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Green and facile synthesis of dihydropyrrol-2-ones and highly substituted piperidines using ethylenediammonium diformate (EDDF) as a reusable catalyst

Mahboobeh Zarei[1] · **Seyed Sajad Sajadikhah**[1]

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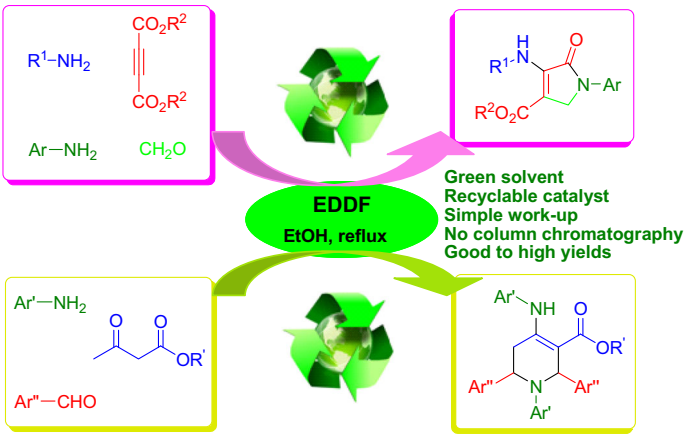
Abstract Extremely facile and efficient procedures have been developed for the synthesis of dihydropyrrol-2-ones and highly substituted piperidines. One-pot four-component reaction of amines, dialkyl acetylenedicarboxylates, and formaldehyde in the presence of ethylenediammonium diformate in ethanol under reflux conditions provides *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates in good to high yields. The same conditions were found useful for the synthesis of highly substituted piperidines via a three (pseudo five)-component reaction of amines, aldehydes, and *β*-ketoesters. It is found that the catalyst is reusable and can be used up to five times without significant loss of its activity.

Graphical Abstract



✉ Seyed Sajad Sajadikhah
sssajadi@pnu.ac.ir

[1] Department of Chemistry, Payame Noor University (PNU), P. O. Box 19395-3697, Tehran, Iran

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Introduction

Development of novel methodologies that reduce pollution in chemical synthesis has received considerable attention due to increasing environmental concerns. In this context, one active area is the use of an eco-friendly recyclable catalyst instead of conventional, toxic, and polluting Brönsted acid catalyst [1, 2]. Ethylenediammonium diformate (EDDF) is a salt (m.p. 132 °C), and recently it was used as a homogeneous catalyst for the synthesis of 4H-pyrans [3], 3-indolochromenes, and 3-indoloxanthenes [4]. Some advantages of EDDF are reusability, low cost, operational simplicity, ease of preparation, and handling. Among the several aspects of green chemistry, the replacement of volatile organic solvents with green solvents such as water and ethanol is of greatest concern [5, 6].

Polyfunctionalized heterocyclic compounds play important roles in drug discovery processes and in the analysis of drugs. In this context, the ubiquity of pyrrol-2-ones in pharmaceuticals and natural products makes them attractive targets for organic synthesis. Dihydropyrrol-2-one and its derivatives are key compounds for the synthesis of bioactive molecules such as Chaetoglobosin A and C [7] and Clausenamide [8]. Moreover, dihydropyrrol-2-ones have been successfully used as HIV integrase [9], herbicidal [10], pesticides [11], anti-tumor and anticancer agents [12], mitomycin antibiotics [13], and also inhibitors of DNA polymerase [14]. Recently, multi-component reactions have been used for one-pot synthesis of dihydropyrrol-2-ones using catalysts such as AcOH, I_2 benzoic acid, TiO_2 nanopowder, and $Cu(OAc)_2{\cdot}H_2O$ [15–20]. However, some of these methods displayed drawbacks, such as performing the reaction in the presence of 200 mol% catalyst at 70 °C and purification of products by preparative TLC [15], long reaction times [17], and environmental pollution caused by use of chlorinated solvent under reflux conditions [18].

