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Novel Proline Based Organocatalysts for Michael Addition of 1,3-Dicarbonyls to Nitrostyrene

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ABSTRACT

A new class of bifunctional proline based organocatalyst was synthesized from L-proline. Excellent enantioselectivity was obtained in the Michael addition of 2,4-pentanedione to various nitro styrene using the new proline based organocatalyst. The construction of contiguous stereocenters via the Michael reaction of substituted 1,3-dicarbonyls to nitro styrene was also carried out with very good yield, enantioselectivity.

Key words: Organocatalyst, Michael addition, Nitro styrene, Enantioselectivity.

INTRODUCTION

In recent years, asymmetric organocatalysis has grown rapidly as an indispensable tool for the synthesis of chiral organic molecules [1]. Multipoint recognition and the activation of reactants by weak hydrogen bonding is the main advantage in non-covalent catalysis. Chiral thioureas play a vital role as non-covalent organocatalysts in enantioselective transformations. The development of thiourea organocatalysts is an expanding research area in the field of asymmetric catalysis [2]. Jacobsen *et al*. reported on the first example of thiourea catalyzed asymmetric Mannich reactions [3]. In 2003, Takemoto reported on a bifunctional thiourea, which comprised of tertiary amine and a thiourea moiety for the concurrent activation of both a nucleophile and an electrophile [4]. The lack of effective bifunctional organocatalysts stimulated us to develop a new class of bifunctional tertiary amine thioureas from *L*-proline. *L*-Proline and its derivatives are well known for their efficiency as organocatalysts in performing various enantioselective transformations via covalent catalysis [6]. The Yong Tong pyrrolidine-thiourea derived from *L*-proline also belongs to this category [7]. Due to our interest in generating new chiral catalyst from an inexpensive chiral organic molecule for example, *L*-proline, [8-10] we continued our efforts to develop new organocatalysts from *L*-proline. We hoped that proline derived non-covalent organocatalysts containing thiocarbamide will emulate the catalytic efficiency of proline derivatives in various enantioselective reactions.

EXPERIMENTAL SECTION

General

All reagents and solvents were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was conducted on GF254 silica gel plates. Nuclear magnetic resonance (NMR) spectra were obtained from Bruker Avance 300 M system, and the chemical shifts of ^{1}H NMR spectra were reported in relation to tetramethyl silane (d = 0). High performance liquid chromatographic (HPLC) analysis was carried out on Agilent 1100 equipped with a diode array ultraviolet (UV) detector; and Daicel Chiralpak AD columns were used for the HPLC analysis.

General procedure for the enantioselective Michael addition of 2,4-pentanedione to nitro styrene:

To a stirred solution of 1a (6.90 mg, 0.0075 mmol, 10 mol %) and nitro styrene (0.15 mmol) in DCE (1.5 mL), 2,4-pentanedione (0.5 mmol) was added. The solution was stirred at ambient temperature for 9–18 h. After the reaction

was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give the product.

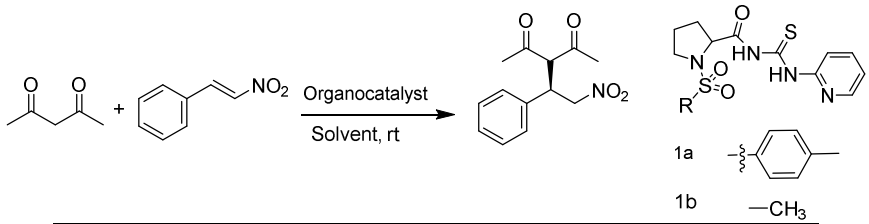
(R)-3-(1-(4-Fluorophenyl)-2-nitroethyl) pentane-2,4-dione (4):
^{1}H NMR (400 MHz, $CDCl_3$): d 7.10-7.20 (m, 2H), 7.05-7.10 (m, 2H), 4.56-4.62 (t, J = 1.0 Hz, 2H), 4.30-4.34 (d, J = 10.45 Hz, 1H), 4.18-4.27 (m, 1H), 2.31 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d 201.6, 200.7, 133.4, 133.8, 130.5, 128.1, 128.7, 126.1, 75.9, 68.9, 39.0, 30.8, 28.3; HPLC (OD-H, hexane/2-propanol = 85/15, flow rate-1 mL/min, 210 nm): tminor = 14.40 min, tmajor = 14.96 min, ee = 97%.

