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Catalyst-free facile and efficient one-pot synthesis of densely functionalized pyrroles and α-amino ketones

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Abstract

An efficient catalyst-free one-pot three-component synthesis of penta-substituted pyrroles has been successfully developed. A variety of penta-substituted pyrroles were straightforwardly synthesized from good to excellent yields (78%–93%) by using easily accessible starting materials under mild conditions. This protocol also provided *α*-amino ketones in good yields (87%–98%) without column chromatography.

1 | INTRODUCTION

Pyrrole, the five-membered heteroaromatic, and its derivatives have emerged as a significant class of heterocyclic compounds due to their wide range of applications in various fields.[1] Pyrrole derivatives are ubiquitous and found to be the core structure in many of the natural and non-natural products.[2] A large number of pyrrole-based alkaloids have been isolated from marine extracts and were found to exhibit remarkable biological activities.[3] Polysubstituted-pyrrole derivatives have been shown to exhibit diverse biological properties in recent years. Some of the important biologically active pyrrole derivatives are shown in Figure 1.

These pyrrole derivatives also demonstrate a range of biological properties such as antibiotic activity.[4] potent inhibitors of HMG-CoA reductase,[5] cytotoxic activity.[6] and antimicrobial,[7] anticancer,[8] antifungal,[9] antiviral,[10] anti-tubercular,[11] and anti-inflammatory agents.[12] Pyrrole derivatives are used as conducting polymers.[13] and also extensively employed in the synthesis of diversely substituted porphyrins and their derivatives.[14]

Because of this wide range of applications of pyrroles in various fields, chemist have continuously endeavored to synthesize novel, densely functionalized pyrrole derivatives by employing simple and efficient synthetic strategies. Various methodologies have been developed for the synthesis of substituted pyrroles including the Paal–Knorr reaction,[15] Hantzsch synthesis,[16] ring-opening reactions,[17] rearrangement reactions,[18] metal-catalyzed reactions,[19] functionalization of pyrroles,[20] cycloadditions, and iodine-mediated reactions.[21] Also, the reactions of α-amino ketones with suitable reacting partners provide densely functionalized pyrroles derivatives. It is one of the simple and efficient methodologies for the synthesis of pyrrole derivatives.[22] This wide range of applications of pyrrole derivatives has inspired the development of novel synthetic routes for the synthesis of penta-substituted pyrroles via α-amino ketones.

α-Amino ketones are another interesting class of compounds that exhibit biological activities. They are also used as intermediates in the synthesis of biologically relevant molecules.[23] The general methods for the synthesis of α-amino ketones involve the condensation of diketone with amine followed by the reduction of the imine functionality, cross-coupling of aldehydes with unactivated imines, and [(*S*)-BINAP]$PdBr_2$-catalyzed cross-coupling reactions of imines with nitriles and silica tungstic acid.

Even though various methodologies have been reported for the synthesis of *α*-amino ketones,[24,25] all these suffer from longer reaction times, expensive reagents, and use of metal catalysts and toxic solvents, which may cause harm to the environment. So, there is a need to develop a simple and environmentally friendly methodology for the synthesis of *α*-amino ketones. In continuation to our work in constructing various