On the other side, piperidines and their analogues have been receiving attention owing to their biological activities such as antimalarial [21], antihypertensive [22], antibacterial [23], anticonvulsant, and anti-inflammatory agents [24]. Additionally, substituted piperidines have been also established as therapeutic agents such as clebopride, cisapride, bamipine, fentanyl, α-methylfentanyl, and indoramine [25]. To date, methods for the synthesis of functionalized piperidines have been reported using multi-component reactions in the presence of L-proline/TFA, $InCl_3$, bromodimethylsulfonium bromide (BDMS), tetrabutylammonium tribromide (TBATB), I_2, cerium ammonium nitrate (CAN), $ZrOCl_2{\cdot}8H_2O$, picric acid, and $BF_3{\cdot}SiO_2$ [21, 26–34]. However, owing to the importance of dihydropyrrol-2-ones and piperidines from pharmaceutical and biological view points, there is still the need to develop green, efficient, and environmentally benign protocols for the synthesis of these heterocycles in the presence of recyclable catalyst. Therefore, in this work EDDF was used as reusable catalyst for the synthesis *N*-aryl-3-amino

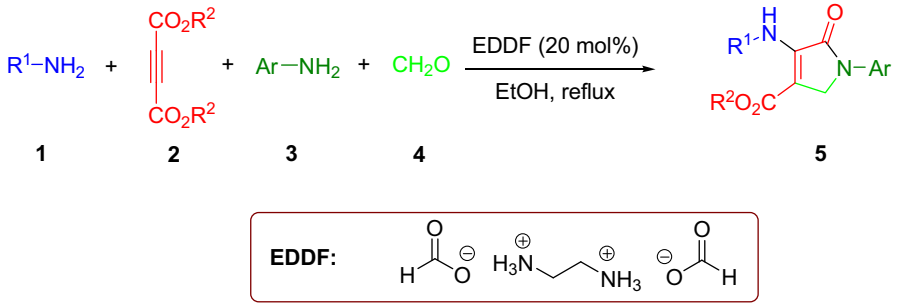
dihydropyrrol-2-one-4-carboxylates and highly functionalized piperidines in ethanol under reflux conditions.

Results and discussion

In continuation of our work on heterocycles synthesis, especially synthesis of dihydropyrrol-2-ones [35–39], herein EDDF was employed as an efficient catalyst for the one-pot four-component synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates in ethanol under reflux conditions (Scheme 1).

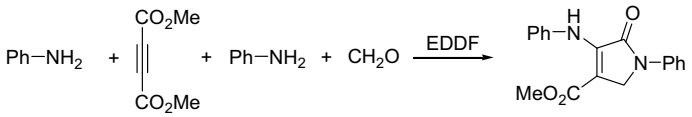
Initially, a mixture of aniline, dimethyl acetylendicarboxylate (DMAD), and formaldehyde in ethanol (5 mL) was treated with 10 mol% of EDDF at ambient temperature. The corresponding dihydropyrrol-2-one **5a** was obtained in 52 % yield after 10 h. To optimize the reaction conditions, the above reaction was carried out under different conditions and the results are summarized in Table 1. The best result was obtained in the presence 20 mol% of catalyst under reflux conditions. Note that control experiments showed that product **5a** was obtained only in trace and low yields when the reaction was examined in the absence of catalyst at ambient temperature and reflux conditions, respectively (Table 1, entries 10 and 11).

Under the optimized reaction conditions, various anilines and dimethyl and/or diethyl acetylenedicarboxylates were used to test the versatility of this reaction, and the results are presented in Table 2. This protocol efficiently coupled anilines with electron donating groups such as Me and OMe, as well as electron withdrawing groups including F, Cl, and Br to produce the expected products **5a**–**h** in good to high yields (Table 2, entries 1–8). Additionally, two different amines were used for the one-pot four-component synthesis of different highly functionalized dihydropyrrol-2-ones **5i**–**q** (Table 2, entries 9–17). Aliphatic amines such as benzyl amine, 1-(pyridin-2-yl)methanamine, cyclohexyl amine, *n*-propyl amine, and *n*-buthyl amine reacted smoothly with dialkyl acetylenedicarboxylates, aromatic amines, and formaldehyde to generate the desired products in high yields. All known compounds have been reported previously in the literature and were characterized by comparison of melting points, IR, and NMR spectra with authentic samples.



