Chapter - 2

Microwave-assisted synthesis of pyrrole-3-methanols

2.1 Introduction

Among the nitrogen-containing heterocycles, pyrroles are widely distributed in bioactive natural products, synthetic medicinal agents, and drug-like compounds.[1-5] The ready availability of suitably substituted and functionalized pyrrole derivatives is essential for the progress of many branches of science including biology, pharmacology, material sciences, agrochemicals, dyes, photographic chemicals, perfumes, and other organic compounds. Pyrrole nucleus is widespread in nature and is the key structural fragment of many important bioactive molecules such as pentabromopseudodiline and pioluteorine, both isolated from bacterial sources prominent in marine natural products.[6] Pyrroles and their derivatives also display many biological activities such as antibacterial, antiviral, antitumor, anti-oxidative and anti-inflammatory activities.[7-14] Nakamuric acid, an axially chiral marinopyrroles also showed good activity against methicillin-resistant Staphylococcus aureus strains and the bacterial red pigment.[15-16] Polysubstituted pyrroles play an important role as promising pharmacophores in medicinal chemistry,[17-18] conducting polymers,[19-20] as well as multiple applications in materials science.[21-26] The pyrrole derivative BM212 [1,5-diaryl-2-methyl-3-(4-methylpiperazine-1-yl)methyl-pyrrole] was shown to possess strong inhibitory activity against both *Mycobacterium tuberculosis* and some nontuberculosis mycobacteria. BM212 was inhibitory to drug-resistant mycobacteria and also exerted bactericidal activity against intracellular bacilli residing in the U937 human histiocytic lymphoma cell line.[27] The compounds like; 5-(3,5-dichlorophenylthio)-4-isopropyl-1-(4-pyridinylmethyl)-1*H*-pyrrol-3-ylmethyl carbamate and 5-(3,5-d ichlorophenylthio)-4-isopropyl-1-(4-pyridinylmethyl)-1H-pyrrole-3-methanol were identified as leads that show potent anti-HIV-1 activity[28] as shown in Figure 2.1.Ningalins and Lamellarins are widely used as anticancer drugs, antibiotics, and protease inhibitors.[29-31] Similar to pyrrole-3-methanol and their structurally related compounds showed multidrug resistance reversal activity against L1210 and HCT116 cell lines.[32-36] and other important biological activity.[37-51]

Recently, tetra-arylpyrroles had shown to possess semiconducting materials properties derived from hexa-(N-pyrrolyl)-benzene in material sciences,[52] glucose sensors based on polypyrrole-latex materials[53] and polypyrrole materials for the detection and discrimination of volatile organic compounds.[54] The derivatives of the 4, 4-difluoro-4-boradipyrrin system (BODIPY) have a strong absorption in the UV and emit very intense fluorescence. Additionally, they have been found to

show platelet aggregation inhibition [55] and hypertensive activities.[56] Some representative examples of pyrrole-containing secondary metabolites are summarized in Figure 2.1.

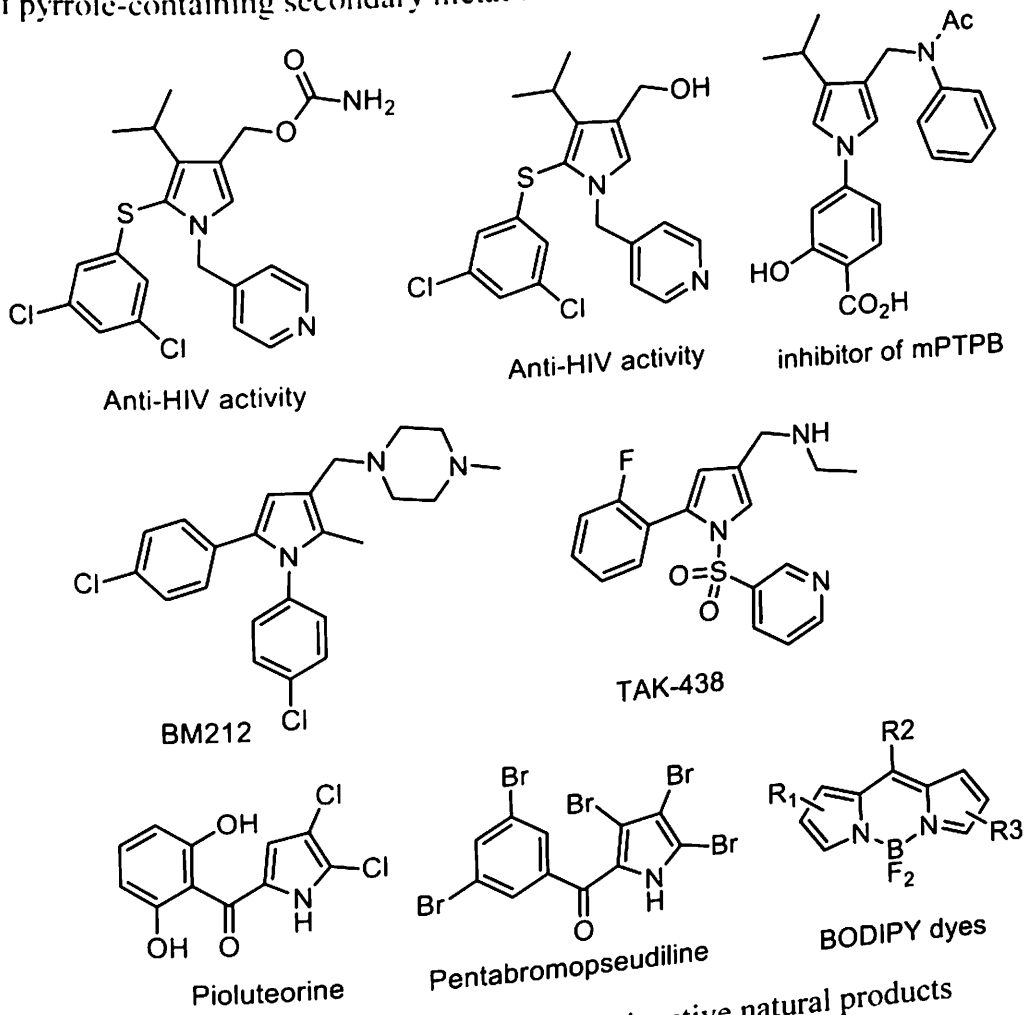
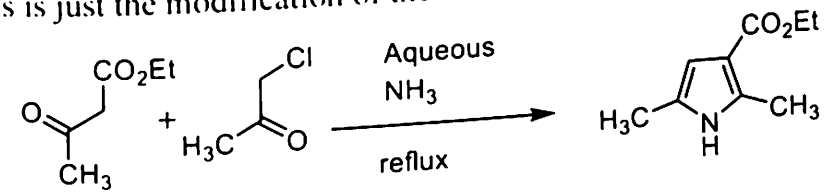


