** when catalyzed by aromatic prolinamides.

Cyclization of 2-methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione to yield the Wieland–Miescher ketone (**2**) with prolinamides **4**–**8** afforded different results. While many other catalysts, as the ones shown by Barbas,[9] yielded only the aldol-type product, these prolinamides rendered the unsaturated ketone **2**, and the aldol intermediate cannot be easily detected in the ^{1}H NMR spectra. The reaction rate is still related to the acidity of the amide proton, but the enantiomeric excesses do not correlate clearly with this parameter (Table 3).

Reaction with the 3,5-bis(trifluoromethylphenyl) prolinamide **6**[10] revealed an initial stage in its ^{1}H NMR spectrum in which the aldol imidazolidinone **12** was formed. Almost simultaneously, a compound **13** started to accumulate. HPLC–MS of an aliquot of this mixture afforded a peak with a quasi-molecular ion at *m*/*z* 487. The presence of olefinic signals (a singlet at 5.68 ppm and a triplet (J=4 Hz) at 5.17 ppm in ^{1}H NMR, and 99.5 ppm for the enamine CH in ^{13}C NMR) suggested the structure shown in Figure 2 for compound **13**. While compound **12** disappeared from the reaction mixture after 6 h, the enamine **13** was still present 24 h later at 20% molar ratio.

Working under conditions similar to those described by Stork,[11] enamine **14** could be obtained in good yield.

3. Conclusion

Prolinamides are among the best catalysts for the Hajos–Parrish and Wieland–Miescher reactions. In these aldol cyclizations catalyzed by aromatic prolinamides, the phenyl ring should be activated with electron withdrawing groups to improve the reaction rates and, in most cases, increase also the enantioselectivities. The behavior of triketones 2-methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione and 2-methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione is different: while cyclopentanedione forms preferentially the imidazolidinone, cyclohexanedione yields the enamine derivative. These enamine compounds can be useful building blocks in the synthesis of steroids and other natural products.

4. Experimental

4.1. General

IR spectra were recorded with a Nicolet IR100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at room temperature with Bruker WP-200-SY, Varian Mercury VS. 2000 or Bruker Advance DRX spectrometer in deuterated chloroform (unless otherwise stated). J values are reported in hertz and chemical shifts are reported in parts per million with the solvent signal as an internal standard. Mass spectra were recorded with an Applied Biosystems QSTAR XL or Waters ZQ 4000. Optical rotations were determined in a PERKIN ELMER digital polarimeter 341. Melting points were taken on a Stuart Cientific SM3P capillary apparatus. The enantiomeric ratio of products was determined by chiral HPLC analysis (Chiralpak® AD-H column, 150×4.6 mm, eluent *n*-hexane/^{i}PrOH, 80:20 v/v %).

4.2. L-Proline chlorhydrate acid chloride (3)

This compound was prepared according to the Fischer procedure.[12] Phosphorus pentachloride (38.0 g, 182 mmol) was suspended in chloroform (100 mL) under argon in an ice–salt bath. L-Proline (20.0 g, 173 mmol) was added to the reaction mixture in small portions, keeping the reaction temperature below 10 °C. After ca. 30 min, the crystalline solid was filtered under argon and dried under vacuum: 25.3 g (149 mmol), 86% yield. Compound **3** is stable under argon and at −20 °C for several months.

4.3. General procedure for the preparation of the prolinamide catalysts 4–8

The appropriate amine (13 mmol) was dissolved in 30 mL of dry THF under argon atmosphere. L-Proline chlorhydrate acid chloride **3** (2.67 g, 15.7 mmol) was added and the mixture was stirred for a few minutes. The progress of the reaction was monitored by TLC and more proline chlorhydrate acid chloride could be added if necessary. When the reaction was finished, a small amount of H_2O (5 mL) was added to hydrolyze the excess of acid chloride **3**. THF was then removed under reduced pressure, the residue dissolved in ethyl acetate, and washed with saturated sodium carbonate solution. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated to dryness. Column chromatography on silica gel (CH_2Cl_2/methanol) gave the desired prolinamides.