Scheme 1 Synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylate **5**

Table 1 Optimization of the reaction conditions for the synthesis **5a**



Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	EtOH	rt	10	10	52
2	MeOH	rt	10	10	50
3	MeCN	rt	10	15	39
4	EtOH	rt	5	14	41
5	EtOH	rt	15	10	59
6	EtOH	rt	20	9	64
7	EtOH	rt	25	9	61
8	EtOH	Reflux	20	3	89
9	EtOH	Reflux	25	3	87
10	EtOH	rt	No catalyst	24	Trace
11	EtOH	Reflux	No catalyst	9	19

[a] Isolated yield

A reasonable mechanism for the synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylate **5** was proposed in Scheme 2. The reaction between amine **1** and dialkyl acetylenedicarboxylate **2** gives intermediate **A**. Next, the reaction of amine **3** with formaldehyde **4** produces imine **B**. Attack of **A** on **B** leads to intermediate **C**, which converts to intermediate **D** by intramolecular cyclization. In the final step, tautomerization of intermediate **D** produces the corresponding dihydropyrrol-2-one **5**.

Recently, we have reported the effective and efficient synthesis of piperidine derivatives using multi-component reactions [40–44]. Motivated from the efficient catalytic activity of EDDF for the synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates, its catalytic activity was examined for the synthesis of highly substituted piperidines **9** via one-pot three (pseudo five)-component reaction of amines, aldehydes and *β*-ketoesters in ethanol under reflux conditions (Scheme 3).

At the outset, the reaction between benzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) was carried out in the presence of EDDF (10 mol%) in ethanol at room temperature. The reaction proceeds smoothly to generate the corresponding highly substituted piperidine **9a** in 48 % yield after 12 h. In order to optimize the reaction conditions, this reaction was considered as the model (Table 3). The best result was achieved in the presence of 25 mol% EDDF in ethanol under reflux conditions (Table 3, entry 11). To illustrate the need for catalytic amounts of EDDF in these reactions, the model reaction was also studied in the absence of the catalyst in ethanol, where no product was obtained at room temperature and under reflux conditions, even after 24 and 10 h, respectively (Table 3, entries 12 and 13).

Using the optimized reaction conditions, a series of highly substituted piperidines were prepared in good to high yields from the reaction between aromatic anilines, methyl/ethyl acetoacetate, and different aromatic aldehydes. As indicated in Table 4,

Table 2 Synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates **5a–q**

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	Mp (°C) (Lit. mp)[b]
1	Ph	Me	Ph	**5a**	3	89	150–152 (155–156) [16]
2	4-F-C_6H_4	Me	4-F-C_6H_4	**5b**	3	88	163–165 (163–165) [35]
3	4-Cl-C_6H_4	Me	4-Cl-C_6H_4	**5c**	2.5	91	170–172 (173–174) [16]
4	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5d**	3	87	163–175 (168–170) [16]
5	Ph	Et	Ph	**5e**	3.5	84	137–139 (138–140) [15]
6	4-Cl-C_6H_4	Et	4-Cl-C_6H_4	**5f**	3	86	168–170 (168–170) [37]
7	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5g**	2.5	80	164–166 (169–171) [15]
8	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5h**	3.5	79	152–154 (152–154) [36]
9	$PhCH_2$	Me	Ph	**5i**	2.5	85	135–137 (140–141) [15]
10	$PhCH_2$	Me	4-Me-C_6H_3	**5j**	2.5	90	144–146 (144–146) [38]
11	C_5H_4N-2-CH_2	Me	4-Br-C_6H_4	**5k**	3	70	160–162 (159–161) [39]
12	C_5H_4N-2-CH_2	Me	4-Me-C_6H_3	**5l**	3	72	106–108 (106–108) [37]
13	Cyclohexyl	Et	Ph	**5m**	3	89	103–105 (107–108) [15]
14	*n*-C_3H_7	Et	Ph	**5n**	3	88	76–78 (78–79) [15]
15	*n*-C_4H_9	Me	4-F-C_6H_4	**5o**	2.5	87	81–83 (81–83) [38]
16	*n*-C_4H_9	Me	4-Cl-C_6H_4	**5p**	3	85	91–93 (92–94) [39]
17	*n*-C_4H_9	Et	4-Br-C_6H_4	**5q**	3	86	95–97 (94–96) [35]