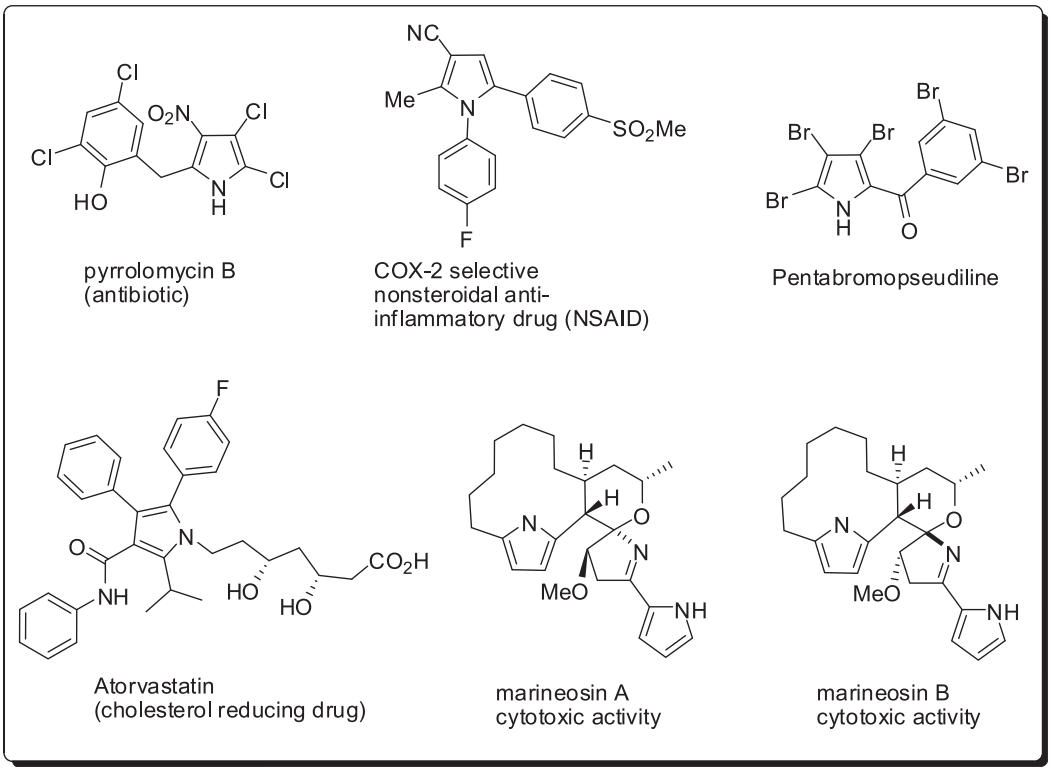


FIGURE 1 Representative examples of biologically active pyrroles

important mono.[26] and fused-ring.[27] heterocyclic compounds [26,27], here we report the design and development of a one-pot synthesis of densely functionalized pyrroles and α-amino ketones.

2 | RESULTS AND DISCUSSION

In the initial studies, a reaction between benzoin (**1**) with aniline in presence of trifluoroacetic acid and 2 mL of 1,2-dichloroethane (DCE) at reflux temperature was performed. The progress of the reaction was monitored by TLC, and it was observed that after 120 min the starting materials were completely consumed. After completion of the reaction, the reaction mixture was subjected to the usual work-up and the crude reaction mixture obtained was purified by column chromatography to afford the desired product **2a** in 86% (Table 1, entry 1). The structure of the product thus obtained was confirmed by the analysis of ^{1}H and ^{13}C NMR data. Encouraged with the result obtained, we proceeded for optimization of the reaction conditions to improve the yield of product **2a.** Therefore we carried out the reactions of benzoin (**1**) and aniline in DCE in the presence of other Brønsted acids such as methane sulfonic acid and triflic acid (TfOH). In the presence of methane sulfonic acid, the reaction was completed in 120 min and the product **2a** was delivered in 84% yield (Table 1, entry 2). The reaction mediated by TfOH was completed in 90 min to provide the corresponding product **2a** in 91% yield (Table 1, entry 3).

When the reaction of benzoin (**1**) and aniline was carried out in presence of molecular iodine in DCE, the reaction failed to afford the expected product and the starting materials were recovered. The neat reaction of benzoin (**1**) and aniline also could not afford the desired product (Table 1, entry 4 & 5). Surprisingly, when the reaction of benzoin (**1**) and aniline was performed in acetic acid, the reaction was completed in 30 min. After completion of the reaction, 3 mL of water was added and the precipitate thus obtained was filtered, washed with water, and dried under vacuum to afford the expected product **2a** in 96% yield (Table 1, entry 6). The product obtained was confirmed by ^{1}H and ^{13}C NMR analysis.

From the above optimization reactions, acetic acid was found to be the best reagent in the current protocol. Encouraged with the result obtained, we further decided to explore the reactivity of benzoin with other aniline derivatives using the present methodology. For this purpose, we chose various substituted aniline derivatives to test their scope of reactivity with benzoin. When the reaction of benzoin (**1**) with 1-naphthylamine under standard conditions was performed, the reaction proceeded smoothly and afforded the desired product **2b** in 98% yield (Scheme 1). Further, the reactions of para-substituted anilines such as

