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ORIGINAL PAPER

$Al(H_2PO_4)_3$ as an efficient and reusable catalyst for the multi-component synthesis of highly functionalized piperidines and dihydro-2-oxypyrroles

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Abstract Extremely facile and efficient procedures have been developed for the synthesis of highly functionalized piperidines and dihydro-2-oxypyrroles via one-pot multi-component reactions in the presence of $Al(H_2PO_4)_3$ as a heterogeneous and eco-friendly catalyst under mild conditions. The multi-component reaction of aromatic aldehydes, aromatic amines, and β-keto esters catalyzed by $Al(H_2PO_4)_3$ in EtOH at room temperature provides highly functionalized piperidines in good to excellent yields. The structure as well as the relative stereochemistry of these functionalized piperidines was confirmed by single X-ray crystallographic analysis. The same catalyst was found useful for the synthesis of polyfuntionalized dihydro-2-oxypyrroles using a four-component reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde in MeOH at ambient temperature. It is found that the catalyst is recyclable and can be used up to five times without significant loss of its activity.

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Keywords Heterocycle · Piperidine · Dihydro-2-oxypyrrole · Multi-component reaction · Reusable catalyst · $Al(H_2PO_4)_3$

Introduction

The design of novel multi-component reactions (MCRs) has received great attention from research groups in medicinal chemistry, drug discovery and materials science due to their significant advantages over conventional linear-type syntheses, including simple procedures, environmental friendliness, atom economy, and the ability to generate architecturally complex molecules in one synthetic step [1, 2].

Polyfunctionalized heterocyclic compounds are playing important roles in drug discovery processes and in the analysis of drugs. In particular, piperidines and their analogues have been receiving attention owing to their biological activities [3, 4], such as antimalarial [5], antihypertensive [6], antibacterial [7], anticonvulsant, and anti-inflammatory agents [8]. Also, substituted piperidines have been established as therapeutic agents such as clebopride, cisapride, bamipine, fentanyl, α-methylfentanyl, and indoramine [9]. To date, methods for the synthesis of functionalized piperidines have been reported using MCRs in the presence of L-proline/TFA [5], $InCl_3$ [10, 11], bromodimethylsulfonium bromide (BDMS) [12], tetrabutylammonium tribromide (TBATB) [13], iodine [14], cerium ammonium nitrate (CAN) [15], $ZrOCl_2{\cdot}8H_2O$ [16], picric acid [17], $BF_3{\cdot}SiO_2$ [18], and $FeCl_3/SiO_2$ nano particles [19].

On the other hand, the ubiquity of pyrrol-2-ones in pharmaceuticals and natural products makes them attractive targets for organic synthesis. Pyrrol-2-one and its derivatives are key compounds for the synthesis of bioactive molecules such as Chaetoglobosin A and C [20], and Clausenamide

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[21]. Moreover, dihydro-2-oxypyrrols have been successfully used as HIV integrase [22], herbicidal [23], pesticides [24], anti-tumor and anticancer agents [25], mitomycin antibiotics [26], and also inhibitor of DNA polymerase [27]. As a result, tremendous progress has been made in accessing substituted pyrrol-2-ones, some of which rely on multistep routes [28–31]. Recently, multi-component reactions have been used for one-pot synthesis of dihydropyrrol-2-ones using catalysts such as AcOH [32], and I_2 [33]. However, owing to the importance of piperidines and dihydropyrrol-2-ones from pharmaceutical and biological view points, there is still the need to develop efficient, mild, and environmentally benign protocols for the synthesis of these heterocycles.

During the past decade, the use of solid acidic catalysts has received considerable attention in organic synthesis due to their important advantages such as environmental compatibility, reusability, low cost, non-toxicity, operational simplicity, ease of handling, and isolation from the reaction mixture. In this respect, aluminum tris(dihydrogen phosphate) [$Al(H_2PO_4)_3$] is well known as an efficient heterogeneous catalyst for organic synthesis [34–39].

In this article, we report simple and efficient procedures for the synthesis of various highly functionalized piperidines and dihydro-2-oxypyrroles under mild reaction conditions.

Experimental

General

Melting points and IR spectra were obtained on an Electrothermal 9100 apparatus and a JASCO FT/IR-460 plus spectrometer, respectively. The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avanve instrument with $CDCl_3$ as solvent at 400 and 100 MHz, respectively. The mass spectra were recorded on an Agilent Technology (HP) mass spectrometer, operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. All chemicals were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

Preparation of the catalyst $Al(H_2PO_4)_3$

The catalyst was prepared by taking a mixture of alumina (neutral) and concentrated phosphoric acid (88 %) in a silica boat, maintaining the molar ratio of alumina–H_3PO_4 as 1:3, and heating at 200–220 °C in a hot sand bath. The mixture was stirred at the stipulated temperature until the swampy mass solidified, and then the temperature was lowered to around 100 °C. The whole solidified product was then placed in a vacuum desiccator and cooled to ambient temperature. The catalyst thus prepared was finally transferred and stored in an air tight sample vial [34, 35].

