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GREEN AND CONVENIENT SYNTHESIS OF POLYFUNCTIONALIZED PIPERIDINES CATALYZED BY ASCORBIC ACID UNDER AMBIENT TEMPERATURE

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ABSTACT: The Knoevenagel intramolecular aza-Diels-Alder imin-based reaction in ethanol media can be used to efficiently manufacture polyfunctionalized piperidines in a moderate and environmentally friendly manner. In this procedure, ascorbic acid is used as a green and biodegradable catalyst. The condensation method, which has five components, efficiently enables the reaction between 1,3-dicarbonyl compounds, aromatic aldehydes, and different amines, resulting in the creation of products with good to high yields. Several fundamental characteristics characterize the proposed strategy. These include the use of an environmentally benign, biodegradable, and widely available catalyst. Furthermore, the method employs a simple work-up procedure that does not necessitate column chromatographic separation. The reaction conditions used are mild, ensuring that any potentially toxic organic solvents are avoided. Furthermore, the procedure is highly efficient and adheres to atomic economics principles.

Keywords: *Ascorbic acid, Polyfunctionalized piperidines, Green procedure, Ethanol media, Simple work-up*

1. INTRODUCTION

Polyfunctionalized heterocyclic compounds are essential components of many natural products and synthetic molecules with enormous potential for use in biology and the development of synthetic therapies. In extensively substituted piperidines, both synthetic medicines and naturally generated monocyclic and bicyclic alkaloids are prevalent. Furthermore, piperidine and its derivatives have a wide range of biological actions, such as antihypertensive, antimalarial, neuroprotective, antibacterial, anticonvulsant, and anti-inflammatory properties. As a result, these molecules are extremely important in the field of pharmaceutical research and development. It is important to note that substituted piperidines are effective therapeutic agents for viral infections, diabetes, influenza, AIDS, and cancer metastases. Furthermore, recent research has shown that certain tetrahydropyridine (THP) derivatives can inhibit the enzymatic activity of farnesyl transferase. Solvents and catalysts are two of the most important components in green chemistry. In recent years, researchers have struggled to synthesize target molecules utilizing ecologically friendly and sustainable catalysts while avoiding harsh reaction conditions. Green catalysts for multi-component reactions (MCRs) have sparked substantial interest in organic and medicinal science.

Because piperidines are so important, current research has used multi-

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component techniques to synthesis them, utilizing the following constituents: The compounds listed are VCl3, BF3.SiO2, Ph3CCl, LaCl3.7H2O, tartaric acid, iodine, ZrOCl2.8H2O, ZrCl4, Tetra butyl ammonium tri bromide (TBATB), Bi(NO3)3.5H2O,bromodimethylsulfoniu m bromide (BDMS), cerium ammonium nitrate (CAN), p-toluenesulfonic acid monohydrate (p-TsOH•H2O), Fe@Si-Gu-Prs, SbCl3, glutamic acid, and SbI3. Although these methods have certain advantages, they also have some drawbacks. These constraints include the need for multiple procedural steps, the use of potentially hazardous organic solvents or catalysts containing transition metals, a time-consuming setup process, relatively high catalyst costs, waste disposal challenges, and suboptimal yields.

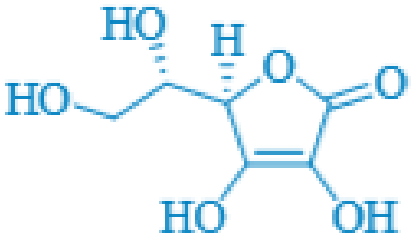
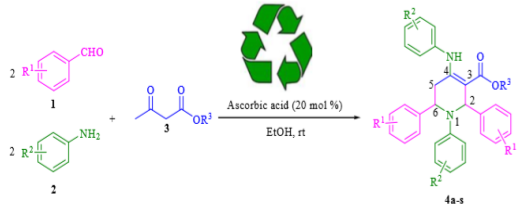


Fig. 1. Structure of ascorbic acid.