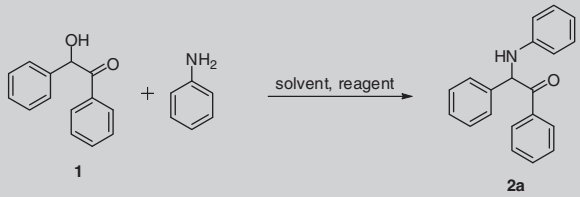
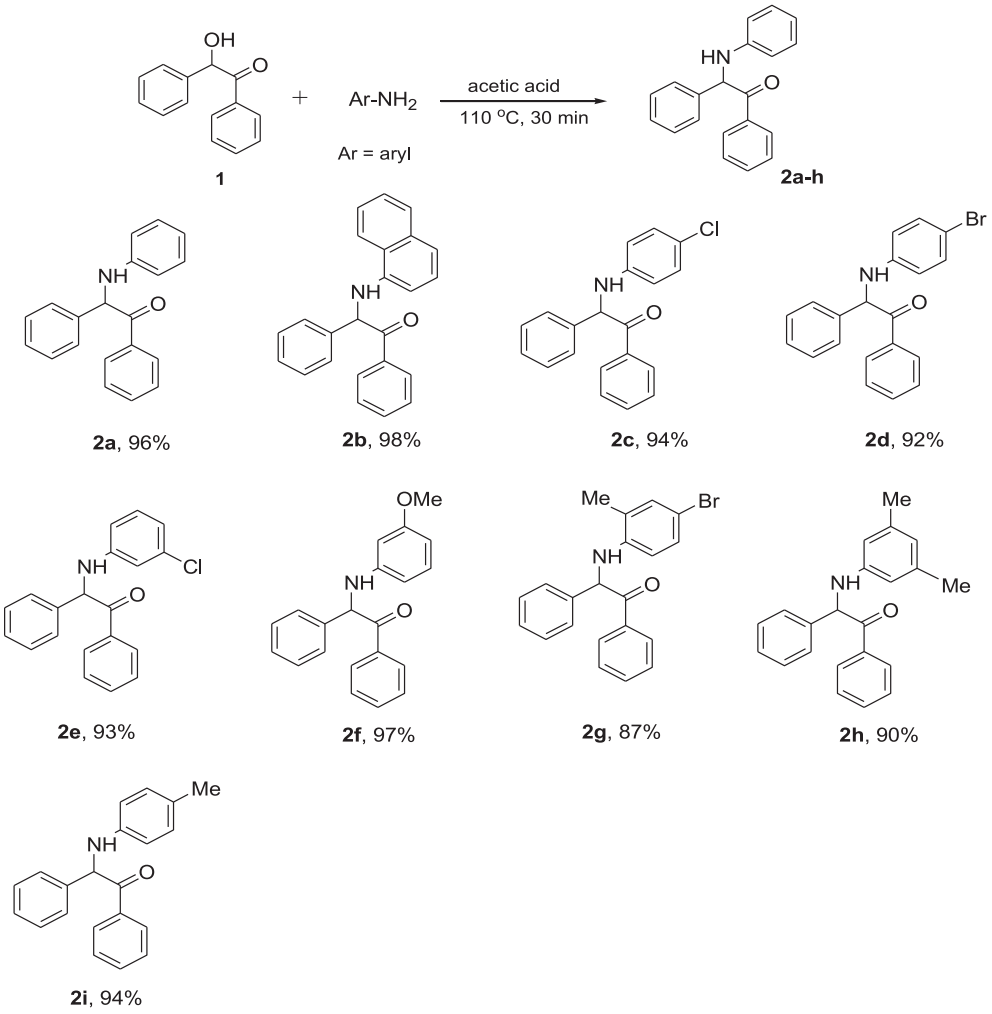


TABLE 1 Optimization of reaction conditions

S. no.	Reagent	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
1	CF_3COOH	DCE	Reflux	120	86
2	CH_3SO_3H	DCE	Reflux	120	84
3	TfOH	DCE	Reflux	90	91
4	I_2	DCE	Reflux	120	-
5	Neat		100°C	120	-
6	-	AcOH	110°C	30	96

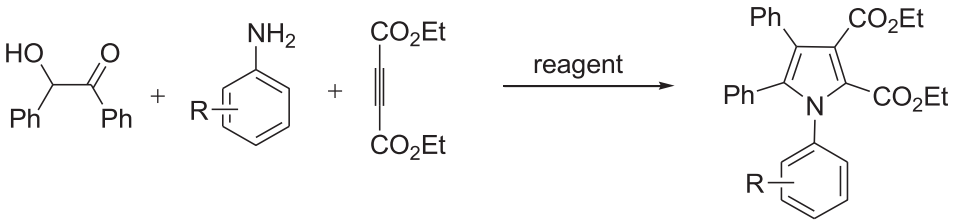
Note: All the reactions were carried out with **1** (1 mmol) and aniline (1 mmol) in 2 ml of solvent.
[a]Yields of pure and isolated product.