General procedure for synthesis of highly functionalized piperidine **4**

First, a solution of aromatic amine **2** (2 mmol) and *β*-ketoester **3** (1 mmol) in EtOH (5 mL) was stirred for 30 min in the presence of $Al(H_2PO_4)_3$ (0.2 g) at ambient temperature. Next, the aromatic aldehyde **1** (2 mmol) was added and the reaction mixture was allowed to stir for the appropriate time. After completion of the reaction as monitored by TLC, the solid material was filtered off, dried, and then dissolved in acetone or CH_2Cl_2 (10 mL). The catalyst was filtered and the solvent was evaporated under vacuum. The obtained solid was washed with EtOH (3 × 2 mL) to give the pure product **4**. Physical and spectral data for selected products are represented below.

Ethyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (4n)

White solid; IR (KBr, cm^{-1}) ν = 3,270 (NH), 1,656 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.82 (dd, J = 15.2, 2.4 Hz, 1H, H′-5), 2.91 (dd, J = 15.2, 5.6 Hz, 1H, H″-5), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.39 (dq, J = 10.8, 7.2 Hz, 1H, OCH_aH_b), 4.52 (dq, J = 10.8, 7.0 Hz, 1H, OCH_aH_b), 5.13 (d, J = 2.8 Hz, 1H, H-6), 6.40 (d, J = 6.8 Hz, 2H, ArH), 6.42 (s, 1H, H-2), 6.57 (d, J = 8.4 Hz, 2H, ArH), 6.65 (t, J = 7.2 Hz, 1H, ArH), 6.84–6.88 (m, 4H, ArH), 7.09–7.29 (m, 9H, ArH), 10.35 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6 (OCH_2CH_3), 33.8 (C-5), 54.5 (C-2), 55.2 (OCH_3), 55.3 (OCH_3), 57.5 (C-6), 59.6 (OCH_2CH_3), 98.4 (C-3), 113.1, 113.6, 114.0, 116.2, 125.6, 125.7, 127.5, 127.7, 128.9, 134.8, 136.2, 138.0, 147.1, 156.1 (C-4), 158.1, 158.5, 168.4 (C=O); MS (EI, 70 eV) *m/z* (%): 534 (M^+, 13), 461 (4), 427 (41), 322 (80), 211 (79), 210 (100), 134 (5), 104 (5), 77 (41). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 855712 for **4n**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk), or via www.ccdc.cam.ac.uk/data request/cif.

Ethyl 4-(4-methoxyphenylamino)-2,6-bis(3-bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4p)

White solid; mp: 198–200 °C; IR (KBr, cm^{-1}) ν = 3,324 (NH), 1,655 (C=O); ^1H NMR (400 MHz, $CDCl_3$):

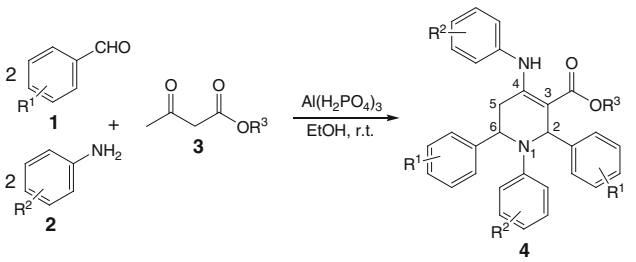
δ = 1.48 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.65 (dd, J = 15.2, 2.4 Hz, 1H, H′-5), 2.78 (dd, J = 15.2, 5.4 Hz, 1H, H″-5), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.30–4.34 (m, 1H, OCH_aH_b), 4.47–4.52 (m, 1H, OCH_aH_b), 5.03 (br s, 1H, H-6), 6.29 (d, J = 7.6 Hz, 2H, ArH), 6.32 (s, 1H, H-2), 6.42 (d, J = 9.2 Hz, 2H, ArH), 6.71 (d, J = 9.2 Hz, 2H, ArH), 6.74 (d, J = 8.8 Hz, 2H, ArH), 7.09–7.29 (m, 4H, ArH), 7.37 (d, J = 7.6 Hz, 1H, ArH), 7.43 (d, J = 7.6 Hz, 1H, ArH), 7.55 (s, 1H, ArH), 10.16 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9 (OCH_2CH_3), 33.5 (C-5), 55.4 (OCH_3), 55.6 (OCH_3), 57.5 (C-6), 59.7 (OCH_2CH_3), 96.4 (C-3), 114.1, 114.3, 114.6, 122.6, 122.7, 125.2, 125.4, 128.1, 129.5, 129.6, 129.7, 129.9, 130.3, 130.4, 130.5, 140.8, 145.5, 146.9, 151.4, 156.6 (C-4), 158.1, 167.9 (C=O); MS (EI, 70 eV): m/z (%) = 696 (M+4, 3), 694 (M+2, 5), 692 (M^+, 3), 568 (8), 402 (100), 328 (30), 290 (68), 275 (46), 167 (20), 77 (10); Anal. Calcd for $C_{34}H_{32}Br_2N_2O_4$: C 58.97, H 4.66, N 4.05. Found: C 59.25, H 4.75, N 4.17.

