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Research Article

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One-pot synthesis of substituted dihydro-2-oxypyrroles catalyzed by (*S*)-camphorsulfonic acid

Xiaojuan Yang

College of Chemistry and Chemical Engineering, Xinxiang University, Xinxiang, Henan, P. R. China

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ABSTRACT

A mild and efficient synthesis of substituted dihydro-2-oxypyrroles has been developed for the one-pot, four-component condensation reaction of dialkylacetylene dicarboxylate, amines and formaldehyde using (S)-camphorsulfonic acid as the catalyst at room temperature. The use of (S)-Camphorsulfonic acid makes this process quite simple, more convenient and environmentally friendly

Keywords: (*S*)-Camphorsulfonic acid; Dialkylacetylene dicarboxylate; Multicomponent reactions

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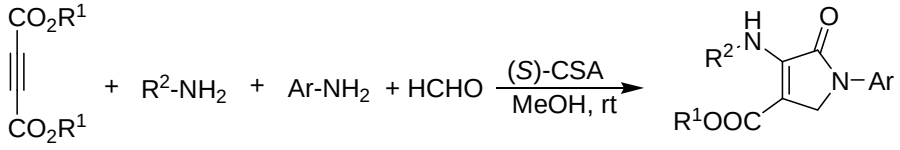
INTRODUCTION

Synthesis of five-membered nitrogen heterocyclic compounds such as dihydropyrroles and their analogues is very important because of their biological activities such as inhibitors of the human immunodeficiency virus (HIV) integrase [1], human mitotic kinesin Eg5 [2], vascular endothelial growth factor receptors (VEGFR) [3], annexin A2-S100A10 protein interaction [4], CD45 protein tyrosine phosphatase [5]. In addition, their anti-tumor activity [6] as well as useful intermediates [7-8] increasingly necessitate new research.

In synthetic organic chemistry, multicomponent reactions (MCRs) have gained considerable popularity in recent years due to their flexible, convergent, and atom-efficient nature. The MCRs are an ideal synthetic tool to generate multiple molecular scaffolds and to increase structural and skeletal diversity [9-10]. Recently, four-component one-pot condensation of dialkylacetylene dicarboxylate, amines, and formaldehyde has been reported for the construction of substituted dihydro-2- oxypyrroles under different conditions [11-13]. Although, these approache are satisfactory for synthesis of substituted dihydro-2-oxypyrroles, the harsh reaction conditions, expensive reagents, use of toxic organic solvents and long reaction times limit the use o these methods. Therefore, there still remains a high demand for the development of more general, efficient, economically viable, and eco-compatible protocol to assemble such scaffolds. Over the past few years, camphorsulfonic acid (CSA) has emerged as a highly efficient and effective potential organic acid catalyst imparting high stereoselectivity in various chemical transformations [14-16]. CSA is mostly soluble in many polar solvents. Hence the problems arising from the use of heterogeneous catalysts, like lower reactivity, extended reaction times and sometimes toxicity, can be removed by taking advantage of such a wide solubility range of CSA.

In continuation of our work to develop new catalysts for organic transformations, here we report mild, efficient and environmentally benign catalyst for the preparation of substituted dihydro-2-oxypyrroles from dialkylacetylene dicarboxylate, amines, and formaldehyde in MeOH using catalytic amounts of (*S*)-CSA as a homogenous catalyst catalysts at room temperature (Scheme 1)



Scheme 1

EXPERIMENTAL SECTION

NMR spectra were determined on Bruker AV-400 spectrometer at room temperature using TMS as internal standard, coupling constants (*J*) were measured in Hz; Elemental analysis were performed by a Vario-III elemental analyzer; Melting points were determined on a XT-4 binocular microscope and were uncorrected; Commercially available reagents were used throughout without further purification unless otherwise stated.