SCHEME 1 Acetic acid-mediated synthesis of α-aminoketones

4-chloroaniline and 4-bromoaniline were carried out with benzoin (**1**) under similar conditions, both the reactions were completed in 30 min and delivered the products **2c** and **2d** in 94% and 92% yields, respectively (Scheme 1). When the 3-chloro aniline and 3-methoxy aniline were subjected to reaction with benzoin (**1**) under standard

SCHEME 2 Designed synthetic plan for the synthesis of penta-substituted pyrroles



reaction conditions, the reactions underwent smoothly and provided the respective products **2e** and **2f** in 93% and 97% yields, respectively (Scheme 1). We also examined the reactivity of disubstituted anilines using the current methodology. The reaction of 4-bromo 2-methyl aniline under the optimized reaction conditions gave the corresponding product **2g** in 87% yield. Similarly, the 3,5-dimethylaniline and 4-methylaniline also provided the expected product **2h** and **2i** in 90% and 94% yields, respectively (Scheme 1).

From a literature survey, it was very clear that these α-amino ketones are very good precursors for the synthesis of densely functionalized heterocyclic derivatives. So, after synthesizing various substituted α-amino ketones, we envisioned that these α-amino ketones could be employed as substrates for the synthesis of penta-substituted pyrroles. Accordingly, we designed a one-pot synthetic strategy for the synthesis of penta-substituted pyrroles from the readily available starting materials (Scheme 2).

We envisaged that the reaction of benzoin (**1**) with aniline derivatives in acetic acid would provide the α-amino ketones, which can be further reacted with dialkyl acetylene dicarboxylates to provide the densely functionalized pyrroles. According to the synthetic plan demonstrated, a one-pot reaction, whose initial step was the reaction of benzoin (**1**) with aniline in acetic acid at 110°C for 30 min, gave the α-aminoketone. To this reaction mixture at the same temperature, diethyl acetylene dicarboxylate was added and the progress of the reaction was monitored by TLC. The reaction was completed in 30 min, and after the usual work-up and purification by column chromatography provided diethyl 1,4,5-triphenyl-1*H*-pyrrole-2,3-dicarboxylate **3a** in 91% yield (Scheme 3).

The one-pot synthetic strategy for the synthesis of densely functionalized pyrroles was also extended to other aniline derivatives. Different mono- and di-substituted aniline derivatives were allowed to react with benzoin (**1**) and diethyl acetylene dicarboxylate under standard conditions; the details are given in Scheme 3. The reaction of naphthylamine with benzoin (**1**) and diethyl acetylene dicarboxylate in acetic acid provided the product **3b** in 93% yield. When the para-substituted anilines such as 4-chloroaniline and 4-bromoaniline were subjected to the one-pot reaction, the reactions underwent smoothly to afford the respective products **3c** and **3d** in 83% and 81% yields, respectively The meta-substituted anilines (3-chloroaniline and 3-methoxyaniline) also reacted efficiently and delivered the products **3e** and **3f** in 86%, and 88% yields, respectively.