Scheme 1. Synthesis of highly substituted piperidine

As a result, it is still advantageous to investigate more broadly applicable, environmentally friendly, practicable, and successful routes to this class of considerably substituted piperidines. Because of its natural origin, cost-effectiveness, environmental friendliness, and high efficacy, ascorbic acid (Figure 1) has received substantial attention as a catalyst in the field of organic chemistry in recent decades. Ascorbic acid's numerous applications in medicine and food have been widely documented. Ascorbic acid, often known as vitamin C, has metabolic and antioxidant properties that make it an essential component of the human diet. L-ascorbic acid is important in plant biology because it is a crucial chemical that serves as both an antioxidant and a hormone signaling modulator, having a substantial impact on various aspects of plant development. Plants are the primary source of vitamin C in the human body. In this paper, we offer a simple and environmentally friendly method for synthesizing widely substituted piperidines. At room temperature, anilines, -ketoesters, and aromatic aldehydes are mixed in ethanol to form a five-component reaction. Notably, a catalytic amount of ascorbic acid serves as the catalyst in the reaction (Scheme 1).

2. RESULTS AND DISCUSSION

The catalytic activity of ascorbic acid in the synthesis of highly substituted piperidines was investigated in order to optimize the reaction conditions. To test the catalytic activity of ascorbic acid in a model system, 2 mmol of benzaldehyde, 2 mmol of aniline, and 1 mmol of methyl acetoacetate were combined in a multi-component reaction. The use of a catalyst is required for the aforementioned transformation, as proven by the lack of discernable product production under ambient circumstances and at a temperature of 50

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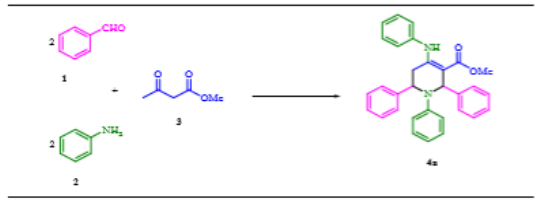
°C for roughly 24 hours, as shown in Table 1, entries 1 and 2. The ideal conditions were identified by manipulating different influential variables in the process, such as temperature, solvent concentration, and catalyst quantity. Following that, the model reaction was run with various concentrations of ascorbic acid to identify the best amount of catalyst. The model reaction investigated several catalyst loadings, specifically 5, 10, 15, 20, and 25 mol%. As indicated in Table 1, entry 3, reducing the amount of catalyst employed to 5 mol% resulted in a drop in the yield of the related product.

Table 1. Optimization of the Reaction Condition in the Synthesis 4a[a]



Entry	Ascorbic acid (mol %)	Solvent	Time (h)	Isolated yields (%)
1	Catalyst free	EtOH	24	Not product
2	Catalyst free	EtOH, 50 °C	24	Not product
3	5	EtOH	24	26
4	10	EtOH	18	48
5	15	EtOH	14	71
6	20	EtOH	11	86
7	20	EtOH, 50 °C	9	72
8	20	H_2O	18	trace
9	20	Solvent free	18	34
10	20	Solvent free, 50 °C	14	27
11	20	CH_2Cl_2	24	29
12	20	MeOH	14	65
13	20	$CHCl_3$	24	23
14	20	CH_3CN	18	38
15	25	EtOH	11	87

Under various solvent systems and temperature conditions, benzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and a catalyst are used in the experiment.

The experimental examination includes gradually increasing the concentration of the catalyst from 5 to 10, 15, and 20 mol%. The observed results, as shown in Table 1, entries 3-6, revealed a reduction in reaction time and an increase in product yield. Based on the results of the optimization, notably entry 6, it can be deduced that the catalyst with the highest efficacy for this particular reaction was ascorbic acid at a concentration of 20 mol%. A research was also conducted to assess the effect of temperature on the yield of the reaction.

When done at 50 °C, the reaction incorporating ascorbic acid at a concentration of 20% indicated a high reaction rate. Nonetheless, the observed yield of the matching product was determined to be only 72%, as shown in Table 1. According to the data in Table 1, item 15, increasing the catalyst quantity did not result in an increase in yield. The analysis of the reaction without the presence of a solvent, using a catalyst concentration of 20 mol% at both room temperature and 50 °C, produced a reaction product with a lower yield and a longer reaction time. This discovery shows that the presence of a solvent is critical to the progression of this reaction (see Table 1, entries 9, 10). As a result, the careful selection of a suitable solvent is critical for the successful completion of the synthesis.

The research involved analyzing the model reaction using several solvents, as well as the addition of 20 mol% ascorbic acid, in order to determine the best solvent. The results showed that using H2O, CH2Cl2, MeOH, CHCl3, and CH3CN as solvents resulted in a lower yield of the intended product. The highest observed yield was attained when ethanol was utilized as the reaction solvent, rather than other solvents or a solvent-free condition. Table 1 offers a concise summary of the results of the aforementioned comparative investigation. We used the optimum conditions stated in

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Scheme 1 and Table 2 to facilitate the condensation reaction between aromatic aldehydes (1, 2 mmol), amines (2, 2 mmol), and methyl/ethyl acetoacetate (3, 1 mmol) for the aim of creating highly substituted piperidines.