General procedure for the preparation of 5

A mixture of dialkyl acetylenedicarboxylate **1** (1 mmol) and amine **2** (1 mmol) in MeOH (5 mL) was stirred for 10-15 min. Then, amine **3** (1 mmol), formaldehyde **4** (1.5 mmol) and (*S*)-CSA 0.1 mmol) were added in succession. The reaction mixture was stirred at ambient temperature for the appropriate time (see Table 2). After completion of the reaction (TLC), the solid precipitate was filtered off and washed with ethanol to give the pure product **5**.

Compound **5f**. Brown solid, m.p. 170-171°C; IR (KBr, cm^{-1}): 3286, 2942, 2927, 2865, 1678, 1642; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (t, J = 7.2 Hz, 3H), 3.76 (s, 6H), 4.22 (q, J = 7.2 Hz, 2H), 4.53 (s, 2H), 6.83-7.70 (m, 8H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 48.5, 55.5, 55.6, 60.9, 101.0, 114.0, 114.5, 122.2, 126.2, 131.5, 132.1, 144.2, 156.8, 157.2, 164.1, 164.3; Anal. Calcd for $C_{21}H_{22}N_2O_5$: C 65.96, H 5.80, N 7.33; found: C 66.02, H 5.76, N 7.30.

Compound **5q**. White solid, m.p. 142-143 °C; IR (KBr, cm^{-1}): 3308, 2951, 2932, 2874, 1702, 1646; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.42 (s, 2H), 5.12 (d, J = 7.2 Hz, 2H), 7.02 (s, 1H), 7.25-7.40 (m, 7H), 7.73 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 48.1, 51.3, 59.4, 99.2, 120.4, 127.3, 127.2, 129.1, 129.4, 130.5, 138.2, 139.3, 164.3, 165.7; Anal. Calcd for $C_{19}H_{17}ClN_2O_3$: C 63.96, H 4.80, N 7.85; found: C 64.02, H 4.82, N 7.80.

RESULTS AND DISCUSSION

In our initial study, the optimum amount of catalyst was identified initially. Therefore, the model reactions were conducted using dimethyl acetylenedicarboxylate, aniline and formaldehyde in MeOH at room temperature in the presence of various catalytic amounts of (*S*)-CSA. The screening results from these reactions are summarised in Table 1. 5, 10, 15 and 20 mol% (*S*)-CSA were used to mediate the reaction, it was found that 10 mol% (*S*)-CSA in MeOH at room temperature is sufficient to initiate the reaction (Table 1, entry 3). In addition, the above reaction was also examined in various solvents (Table 1, entries 6-10). The results indicated that different solvents affected the efficiency of the reaction. DMSO, DMF and $CHCl_3$ afforded lower yields. (Table 1, entries 6-8), while when CH_3CN and EtOH were used, better results were obtained (Table 1, entries 9 and 10). However, the best result was obtained when the reaction was carried out in MeOH (Table 1, entry 3).

Table 1. Reaction conditions optimisation for the synthesis of 5a[a]

Entry	Solvent	Catalyst/ mol%	Time/ h	Yield/ %[b]
1	MeOH	-	24	Trace
2	MeOH	5	5	61
3	MeOH	10	2	92
4	MeOH	15	2	92
5	MeOH	20	2	91
6	DMSO	10	10	20
7	DMF	10	10	22
8	$CHCl_3$	10	10	43
9	CH_3CN	10	3	75
10	EtOH	10	3	82

[a]Reaction conditions: dimethyl acetylenedicarboxylate (1 mmol), aniline (2 mmol); formaldehyde (1.5 mmol); rt