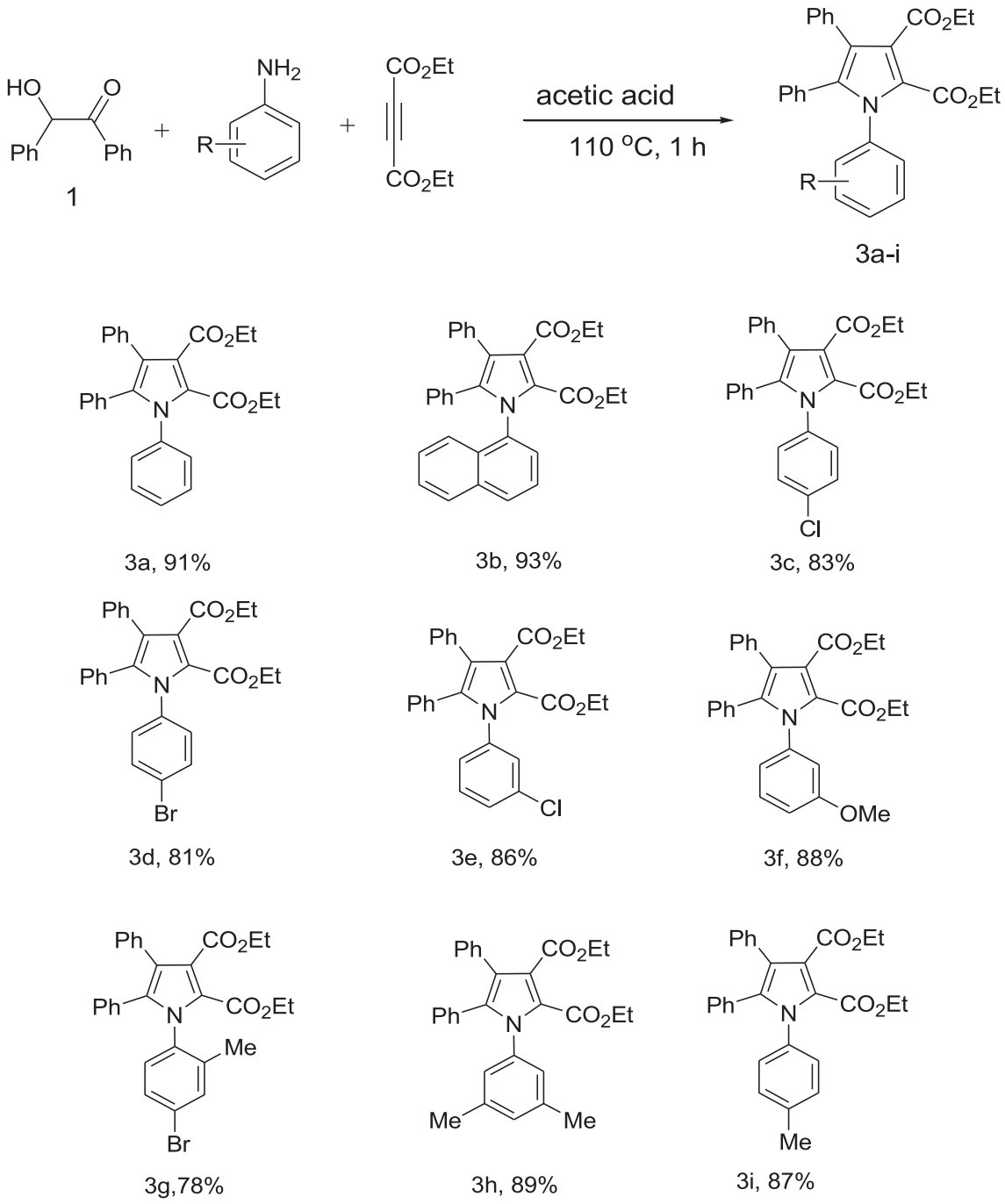
Further, we explored the possibility of reactivity of disubstituted anilines in the current protocol. The reactions of 4-bromo,2-methylaniline and 3,5-dimethylaniline with benzoin and diethyl acetylene dicarboxylate gave their respective penta-substituted pyrroles **3g** and **3h** in 78% and 89% yield, respectively. The reaction of 4-methylaniline also underwent successfully and provided the product **3i** in 87% isolated yield. All the products obtained were well characterized using modern analytical techniques.

2.1 | Mechanism

The plausible reaction mechanism for one-pot synthesis of penta-substituted pyrroles is shown in Scheme 4. The initial reaction of benzoin with aniline in the presence of acetic acid gave the α-aminoketone by dehydration. Thus obtained α-aminoketone reacted in situ with diethyl acetylene dicarboxylate, and the nitrogen atom of α-aminoketone underwent Michael addition with diethyl acetylene dicarboxylate, which in turn underwent intramolecular cyclization by reacting with the keto carbon. The intermediate obtained further underwent aromatization by the elimination of water molecule to give the penta-substituted pyrrole diethyl 1,4,5-triphenyl-1*H*-pyrrole-2,3-dicarboxylate (**3a**).