(R)-3-(2-Nitro-1-phenylethyl) pentane-2,4-dione (5):
^{1}H NMR (400 MHz, $CDCl_3$): d 7.20-7.26 (m, 3H), 7.24-7.30 (m, 2H), 4.55 (dd, J = 12.43, 7.45 Hz, 1H), 4.54 (dd, J = 12.3, 5.2 Hz, 1H), 4.10-4.19 (m, 2H), 4.29 (d, J = 11.1 Hz, 1H), 4.21-4.29 (m, 1H), 2.32 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): d 201.2, 200.7, 135.3,129.8, 128.8, 127.4, 78.6, 70.3, 42.5, 30.7, 29.8; HPLC (AD-H, hexane/IPA = 90.1/9.9, flow rate-1.0 mL/min, 210 nm): tminor = 9.82 min, tmajor = 11.90 min; ee = 98%.

RESULTS AND DISCUSSION

In the literature, conjugate additions were found to be suitable reactions for examining the catalytic efficacy of new proline based thiocarbamide organocatalytic systems [11]. Hence, the Michael addition of 2,4-pentanedione to nitrostyrene was chosen as the model reaction to evaluate the efficiency of an organocatalyst. A solution of nitrostyrene in toluene was treated with 10 mol % of N-(pyridin-2-ylcarbamothioyl)-1-tosylpyrrolidine-2-carboxamide 1a at room temperature, followed by the addition of 2,4-pentanedione. Michael adduct was isolated in 76% yield with 87% ee in 40 h (Table 1, entry 1). The 1-(methylsulfonyl)-N-(pyridin-2-ylcarbamothioyl)pyrrolidine-2-carboxamide (1b) poorly catalyze the reaction under identical conditions (Table 1, entry 2). N-(pyridin-2-ylcarbamothioyl)-1-tosylpyrrolidine-2-carboxamide 1a catalyzed the Michael addition of 2,4-pentanedione to nitrostyrene with great efficiency to yield the product in 98% yield and with 96% enantioselectivity (Table 1, entry 3). These results demonstrate unequivocally the requirement of a stereogenic centre at the carbon bearing a thiocarbamide moiety in organocatalyst 1a scaffold for its effective asymmetric induction. Encouraged by this observation, we screened various polar and non-polar solvents, in which dichloroethane was identified as the most suitable reaction medium (Table 1, entries 4–7). Using 10 mol % of catalyst 1a, Michael adduct was isolated in 98% yield with 96% enantioselectivity within 12 h at ambient temperature in dichloroethane.

Table 1. Screening of the organocatalysts and solvent for Michael addition reaction[a]

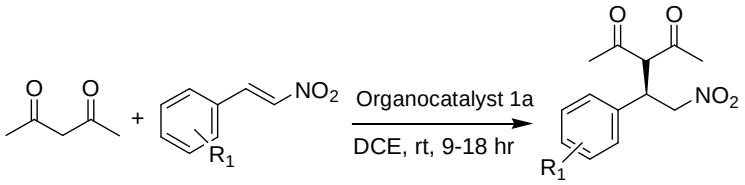


Entry	Organocatalyst (mol %)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	1a(10)	Toluene	40	76	87
2	1b(10)	Toluene	46	30	-
3	1a(10)	DCE	10	98	96
4	1a(10)	DCM	32	89	80
5	1a(10)	Chloroform	32	91	83
6	1a(10)	THF	38	65	87
7	1a(10)	Cyclohexane	30	70	90
8	1a(5)	DCE	12	92	94

[a]Reaction conditions: 2,4-pentanedione (0.5 mmol) was added to an agitated solution of nitrostyrene (0.15 mmol) and catalyst 1 (x mol %) in solvent at ambient temperature for the time mentioned.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis.

Lowering the catalyst loading to 5 mol % did not affect either the yield or the enantioselectivity (Table 1; entry 8). Thus the Michael addition of 2,4-pentanedione with nitrostyrene was achieved with quantitative yield and excellent enantioselectivity using 10 mol % of the newly designed proline based thiourea organocatalyst 1a.

Table 2 Asymmetric Michael addition reaction of 2,4-pentanedione to nitro styrene[a]



Entry	R_1	Catalyst	Yield[b] (%)	ee[c] (%)
1	Ph	1a	97	94
2	3-Cl	1a	84	96
3	4-Cl	1a	90	95
4	4-F	1a	91	97
5	2-NO2	1a	93	98
6	2-OMe	1a	51	92
7	3,4-OMe	1a	63	95
8	4-OH, 3-OMe	1a	68	93
9	4-Me	1a	88	94
10	4-OMe	1a	62	92

[a]Reaction conditions: 2,4-pentanedione 10 (0.5 mmol) was added to an agitated solution of nitro olefin (0.15 mmol) and catalyst 1a (10 mol %) in DCE as solvent at ambient temperature for the time mentioned.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis.

CONCLUSION

The catalytic performance of the resultant synthetic products for the Michael addition reactions between 2,4-pentanedione and nitrostyrene has been evaluated. It has been found that out of two organocatalysts 1a was found to be efficient for the Michael addition reactions under investigation and it have excellent to high yields, dosages of 10 mol % in the solvent dichloroethane.

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