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p-Toluenesulfonic acid doped polystyrene (PS-PTSA): solvent-free microwave assisted cross-coupling-cyclization–oxidation to build one-pot diversely functionalized pyrrole from aldehyde, amine, active methylene, and nitroalkane

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ABSTRACT

A solvent-free environmentally benign approach for the synthesis of diversified pyrrole derivatives has been described by the one-pot multicomponent reaction of aldehydes, nitroalkane, amine, and enolizable active C–H reactant using polystyrene supported *p*-toluenesulfonic acid (PS-PTSA) under microwave irradiation. In comparison to the conventional methods, this efficient green protocol provides remarkable advantages such as good to excellent yields, shorter reaction time, low cost, easy work-up procedure, and bypass for use of hazardous transition metal catalyst and organic solvent.

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Introduction

Over the last few decades, great efforts have been devoted to synthesize libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents.[1] Pyrrole is well reported as 'privileged scaffolds', each original substituent or a new combination of substituents in the pyrrole cycle endows the compounds with wide range of biological activities.[2–6] Tetrasubstituted pyrroles are of paramount importance owing to their antibacterial,[7] antiviral, antitumor,[8] and antioxidant[9] activities and ability of inhibiting the cytokine-mediated diseases.[10] In addition, pyrroles are employed as special dyes, insecticides,[11] and versatile building blocks in organic synthesis as well as in materials chemistry.[12] Therefore, chemists are more concerned for the development of efficient methodologies for the synthesis of polyfunctionalized pyrroles.[13] As a consequence, a lot of amazing progress has been achieved in the elaboration of elegant synthetic methodologies allowing structurally diverse pyrroles to be prepared.

Among numerous approaches to the synthesis of pyrroles, multicomponent coupling reactions are always of great interest. Over the last decade, a number of methodologies have been devoted for the synthesis of this valuable precursor.[14,15] However, these methods have some lack of efficiencies, such as high reaction temperatures, long reaction time, expensive catalysts, unsatisfactory yields, and complex work-up procedures.

Consequently, chemists are interested to find a more convenient and efficient method for the synthesis of pyrroles. Nowadays use of green chemical process is gaining importance in global chemical industry due to environmental aspects. Currently, multi-component one-pot syntheses under microwave-assisted organic synthesis are accepted widely as environmentally benign, efficient synthetic methodology, and easy work-up procedures.[16] The main advantages of this method in comparison to common laboratory techniques are reduction of the reaction time, increased reaction efficiency, high product purity, improved selectivity, reduced byproduct formation, and use of milder reaction conditions. Moreover microwave promoted, especially when either one of the substrates or the products is a liquid and can be used as the solvent of the reaction are particularly welcome. In the recent years, heterogeneous catalysts have found increased application in organic synthesis[17] as they are efficient, easily recovered, and recycled.

In this context polystyrene supported *p*-toluenesulfonic acid (PS-PTSA) is synthetically useful as an efficient proton source

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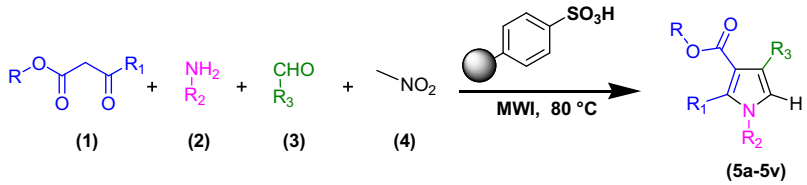


Scheme 1. Synthesis of tetrasubstituted pyrrole derivative catalyzed by PS-PTSA.

was found in organic reactions. Because *p*-toluene sulfonic acid is a strong organic acid, it is widely used as a catalyst in the organic reactions. Nevertheless, it is easily soluble in aqueous as well as in the organic solvent, so that reuse and separation from the reaction mixture are tedious and inconvenient. On the other hand polystyrene-supported *p*-toluene sulfonic acid (PS-PTSA) is a tightly bound complex of styrene-divinylbenzene copolymer and PTSA. The unique feature of polystyrene-supported *p*-toluene sulfonic acid, over conventional acid catalysts is ease of handling, stability, recyclability, cost effective, and tunable Lewis acidity. It could be successively used in multicomponent reactions such as Knoevenagel condensation and Michael-type addition.[18] These reactions are known to be useful for the synthesis of biological interesting compounds. Despite its great importance, only a few papers reported on its catalytic application in organic transformation.[18–22]

In continuation of our interest to investigate environmentally friendly reaction methodology by microwave irradiation (MWI) under solvent-free heterogeneous organic synthesis[17f] the literature survey revealed that there are no reports on MWI mediated PS-PTSA catalyzed synthesis for diversely functionalized tetrasubstituted pyrrole. Herein, we wish to report a simple and useful synthetic protocol, microwave assisted synthesis of tetra-substituted pyrroles by employing PS-PTSA as a catalyst through one-pot four-component condensation reaction of aldehydes, amines, β-ketoesters, and nitroalkanes at 80 °C as shown in Scheme 1.