2.2 | Conclusion

In summary, a facile and efficient methodology was developed for the synthesis of α-amino ketones from readily available starting materials mediated by acetic acid. The current protocol does not require any column chromatography purification and provides the various α-amino ketones in high yields. Further, these α-amino ketones could be effectively exploited in the synthesis of penta-substituted pyrroles by reacting them with diethyl acetylene dicarboxylates. The methodology is simple,



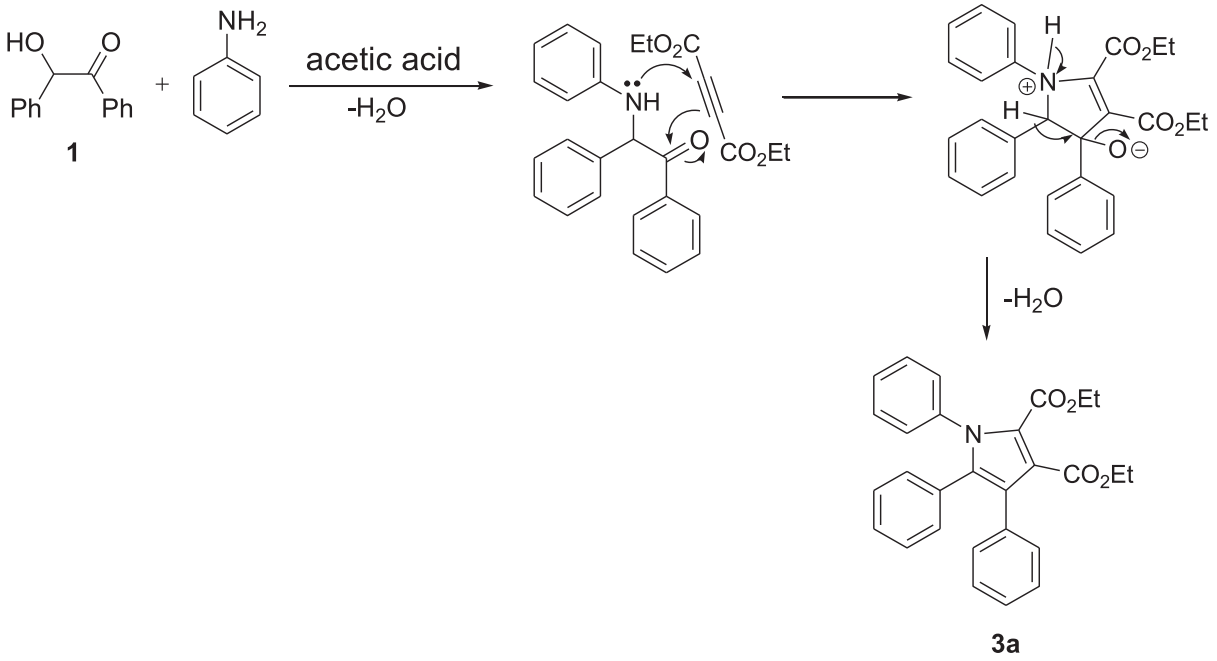
SCHEME 3 Synthesis of densely functionalized pyrrole derivatives

easy to handle, and provides an easy access for the synthesis of densely functionalized pyrroles in high yields.

3 | EXPERIMENTAL

All the chemicals were procured from Avra Chemicals Pvt. Ltd., Hyderabad, India, and the reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent. The synthesized compounds were characterized by ^{1}H NMR using a Bruker AMX 400-MHz NMR instrument using TMS as internal standard (δ in ppm). ^{13}C NMR was recorded at 100 MHz. The elemental analysis was done on a Perkin-Elmer 2400 series instrument. All the melting points were determined using the Meltemp apparatus in open capillaries, and expressed in °C and are uncorrected.

General procedure for synthesis of 2a–i: To a mixture of benzoin (**1**) (1.0 mmol, 0.212 g) and aniline (1.0 mmol, 0.093 g) was added 2 ml of acetic acid and



SCHEME 4 Plausible reaction mechanism for the one-pot synthesis of penta-substituted pyrroles

allowed to heat to 110°C for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction as shown by TLC, the reaction mixture was diluted with 5 mL of water and the precipitate thus obtained was filtered and dried under vacuum to obtain the product 1,2-diphenyl-2-(phenylamino)ethanone (**2a**) in 96% yield.

General procedure for synthesis of 3a–i: To a mixture of benzoin (**1**) (1.0 mmol, 0.212 g) and aniline (1.0 mmol, 0.093 g) was added 2 mL of acetic acid and allowed to heat to 110°C for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction as shown by TLC, diethyl acetylene dicarboxylate (1.0 mmol, 0.170 g) was added to the reaction mixture, which was stirred at the same temperature for more than 30 min. Then the reaction mixture was diluted with 5 mL of water. The organic layer was separated, washed with water (2 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The purification of reaction mixture by silica gel column chromatography using 5% ethyl acetate in hexanes as eluent afforded the product diethyl 1,4,5-triphenyl-1*H*-pyrrole-2,3-dicarboxylate (**3a**) in 91% yield.