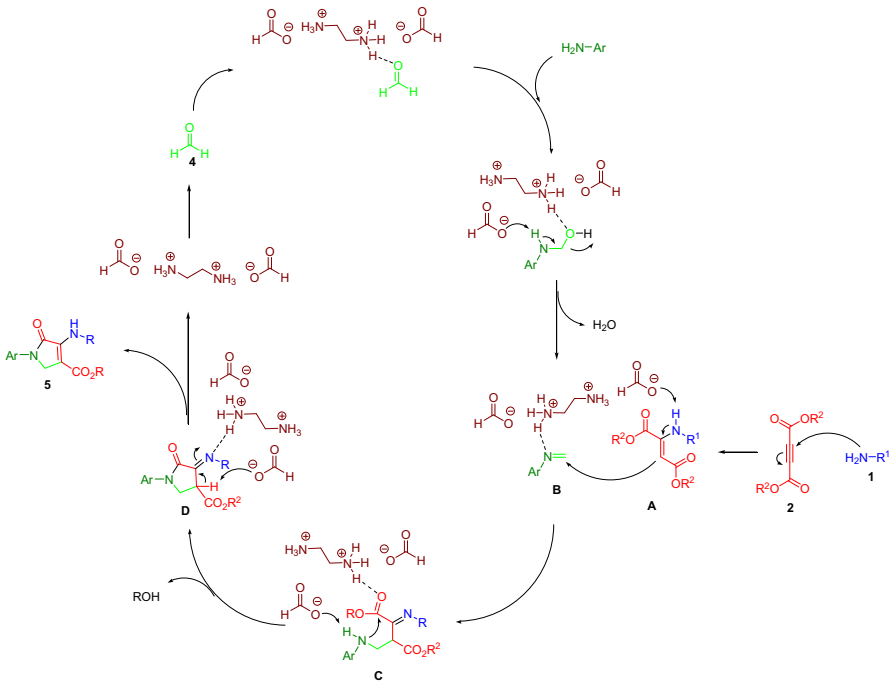
[a] Isolated yield

[b] Literature references for known compounds

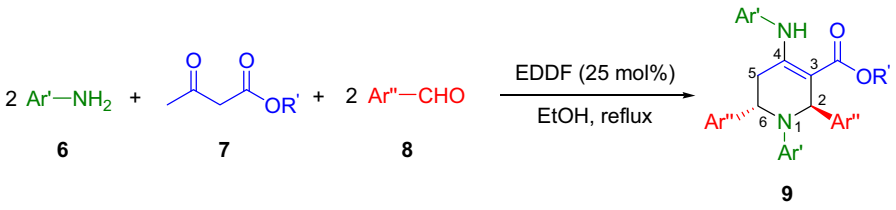
aniline and its derivatives containing electron withdrawing and/or electron donating groups reacted efficiently with benzaldehyde and substituted benzaldehydes to give the corresponding products **9** in good to high yields. However, *p*-nitro benzaldehyde gives the corresponding product in low yield (Table 4, entry 8), which is caused by the formation of more stable imine due to extra conjugation in the presence of a nitro group, which is less reactive [30]. The relative stereochemistry of this class of compounds has been confirmed by single X-ray crystallographic analysis in authentic literature [26–30, 36, 40, 43], and stereochemistry of our products was proved by comparison of spectroscopic data of some products with authentic samples.

On the basis of the previous literature [28–31], the proposed mechanism for the formation of piperidine **9** is illustrated in Scheme 4. First, aniline **6** reacts with *β*-ketoester **7** and aldehyde **8** in the presence of EDDF to give enamine **E** and imine **F**, respectively. Next, the reaction between enamine **E** and activated imine **F** leads to intermediate **G** through intermolecular Mannich-type reaction. The intermediate **G** reacts with aldehyde **8** to generate intermediate **H**. Then, tautomerization of **H** generates intermediate **I**, which immediately undergoes intramolecular Mannich-type reaction to produce intermediate **J**. Eventually, tautomerization of the intermediate **J** generates the desired piperidine **9** due to conjugation with the ester group.

In general, at the beginning of both reactions for the synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates **5** and piperidines **9**, the reagents were completely soluble in reaction medium to form a homogeneous mixture. But, at the end of the reactions, the products were precipitated and separated by simple filtration.