Prolinamides **4** and **5** are known and their physical and spectroscopic properties are consistent with literature.[7i]

4.4. (*S*)-*N*-(3,5-Bis(trifluoromethyl)phenyl)pyrrolidine-2-carboxamide (6)

Pale yellow oil, yield 68%. $[\alpha]_D^{25}$ −37.52 (*c* 1.33, $CHCl_3$); ^{1}H NMR: δ 1.74–1.81 (m, 2H), 2.01–2.14 (m, 1H), 2.15–2.30 (m, 1H), 2.95–3.2 (m, 2H), 3.90 (dd, J_1=9 Hz, J_2=3 Hz, 1H), 7.58 (s, 1H), 8.12 (s, 2H), 10.13 (s, 1H, NH) ppm; ^{13}C NMR: δ 26.5, 30.9, 47.6, 61.2, 117.3, 119.1, 126.1, 132.1, 139.4, 174.3 ppm; IR (ν): 1625, 1696, 2922, 3247 cm^{-1}; ESIHRMS calcd for $C_{13}H_{13}N_2OF_6$ $[M+H]^+$: 327.0927, found: 327.0904.

4.5. (*S*)-*N*-(3,5-Bis(methoxycarbonyl)phenyl)pyrrolidine-2-carboxamide (7)

White solid, yield 76%; mp: 130–131 °C; $[\alpha]_D^{25}$ −30.18 (*c* 1.12, EtOH); ^{1}H NMR: δ 1.73–1.80 (m, 2H), 1.90–2.30 (m, 2H), 2.90–3.10 (m, 2H), 3.85–3.96 (m, 1H), 3.94 (s, 6H), 8.40 (s, 1H), 8.46 (s, 2H) ppm; IR (ν): 1462, 1586, 1729, 2854, 2924 cm^{-1}; ESIHRMS calcd for $C_{15}H_{19}N_2O_5$ $[M+H]^+$: 307.1288, found: 307.1284.

4.6. (*S*)-*N*-Methyl-*N*-phenyl-pyrrolidine-2-carboxamide (8)

White solid, yield 83%; mp: 96–98 °C; $[\alpha]_D^{25}$ −37.80 (*c* 1.29, $CHCl_3$); ^{1}H NMR: δ 1.52–1.68 (m, 2H), 2.67 (m, 2H), 2.80–3.15 (m, 2H), 3.20 (s, 3H), 3.46–3.60 (m, 1H), 7.19 (dd, J_1=6 Hz, J_2=1.4 Hz, 2H), 7.35–7.43 (m, 3H) ppm; ^{13}C NMR: δ 26.9, 31.8, 38.0, 48.0, 58.8, 127.9 (×2), 128.3, 129.9 (×2), 143.3, 174.6 ppm; ESIHRMS calcd for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1335, found: 205.1323.

4.7. Preparation of L-proline-*n*-butyl ester (9)

L-Proline (5 g, 43.4 mmol), thionyl chloride (5 mL, 68 mmol), and *n*-butanol (50 mL) were refluxed together for 2 h. The solvent was removed under reduced pressure and the crude residue was extracted with ethyl acetate (50 mL) and added to aqueous sodium carbonate (10% w/v, 100 mL). The organic layer was dried over Na_2SO_4, and the organic solvent was evaporated to dryness to afford butyl ester **9** as an oily compound (85% yield). $[\alpha]_D^{25}$ −37.86 (*c* 1.38, $CHCl_3$); ^{1}H NMR: δ 0.90 (t, *J*=7.2 Hz, 3H), 1.29–1.40 (m, 2H), 1.56–1.89 (m, 5H), 2.03–2.20 (m, 1H), 2.81–2.92 (m, 1H), 3.02–3.11 (m, 1H), 3.71 (dd, J_1=8.8 Hz, J_2=5.8 Hz, 1H), 4.09 (t, *J*=6.7 Hz, 2H) ppm; ^{13}C NMR: δ 13.9, 19.3, 25.7, 30.5, 30.9, 47.3, 60.0, 64.9, 175.8 ppm; IR (ν): 1469, 1677, 1742, 2858, 2917 cm^{-1}; ESIHRMS calcd for $C_9H_{18}NO_2$ $[M+H]^+$: 172.1332, found: 172.1326.