The experimental conditions included using a 20% mol% concentration of ascorbic acid as a catalyst in ethanol at room temperature. Motivated by the impressive results obtained under the aforementioned conditions, and with the goal of demonstrating the versatility and breadth of this approach, we used a variety of aromatic aldehydes and amines with electron-withdrawing or electron-donating functional groups to generate extensively substituted piperidines. It was discovered that substituents had a considerable impact on aromatic ring yields within the context of these reaction circumstances. Both families of aromatic aldehydes and amines, which include substituents in their aromatic rings that can either withdraw or give electrons, demonstrated remarkable reactivity. As a result, the necessary compounds were formed in a short reaction time with yields ranging from excellent to extraordinary. Furthermore, methyl/ethyl acetoacetate was utilized. There were no significant differences in product yields or reaction speeds across all of these adjustments. Table 2 summarizes the research findings in detail.

Scheme 2 depicts the potential pathways for the synthesis of piperidines with a high amount of substitution in the presence of ascorbic acid. Enamine A and imine B were created by combining aromatic aldehyde 1 and -ketoester 3 in the presence of amine 2 and ascorbic acid as a catalyst. Following that, enamine A and imine B were used in an intermolecular Mannich-type reaction, which produced intermediate C. The chemical interaction between intermediate C and aldehyde 1 produces intermediate D. Tautomerization resulted in the production of intermediate E. The intermediate underwent a quick intramolecular Mannich reaction, resulting in the formation of intermediate F. The presence of the ester group aided the conjugation process in Scheme 2, resulting in the tautomerization of intermediate F and the formation of the desired piperidine derivative 4.

Table 3 presents a comparative review of several catalysts reported in the literature, with a focus on their catalytic efficiency in the synthesis of highly substituted piperidines. The findings of the study reveal that ascorbic acid has significant potential as a low-cost, biodegradable, and environmentally sustainable alternative catalyst for the synthesis of these biologically active heterocyclic molecules. This substitution results in extremely high yields and faster reaction kinetics.

3. EXPERIMENTAL

The melting points and infrared spectra of the compounds were determined using a JASCO FTIR 460 Plus spectrometer and an Electro thermal 9100 equipment. In addition, 1H NMR and nuclear magnetic resonance spectra were obtained on a Bruker DRX-400 Avance apparatus using CDCl3 as a solvent. Merck, Fluka, and Acros supplied all of the reagents and solvents, which were used without extra purification.

General Procedure for the Synthesis of Highly Functionalized Piperidine (4a-s)

A solution comprising 1.0 mmol of -ketoester 3 and 2.0 mmol of aromatic

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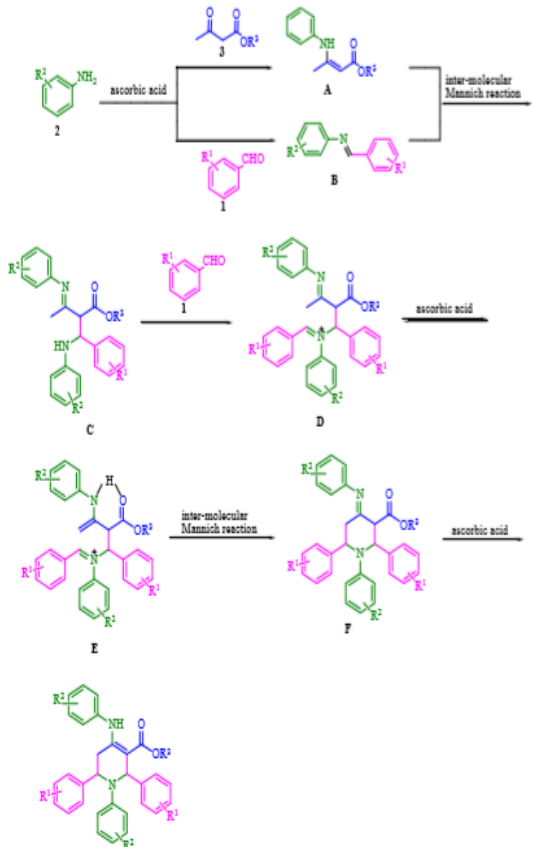
amine 2 in 5 ml of ethanol was agitated for 20 minutes at room temperature in the presence of 20% ascorbic acid. The reaction mixture was agitated for the time indicated in Table 2 after the addition of aromatic aldehyde 1 (2.0 mmol). The reaction was monitored using thin-layer chromatography (TLC) using a solvent mixture of n-hexane and ethyl acetate in a 3:1 ratio. The dense precipitate was removed by filtration after the reaction was completed, and the pure product 4 was obtained by washing it with ethanol (3 2 ml).