Diethyl 1,4,5-triphenyl-1*H*-pyrrole-2,3-dicarboxylate (3a)

Yield: 91%, yellow solid, m.p. 88–90°C; IR: (cm^{-1}) 1712, 1603, 1546; ^{1}H NMR (400 MHz, $CDCl_3$): 7.31–7.26 (m, 3H), 7.22–7.15 (m, 7H), 7.12–7.01 (m, 3H), 6.87–6.93 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.90, 14.05, 60.74, 61.20, 122.71, 123.01, 123.10, 126.70, 127.72, 127.81, 127.92, 128.29, 128.38, 128.56, 129.94, 130.23, 131.13, 133.41, 136.79, 138.20, 160.04, 166.24; Anal. Calcd. for $C_{28}H_{25}NO_4$: C, 76.52; H, 5.73; N, 3.19; O, 14.56; Found: C, 76.64; H, 5.61; N, 3.07.

Diethyl 1-(naphthalen-1-yl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3b)

Yield: 93% as orange solid. m.p., 129–130°C; IR (cm^{-1}) 1706, 1590, 1520; ^{1}H NMR (400 MHz, $CDCl_3$): 7.85–7.76 (m, 2H), 7.50–7.42 (m, 3H), 7.39–7.29 (m, 2H), 7.27–7.15 (m, 5H), 6.99–6.93 (m, 1H), 6.91–6.80 (m, 4H), 4.30 (q, J = 7.1 Hz, 2H), 3.98–3.84 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.1 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$):13.50, 14.04, 60.38, 61.26122.75, 123.08, 123.43, 123.60, 124.63, 126.33, 126.68, 127.23, 127.60, 127.79, 127.95, 128.04, 128.93, 129.86, 130.19, 130.58, 131.78, 133.42, 135.19, 137.71, 159.53, 166.4; Anal. Calcd. for $C_{32}H_{27}NO_4$: C, 78.51; H, 5.56; N, 2.86; O, 13.07; Found: C, 78.43; H, 5.63; N, 2.77.

Diethyl 1-(4-chlorophenyl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3c)

Yield: 83%; yellow solid. m.p. 119–120°C; IR: (cm^{-1}) 1710, 1545, 1520 , ^{1}H NMR (400 MHz, $CDCl_3$): 7.28–7.23 (m, 2H), 7.22–7.15 (m, 5H), 7.14–7.05 (m, 5H), 6.92–6.87 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):13.82, 13.95, 60.76, 61.16, 122.83, 123.22, 123.33, 126.75, 126.92, 127.88, 127.92, 128.49, 128.88, 129.19, 129.79, 131.01, 133.04, 133.81, 136.77,

139.26, 159.69, 165.93; Anal. Calcd. for $C_{28}H_{24}ClNO_4$: C, 70.96; H, 5.10; Cl, 7.48; N, 2.96; O, 13.50; Found: C, 70.99; H, 5.07; Cl, 7.39; N, 2.89.

Diethyl 1-(4-bromophenyl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3d)

Yield: 81%; m.p. 124–125°C; IR (cm^{-1}) 1711, 1551, 1491; ^1H NMR (400 MHz, $CDCl_3$): 7.40 (d, J = 8.8 Hz, 2H), 7.23–7.15 (m, 5H), 7.14–7.01 (m, 5H), 6.92–6.86 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 6.8 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):13.86, 13.96, 60.75, 61.20, 122.21, 122.43, 123.12, 123.37, 126.75, 127.90, 127.94, 129.74, 130.10, 130.99, 131.52, 133.00, 136.84, 137.17, 159.70, 166.04; Anal. Calcd. for $C_{28}H_{24}BrNO_4$: C, 64.87; H, 4.67; Br, 15.41; N, 2.70; O, 12.35; Found: C, 64.94; H, 4.56; Br, 15.52; N, 2.61.