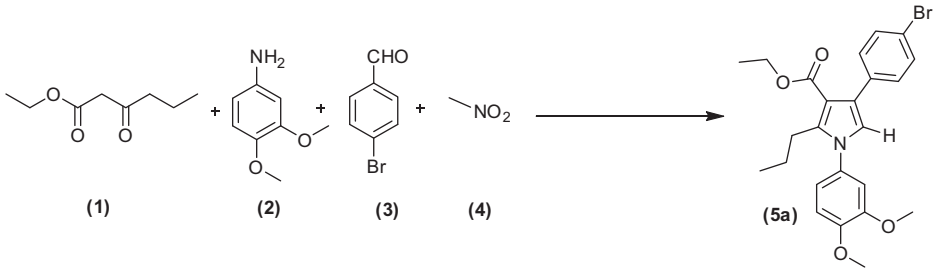
Result and discussions

The strategy provided two new C–C bonds and two C–N bonds in a single operation through condensation and intramolecular cyclization sequence. On the basis of a proposed scheme, a number of starting materials are readily available for the synthesis of a small combinatorial library of tetra substituted pyrrole derivatives.

Accordingly, to investigate the reaction conditions, we carried out the reaction between ethyl 3-oxohexanoate (**1**, 1 mmol), 3,4-dimethoxybenzenamine (**2a**, 1 mmol), 4-bromobenzaldehyde (**3**, 1 mmol), and nitromethane (**4**, 1 ml) as a model.

It was investigated by utilizing different catalysts under both conventional and microwave conditions without solvent. Catalysts such as $Y(OAc)_3{\cdot}H_2O$, $GaBr_3$, $GaCl_3$, and PTSA either completely impede the reaction or diminish the yield of the product (Table 1, entries 1–4).

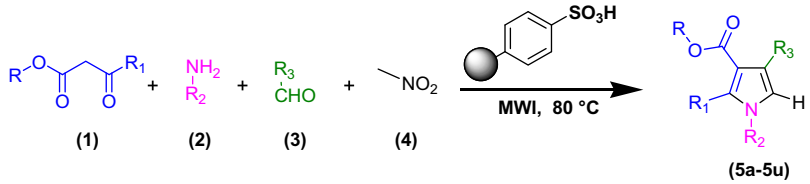
Table 1
Optimization of reaction conditions in the synthesis of **5a**[a]



Entry	Catalyst (mol %)	Solvent	Temp (°C)	Conventional		Microwave	
				Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)
1	$Y(OAc)_3{\cdot}H_2O$ (5)	Neat[d]	80	240	30	142	45
2	$GaBr_3$ (5)	Neat[d]	80	310	35	156	55
3	$GaCl_3$ (5)	Neat[d]	80	280	30	152	52
4	PTSA (5)	Neat[d]	80	255	45	126	53
5	STA (5)	Neat[d]	80	220	75	88	85
6	$FeCl_3{\cdot}SiO_2$ (5)	Neat[d]	80	245	60	91	74
7	TiO_2–SiO_2 (5)	Neat[d]	80	290	60	80	78
8	InF_3 (5)	Neat[d]	80	324	65	123	75
9	K-10 (5)	Neat[d]	80	334	60	156	77
10[c]	PS-PTSA (5 mg)	Neat[d]	80	245	85	56	93, 91, 90, 87, 86, 86, 85
11	PS-PTSA (2 mg)	Neat[d]	80	266	65	69	75
12	PS-PTSA (3 mg)	Neat[d]	80	254	70	62	85
13	PS-PTSA (8 mg)	Neat[d]	80	249	85	56	93
14	PS-PTSA (5 mg)	H_2O	80	310	60	146	76
15	PS-PTSA (5 mg)	[Bmim][Cl]	80	251	55	139	65
16	PS-PTSA (5 mg)	Toluene	80	263	60	141	75
17	PS-PTSA (5 mg)	Ethanol	80	253	65	112	79
18	PS-PTSA (5 mg)	Neat[d]	40	292	68	108	80
19	PS-PTSA (5 mg)	Neat[d]	60	248	85	78	83