Methyl 4-(p-tolylamino)-2,6-diphenyl-1-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (4q)

White solid; mp: 190–192 °C; IR (KBr, cm^{-1}) ν = 3,310 (NH), 1,650 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.78 (dd, J = 15.2, 2.4 Hz, 1H, H′-5), 2.88 (dd, J = 15.2, 6.0 Hz, 1H, H″-5), 3.96 (s, 3H, OCH_3), 5.16 (d, J = 3.6 Hz, 1H, H-6), 6.20 (d, J = 8.4 Hz, 2H, ArH), 6.46 (s, 1H, H-2), 6.48 (d, J = 8.8 Hz, 2H, ArH), 6.92 (t, J = 8.0 Hz, 4H, ArH), 7.20–7.31 (m, 10H, ArH), 10.22 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1 (CH_3), 20.9 (CH_3), 33.6 (C-5), 50.9 (OCH_3), 55.2 (C-2), 58.2 (C-6), 97.5 (C-3), 112.9, 125.1, 126.0, 126.2, 126.4, 126.7, 127.1, 128.2, 128.6, 129.4, 135.2, 135.6, 143.0, 144.3, 144.8, 156.6 (C-4), 168.6 (C=O); MS (EI, 70 eV): m/z (%) = 488 (M^+, 28), 429 (9), 411 (91), 379 (37), 322 (29), 292 (81), 194 (80), 104 (19), 91 (100), 77 (37), 59 (11); Anal. Calcd for $C_{33}H_{32}N_2O_2$: C 81.12, H 6.60, N 5.73. Found: C 81.33, H 6.68, N 5.84.

General procedure for synthesis of highly functionalized dihydro-2-oxypyrrole **9**

A mixture of amine **5** (1 mmol) and dialkyl acetylenedicarboxylate **6** (1 mmol) in methanol (3 mL) was stirred for 20 min. Next, aromatic amine **7** (1 mmol), formaldehyde **8** (1.5 mmol), and $Al(H_2PO_4)_3$ (0.1 g) were added successively. The reaction mixture was allowed to stir at ambient temperature for the appropriate time (see Table 5). The progress of the reaction was monitored by TLC. After completion, the solid material was separated, dried, and then dissolved in acetone or $CHCl_3$ (10 mL). The catalyst was filtered and the solvent was evaporated under vacuum. The obtained solid was washed with EtOH (3 × 2 mL) to give the pure product **9**.

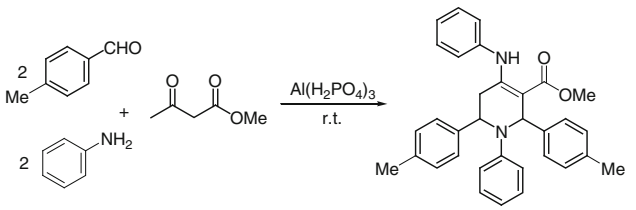


Scheme 1 Synthesis of highly funtionalized piperidine **4**

Ethyl 4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (9h)

Pall yellow solid; mp: 152–154 °C; IR (KBr, cm^{-1}) ν = 3,264 (NH), 1,692, 1,640 (2C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.23 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.49 (s, 2H, CH_2–N), 6.87 (d, J = 9.2 Hz, 2H, ArH), 6.93 (d, J = 9.2 Hz, 2H, ArH), 7.12 (d, J = 8.8 Hz, 2H, ArH), 7.69 (d, J = 9.2 Hz, 2H, ArH), 8.03 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 48.4 (CH_2–N), 55.4 (OCH_3), 55.5 (OCH_3), 60.1 (OCH_2CH_3), 101.3, 113.5, 114.2, 120.9, 124.8, 131.7, 132.0, 143.7, 156.8, 157.0, 163.5 (C=O),

Table 1 Optimization of the reaction conditions for the synthesis **4a**



Entry	Solvent	Catalyst (g)	Time (h)	Yield (%)[a]
1	EtOH	0.05	12	57
2	MeOH	0.05	12	54
3	CH_2Cl_2	0.05	12	38
4	EtOAc	0.05	12	35
5	MeCN	0.05	12	46
6	EtOH	0.1	12	74
7	EtOH	0.15	11	83
8	EtOH	0.2	10	87
9	EtOH	0.25	10	84
10	EtOH	0.3	10	80
11	MeOH	0.2	10	85
12	EtOH	No catalyst	24	–

[a] Yield of isolated product

164.8 (C=O); Anal. Calcd for $C_{21}H_{22}N_2O_5$: C 69.96, H 5.80, N 7.33. Found: C 70.14, H 5.89, N 7.30.