Diethyl 1-(3-chlorophenyl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3e)

Yield: 86%, m.p. 112–113°C; IR (cm^{-1}) 1712, 1542, 1522, ^1H NMR (400 MHz, $CDCl_3$): 7.31–7.36 (m, 1H), 7.24–7.15 (m, 7H), 7.14–7.02 (m, 4H), 6.91 (d, J = 7.0 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$):13.82, 13.95, 60.76, 61.16, 122.83, 123.22, 123.33, 126.75, 126.92, 127.88, 127.92, 128.49, 128.88, 129.19, 129.79, 131.01, 133.04, 133.81, 136.77, 139.26, 159.69, 165.93; Anal. Calcd. For $C_{28}H_{24}ClNO_4$: C, 70.96; H, 5.10; Cl, 7.48; N, 2.96; O, 13.50; Found: C, 70.91; H, 5.03; Cl, 7.54; N, 2.83.

Diethyl 1-(3-methoxyphenyl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3f)

Yield: 88%, yellow thick liquid. IR (cm^{-}1) 1706, 1586, 1524; ^1H NMR (400 MHz, $CDCl_3$): 7.23–7.14 (m, 6H), 7.12–7.02 (m, 3H), 6.92 (d, J = 7.6 Hz, 2H), 6.86–6.76 (m, 2H), 6.69 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$):13.92, 14.04, 55.34, 60.79, 61.15, 114.23, 120.92, 122.42, 123.02, 123.29, 126.69, 127.75, 127.83, 127.90, 128.98, 129.96, 130.28, 131.02, 133.41, 136.56, 139.11, 159.41, 160.05, 166.13; Anal. Calcd. for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98; O, 17.04; Found: C, 74.26; H, 5.71; N, 2.88.

Diethyl 1-(4-bromo-2-methylphenyl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3g)

Yield: 78%, white solid; m.p. 126–127°C; IR (cm^{-1}) 1710, 1596, 1534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$):7.33–7.25 (m, 2H), 7.23–7.04 (m, 9H), 6.95–6.86 (m, 2H), 4.32–4.22 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.95 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H), ^{13}C NMR (400 MHz, $CDCl_3$):13.90, 14.05, 17.56, 60.74, 61.30, 121.94, 122.51, 123.28, 123.67, 126.79, 128.00, 128.05, 129.09, 129.82, 129.87, 130.67, 130.73, 133.14, 133.17, 136.65, 136.70, 138.46, 159.63, 166.26; Anal. Calcd. for $C_{29}H_{26}BrNO_4$: C, 65.42; H, 4.92; Br, 15.01; N, 2.63; O, 12.02; Found: C, 65.55; H, 4.85; Br, 15.13; N, 2.52.

Diethyl 1-(3,5-dimethylphenyl)-4,5-diphenyl-1*H*-pyrrole-2,3-dicarboxylate (3h)

Yield: 89%, m.p. 91–92°C; IR (cm^{-1}) 1712, 1603, 1546; ^1H NMR (400 MHz, $CDCl_3$): 7.22–7.15 (m, 5H), 7.12–7.01 (m, 3H), 6.94–6.88 (m, 3H), 6.77 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 2.22 (s, 6H), 1.20 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H), ^{13}C NMR (400 MHz, $CDCl_3$): 13.90, 14.03, 21.13, 60.71, 61.03, 121.97, 122.94, 123.65, 126.13, 126.58, 127.59, 127.68, 127.84, 129.91, 130.02, 130.40, 131.10, 133.62, 136.48, 137.85, 137.88, 160.26, 166.12; Anal. Calcd. for $C_{30}H_{29}NO_4$: C, 77.06; H, 6.25; N, 3.00; O, 13.69; Found: C, 77.20; H, 6.14; N, 3.11.

Diethyl 4,5-diphenyl-1-*p*-tolyl-1*H*-pyrrole-2,3-dicarboxylate (3i)

Yield: 87%, yellow solid; m.p. 88–89°C, IR (cm^{-1}) 1708, 1548, 1519; ^1H NMR (400 MHz, $CDCl_3$): 7.25–7.19 (m, 5H), 7.14–7.05 (m, 7H), 6.98–6.88 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$):13.90, 14.02, 21.19, 60.67, 61.11, 122.49, 122.88, 123.04, 126.62, 127.61, 127.75, 127.86, 128.17, 129.00, 129.92, 130.29, 131.11, 133.46, 135.50, 136.81, 138.07, 160.05, 166.24; Anal. Calcd. for $C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09; O, 14.11; Found: C, 76.96; H, 5.94; N, 2.98.

ACKNOWLEDGMENTS

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

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