Scheme 2 Suggested mechanism for the synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates **5**



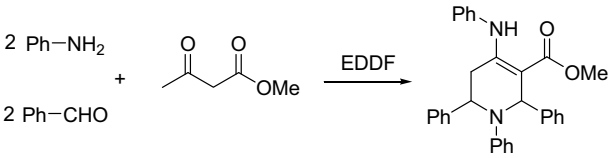
Scheme 3 Synthesis of highly substituted piperidine **9**

No column chromatography technique was used for products purification. This avoids use of large amounts of volatile organic solvents, as the solvent is generally the main source of waste as well as environmental pollutions.

The reusability of the catalyst is an important factor from an economical and environmental point of views and has attracted much attention in recent years. Thus, the reusability of EDDF was examined in the synthesis of dihydropyrrol-2-one **5a** and highly functionalized piperidine **9f** as two examples. After completion of the reaction, solid product was separated and the filtrated ethanol containing catalyst was evaporated under reduced pressure and catalyst was recovered and reused. The results show that EDDF can be used up to five times without significant loss of its activity (Table 5).

In conclusion, we have developed simple and green methods for the one-pot multi-component synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates

Table 3 Optimization of the reaction conditions for the synthesis **9a**



Entry	Solvent	Temperature (°C)	Catalyst (mol%)	Time (h)	Yield (%)[a]
1	EtOH	rt	10	12	48
2	MeOH	rt	10	12	49
3	MeCN	rt	10	16	36
6	EtOH	rt	5	15	37
7	EtOH	rt	15	12	57
8	EtOH	rt	20	12	64
9	EtOH	rt	25	10	69
10	EtOH	rt	30	10	69
11	EtOH	Reflux	25	6	81
12	EtOH	rt	No catalyst	24	–
13	EtOH	Reflux	No catalyst	10	–

[a] Isolated yield

and highly substituted piperidines using EDDF as a homogeneous catalyst in ethanol under reflux conditions. The noteworthy aspects of these procedures are green solvent, high atom economy, good to high yields, readily available starting material, recyclable catalyst, and operational simplicity. Moreover, all products were obtained through simple filtration and no need to column chromatography, which reduces the waste as well as environmental pollutions.

Experimental

Preparation of the catalyst EDDF

Ethylenediamine (10 mL, 0.15 mol) was diluted with acetone (15 mL) and was added dropwise to a previously cooled and stirred mixture of 90 % formic acid (aq.) (12.5 mL, 0.30 mol) and acetone (15 mL). The reaction mixture was maintained at 0 °C under continuous stirring for 2 h. The precipitated EDDF as a white solid was filtered, washed with acetone, and dried at 50 °C under vacuum [3].

General procedure for synthesis of *N*-aryl-3-amino dihydropyrrol-2-one-4-carboxylates 5

A mixture of amine **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1 mmol) in ethanol (5 mL) was stirred for 30 min at room temperature. Next, aromatic amine **3**

Table 4 Synthesis of substituted piperidines **9a–s**

Entry	Ar′	R′	Ar″	Product	Time (h)	Yield (%)[a]	Mp (°C) (Lit. mp)[b]
1	Ph	Me	Ph	**9a**	6	81	182–184 (185–186) [30]
2	Ph	Me	4-Me-C_6H_4	**9b**	5.5	89	214–217 (215–217) [30]
3	Ph	Et	3-Me-C_6H_4	**9c**	6	82	150–152 (149–151) [44]
4	Ph	Et	3-Br-C_6H_4	**9d**	6.5	84	164–166 (164–167) [44]
5	Ph	Me	4-F-C_6H_4	**9e**	6	87	190–192 (193–195) [30]
6	Ph	Me	4-Cl	**9f**	6	88	219–222 (225–227) [30]
7	Ph	Me	4-OMe-C_6H_4	**9g**	8	80	182–184 (186–188) [30]
8	Ph	Me	4-NO_2-C_6H_4	**9h**	10	47	234–236 (239–241) [30]
9	4-OMe-C_6H_4	Et	3-Br-C_6H_4	**9i**	7	77	197–199 (198–200) [36]
10	3,4-Cl_2-C_6H_3	Et	4-Me-C_6H_4	**9j**	6	76	174–176 (173–175) [41]
11	4-Br-C_6H_4	Et	4-Me-C_6H_4	**9k**	6.5	88	233–235 (234–236) [43]
12	4-Me-C_6H_4	Me	Ph	**9l**	6	83	186–188 (190–192) [36]
13	4-Me-C_6H_4	Me	4-F-C_6H_4	**9m**	6	89	200–202 (200–202) [41]
14	4-Me-C_6H_4	Et	4-Me-C_6H_4	**9n**	6	90	171–173 (169–171) [40]
15	4-Cl-C_6H_4	Me	4-Br-C_6H_4	**9o**	6	82	164–166 (160–163) [21]
16	4-Br-C_6H_4	Et	Ph	**9p**	7	85	194–196 (196–198) [40]
17	4-F-C_6H_4	Me	4-Me-C_6H_4	**9q**	6	88	198–201 (199–201) [43]
18	4-Cl-C_6H_4	Me	4-Me-C_6H_4	**9r**	6.5	84	204–206 (204–206) [44]
19	4-F-C_6H_4	Et	4-Me-C_6H_4	**9s**	6	87	182–184 (183–185) [31]