Methyl 4-(benzylamino)-1-(4-fluorophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (9l)

White solid; mp: 166–168 °C; IR (KBr, cm^{-1}) ν = 3,316 (NH), 1,700, 1,644 (2C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 4.42 (s, 2H, CH_2–N), 5.13 (d, *J* = 6.4 Hz, 2H, C*H*$_2$–NH), 8.90 (br s, 1H, NH), 7.09–7.13 (m, 2H, ArH), 7.29–7.38 (m, 5H, ArH), 7.72–7.75 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.5 (CH_2–NH), 48.2 (CH_2–N), 51.1 (OCH_3), 97.3, 115.1 (d, *J* = 22.0 Hz), 115.7, 116.0, 121.1 (d, *J* = 8.0 Hz), 125.1 (d, *J* = 8.0 Hz), 127.4, 127.5, 128.7, 134.8 (d, *J* = 8.0 Hz), 139.4, 159.8 (d, *J* = 243.0 Hz), 164.3 (C=O), 165.4 (C=O); MS (EI, 70 eV): *m/z* (%) = 340 (M^+, 51), 325 (14), 308 (30), 281 (26), 279 (37), 201 (9), 177 (10), 142 (10), 122 (18), 105 (10), 95 (20), 91 (100), 65 (21); Anal. Calcd for $C_{19}H_{17}FN_2O_3$: C 67.05, H 5.03, N 8.23. Found: C 67.33, H 5.15, N 8.40.

Methyl 4-(butylamino)-1-phenyl-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (9n)

White solid, mp: 61–63 °C (lit. mp: 60 °C) [33]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3H, CH_3), 1.42 (sextet, *J* = 7.2 Hz, 2H, CH_2), 1.64 (quintet, *J* = 7.2 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.85 (t, *J* = 7.2 Hz, 2H, C*H*$_2$–NH), 4.45 (s, 2H, C*H*$_2$–N), 6.85 (br, 1H, NH), 7.18 (d, *J* = 7.6 Hz, 1H, ArH), 7.40 (d, *J* = 7.6 Hz, 2H, ArH), 7.73 (d, *J* = 7.6 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 19.9(CH_2), 33.3 (CH_2), 42.7 (CH_2–NH), 47.7 (CH_2–N), 51.0 (OCH_3), 96.1, 118.4, 125.2, 128.8, 138.4, 164.5 (C=O), 165.6 (C=O).

Methyl 4–(butylamino)-1-(3,4-dichlorophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (9p)

White solid; mp: 97–99 °C; IR (KBr, cm^{-1}) ν = 3,335 (NH), 2,933, 2,853, 1,711, 1,642 (2C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3H, CH_3), 1.44 (sextet, *J* = 7.2 Hz, 2H, CH_2), 1.63 (quintet, *J* = 7.2 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.87 (2H, t, *J* = 7.2 Hz, C*H*$_2$–NH), 4.39 (s, 2H, C*H*$_2$–N), 6.75 (br s, 1H, NH), 7.46 (d, *J* = 8.8 Hz, 1H, ArH), 7.67 (dd, *J* = 9.0, 2.8 Hz, 1H, m, ArH), 8.00 (d, *J* = 2.8 Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 19.8 (CH_2), 33.3 (CH_2), 42.6 (CH_2–NH), 47.6 (CH_2–N), 51.0 (OCH_3), 96.1, 117.9, 120.5, 128.1, 130.5, 133.0, 138.2, 144.0, 164.5 (C=O), 165.5 (C=O); MS (EI, 70 eV): *m/z* (%) = 358 (M+2, 37), 356 (M^+, 57), 341 (8), 315 (51), 313 (78), 299 (55), 297 (100), 283 (52), 281 (78), 241 (16), 213 (13), 187

Table 2 Synthesis of highly substituted piperidine **4a–t**

Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	M.p. (°C)	Lit. M.p. (°C) [Ref][b]
1	4-Me	H	Me	**4a**	10	87	214–217	215–217 [12]
2	4-Me	H	Et	**4b**	10	85	228–230	228–231 [12]
3	4-F	H	Me	**4c**	10	84	192–194	193–195 [14]
4	4-Cl	H	Me	**4d**	10	85	188–190	189–191 [10]
5	4-OMe	H	Me	**4e**	12	79	178–181	180 [5]
6	4-NO_2	H	Me	**4f**	16	32	238–240	239–241 [5]
7	H	H	Me	**4g**	12	80	190–192	194 [5]
8	H	4-Cl	Et	**4h**	12	80	198–201	202 [5]
9	3-Cl	4-OMe	Me	**4i**	14	74	159–161	160 [5]
10	4-Me	4-Br	Me	**4j**	10	77	228–231	230–232 [12]
11	4-Me	4-Me	Me	**4k**	10	82	204–205	206–208 [12]
12	3-Me	H	Me	**4l**	11	80	126–128	131–134 [15]
13	4-Br	4-Cl	Me	**4m**	12	76	160–162	159–160 [15]
14	4-OMe	H	Et	**4n**	12	83	166–168	166–168 [41]
15	4-Me	4-Cl	Me	**4o**	10	81	204–206	204–206 [42]
16	3-Br	4-OMe	Et	**4p**	14	79	198–200	–
17	H	4-Me	Me	**4q**	10	78	190–192	–
18	4-Me	4-F	Et	**4r**	10	79	183–185	183–185 [41]
19	3-Br	H	Et	**4s**	10	82	165–167	164–167 [42]
20	4-F	4-Me	Me	**4t**	10	80	200–202	200–202 [41]

[a] Yield of isolated product

[b] The references of known products in the literature

13), 172 (23), 145 (15), 112 (17), 97 (20), 81 (39), 69 (75), 55 (60); Anal. Calcd for $C_{16}H_{18}Cl_2N_2O_3$: C 53.79, H 5.08, N 7.84. Found: C 53.97, H 5.21, N 7.93.