Table 2. Synthesis of Highly Substituted Piperidines

Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	M.p. (°C)	Lit.M.p. (°C)
1	H	H	Me	4a	11	86	170-172	169-171[34]
2	H	H	Et	4b	11	84	174-176	173-175[34]
3	H	4-Me	Et	4c	8	88	195-197	196-198[28]
4	H	4-Cl	Et	4d	12	82	205-207	203-205[34]
5	4-OMe	H	Me	4e	10	85	187-189	187-188[28]
6	4-OMe	4-Cl	Me	4f	14	79	194-196	194-195[45]
7	4-OMe	H	Et	4g	10	84	167-169	166-168[34]
8	4-NO_2	H	Me	4h	9	83	241-243	239-241[35]
9	4-NO_2	H	Et	4i	9	85	246-248	247-250[45]
10	4-Me	H	Me	4j	8	87	214-216	212-214[28]
11	4-Me	4-F	Me	4k	7	89	197-199	199-201[29]
12	4-Me	4-F	Et	4l	7	86	187-189	186-187[31]
13	4-Me	4-Cl	Et	4m	9	82	220-222	218-220[28]
14	4-Me	4-Br	Et	4n	11	79	232-234	234-236[28]
15	4-Me	3,4-Cl_2-C_6H_3	Et	4o	13	76	174-176	173-175[45]
16	4-Br	4-Cl	Me	4p	14	74	163-165	160-165[35]
17	4-F	H	Me	4q	7	88	179-181	180[45]
18	4-F	4-Me	Me	4r	9	87	202-204	203-205[31]
19	4-Cl	H	Me	4s	8	83	188-190	189-191[28]

[a]Isolated yield.



Scheme 2. A mechanistic strategy for the production of highly substituted piperidines is proposed.

Table 3. Comparing Various Catalysts' Catalytic Capabilities Published in the Literature for Piperidinesa Synthesis

Entry	Catalyst	Conditions	Time/Yield (%)	Ref.
1	Ph_3CCl	MeOH, 50 °C	5 h/79	[29]
2	Tartaric acid	MeOH, r.t.	14 h/79	[31]
3	I_2	MeOH, r.t.	8 h/81	[32]
4	$ZrOCl_2.8H_2O$	EtOH, reflux	3.5 h/80	[33]
5	$ZrCl_4$	EtOH, r.t.	9 h/90	[34]
6	$InCl_3$	CH_3CN, r.t.	24 h/60	[35]
7	TBATB	EtOH, r.t.	24 h/74	[37]
8	$Bi(NO_3)_3.5H_2O$	EtOH, r.t.	12 h/81	[38]
9	BDMS	CH_3CN, r.t.	3 h/75	[39]
10	CAN	CH_3CN, r.t.	20 h/82	[40]
11	*p*-TsOH-H_2O	EtOH, r.t.	10 h/78	[41]
12	Ascorbic acid	EtOH, r.t.	11 h/86	This work

aPredicted on the benzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate

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(1 mmol) five-component reaction.described using spectroscopic data comparison (1H NMR). The following represents the product spectrum data:**Methyl-1-phenyl-4-(4 chlorophenylamino)-2,6-bis(4 methoxyphenyl)-1,2,5,6-tetrahydropyridine-3- carboxylate (4f).** Yield: 79%; m. p.: 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (1H, dd, J = 15.2, 2.4 Hz, H′-5), 2.86 (1H, dd, J = 15.2, 5.6 Hz, H″-5), 3.81, 3.83, 3.97 (9H, 3s, 3OCH_3), 5.07 (1H, d, J = 3.6 Hz, H-6), 6.28 (2H, d, J = 8.0 Hz, ArH), 6.32 (1H, s, H- 2), 6.46 (2H, d, J = 8.0 Hz, ArH), 6.83-7.20 (12H, m, ArH), 10.25 (1H, s, NH).