Next, we prepared a range of substituted dihydro-2-oxypyrroles under the optimized conditions (Table 2). Both anilines containing an electron-withdrawing or –donating group reacted with dimethyl and/or diethyl acetylenedicarboxylate and formaldehyde in the presence of (*S*)-CSA in this one-pot condensation to afford excellent yields of corresponding substituted dihydro-2-oxypyrroles. To explore the scope and generality of this procedure, different functionalized dihydro-2- oxopyrroles were synthesized by means of a one-pot four-component reaction between two different amines, dialkyl acetylenedicarboxylates and formaldehyde, in the presence of (*S*)-CSA in methanol at room temperature. Most of aromatic and aliphatic amines are easily reacted in these condensations. All the products were characterized by comparison of their IR, ^{1}H NMR and ^{13}C NMR spectroscopic data and their melting points with reported. Furthermore, the reaction was scaled up to the 10 mmol scale; excellent results were still obtained in the required time as mentioned in Table 2. Additionally, for large scale synthesis we also investigated the recyclability of (*S*)-Camphorsulfonic acid for five consecutive cycles with almost the same catalytic activity. After completion of each reaction, the crude product (insoluble in MeOH) was filtered and it was washed with EtOH.

Table 2. Preparation of substituted dihydro-2-oxypyrroles[a]

Entry	R^1	R^2	Ar	Time/ h	Product	Yield/ %[b]	M.p./°C (lit.)
1	Me	C_6H_5	C_6H_5	2	**5a**	92	158-159 (159-160 [11])
2	Me	4-F- C_6H_4	4-F- C_6H_4	2	**5b**	91	163-164 (163-165 [12])
3	Me	3-Me-C_6H_4	3-Me-C_6H_4	2.5	**5c**	87	118-119 (118-119 [11])
4	Me	4-MeO-C_6H_4	4-MeO-C_6H_4	2	**5d**	88	174-175 (176-177 [13])
5	Et	C_6H_5	C_6H_5	2	**5e**	90	138-139 (139-140 [13])
6	Et	4-MeO-C_6H_4	4-MeO-C_6H_4	2	**5f**	86	170-171
7	Et	4-Br-C_6H_4	4-Br-C_6H_4	2	**5g**	86	168-170 (168-170 [12])
8	Et	4-Me-C_6H_4	4-Me-C_6H_4	3	**5h**	85	129-130 (129-131 [12])
9	Me	4-Me-C_6H_4	C_6H_5	3	**5i**	89	135-136 (136-137 [11])
10	Me	C_6H_5	4-Me-C_6H_4	2	**5j**	89	154-156 (153-154 [11])
11	Me	4-Br-C_6H_4	4-Me-C_6H_4	2	**5k**	86	205-206 (207-208 [11])
12	Me	4-NO_2-C_6H_4	C_6H_5	2	**5l**	83	136-138 (136-137 [11])
13	Me	C_6H_4-CH_2	C_6H_5	2.5	**5m**	84	140-141 (139-140 [13])
14	Me	C_6H_4-CH_2	4-MeO-C_6H_4	3	**5n**	79	129-130 (129-130 [13])
15	Me	C_6H_4-CH_2	4-Br-C_6H_4	3	**5o**	85	121-122 (120-121 [13])
16	Et	C_6H_4-CH_2	C_6H_5	3	**5p**	86	125-126 (126-128 [12])
17	Et	C_6H_4-CH_2	4-Cl-C_6H_4	3	**5q**	87	142-143
18	Me	cyclohexanyl	C_6H_5	3	**5r**	85	95-97 (96-97 [13])
19	Me	cyclohexanyl	4-MeO-C_6H_4	3	**5s**	87	126-127 (128-129 [13])
20	Me	*n*-C_4H_9	C_6H_5	3	**5t**	83	59-60 (60-62 [12])

[a]Reaction conditions: dialkylacetylene dicarboxylate (1 mmol); amine (1 mmol); aromatic amine (1 mmol); formaldehyde (1.5 mmol); (S)-CSA (0.1 mmol); rt.
[b]Isolated yield

CONCLUSION

In summary, we have successfully developed a (*S*)-CSA catalysed facile, efficient and economic procedure for the synthesis of substituted dihydro-2-oxypyrroles. This general synthetic protocol offers several advantages including short reaction times, readily available starting materials, recyclability of the catalyst and high isolated yields of the products. To the best of our knowledge this is the first report of (*S*)-CSA catalysed synthesis of substituted dihydro-2-oxypyrroles.

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