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Recyclable L-proline organocatalyst for Wieland–Miescher ketone synthesis

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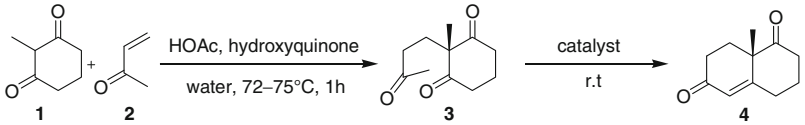
Abstract. Wieland–Miescher ketone **4** was synthesised using L-proline catalyst in the ionic liquid medium via non-selective conjugated addition reaction followed by an enantioselective intermolecular Aldol condensation reaction of triketone **3** intermediate. Short reaction time, recycling of the catalyst, good yield and selectivity are major outcomes of this proposed protocol.

Keywords. L-proline; ionic liquid; Wieland–Miescher ketone.

1. Introduction

Wieland–Miescher ketone analogues are very useful building blocks to synthesise various biologically active compounds such as steroids, terpenoids and taxol.[1] Wieland–Miescher ketone analogues can be synthesized via two different methods (Hajos–Parrish–Eder–Sauer–Wiechert reaction and Robinson annulation reaction).[1] Various catalysts such as antibody 38 C2 (96% ee),[2a] β-amino acid (1*R*,2*S*)-cispentacin (86% ee),[2b] prolinethiomides (86% ee),[2c] etc. were tested to improve the yield and stereoselectivity of the Wieland–Miescher ketone analogue synthesis.[1b] Hanessian *et al* documented that *cis*-(2*S*, 4*S*, 5*S*)-4, 5-methanoproline as an alternative catalyst of L-proline, offers the Wieland–Miescher ketone analogues with 93% enantiomeric excess along with good yield, whereas catalysis with *trans*-(2*S*, 4*S*, 5*S*)-4,5-methanoproline proceeded at much slower rate than L-proline and offers enone with lower selectivity (83% ee).[3] There are relatively few examples where primary amino acids were used as enantioselective catalyst for this reaction such as L-phenylalanine gave (*S*) enone 85% yield with 25% e.e., while L-*tert*-leucine offers (*S*)-ketone with higher yield (95%) but lesser enantiomeric excess (only 2%).[4a] Various proline derivatives such as D-proline (6 days, 82% yield), L-proline (5 days, 56% yield) etc. were also tested with or without solvent system to catalyse the Wieland–Miescher ketone synthesis.[4b–h] Despite these numerous investigations, L-proline remains the most interesting catalyst known for this reaction[4b–h,5] (scheme 1), but along with L-proline and other alternative organocatalysts for Wieland–Miescher ketone analogues synthesis suffers from several drawbacks such as long reaction time, high catalyst loading, low catalyst solubility, requirement of polar solvents (Dimethyl sulfoxide (DMSO) and Dimethylformamide (DMF)), costly starting materials for catalyst synthesis, tedious work-up procedure at product isolation step, etc. Various protocols along with ionic liquids, have been reported by different groups time to time in order to overcome the above mentioned demerits of organocatalysed reactions.[6,7] Kodo *et al.* studied polymer bound (*S*)-proline as catalyst[8] while Agami *et al.* described proline catalysed aldol-cyclodehydrations of acyclic diketones.[9] *D*-phenylanaline and *D*-camphorsulfonic acid was tested in [hmim] PF_6 along with dimethylimidazolidinone was tested for Wieland–Miescher ketone analogues synthesis.[10] Although, 81% yield and 74% ee



Scheme 1. Two-step synthesis of Wieland–Miescher ketone **4**.

along with five times recycling of the catalytic system were the major outcomes of this process, the proposed protocol suffers high catalyst loading, requirement of polar solvent (as co-solvent), longer reaction time and continuous drop in yield and selectivity during recycling of the catalytic system, etc.

In this report, we optimized the reaction conditions of the L-proline-catalysed Wieland–Miescher ketone **4** synthesis. During the reaction, L-proline was found active, recoverable and relatively inexpensive in [pyC_4]NTf_2 with respect to conventional solvents. High polarity of ionic liquid is expected to work as an activating and stabilizing solvent for the L-proline to catalyse Wieland–Miescher ketone **4**.