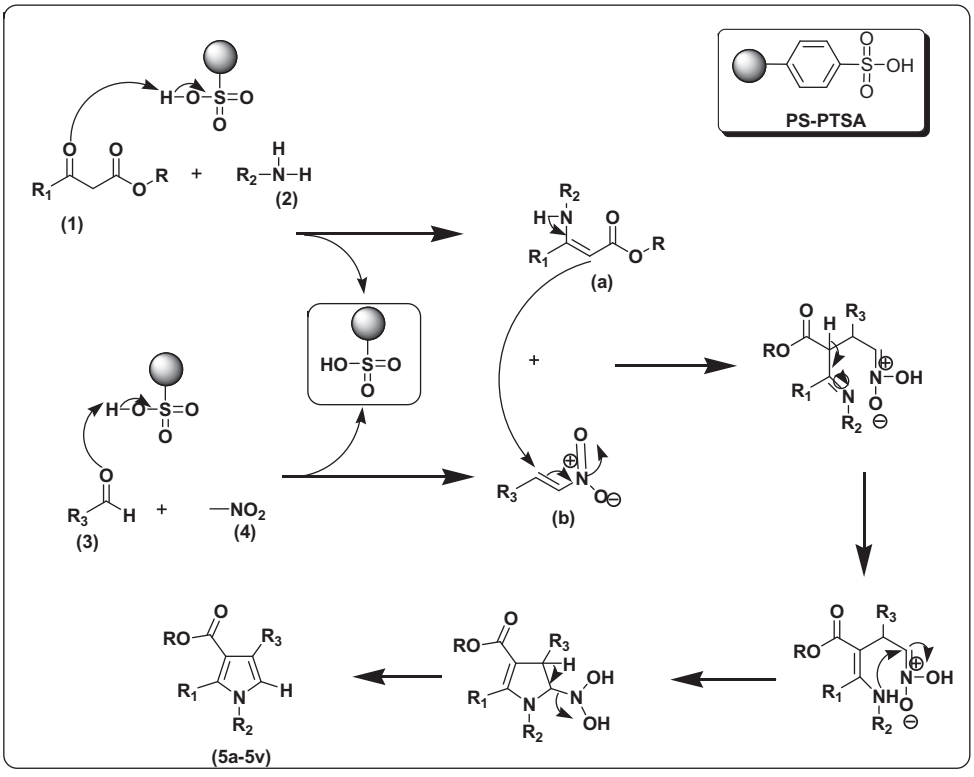
[a] Reaction of ethyl 3-oxohexanoate (**1**, 1 mmol), 3,4-dimethoxybenzenamine (**2a**, 1 mmol), 4-bromobenzaldehyde (**3**, 1 mmol), and nitromethane (**4**, 1 ml).
[b] Isolated yield.
[c] Catalyst was reused seven times.
[d] Nitromethane itself as reagent as well as solvent.

Table 2
Microwave-assisted synthesis of tetra substituted pyrrole[a]



Entry	R	R_1	R_2	R_3	Products	Time (min)	Yield[b] (%)
1	Et	Pr	3,4-$OCH_3C_6H_3$	4-BrC_6H_4	**5a**	56	93
2	Et	Pr	4-BrC_6H_4	4-ClC_6H_4	**5b**	55	91
3	Et	Pr	3,4-$OCH_3C_6H_3$	Ph	**5c**	51	92
4	Et	Pr	4-$OCH_3C_6H_4$	4-BrC_6H_4	**5d**	53	91
5	Et	Pr	3,4-$OCH_3C_6H_3$	2-$CH_3C_6H_4$	**5e**	52	89
6	Et	Pr	3,4-$OCH_3C_6H_3$	2-BrC_6H_4	**5f**	61	90
7	Et	Pr	3,4-$CH_3C_6H_3$	4-ClC_6H_4	**5g**	54	92
8	Et	Pr	3,4-$OCH_3C_6H_3$	4-ClC_6H_4	**5h**	52	89
9	Et	Pr	3,4-$OCH_3C_6H_3$		**5i**	57	91
10	Et	Pr	3,4-$OCH_3C_6H_3$	4-$C(CH_3)_2C_6H_4$	**5j**	59	93
11	Et	Pr	3,4-$OCH_3C_6H_3$	2-Cl-6-FC_6H3	**5k**	64	89
12	Et	Pr	3,4-$OCH_3C_6H_3$	4-FC_6H_4	**5l**	56	92
13	Me	Me	3,4-$CH_3C_6H_3$	4-FC_6H_4	**5m**	55	87
14	Et	Pr	3,4-$CH_3C_6H_3$	4-FC_6H_4	**5n**	62	84
15	Et	Pr	4-$OCH_3C_6H_4$	4-FC_6H_4	**5o**	53	88
16	Et	Pr	3,4-$OCH_3C_6H_3$	4-$CH_3C_6H_4$	**5p**	58	81
17	Et	Pr	5-Amino indane	Ph	**5q**	63	83
18	Et	Pr	3,4-$OCH_3C_6H_3$	2-$CH_3C_6H_4$	**5r**	57	85
19	Et	Pr	3,4-$CH_3C_6H_3$	2-Cl-6-FC_6H3	**5s**	66	91
20	Me	Me	3,4-$CH_3C_6H_3$	2-Cl-6-FC_6H3	**5t**	59	90
21	Et	Pr	4-$OCH_3C_6H_4$	4-$C(CH_3)_2C_6H_4$	**5u**	60	88
22	Me	Me	$-CH(CH_3)_2$	4-ClC_6H_4	**5v**	76	78

[a] Reaction of β-ketoesters (**1**, 1 mmol), amines (**2** 1 mmol), aldehydes (**3**, 1 mmol), and nitroalkanes (**4**, 1 ml) catalyzed by PS-PTSA under microwave irradiation at 80 °C.
[b] Isolated yield.