Results and discussion

In continuation of our work on heterocycles synthesis, especially synthesis of piperidines [40–42], herein, we employed $Al(H_2PO_4)_3$ as an efficient and recyclable heterogeneous catalyst for the one-pot three (in situ five)-component synthesis of highly functionalized piperidines in EtOH at ambient temperature (Scheme 1).

First, the reaction between 4-methylbenzaldehyde (2 mmol), aniline (2 mmol) and methyl acetoacetate (1 mmol) was carried out in the presence of $Al(H_2PO_4)_3$ (0.05 g) in EtOH at ambient temperature. The reaction proceeds smoothly to generate the corresponding highly substituted piperidine **4a** in 57 % yield after 12 h. In order to optimize the reaction conditions, this reaction was considered as the model (Table 1). The best result was achieved in the presence of 0.2 g of $Al(H_2PO_4)_3$ in EtOH at ambient temperature (Table 1, Entry 8). To illustrate the need for catalytic amounts of $Al(H_2PO_4)_3$ in these reactions, the model reaction was also studied in the absence of the catalyst in EtOH, where no product was obtained at room temperature even after 24 h (Table 1, Entry 12).

Using the optimized reaction conditions, a series of highly substituted piperidines were prepared in good to high yields from the reaction between aromatic aldehydes, anilines, and methyl/ethyl acetoacetate in the presence of $Al(H_2PO_4)_3$ as a catalyst. As indicated in Table 2, benzaldehyde and its derivatives containing electron withdrawing and/or electron donating groups reacted efficiently with aniline and substituted anilines to give the corresponding products **4** in good to high yields. However, *p*-nitro benzaldehyde gives the corresponding product in low yield (Table 2, Entry 7), 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 [14].

All known products have been reported previously in the literature and were characterized by comparison of IR and

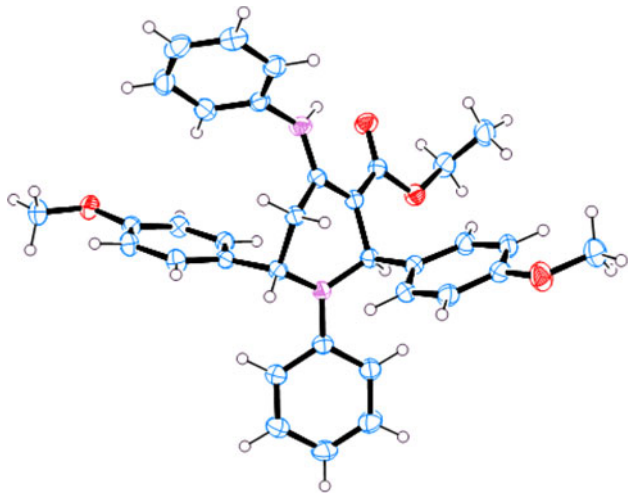
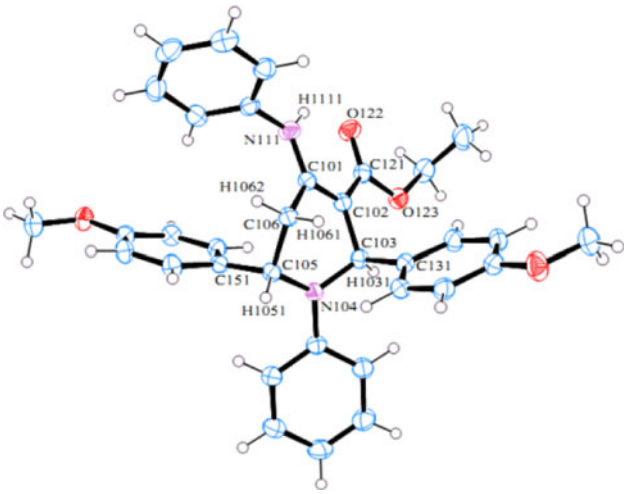