2. Experimental

All the chemicals were purchased from Sigma Aldrich and SD fine chemicals. Commercially supplied reagents were used as provided. Organic solvents were dried up as per their specifications. The work-up and purification procedure were carried out with reagent-grade solvents. Nuclear magnetic resonance (NMR) spectra were recorded on standard Bruker 300WB spectrometer with an Avance console at 300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively. Enantiomeric excesses were determined by chiral-phase HPLC: Waters 600E System Controller and a Waters 996 Photodiode Array Detector Column with Chiralcel OD-H column from Daicel Chemical Industries Ltd., eluting with n-hexane and ethyl acetate. Ionic liquids were synthesised as per their standard reported procedure.[11] The detailed ^{1}H NMR and ^{13}C NMR were found similar as per reported data.[7]

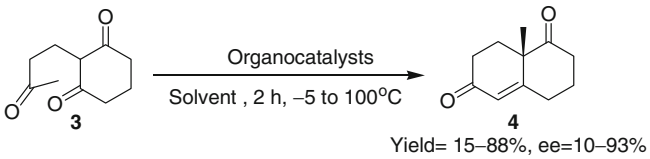
2.1 *General experimental procedure*

2.1a *2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione or triketone **3***: A 100 mL, round-bottomed flask equipped with a thermometer and a reflux condenser capped with an argon-inlet tube was charged with 1.26 g (10 mmol) of 2-methylcyclohexane-1, 3-dione **1** and 10 mL of distilled water. To the well-stirred suspension were added 0.023 mL of acetic acid, 0.008 g of hydroquinone and 1.42 g (20 mmol) of freshly distilled methyl vinyl ketone **2**. The reaction mixture was stirred under argon at 72–75°C for 1 h, cooled to room temperature, treated with sodium chloride (1.03 g), and poured into a separatory funnel containing ethyl acetate (4 × 5 mL). The organic phase was collected and aqueous phase was extracted twice with ethyl acetate (2 mL each time). The combined extracts were further washed with two 20 mL portions of saturated brine, dried over anhydrous magnesium sulphate, filtered, and concentrated. The residue was further purified via column chromatography using ethyl acetate and the hexane mixture (1:2) which offers the titled product **3** as pale-yellow oil in good yield (1.78 g, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) 2.53–2.78 (m, 4H), 2.23–2.38 (m, 2H), 2.09 (s, 3H), 1.81–2.07 (m, 4H), 1.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 17.8, 20.2, 29.7, 30.1, 37.9, 38.5, 64.5, 207.7, 210.2.

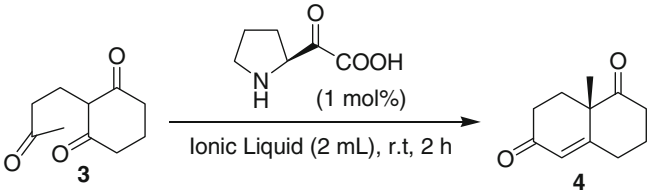
2.1b *(S)-8a-Methyl-3, 4, 8, 8-tetrahydro-1, 6 (2H, 7H)-naphthalen edione (3-S) **(4)***: 50 mL, one-necked, round-bottomed flask, was charged with L-proline (0.5–1.5 mol%) or other catalyst and a solution of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione **3** (1 mmol) in ionic liquid (1–3 mL) or organic solvent (2 mL) or water (2 mL). The mixture was allowed to stir at room temperature for 2 h. Further, volatile organic materials was evaporated from the reaction slurry under vacuum. The reaction product was further extracted with diethyl ether (5 × 2 mL) by vigorous stirring followed by decantation of the upper diethyl ether layer. Evaporation of the combined organic layer and the subsequent medium pressure-filtration chromatography (FC) purification of residue (eluent: AcOEt: *n*-hexane=1: 3) offered the titled product **4**. A new portion of reactants was added to recycle the catalytic system. ^{1}H NMR (300 MHz, $CDCl_3$) 1.43 (s, 3H), 1.60–1.77 (m, 2H), 2.06–2.19 (m, 3H), 2.40–2.53 (m, 4H), 2.63–2.77 (m, 2H), 5.83 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 23.5, 23.9, 30.2, 32.4, 34.2, 38.3, 51.2, 126.4, 166.5, 199, 211.7. $[\alpha]_D^{20}$ + 1.8 (c = 1.2, $CHCl_3$), HPLC Chiral OD-H, Hexanes/IPrOH 90/10, 0.5 mL.min^{-1}, minor t = 40.7 min, major t = 31.0 min.

3. Result and discussion

Synthesis of Wieland–Miescher ketone **4** proceeds via non-selective conjugated addition reaction followed by an enantioselective intermolecular Aldol condensation reaction of triketone **3** intermediate. The intermediate, triketone **3** was synthesised as per reported procedure by the reaction between methyl vinyl ketone **2** and 2-methylcyclohexane-1, 3-dione **1**.[1,2] The isolated yield of triketone **3** was 97%. The identity of the intermediate triketone **3** was confirmed by ^{1}H NMR and ^{13}C NMR (scheme 2). Later structurally confirmed, triketone **3** was used for the synthesis of Wieland–Miescher ketone **4** under different reaction conditions,



Scheme 2. Organocatalysts/ionic liquid catalytic system for Wieland–Miescher ketone **4** synthesis under different parameters.