Scheme 2. Schematic presentation of PS-PTSA catalyst activity in the synthesis of **5a**–**5v**.

Due to numerous advantages with heterogeneous solid acid catalyzed reactions, the reaction was performed with STA, $FeCl_3.SiO_2$, TiO_2–SiO_2, InF_3, and K-10 and obtained moderate product yields (Table 1, entries 5–9). Subsequently the reaction was performed in the presence of PS-PTSA, to obtain the desired product (**5a**) in high yields (Table 1, entry 10).

When studied the required amount of PS-PTSA catalyst for maximum efficiency it was found that 5 mg PS-PTSA (Table 1, entry 10) was efficient to get optimum product yield. Additional amount of catalyst did not increase the yields considerably (Table 1). The effect of solvent on the model reaction was studied in both conventional and microwave conditions using 5 mg of PS-PTSA in different solvents and without solvent. The reaction was also studied at varying temperatures (40, 60, and 80 °C). The optimum conversion of reactants to product was achieved when nitromethane itself was employed as a solvent at 80 °C.

The recyclability of the PS-PTSA catalyst was also established by running the same model reaction in seven cycles with recovered PS-PTSA and obtained **5a** in 93%, 91%, 90%, 87%, 86%, 86%, and 85% product yields. This proved that efficiency of the catalyst can be used for multiple usage purpose without much loss of its efficiency (Table 1, entry 10). From all these establishments (Table 1) we concluded that 5 mg of PS-PTSA, at 80 °C MWI are optimized reaction conditions for the synthesis of tetra substituted pyrrole (**5a**–**5u**).

To explore the scope of this present protocol, reactions of several amines, aldehydes, β-ketoesters, and nitromethane in the presence of 5 mg of PS-PTSA were conducted. The results are summarized in Table 2. Thus, we selected the optimized reaction condition to examine the universality of this catalyst application with different electron rich and deficient substrates. It was gratifying to observe that most of the tested substrates exhibited satisfactory reactivity profiles, in all cases leading to a heterocyclization sequence that readily afforded the target structures (Table 2).

All the structures of synthesized (**5a**–**5v**) compounds have been ascertained on the basis of ^{1}H NMR, ^{13}C NMR, and HRMS data.

Presumably the reaction seems to proceed through the following mechanistic pathway as presented in Scheme 2. The catalyst PS-PTSA appears to play a key role as acid in the reaction and accelerate the reaction to help in the formation of the intermediate β-enamino carbonyl (a) and nitrostyrene (b) which then undergoes Michael reaction followed by cyclization leading to the final pyrrole products **5a**–**5v** as shown in Scheme 2.

Conclusion

In conclusion, we demonstrated a facile and environmentally benign method for the synthesis of highly functionalized pyrrole compounds by a one-pot four-component condensation reaction of aldehydes, nitroalkane, amine, and an active methylene compound in the presence of polystyrene supported *p*-toluenesulfonic acid (PS-PTSA) as catalyst under microwave-assistance. This method offers several advantages, including shorter reaction time with excellent yields, a simple work-up procedure, ease of separation, and recyclability of the catalyst, no need of anhydrous condition, no base, or any additional activator required as well as the ability to tolerate a wide variety of benzaldehyde, active methylene compounds, and amine.

Experimental

Synthesis of ethyl 4-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5a)

A mixture of ethyl 3-oxohexanoate (**1**, 1 mmol), 3,4-dimethoxybenzenamine (**2a**, 1 mmol), 4-bromobenzaldehyde (**3**, 1 mmol), nitromethane (**4**, 1 ml), and 5 mg of PS-PTSA was taken in an open vessel in CATA-4R—Scientific Microwave oven and irradiated at 80 °C (140 W) at an ambient pressure for 56 min. The reactions were followed by thin layer chromatography (TLC) using hexane/ethyl acetate as an eluent. After completion of the reaction, the mixture was washed with ethyl acetate and filtered to recover the catalyst. The filtrate was evaporated and the crude product was purified by flash column chromatography on silica gel (200−300 mesh) with ethyl acetate and hexane as eluent to afford the product **5a**. The PS-PTSA catalyst was reused by the way of addition of ethyl acetate to the reaction mixture and filtration followed by drying in a vacuum oven every time.