Fig. 1 ORTEP of the X-ray structure of piperidine **4n**

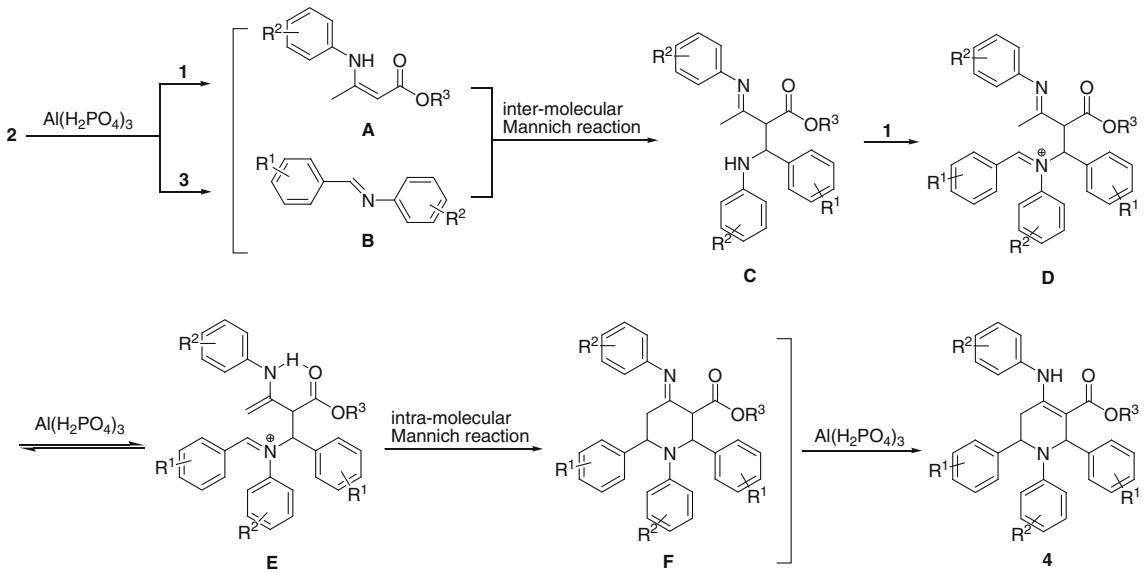
Table 3 Selected bond lengths (Å), bond angles (°), and torsion angles (°) in piperidine structure **4n**



Entry	Bond	Length (Å)
1	C101–C102	1.3682(16)
2	C102–C103	1.5191(16)
3	C103–N104	1.4674(14)
4	N104–C105	1.4638(14)
5	C105–C106	1.5445(16)
6	C106–C101	1.5026(16)

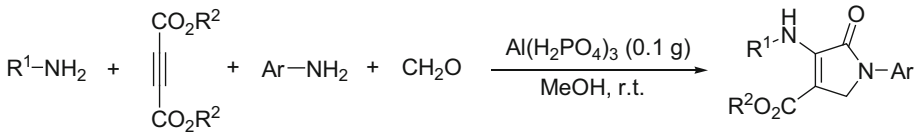
Entry	Atom1	Atom2	Atom3	Angle (°)
1	C102	C101	C106	115.65 (10)
2	C101	C102	C103	117.74 (10)
3	C102	C103	N104	109.96 (9)
4	C103	N104	C105	119.73 (9)
5	N104	C105	C106	109.83 (9)
6	C105	C106	C101	110.50 (9)

Entry	Atom1	Atom2	Atom3	Atom4	Angle (°)
1	C101	C102	C103	N104	44.1 (2)
2	C101	C106	C105	N104	51.0 (1)
3	C101	C106	C105	C151	−75.4 (1)
4	C102	C101	C106	C105	−48.9 (1)
5	C102	C103	N104	C105	−39.7 (2)
6	C103	N104	C105	C106	−6.5 (1)
7	C103	C102	C101	C106	0.2 (2)
8	C105	C106	C101	N111	133.2 (1)
9	C106	C101	C102	C121	−178.7 (1)



Scheme 2 Proposed mechanism for the synthesis of highly functionalized piperidine **4**

Scheme 3 Synthesis of highly substituted dihydro-2-oxypyrrole **9**

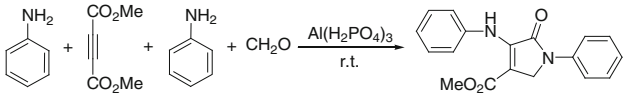


NMR spectra with authentic samples. The structures of new compounds **4p,q** were deduced on the basis of IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. For example, the mass spectrum of **4p** displayed the molecular ion peak (M^{+}) at $m/z = 692$, which is consistent with the proposed structure. The ^{1}H NMR spectrum of **4p** exhibited two doublets of doublets at $\delta = 2.65$ ($J = 15.2, 2.4$ Hz) and $\delta = 2.78$ ($J = 15.2, 5.4$ Hz) for the CH_2 protons of the piperidine ring (H′- H″-5). The methoxy groups appeared as two singlets at $\delta = 3.71$ and 3.80 ppm, respectively. The ethoxy protons were observed as a triplet at 1.48 ppm ($J = 7.2$ Hz) and two multiplets at 4.30–4.52 ppm. One of the methine protons of the piperidine ring (H-6) was observed as a broad singlet at δ 5.03 ppm, and another methine proton (H-2) appeared as a singlet at δ 6.32 ppm. The resonances of aromatic protons were observed as mixture of singlet, doublets, and multiplet at δ 6.29–7.55 ppm. The NH proton was observed as a singlet at δ 10.16 ppm, thus indicating an intramolecular H-bond formation with the vicinal carbonyl group. The ^{13}C NMR spectrum **4p** exhibited 29 distinct signals in agreement with the proposed structure. Furthermore, the structure as well as the relative stereochemistry of piperidine **4**, for example **4n** was further confirmed by single X-ray crystallographic analysis (Fig. 1). Selected bond length, bond angels, and torsion angels for compound **4n** are exhibited in Table 3.