4.8. Preparation of imidazolidinone 11

2-Methyl-2-(3-oxobutyl)-cyclopentane-1,3-dione (224 mg, 1.23 mmol) was dissolved in 0.4 mL of $CDCl_3$ and mixed with 393 mg (1.20 mmol) of the prolinamide catalyst **6**. The reaction mixture was transferred to an NMR tube and allowed to react at 0 °C. After 2 h, the ^{1}H NMR spectrum recorded displayed the presence of the imidazolidinone **11** in 76% yield, according to the integration of the NMR signals. ^{1}H NMR: δ 0.95 (s, 3H, H-8), 1.50–2.50 (m, 14H), 3.10 (m, 2H, H-9), 4.10 (dd, 1H, H-12), 7.43 (s, 2H, H-15), 8.06 (s, 1H, H-17) ppm; ^{13}C NMR: δ 19.0 (C-8), 24.9 (C-7), 25.4 (C-10), 28.9 (C-6), 29.2 (C-3), 30.6 (C-2), 33.4 (C-11), 42.8 (C-4), 47.1 (C-9), 52.3 (C-7a), 63.2 (C-12), 77.9 (C-3a), 82.5 (C-5), 122.0 (C-17), 122.7 (C-18, q, *J*=275 Hz), 129.8 (C-15), 132.8 (C-16, q, *J*=35 Hz), 137.2 (C-14), 176.3 (C-13), 217.8 (C-1); ESI-MS *m*/*z* 491.3 $[M+H]^+$.

4.9. (*S*)-*N*-Phenyl-pyrrolidine-2-carboxamide (15)

Freshly distilled aniline (11.8 mL, 129.4 mmol) was dissolved in dry THF (50 mL) under argon atmosphere and in an ice–salt bath. Compound **3** (11 g, 64.7 mmol) was added in small portions and the progress of the reaction was monitored by TLC. Once the reaction was finished, it was poured into 100 mL of water, Na_2CO_3 (20 g, 188 mmol) was added, and stirred. Steam distillation and cooling afforded, after filtration, the pure compound **15** in 81% yield as a white solid. Prolinamide **15** is a known compound and its physical and spectroscopic properties are consistent with literature.[7j]

4.10. Preparation of enamine 14

2-Methyl-2-(3-oxobutyl)-cyclohexane-1,3-dione (530 mg, 2.7 mmol) and aniline prolinamide **15** (513 mg, 2.7 mmol) were dissolved in toluene (5 mL) and allowed to react at 40 °C and 20 mmHg for 2 h. Additional toluene portions were added under argon atmosphere when the reaction mixture turned viscous. Diethyl ether (20 mL) was then added and the mixture was cooled to −80 °C. The precipitate of the product was filtered under argon (crystals melted before reaching room temperature and decomposed in the presence of oxygen) and dried under vacuum (0.1 mmHg, 100 °C, 3 h) to obtain the enamine **14** (600 mg, 65% yield). $[\alpha]_D^{25}$ −124 (*c* 0.62, $CHCl_3$); ^{1}H NMR: δ 1.20 (s, 3H, H-9), 2.74–1.58 (m, 12H), 3.20 (q, *J*=9.6 Hz, 1H, H-10), 3.58 (t, *J*=9 Hz, 1H, H-10), 4.07 (dd, J_1=9 Hz, J_2=3 Hz, 1H, H-13), 5.05 (s, 1H, H-5), 5.34 (t, *J*=4.8 Hz, 1H, H-4), 7.10 (t, *J*=8 Hz, 1H, H-18), 7.29 (t, *J*=8 Hz, 2H, H-17), 7.48 (d, *J*=8 Hz, 2H, H-16), 8.16 (s, 1H, NH) ppm; ^{13}C NMR: δ 22.2 (C-9), 23.9 (C-3, C-11), 28.9 (C-12), 31.3 (C-8), 35.7 (C-2), 44.8 (C-8a), 49.1 (C-10), 63.6 (C-13), 99.9 (C-5), 115.6 (C-4), 119.8 (C-18), 124.4 (C-17), 128.9 (C-16), 137.3 (C-4a), 139.5 (C-15), 142.3 (C-6), 172.1 (C-14), 215.4 (C-1); IR (ν): 694, 1716, 2923, 3285 cm^{-1}; ESIHRMS calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$: 351.2067, found: 351.2054.

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Supplementary data

^{1}H NMR, ^{13}C NMR, 2D NMR (COSY, HMQC, HMBC), and HRMS spectra of enamine **14** are provided. HRMS of prolinamides **6**–**8** and butyl ester **9** are also included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.050.

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