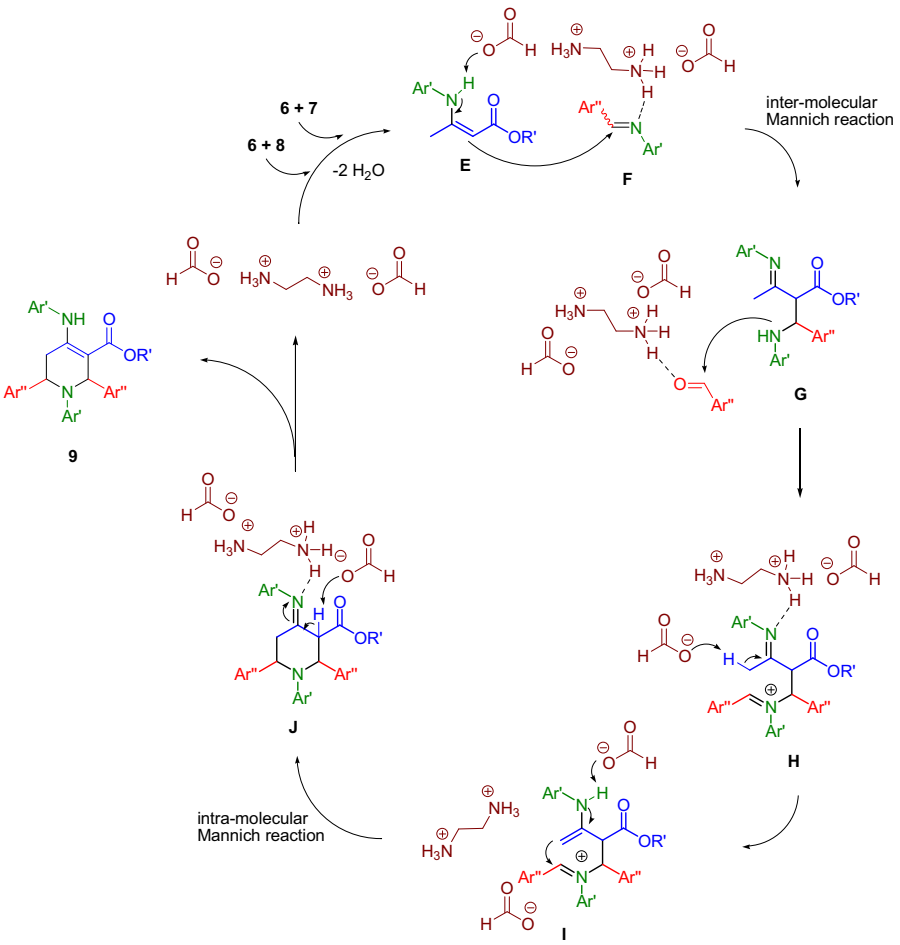
[a] Isolated yield

[b] Literature references for known compounds

(1 mmol), formaldehyde **4** (37 % solution, 1.5 mmol), and EDDF (20 mol%) were added successively. The reaction mixture was allowed to stir under reflux conditions for the appropriate time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to ambient temperature. The solid precipitate was filtered off and washed with ethanol to afford the pure products **5**. In order to recover the catalyst, filtrated solution was evaporated under reduced pressure, and the resulting catalyst was washed with diethyl ether, and dried. The recovered catalyst was reused five times.