Scheme 3. L-proline/ionic liquid catalytic system for Wieland–Miescher ketone **4** synthesis.

in order to achieve the best results with respect to yield and sterioselectivity.

We tested a series of ionic liquids with L-proline (1 mol%) as per scheme 3 and the corresponding results are summarised in table 1, entries 1–6.

Surprisingly, Wieland–Miescher ketone **4** was obtained in good yield (42–88%) and selectivity (61–93%) with L-proline (table 1, scheme 2) in different ionic liquids. Higher yield (88%) and selectivity (93% ee) was found only with $[pyC_4]NTf_2$ reaction medium. After obtaining good catalytic activity of L-proline in $[PyC_4]NTf_2$ with respect to yield and selectivity, we further studied various other reaction parameters such as time, temperature, catalyst loading, solvents such as *N*, *N*-dimethylformamide (DMF), dimethyl sulphoxide (DMSO), *N*-methylpyrrolidine (NMP), tetrahydrofuran (THF), dichloromethane (DCM) and water. All the results were summarised in table 2, entries 1–21.

Lower yield and selectivity (table 2, scheme 2, entry 2) was obtained with smaller quantity (0.50 mol%) of L-proline, while the higher quantity of the L-proline (1.5 mol%, table 2, entry 3) gave almost similar results as we obtained from 1 mol% of L-proline (table 2, entry 1) in $[pyC_4]NTf_2$. Temperature parameters were also optimised (from −5°C to 100°C) (table 2, entries 4–7) for Wieland–Miescher ketone **4** synthesis and it was concluded that at higher temperature L-proline gets decomposed and offers lower yield and selectivity. Lowering the reaction temperature from 0° to −5°C was also not found suitable in terms of yield and selectivity for Wieland–Miescher ketone **4** synthesis (table 2, entries 8–9). No reaction was found at −5°C as the reaction mass gets solidified. Screening conventional organic solvents such as DMF, DMSO, NMP, THF, DCM and water for Wieland–Miescher ketone **4**, was the other major goal of our study in order to understand the behaviour of L-proline catalysts for Wieland–Miescher ketone **4** synthesis (table 2, entries 10–15). While decreasing the polarity of the solvent, the corresponding yield of the Wieland–Miescher ketone **4** also decreased from 35% to 67% and selectivity was found to be between 45% and 69%. In DMSO solvent system with L-proline, Wieland–Miescher ketone responded with 67% yield and 65% ee (table 2, entry 11). Under solventless condition, L-proline also offered the Wieland–Miescher ketone **4** in acceptable yield and selectivity (48% yield, 67% ee) (table 2, entry 16). Apart from L-proline, we also tested other alternative catalysts for Wieland–Miescher ketone **4** synthesis with $[pyC4]NTf_2$ (table 2, entries 17–21) but no such significant increase in yield and selectivity was observed.

To evaluate the possibility of recycling the ionic liquid mediated L-proline catalytic system for Wieland–Miescher ketone **4** synthesis, triketone **3** was allowed to react with $[pyC_4]NTf_2$ immobilised L-proline catalyst and the corresponding product was then extracted with diethyl ether (5 × 2 mL) (scheme 4). A second amount of triketone **3** was added to the previously used $[pyC_4]NTf_2$ immobilised L-proline catalytic system and the process was repeated up to eight times. Surprisingly, there was no significant loss in yield (85–88%) and selectivity (90–93% ee) was observed during the eight recycling runs of L-proline/$[pyC_4]NTf_2$ catalytic system during the Wieland–Miescher ketone **4** synthesis (figure 1).

Table 1. Screening of L-proline with different ionic liquids for Wieland–Miescher ketone **4** synthesis.