Ethyl 4-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5a)

Yield 93%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H), 1.49–1.58 (m, 2H), 2.78 (t, J = 7.7 Hz, 2H), 3.88 (s, 3H), 3.94 (s, 3H), 4.19 (q, J = 7.3 Hz, 2H), 6.62 (s, 1H), 6.81 (s, 1H), 6.88 (dd, J = 2.2, J = 6.2, 1H), 6.93 (d, J = 8.8 Hz, 1H), 7.29 (d, J = 8.87 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.24, 23.79, 28.02, 56.23, 59.60, 110.53, 110.64, 111.05, 119.17, 120.31, 121.59, 125.25, 130.72, 131.03, 132.00, 134.79, 142.16, 149.20, 149.29, 165.51; HRMS (ESI, m/z): calcd for $C_{24}H_{26}BrNO_4$ ($M+H^+$) 471.1045, found: 471.1047.

Ethyl 1-(4-bromophenyl)-4-(4-chlorophenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5b)

Yield 91%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H), 1.45–1.55 (m, 2H), 2.79 (t, J = 8.0 Hz, 2H), 4.18 (q, J = 7.3 Hz, 2H), 6.60 (s, 1H), 7.20 (d, J = 9.5 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H); 7.48 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.18, 14.23, 23.71, 27.83, 59.74, 111.51, 121.19, 122.50, 125.90, 127.85, 128.50, 129.92, 130.67, 132.38, 132.71, 134.07, 137.59, 137.79, 138.49, 141.70, 165.40; HRMS (ESI, m/z): calcd for $C_{22}H_{21}BrClNO_2$ ($M+H^+$) 445.0444, found: 445.0443.

Ethyl 1-(3,4-dimethoxyphenyl)-4-phenyl-2-propyl-1*H*-pyrrole-3-carboxylate (5c)

Yield 92%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.3 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H), 1.83–1.89 (m, 2H), 2.95 (t, J = 7.7 Hz, 2H), 3.75 (s, 3H), 4.02–4.05 (m, 5H), 6.79 (s, 1H), 7.35–7.38 (m, 3H), 7.44–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 13.75, 14.40, 23.55, 39.17, 55.95, 56.36, 61.24, 104.07, 107.90, 120.44, 125.84, 128.43, 129.38, 136.59, 144.92, 145.29, 149.73, 150.18, 153.09, 156.43, 169.06; HRMS (ESI, m/z): calcd for $C_{24}H_{27}NO_4$ ($M+H^+$) 393.1940, found: 393.1938.

Ethyl 4-(4-bromophenyl)-1-(4-methoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5d)

Yield 91%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H), 1.45–1.55 (m, 2H), 2.76 (t, J = 8.2 Hz, 2H), 3.86 (s, 3H), 4.19 (q, J = 7.3 Hz, 2H), 6.59 (s, 1H), 6.97 (d, J = 8.4, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 10.6 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.22, 14.25, 23.66, 27.92, 55.68, 59.60, 110.60, 114.49, 120.28, 121.65, 125.22, 128.11, 130.71, 131.04, 131.90, 134.87, 142.25, 159.59, 165.57; HRMS (ESI, m/z): calcd for $C_{23}H_{24}BrNO_3$ ($M+H^+$) 441.0939, found: 441.0941.

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Ethyl 1-(3,4-dimethoxyphenyl)-2-propyl-4-o-tolyl-1*H*-pyrrole-3-carboxylate (5e)

Yield 89%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 7.3 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H), 1.50–1.60 (m, 2H), 2.29 (s, 3H), 2.84 (t, J = 7.7 Hz, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 4.04 (q, J = 7.3 Hz, 2H), 6.51 (s, 1H), 6.84 (s, 1H), 6.91 (d, J = 7.4, 2H), 7.15 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 7.4 Hz, 2H), 7.22 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 13.85, 14.19, 20.51, 23.71, 27.87, 56.23, 59.18, 110.53, 111.05, 111.92, 119.11, 121.09, 124.92, 125.54, 126.75, 129.23, 130.29, 132.36, 136.37, 137.47, 141.29, 148.99, 149.23, 165.62; HRMS (ESI, m/z): calcd for $C_{25}H_{29}NO_4$ (M+H$^+$) 407.2096, found: 407.2096.

Ethyl 4-(2-bromophenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5f)

Yield 90%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 7.3 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H), 1.50–1.59 (m, 2H), 2.84 (t, J = 7.7 Hz, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 4.07 (q, J = 7.3 Hz, 2H), 6.59 (s, 1H), 6.85 (s, 1H), 6.92 (s, 2H), 7.11–7.15 (m, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 13.83, 14.16, 23.63, 27.71, 56.20, 56.24, 59.36, 110.54, 111.04, 111.99, 119.16, 121.58, 124.99, 125.41, 126.62, 128.05, 131.69, 132.14, 137.79, 141.24, 149.05, 149.23, 165.38; HRMS (ESI, m/z): calcd for $C_{24}H_{26}BrNO_4$ (M+H$^+$) 471.1045, found: 471.1045.