Methyl-1-phenyl-4-(phenylamino)-2,6-bis(4-methyl-phenyl)-1,2,5,6-tetrahydropyridine-3 carboxylate (4j). Yield: 87%; m. p.: 214-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.75 (1H, dd, J = 15.2, 2.4 Hz, H′-5), 2.84 (1H, dd, J = 15.2, 5.6 Hz, H″-5), 3.93 (3H, s, OCH_3), 5.09 (1H, d, J = 3.1 Hz, H-6), 6.32 (2H, d, J = 8.0 Hz, ArH), 6.37 (1H, s, H-2), 6.48 (2H, d, J = 8.8 Hz, ArH), 6.60 (1H, t, J = 7.2 Hz, ArH), 7.00-7.12 (11H, m, ArH), 7.20 (2H, d, J = 8.0 Hz, ArH), 10.29 (1H, s, NH).

Methyl-4-(4-fluorophenylamino)-1-(4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-diptolylpyridine-3-carboxylate (4k). Yield: 89%; m. p.: 197-199 °C; IR (KBr) ν = 3255(NH), 1649 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.66 (dd, 1H, J = 15.1, 2.8 Hz, H′-5), 2.86 (dd, 1H, J = 15.1, 6.0 Hz, H″-5), 3.95 (s, 3H, OCH_3), 5.08 (d, 1H, J = 4.0 Hz, H-6), 6.25-6.28 (m, 2H, ArH), 6.33 (s, 1H, H-2), 6.43-6.48 (m, 2H, ArH), 6.77-6.84 (m, 4H, ArH), 7.05-7.20 (m, 8H, ArH), 10.17 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.0 (CH_3), 21.1 (CH_3), 33.6 (C-5), 51.0 (OCH_3), 55.4 (C-2), 58.1 (C-6), 98.0 (C-3), 113.6 (d, J = 7.0 Hz), 115.2 (d, J = 22.0 Hz), 115.6 (d, J = 22.0 Hz), 126.4 (d, J = 23.0 Hz), 128.0 (d, J = 8.0 Hz), 129.0, 129.4, 133.9 (d, J = 3.0 Hz), 136.0, 136.9, 139.7, 140.6, 143.5, 155.0 (d, $^{1}J_{CF}$ = 233.0 Hz), 156.2 (C-4), 160.7 (d, $^{1}J_{CF}$ = 244.0 Hz), 168.6 (C=O).

Ethyl-4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diptolylpyridine-3-carboxylate (4n). Yield: 79%; m. p.: 232-234 °C; IR (KBr) ν = 3310 (NH), 1652 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (t, 3H, J = 6.8 Hz, OCH_2CH_3), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.74 (d, 1H, J = 15.2 Hz, H′-5), 2.88 (dd, 1H, J = 15.2, 5.6 Hz, H″-5), 4.33-4.39 (m, 1H, OCH_aH_b), 4.45–4.51 (m, 1H, OCH_aH_b), 5.09 (d, 1H, J = 3.6 Hz, H-6), 6.17 (d, 2H, J = 8.0 Hz, ArH), 6.35 (s, 1H, H-2), 6.42 (d, 2H, J = 8.8 Hz, ArH), 7.05-7.24 (m, 12H, ArH), 10.26 (s, 1H, NH); ^{13}C NMR (100 MHz $CDCl_3$) δ (ppm): 14.7 (OCH_2CH_3), 21.0 (CH_3), 21.2 (CH_3), 33.4 (C-5), 55.0 (C-2), 58.1 (C-6), 59.9 (OCH_2CH_3), 99.0 (C-3), 108.2, 114.5, 118.9, 126.2, 126.4, 127.2, 129.0, 129.4, 131.5, 131.9, 136.1, 137.0, 139.1, 140.2, 146.0, 155.2 (C-4), 168.1 (C=O).