General procedure for synthesis of highly functionalized piperidine 9

First, a solution of aromatic amine **6** (2 mmol) and β-ketoester **7** (1 mmol) in ethanol (5 mL) was stirred for 30 min in the presence of EDDF (25 mol%) at ambient temperature. Next, the aromatic aldehyde **8** (2 mmol) was added and the reaction mixture was allowed to stir for appropriate time under reflux conditions. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to ambient temperature. The tick precipitate was filtered off and washed with



Scheme 4 Proposed mechanism for the synthesis of highly substituted piperidine **9**

Table 5 Recyclability of EDDF in the synthesis of compounds **5a** and **9f**

Run no.	Compound **5a**		Compound **9f**	
	Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1	3	89	6	88
2	3	89	6	85
3	3.5	87	6	87
4	3.5	84	7	86
5	4	85	7	82

[a] Isolated yield

ethanol to give the pure product **9**. In order to recover the catalyst, filtrated ethanol was evaporated under reduced pressure, and the resulting catalyst was washed with diethyl ether, and dried. The recovered catalyst was reused next times.

Physical and spectral data for selected products

*Ethyl 4-(4-chlorophenylamino)-1-(4-chlorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (**5f**)*

White solid; IR (KBr, cm^{-1}): *v* 3320 (NH), 1693 (C=O), 1640 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, t, $J = 7.0$ Hz, $OCH_2C\underline{H}_3$), 4.27 (2H, q, $J = 7.0$ Hz, $OC\underline{H}_2CH_3$), 4.52 (2H, s, CH_2), 7.08 (2H, d, $J = 8.2$ Hz, ArH), 7.27 (2H, d, $J = 8.4$ Hz, ArH), 7.38 (2H, d, $J = 8.8$ Hz, ArH), 7.76 (2H, d, $J = 8.8$ Hz, ArH), 8.05 (1H, br s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 48.1, 60.6, 104.3, 120.2, 124.0, 128.5, 129.2, 129.9, 130.2, 137.2, 137.2, 142.6, 163.6, 164.5.

*Methyl 4-(benzylamino)-1-(4-methylphenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (**5j**)*

White solid; IR (KBr, cm^{-1}): *v* 3311 (NH), 1682 (C=O), 1646 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, t, $J = 7.2$ Hz, $OCH_2C\underline{H}_3$), 4.28 (2H, t, $J = 7.2$ Hz, $OC\underline{H}_2CH_3$), 4.41 (2H, s, $C\underline{H}_2$-N), 5.12 (2H, d, $J = 6.4$ Hz, $C\underline{H}_2$-NH), 6.89 (1H, br s, NH), 7.28–7.37 (5H, m, ArH), 7.53 (2H, d, $J = 8.4$ Hz, ArH), 7.71 (2H, d, $J = 8.8$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 46.6, 48.1, 51.1, 97.1, 119.4, 127.3, 127.5, 128.7, 129.6, 134.8, 136.2, 139.5, 164.3, 165.6.

*Methyl 3-(butylamino)-1-(4-chlorophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (**5p**)*

White solid; IR (KBr, cm^{-1}): *v* 3358 (NH), 1699 (C=O), 1635 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, $J = 7.6$ Hz, CH_3), 1.42 (2H, sextet, $J = 7.5$ Hz, CH_2), 1.62 (2H, quintet, $J = 7.6$ Hz, CH_2), 3.80 (3H, s, OCH_3), 3.87 (2H, t, $J = 6.4$ Hz, $C\underline{H}_2$-NH), 4.39 (2H, s, CH_2-N), 6.75 (1H, br s, NH), 7.37 (2H, d, $J = 8.8$ Hz, ArH), 7.75 (2H, d, $J = 8.8$ Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 19.8, 33.3, 42.5, 47.8, 51.1, 96.0, 120.2, 129.1, 130.0, 137.3, 164.5, 165.6.