Ethyl 4-(4-chlorophenyl)-1-(3,4-dimethylphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5g)

Yield 92%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H), 1.47–1.57 (m, 2H), 2.31 (s, 3H), 2.32 (s, 3H), 2.78 (t, J = 8.1 Hz, 2H), 4.18 (q, J = 7.3 Hz, 2H), 6.59 (s, 1H), 7.03 (dd, J = 2.2, J = 5.9, 1H), 7.07 (s, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.20, 14.24, 19.57, 19.93, 23.68, 27.93, 59.54, 110.68, 121.53, 124.08, 125.24, 127.74, 127.86, 129.88, 130.35, 130.68, 132.09, 134.45, 136.80, 137.13, 137.90, 141.96, 165.60; HRMS (ESI, m/z): calcd for $C_{24}H_{26}ClNO_2$ (M+H$^+$) 395.1652, found: 395.1654.

Ethyl 4-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5h)

Yield 89%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H), 1.49–1.58 (m, 2H), 2.78 (t, J = 8.2 Hz, 2H), 3.88 (s, 3H), 3.94 (s, 3H), 4.19 (q, J = 7.3 Hz, 2H), 6.62 (s, 1H), 6.81 (s, 1H), 6.88 (dd, J = 2.2, J = 6.2, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.22, 14.24, 23.77, 28.01, 56.20, 59.58, 110.53, 110.67, 111.05, 119.16, 121.61, 125.23, 127.76, 130.65, 132.00, 132.14, 134.31, 142.12, 149.18, 149.27, 165.51; HRMS (ESI, m/z): calcd for $C_{24}H_{26}ClNO_4$ (M+H$^+$) 427.1550, found: 427.1552.

Ethyl 1-(3,4-dimethoxyphenyl)-2-propyl-4-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (5i)

Yield 91%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H), 1.48–1.57 (m, 2H), 2.77 (t, J = 7.7 Hz, 2H), 3.88 (s, 3H), 3.94 (s, 3H), 4.25 (q, J = 7.3 Hz, 2H), 6.70 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.86–6.89 (m, 1H), 6.92 (d, J = 8.4 Hz, 1H), 7.00–7.02 (m, 1H), 7.18–7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.23, 14.28, 23.73, 28.05, 56.20, 59.64, 110.53, 111.03, 118.56, 119.18, 122.36, 123.89, 126.13, 126.82, 131.85, 136.90, 142.04, 149.19, 149.26, 165.38; HRMS (ESI, m/z): calcd for $C_{22}H_{25}NO_4S$ (M+H$^+$) 399.1504, found: 399.1504.

Ethyl 4-(4-isopropylphenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5j)

Yield 93%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H), 1.26 (d, J = 7.0 Hz, 6H), 1.49–1.59 (m, 2H), 2.79 (t, J = 7.7 Hz, 2H), 2.88–2.95 (m, 1H), 3.88 (s, 3H), 3.93 (s, 3H), 4.18 (q, J = 7.0 Hz, 2H), 6.62 (s, 1H), 6.83 (s, 1H), 6.87–6.93 (m, 2H), 7.19 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.10, 14.24, 23.80, 24.15, 28.02, 33.90, 56.16, 59.43, 110.55, 110.86, 111.01, 119.11, 121.38, 125.68, 126.39, 129.23, 132.25, 133.09, 141.57, 146.83, 149.01, 149.20, 165.77; HRMS (ESI, m/z): calcd for $C_{27}H_{33}NO_4$ (M+H$^+$) 435.2409, found: 435.2407.

Ethyl 4-(2-chloro-6-fluorophenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5k)

Yield 89%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H), 1.51–1.58 (m, 2H), 2.85 (t, J = 7.9 Hz, 2H), 3.90 (s, 3H), 3.94 (s, 3H), 4.08 (q, J = 7.0 Hz, 2H), 6.66 (s, 1H), 6.86 (s, 1H), 6.93 (s, 2H), 6.98–7.03 (m, 1H), 7.17–7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 13.87, 14.18, 23.60, 27.83, 56.22, 56.27, 59.30, 110.57, 111.04, 112.02, 113.43, 113.67, 115.09, 119.22, 122.62, 124.70, 128.19, 128.28, 132.10, 141.72, 149.13, 149.25, 162.33 (C–F, d, J = 243 Hz), 165.10; HRMS (ESI, m/z): calcd for $C_{24}H_{25}ClFNO_4$ (M+H$^+$) 445.1456, found: 445.1456.

Ethyl 4-(4-fluorophenyl)-1-(3,4-dimethoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5l)

Yield 92%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H), 1.51–1.57 (m, 2H), 2.79 (t, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.94 (s, 3H), 4.18 (q, J = 7.0 Hz, 2H), 6.61 (s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 8.8, 2H), 7.35–7.40 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.18, 14.24, 23.77, 28.02, 56.20, 59.51, 110.54, 111.05, 114.30, 114.51, 119.15, 121.50, 125.42, 129.88, 130.83, 130.91, 131.80, 132.08, 141.95, 149.14, 149.27, 163.01 (C–F, d, J = 243 Hz), 165.58; HRMS (ESI, m/z): calcd for $C_{24}H_{26}FNO_4$ (M+H$^+$) 411.1845, found: 411.1844.