Figure 2.1 Some pyrrole-containing bioactive natural products

2.2 General Synthesis of Pyrrole Derivatives

Due to the high commercial impact of substituted pyrroles, a series of efficient methods including Hantzsch,[57] Barton–Zard[58] and Paal-Knorr synthesis [59-63] were developed by synthetic chemists. In addition to these famous routes, a number of methods have been developed including; tandem reactions,[64] rearrangements of *o*-vinyl oximes,[65] [3+2] cycloaddition of 1,3-dipolar reagents with alkynes,[66] hydroamination of diynes,[67] and olefin cross-metathesis[68]are the predominantly applied strategies to provide easy access to pyrroles. However, most of these methods are limited to the use of elaborately designed starting materials, suffer from low efficiency and selectivity and sometimes required harsh conditions. Moreover, the involvement of aldimines in [3+2] cycloaddition/annulation reactions with different C3-synthons to synthesize functionalized pyrroles have recently been studied extensively.[69-73]

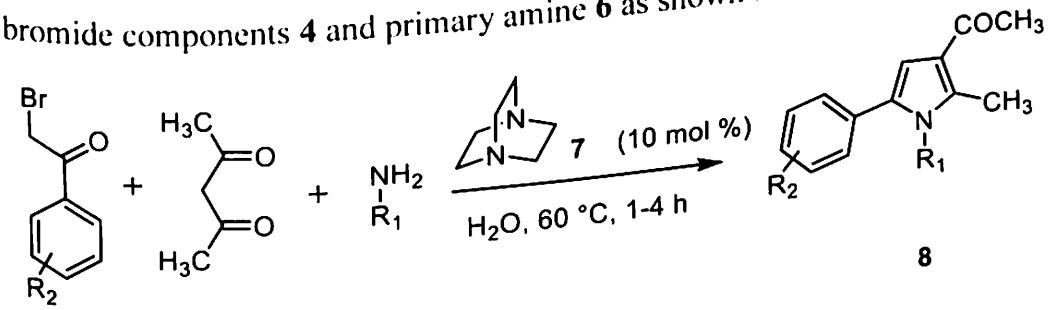
Hantzsch developed a brief note in 1890, between an equimolecular mixture of acetoacetic ester **1** and chloroacetone **2** under reflux in concentrated aqueous ammonia afforded a new compound, which he correctly identified as a pyrrole derivative **3** shown in Scheme 2.1.[74-75] Actually, Hantzsch synthesis is just the modification of the Feist-Benary synthesis of furans.