*Ethyl 2,6-bis(3-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**9d**)*

White solid; IR (KBr, cm^{-1}): *v* 3223 (NH), 1656 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (3H, t, $J = 7.2$ Hz, $OCH_2C\underline{H}_3$), 2.79 (1H, d, $J = 15.1$ Hz, H′-5), 2.88 (1H, dd, $J = 15.2$, 5.2 Hz, H″-5), 4.38 (1H, dq, $J = 10.8$, 7.2 Hz, OCH_aH_b), 4.54 (1H, dq, $J = 10.8$, 7.0 Hz, OCH_aH_b), 5.14 (1H, br, H-6), 6.41 (2H, d, $J = 8.2$ Hz, ArH), 6.42 (1H, s, H-2), 6.51 (2H, d, $J = 8.0$ Hz, ArH), 6.70 (1H, t, $J = 7.2$ Hz, ArH), 7.09–7 .27 (9H, m, ArH), 7.30 (1H, s, ArH), 7.39 (1H, d, $J = 7.6$ Hz, ArH), 7.44 (1H, d, $J = 7.6$ Hz, ArH), 7.60 (1H, s, ArH), 10.34 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.9, 33.6, 55.0, 57.5, 59.9, 97.3, 113.1, 116.9, 1 22.7, 123.9, 1 25.1, 125.2, 126.1, 126.2, 129.1, 129.4, 129.6, 129.7, 129.8, 130.3, 130.4, 137.6, 145.1, 146.3, 146.6, 155.8, 167.9.

*Methyl 4-(4-methylphenylamino)-1-(4-methylphenyl)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**9l**)*

White solid; IR (KBr, cm^{-1}): *v* 3308 (NH), 1652 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 2.20 (3H, s, CH_3), 2.30 (3H, s, CH_3), 2.78 (1H, dd, $J = 15.2$, 2.4 Hz, H′-5), 2.89 (1H, dd, $J = 15.2$, 5.8 Hz, H″-5), 3.96 (3H, s, OCH_3), 5.16 (1H, d, $J = 3.6$ Hz, H-6), 6.21 (2H, d, $J = 8.8$ Hz, ArH), 6.46 (1H, s, H-2), 6.49 (2H, d, $J = 8.8$ Hz, ArH), 6.92 (4H, t, $J = 8.4$ Hz, ArH), 7.20–7.33 (10H, m, ArH), 10.22 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.1, 20.9, 33.6, 50.9, 55.2, 58.2, 97.5, 112.9, 125.1, 126.0, 126.2, 126.4, 126.7, 127.1, 128.2, 128.6, 129.4, 135.2, 135.6, 143.1, 144.3, 144.8, 156.6, 168.6.

*Ethyl 4-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,6-bis(4-methylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (**9s**)*

White solid; IR (KBr, cm^{-1}): *v* 3298 (NH), 1655 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ 1.49 (3H, t, $J = 7.2$ Hz, $OCH_2\underline{CH_3}$), 2.36 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.67 (1H, dd, $J = 15.2$, 2.4 Hz, H′-5), 2.86 (1H, dd, $J = 15.2$, 5.8 Hz, H″-5), 4.36 (1H, dq, $J = 10.5$, 7.2 Hz, OCH_aH_b), 4.49 (1H, dq, $J = 10.5$, 6.8 Hz, OCH_aH_b), 5.08 (1H, d, $J = 3.6$ Hz, H-6), 6.24–6.29 (2H, m, ArH), 6.35 (1H, s, H-2), 6.44–6.49 (2H, m, ArH), 6.77–6.86 (4H, m, ArH), 7.05–7.23 (8H, m, ArH), 10.22 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8, 21.0, 21.1, 33.6, 55.4, 58.1, 59.7, 98.3, 113.5 (d, $J = 7.0$ Hz), 115.3 (d, $J = 22.2$ Hz), 115.6 (d, $J = 23.0$ Hz), 127.0 (d, $J = 23.0$ Hz), 127.9 (d, $J = 9.1$ Hz), 129.0, 129.4, 134.1 (d, $J = 3.0$ Hz), 135.9, 136.9, 139.7, 140.7, 143.6, 155.1 (d, $^1J_{CF} = 234.0$ Hz), 156.0, 160.6 (d, $^1J_{CF} = 245.0$ Hz), 168.2.

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