On the basis of the previous literature [12–15, 40–42], the proposed mechanism for the formation of piperidine **4** is illustrated in Scheme 2. First, *β*-ketoester **3** and aldehyde **1** react with aniline **2** in the presence of $Al(H_2PO_4)_3$ to give

Table 4 Optimization of the reaction conditions for the synthesis **9a**

synthesis **9a**



Entry	Solvent	Catalyst (g)	Time (h)	Yield (%)[a]
1	EtOH	0.05	7	65
2	MeOH	0.05	5	73
3	EtOAc	0.05	10	34
4	MeCN	0.05	9	59
5	MeOH	0.1	5	81
6	MeOH	0.15	5	81
7	MeOH	0.2	5	78
8	MeOH	No catalyst	24	Trace

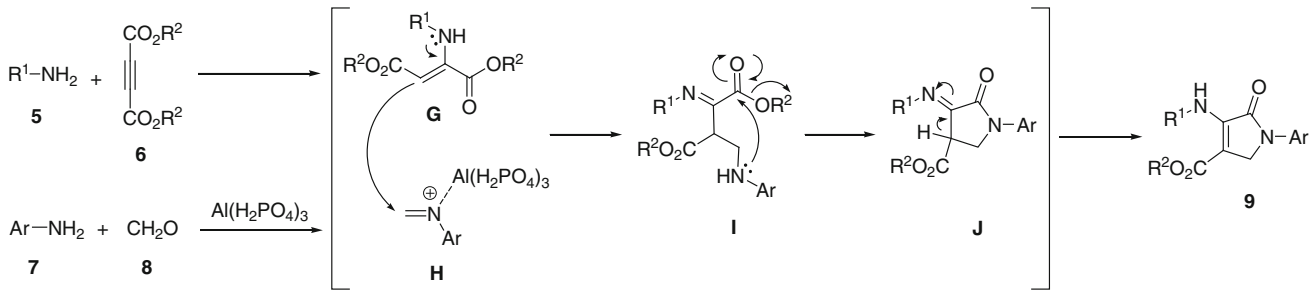
[a] Yield of isolated product

Table 5 Synthesis of highly functionalized dihydro-2-oxypyrroles **9a-p**

Entry	R^1	R^2	Ar	Product	Time (h)	Yield (%)[a]	Mp (°C)	Lit. mp (°C) [Ref][b]
1	Ph	Me	Ph	**9a**	5	81	154–155	155–156 [33]
2	Ph	Et	Ph	**9b**	5	80	136–138	138–140 [32]
3	4-Me–C_6H_4	Me	4-Me–C_6H_4	**9c**	5	82	177–179	177–178 [33]
4	4-Me–C_6H_4	Et	4-Me–C_6H_4	**9d**	5	79	128–130	131–132 [33]
5	4-F–C_6H_4	Et	4-F–C_6H_4	**9e**	6	83	171–173	172–173 [32]
6	4-Cl–C_6H_4	Me	4-Cl–C_6H_4	**9f**	6	81	175–177	173–174 [33]
7	4-Br–C_6H_4	Et	4-Br–C_6H_4	**9g**	5	84	166–168	169–171 [32]
8	4-OMe–C_6H_4	Et	4-OMe–C_6H_4	**9h**	6	77	152–154	–
9	$PhCH_2$	Me	4-OMe–C_6H_4	**9i**	5	79	124–126	129–130 [33]
10	$PhCH_2$	Me	Ph	**9j**	5	83	138–140	140–141 [32]
11	$PhCH_2$	Et	Ph	**9k**	6	83	129–131	130–132 [32]
12	$PhCH_2$	Me	4-F–C_6H_4	**9l**	5	80	166–168	–
13	$PhCH_2$	Me	4-Cl–C_6H_4	**9m**	5.5	79	145–147	147–148 [33]
14	*n*-C_4H_9	Me	Ph	**9n**	6	76	61–63	60 [33]
15	*n*-C_4H_9	Me	4-Br–C_6H_4	**9o**	5	82	109–111	108–109 [33]
16	*n*-C_4H_9	Me	3,4-Cl_2–C_6H_3	**9p**	5	78	97–99	–

[a] Isolated yield

[b] References refer to known products as mentioned in the literature



Scheme 4 Suggested mechanism for the synthesis of polyfunctionalized dihydro-2-oxypyrrole **9**

enamine **A** and imine **B**, respectively. Next, the reaction between enamine **A** and imine **B** leads to intermediate **C** through intermolecular Mannich-type reaction. The intermediate **C** reacts with aldehyde **1** to generate intermediate **D**. Then, tautomerization of **D** generates intermediate **E**, which immediately undergoes intramolecular Mannich-type reaction to produce intermediate **F**. In the final step, tautomerization of the intermediate **F** generates the desired piperidine **4** due to conjugation with the ester group.

Motivated from the efficient catalytic activity of $Al(H_2PO_4)_3$ for the synthesis of highly functionalized piperidines, we explored its catalytic activity for the synthesis of polyfunctionalized dihydro-2-oxypyrroles **9** via one-pot four-component reaction of amines, dialkyl acetylenedicarboxylates and formaldehyde at room temperature (Scheme 3).