Methyl 4-(4-fluorophenyl)-2-methyl-1-(3,4-dimethylphenyl)-1*H*-pyrrole-3-carboxylate (5m)

Yield 87%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.32 (s, 3H), 2.42 (s, 3H), 3.69 (s, 3H), 6.63 (s, 1H), 6.99–7.04 (m, 3H), 7.04 (s, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.34–7.7.39 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ; 12.88, 19.54, 19.94, 50.69, 111.08, 114.44, 114.66, 121.19, 123.71, 125.54, 127.46, 130.42, 130.72, 130.81, 131.78, 136.76, 136.96, 137.09, 138.00, 160.69, 163.11 (C–F, d, J = 242 Hz), 166.69; HRMS (ESI, m/z): calcd for $C_{21}H_{20}FNO_2$ (M+H$^+$) 337.1478, found: 337.1477.

Ethyl 4-(4-fluorophenyl)-1-(3,4-dimethylphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5n)

Yield 84%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.3 Hz, 3H), 1.16 (t, J = 7.3 Hz, 3H), 1.50–1.55 (m, 2H), 2.31 (s, 3H), 2.32 (s, 3H), 2.79 (t, J = 8.0 Hz, 2H), 4.17 (q, J = 7.3 Hz, 2H), 6.58 (s, 1H), 6.99 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 9.5 Hz, 1H), 7.08 (s, 1H), 7.16 (d, J = 8.42 Hz, 1H), 7.21 (d,

J = 7.7 Hz, 1H), 7.35–7.39 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.21, 19.58, 19.94, 23.70, 27.96, 59.50, 110.76, 114.30, 114.51, 116.80, 117.03, 121.44, 124.10, 125.41, 127.89, 130.35, 130.87, 130.95, 131.36, 131.45, 136.89, 137.08, 137.91, 141.82, 160.64, 163.08 (C–F, d, J = 244 Hz), 165.69; HRMS (ESI, m/z): calcd for $C_{24}H_{26}FNO_2$ (M+H$^+$) 379.1947, found: 379.1948.

Ethyl 4-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5o)

Yield 88%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J = 7.5 Hz, 3H), 1.16 (t, J = 8.9 Hz, 3H), 1.46–1.54 (m, 2H), 2.77 (t, J = 9.9 Hz, 2H), 3.86 (s, 3H), 4.17 (q, J = 7.3 Hz, 2H), 6.58 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.35–7.38 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.19, 23.65, 27.92, 55.64, 59.50, 110.70, 114.30, 114.45, 114.54, 121.56, 125.39, 128.10, 130.84, 130.92, 131.84, 131.98, 142.04, 159.54, 160.64, 163.08 (C–F, d, J = 244 Hz), 165.64; HRMS (ESI, m/z): calcd for $C_{23}H_{24}FNO_3$ (M+H$^+$) 381.1740, found: 381.1742.

Ethyl 1-(3,4-dimethoxyphenyl)-2-propyl-4-*p*-tolyl-1*H*-pyrrole-3-carboxylate (5p)

Yield 81%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.17 (t, J = 7.3 Hz, 3H), 1.50–1.59 (m, 2H), 2.35 (s, 3H), 2.79 (t, J = 7.7 Hz, 2H), 3.86 (s, 3H), 3.91 (s, 3H), 4.19 (q, J = 7.3 Hz, 2H), 6.62 (s, 1H), 6.83 (s, 1H), 6.87 (dd, J = 2.2, J = 6.2, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.11, 14.15, 21.13, 23.70, 27.92, 56.05, 59.34, 110.47, 110.73, 110.95, 119.03, 121.27, 126.23, 128.28, 129.09, 129.54, 129.74, 132.11, 132.63, 135.66, 141.50, 148.94, 149.12, 165.65; HRMS (ESI, m/z): calcd for $C_{25}H_{29}NO_4$ (M+H$^+$) 407.2096, found: 407.2097.

Ethyl 1-(2,3-dihydro-1*H*-inden-5-yl)-4-phenyl-2-propyl-1*H*-pyrrole-3-carboxylate (5q)

Yield 83%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.4 Hz, 3H), 1.14 (t, J = 7.4 Hz, 3H), 1.48–1.58 (m, 2H), 2.11–2.18 (m, 2H), 2.80 (t, J = 7.7 Hz, 2H), 2.96 (t, J = 7.7 Hz, 4H), 4.17 (q, J = 7.3 Hz, 2H), 6.62 (s, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 7.40–7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.14, 14.21, 23.67, 25.70, 27.89, 32.65, 32.96, 59.46, 110.79, 121.55, 122.89, 124.80, 126.20, 127.61, 129.24, 129.49, 132.23, 137.23, 137.23, 139.14, 144.61, 145.65, 165.85; HRMS (ESI, m/z): calcd for $C_{25}H_{27}NO_2$ (M+H$^+$) 373.2041, found: 373.2040.