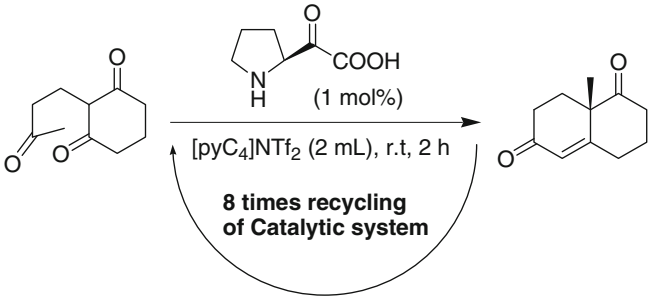
Entry	Ionic liquid (2mL)	Results	
		Yield (%)[1]	ee (%)[2]
1	$[bmim][PF_6]$	68	65
2	$[pyC_4][PF_6]$	42	73
3	$[tmba][PF_6]$	28	61
4	$[bmim][NTf_2]$	76	78
5	$[pyC_4][NTf_2]$	88	93
6	$[tmba][NTf_2]$	74	74

[1]Isolated yields after column chromatography
[2]Determined by HPLC

Table 2. Screening reaction parameters for Wieland–Miescher ketone **4** synthesis.

Entry	Solvent (2mL)	Catalyst	T/°C	Yield (%)[1]	ee (%)[2]
1	$[pyC_4][NTf_2]$	L-proline (1 mol %)	rt	88	93
2	$[pyC_4][NTf_2]$	L-proline (0.5 mol %)	rt	67	66
3	$[pyC_4][NTf_2]$	L-proline (1.5 mol %)	rt	75	79
4	$[pyC_4][NTf_2]$ (1 mL)	L-proline (1 mol %)	rt	72	79
5	$[pyC_4][NTf_2]$ (3 mL)	L-proline (1 mol %)	rt	78	81
6	$[pyC_4][NTf_2]$	L-proline (1 mol %)	100	15	75
7	$[tmba][NTf_2]$	L-proline (1 mol %)	50	38	78
8	$[tmba][NTf_2]$	L-proline (1 mol %)	−5	nd	–
9	$[tmba][NTf_2]$	L-proline (1 mol %)	0	25	54
10	DMF	L-proline (1 mol %)	rt	63	69
11	DMSO	L-proline (1 mol %)	rt	67	65
12	NMP	L-proline (1 mol %)	rt	55	67
13	THF	L-proline (1 mol %)	rt	40	69
14	DCM	L-proline (1 mol %)	rt	35	49
15	Water	L-proline (1 mol %)	rt	37	45
16	Neat	L-proline (1 mol %)	rt	48	67
17	$[pyC_4][NTf_2]$	L-hydroxyproline (1 mol %)	rt	65	74
18	$[pyC_4][NTf_2]$	(S)-phenylanaline (1 mol %)	rt	48	68
19	$[pyC_4][NTf_2]$	2-(S)-trans-4-hydroxyproline (1 mol %)	rt	15	58
20	$[pyC_4][NTf_2]$	(S)-proline ethyl ester (1 mol %)	rt	25	10
21	$[pyC_4][NTf_2]$	(S)-azetidine-2-carboxylic acid (1 mol %)	rt	68	72

[1]Isolated yields after column chromatography
[2]Determined by HPLC
rt, Room temperature



Scheme 4. Recycling parameters for Wieland–Miescher ketone **4** synthesis.

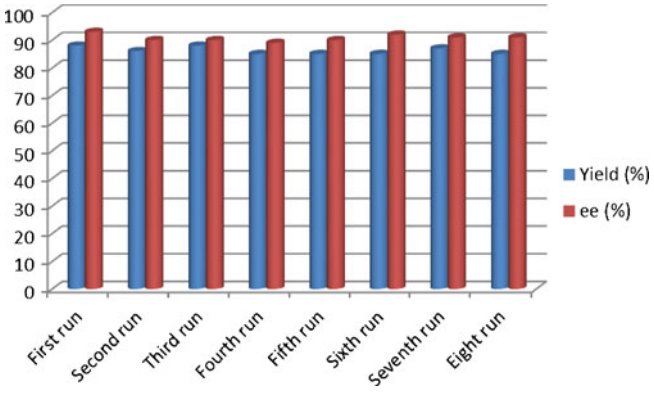


Figure 1. Recycling of $[pyC_4]NTf_2$/L-proline catalytic system for Wieland–Miescher ketone **4.**

4. Conclusion

We explored the application of L-proline for the synthesis of Wieland–Miescher ketone **4**. In this report, we optimised reaction parameters such as time, temperature as well as quantity of catalyst for the synthesis of Wieland–Miescher ketone **4**. As a result of our comprehensive study, L-proline (1 mol%) was found suitable for the synthesis of Wieland–Miescher ketone **4** with good yield (88%) and selectivity (93% ee) at room temperature. Eight times recycling of the $[pyC_4]$ NTf_2/L-proline catalytic system for the synthesis of Wieland–Miescher ketone **4** is the major outcome of the proposed protocol.

Supplementary information

The electronic supporting information can be seen in www.ias.ac.in/chemsci.

Acknowledgement

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