To find the optimal conditions, the reaction of aniline, dimethyl acetylendicarboxylate (DMAD), and formaldehyde was performed using different quantities of $Al(H_2PO_4)_3$ in different solvents at ambient temperature (Table 4). The use of 0.1 g of catalyst in MeOH resulted in the highest yield in 5 h (Table 4, Entry 5). Note that a control experiment showed that product **9a** was obtained only in trace yield

Table 6 Reusability of $Al(H_2PO_4)_3$ in the synthesis of compounds **4a** and **9a**

Run no.	Compound **4a**		Compound **9a**	
	Time (h)	Yield (%)[a]	Time (h)	Yield (%)[a]
1	10	87	5	81
2	10	86	5	81
3	10	84	5	79
4	12	81	6	74
5	14	80	6	75

[a] Isolated yield

Table 7 Comparison result of $Al(H_2PO_4)_3$ with the reported catalysts in literature for the synthesis of highly functionalized piperidines **4a** and **4 g** and dihydro-2-oxypyrrole **9b**

Compound	Catalyst/conditions	Time (h)	Yield (%)	Ref.
4a	$InCl_3/CH_3CN$, r.t.	24	50	[10]
	$BDMS/CH_3CN$, r.t.	3	80	[12]
	TBATB/EtOH, r.t.	10	78	[13]
	I_2/MeOH, r.t.	8	84	[14]
	CAN/CH_3CN, r.t.	22	85	[15]
	p-TsOH·H_2O/EtOH, r.t.	7	89	[41]
	Oxalic acid dihydrate/ EtOH, r.t.	12	81	[40]
	$Al(H_2PO_4)_3$/EtOH, r.t.	10	87	–
4g	L-proline/TFA/CH_3CN, 20-30 °C	17	70	[5]
	$InCl_3/CH_3CN$, r.t.	24	60	[10]
	$BDMS/CH_3CN$, r.t.	3	75	[12]
	TBATB/EtOH, r.t.	24	74	[13]
	I_2/MeOH, 55 °C	8	81	[14]
	CAN/CH_3CN, r.t.	20	82	[15]
	$ZrOCl_2·8H_2O$/EtOH, reflux	3.5	80	[16]
	p-TsOH·H_2O/EtOH, r.t.	10	78	[41]
	Oxalic acid dihydrate/ EtOH, r.t.	12	78	[40]
	$Al(H_2PO_4)_3$/EtOH, r.t.	12	80	–
9b	AcOH/EtOH, 70 °C	4	85	[32]
	I_2/MeOH, r.t.	1	81	[33]
	$Al(H_2PO_4)_3$/MeOH, r.t.	5	80	–

when the reaction was examined in the absence of catalyst (Table 4, Entry 8).

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 have been summarized in Table 5. 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 **9a–h** in good to high yields (Table 5, entries 1–8). Additionally, two different amines were used for the one-pot four-component synthesis of different highly functionalized dihdro-2-oxypyrroles **5i–p** (Table 5, entries 9–16). Aliphatic amines such as benzyl amine and *n*-butyl amine reacted smoothly with dialkyl acetylenedicarboxylates, aromatic amines, and formaldehyde to generate the desired products in high yields. The structures of these products were also characterized on the basis of IR, ^1H, and ^{13}C NMR, Mass spectra and elemental analysis.

A reasonable mechanism for the synthesis of dihydeo-2-oxypyrrole **9** was proposed (Scheme 4). The reaction between amine **5** and dialkyl acetylenedicarboxylate **6**, and also reaction of amine **7** whit formaldehyde **8**, give intermediate **G** and imine **H**, respectively. Attack of **G** on **H** leads to intermediate **I**, which converts to intermediate **J** by intamolecular cyclization. In the final step, tautomerization of intermediate **J** produces the corresponding dihydeo-2-oxypyrrole **9**.

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 $Al(H_2PO_4)_3$ was examined in the synthesis of highly functionalize piperidine **4a** and dihydro-2-oxypyrrole **9a** as two examples. Since $Al(H_2PO_4)_3$ is a heterogeneous catalyst, it was separated and reused after being washed with $CHCl_3$ and dried at 100 °C for 60 min. The results show that the catalyst can be used up to five times without significant loss of its activity (Table 6).

To compare the applicability of the $Al(H_2PO_4)_3$ with the reported catalysts in the literature for the synthesis of highly functionalized piperidines and dihydro-2-oxypyrroles, we have tabulated the results of these catalysts in Table 7. As shown in Table 7, $Al(H_2PO_4)_3$ can act as effective catalyst with respect to reaction times and yields of products.

In conclusion, we have developed simple and efficient methods for the one-pot multi-component synthesis of highly functionalize piperidines and dihydro-2-oxypyrroles using $Al(H_2PO_4)_3$ as catalyst under mild reaction conditions. The noteworthy aspects of these procedures are high atom economy, high to excellent yields, inexpensive and reusable catalyst, operational simplicity, and lack of need for complex separation and column chromatography.

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