Ethyl 1-(3,4-dimethoxyphenyl)-2-propyl-4-*m*-tolyl-1*H*-pyrrole-3-carboxylate (5r)

Yield 85%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.3 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H), 1.81–1.90 (m, 2H), 2.40 (s, 3H), 2.94 (t, J = 7.7 Hz, 2H), 3.76 (s, 3H), 4.01–4.06 (m, 5H), 6.82 (s, 1H), 7.16 (d, J = 9.5, 2H), 7.25 (d, J = 8.1, 2H), 7.30–7.39 (m, 2H), 7.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 13.75, 14.38, 21.50, 23.54, 39.16, 55.96, 56.33, 61.18, 104.19, 107.85, 120.46, 126.49, 128.27, 129.13, 129.94, 136.45, 138.06, 145.10, 145.27, 149.65, 153.04, 156.36, 169.10; HRMS (ESI, m/z): calcd for $C_{25}H_{29}NO_4$ (M+H$^+$) 407.2096, found: 407.2098.

Ethyl 4-(2-chloro-6-fluorophenyl)-1-(3,4-dimethylphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5s)

Yield 91%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (t, J = 7.3 Hz, 3H), 1.00 (t, J = 7.3 Hz, 3H), 1.51–1.57 (m, 2H), 2.31 (s, 3H), 2.33 (s, 3H), 2.85 (t, J = 8.1 Hz, 2H), 4.07 (q, J = 7.3 Hz, 2H), 6.63 (s, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.12 (s, 1H), 7.20–7.24 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.21, 19.58, 19.94, 23.70, 27.96, 59.50, 110.76, 114.30, 114.51, 116.80, 117.03, 121.44, 124.10, 127.89, 130.35, 130.87, 130.95, 131.36, 131.45, 137.08, 137.91, 141.82, 162.37 (C–F, d, J = 245 Hz), 165.69; HRMS (ESI, m/z): calcd for $C_{24}H_{25}ClFNO_2$ (M+H$^+$) 413.1557, found: 413.1556.

Methyl 4-(2-chloro-6-fluorophenyl)-2-methyl-1-(3,4-dimethylphenyl)-1*H*-pyrrole-3-carboxylate (5t)

Yield 90%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.15 (s, 3H), 2.42 (s, 3H), 3.65 (s, 3H), 6.48 (s, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 7.02 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.13–7.7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 19.01, 19.87, 47.12, 52.01, 115.65, 116.12, 117.20, 118.38, 120.49, 122.25, 125.96, 126.60, 129.06, 130.33, 132.08, 132.93, 138.41, 142.76, 153.46, 162.34 (C–F, d, J = 242 Hz 164.99; HRMS (ESI, m/z): calcd for $C_{21}H_{19}ClFNO_2$ (M+H$^+$) 371.1088, found: 371.1086.

Ethyl 4-(4-isopropylphenyl)-1-(4-methoxyphenyl)-2-propyl-1*H*-pyrrole-3-carboxylate (5u)

Yield 88%; brown sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H), 1.26 (d, J = 7.0 Hz, 6H), 1.46–1.54 (m, 2H), 2.77 (t, J = 8.1 Hz, 2H), 2.87–2.94 (m, 1H), 3.84 (s, 3H), 4.18 (q, J = 7.3 Hz, 2H), 6.60 (s, 1H), 6.96 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 9.2 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ; 14.35, 14.83, 24.39, 24.89, 28.02, 34.63, 56.32, 60.14, 111.53, 115.12, 122.16, 126.40, 127.08, 128.80, 129.99, 132.86, 133.90, 142.37, 147.50, 160.15, 166.55, 168.08; HRMS (ESI, m/z): calcd for $C_{26}H_{31}NO_3$ (M+H$^+$) 405.2303, found: 405.2304.

Methyl 4-(4-chlorophenyl)-1-isopropyl-2-methyl-1*H*-pyrrole-3-carboxylate (5v)

Yield 78%; brown sticky liquid; ^{1}H NMR (400 MHz, CDCl3): δ 1.41 (d, J = 4 Hz, 6H), 2.53 (s, 3H), 3.64 (s, 3H), 4.35 (m, 1H), 6.61 (s, 1H), 7.35 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl3) δ 11.03, 23.07, 47.05, 50.32, 115.20, 124.81, 127.52, 130.19, 131.63, 134.65, 135.64, 166.14; HRMS (ESI, m/z): calcd for C16H18ClNO2 (M+H$^+$) 291.1026; found: 291.1024.

Supplementary data

Supplementary data (all compounds NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.126.

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