Ethyl-4-(3,4-dichlorophenylamino)-1-(3,4-dichloro-phenyl)-2,6-bis(4-methylphenyl)-1,2,5,6-tetrahydro-2,6-diptolylpyridine-3-carboxylate (4o). Yield: 76%; m. p.: 174-176 °C; IR (KBr) ν = 3301 (NH), 1660 (C=O) cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):

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1.50 (t, 3H, J = 6.4 Hz, OCH_2CH_3), 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.73 (d, 1H, J = 15.2 Hz, H′-5), 2.90 (dd, 1H, J = 15.2, 5.6 Hz, H″-5), 4.31-4.40 (m, 1H, OCH_aH_b), 4.46–4.54 (m, 1H, OCH_aH_b), 5.08 (br s, 1H, H-6), 6.15 (d, 2H, J = 7.2 Hz, ArH), 6.36 (s, 1H, H-2), 6.42 (d, 2H, J = 7.6 Hz, ArH), 6.95-7.25 (m, 10H, ArH), 10.24 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.8 (OCH_2CH_3), 21.6 (CH_3), 21.8 (CH_3), 33.4 (C-5), 55.3 (C-2), 58.3 (C-6), 59.8 (OCH_2CH_3), 98.9 (C-3), 108.3, 114.6, 119.1, 123.5, 123.5, 126.9, 127.2, 127.4, 127.4, 128.2, 128.2, 128.7, 131.5, 131.9, 137.0, 138.0, 138.4, 142.2, 143.3, 146.0, 155.3 (C-4), 168.1(C=O).

Methyl-4-(4-methylphenylamino)-1-(4-fluorophenyl)-1-(4-methylphenyl)-1,2,5,6-tetrahydro-2,6-diptolyl-pyridine-3-carboxylate (4r). Yield: 87%; m. p.: 202- 204 °C; IR (KBr) ν = 3264 (NH), 1658 (C=O) cm-1; 1H NMR (400 MHz, CDCl3) δ (ppm): 2.20 (s, 3H, CH3), 2.31 (s, 3H, CH3), 2.75 (dd, 1H, J = 15.1, 2.4 Hz, H′-5), 2.83 (dd, 1H, J = 15.1, 5.6 Hz, H″-5), 3.95 (s, 3H, OCH3), 5.11 (br s, 1H, H-6), 6.31 (d, 2H, J = 8.4 Hz, ArH), 6.37 (s, 1H, H-2), 6.42 (d, 2H, J = 8.8 Hz, ArH), 6.92 (d, 2H, J = 8.4 Hz, ArH), 7.97-7.02 (m, 6H, ArH), 7.12-7.15 (m, 2H, ArH), 7.27-7.31 (m, 2H, ArH), 10.22 (s, 1H, NH); 13C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.1 (CH_3), 33.7 (C-5), 51.0 (OCH_3), 54.7 (C-2), 57.3 (C-6), 97.2 (C-3), 113.0, 114.9 (d, J = 21.0 Hz), 115.4 (d, J = 21.0 Hz), 125.6, 125.8, 127.9 (d, J = 8.0 Hz), 128.2 (d, J = 7.0 Hz), 129.6, 135.0, 135.9, 138.4, 139.7, 144.5, 156.4 (C-4), 161.5 (d, $^1J_{CF}$ = 243.0 Hz), 161.9 (d, $^1J_{CF}$ = 244.0 Hz), 168.4 (C=O).

Methyl--1-phenyl-4-(phenylamino)-2,6-bis(4-chloro-phenyl)-1,2,5,6-tetrahydropyridine-3 carboxylate (4s). Yield: 83%; m. p.: 188-190 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.75 (1H, dd, J = 15.2, 2.4 Hz, H′-5), 2.86 (1H, dd, J = 15.2, 5.6 Hz, H″-5), 3.94 (3H, s, OCH_3), 5.11 (1H, d, J = 3.6 Hz, H-6), 6.39 (2H, d, J = 7.8 Hz, ArH), 6.40 (1H, s, H-2), 6.56 (2H, d, J = 8.0 Hz, ArH), 6.64 (1H, t, J = 7.0 Hz, ArH), 7.04-7.27 (13H, m, ArH), 10.26 (1H, s, NH).

4. CONCLUSIONS

Ascorbic acid, a renowned ecologically benign catalyst, has been shown to be a valuable aid in the synthesis of highly substituted piperidines. This is a multi-component reaction that comprises aromatic aldehydes, anilines, and -ketoesters and is carried out in an ethanol solvent. The use of ascorbic acid as a catalyst allows for the synthesis of these molecules to be simple and gentle. The use of a green, highly efficient, and easily accessible catalyst is an example of a competitive alternative synthetic approach for the synthesis of these physiologically active molecules. In addition to using ethanol as the medium, this technique provides a straightforward and cleaner reaction profile, resulting in good to high yields and quick reaction durations. It also makes product purification easier and eliminates the need for toxic organic solvents.

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