1 **2** **3**

Scheme 2.1 The first multi-component synthesis of pyrrole

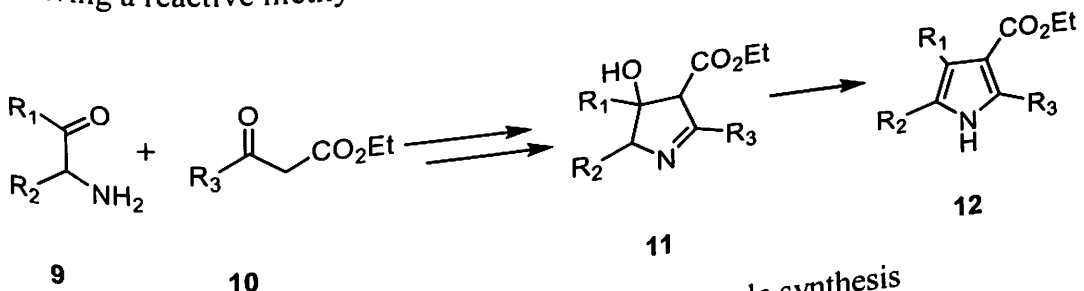
Meshram and co-workers reported a base-catalyzed variant of the Hantzsch pyrrole **8** synthesis through the organic base 1, 4-diazabicyclo [2.2.2] octane (DABCO) **7** as a catalyst and water as the reaction medium. This scheme lacked generality since it was limited to a single diketone substrate **5** and substitutions were restricted to the positions 1 and 5, from variations in the phenacyl bromide components **4** and primary amine **6** as shown in Scheme 2.2.[76]



4 **5** **6** **8**

Scheme 2.2 Hantzsch method for the pyrrole synthesis

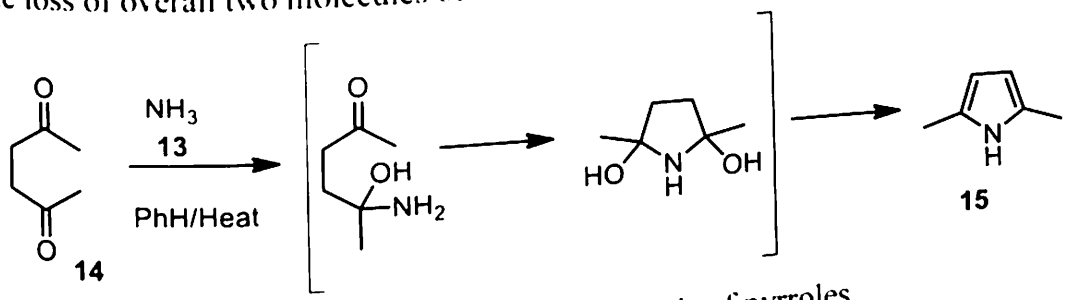
Knorr and co-workers reported the ring closing reaction approach in the presence of the base to access substituted pyrroles **12**. This method involves the condensation of α-amino ketones **9** with ketone **10** having a reactive methylene group alpha to the carbonyl group as illustrated in Scheme 2.3.[77]



9 **10** **11** **12**

Scheme 2.3 Knorr method for the pyrrole synthesis

Paal-Knorr reported the synthesis of pyrroles where 1, 4-dicarbonyl unit provides four carbon atoms of the ring and amine group provides the nitrogen atom of the pyrrole (Scheme 2.4).[78-79] This method involving the nucleophilic addition of the amine **13** to the dicarbonyl carbon atoms **14** and the loss of overall two molecules of water affords the pyrrole **15**.

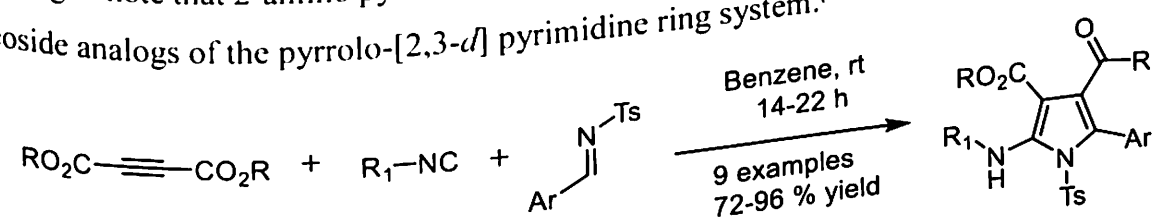


14 **15**

Scheme 2.4 Paal-Knorr synthesis of pyrroles

2.2.1 Utilization of imines for Pyrroles Synthesis

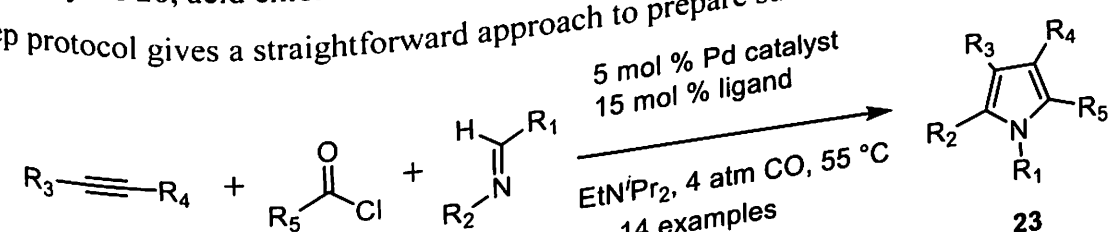
Additionally, a number of methods have been developed for the synthesis of substituted pyrroles in which imine is involved as one of the counterpart substrates. In this context, Nair and co-workers reported the multi-component reaction of DMAD **16**, isocyanides **17** and N-tosylimines **18**, to the synthesis of 2-amino pyrrole systems **19** in excellent yields shown in Scheme 2.5.[80] It is interesting to note that 2-amino pyrrole systems have found use as synthetic precursors for acyclic nucleoside analogs of the pyrrolo-[2,3-*d*] pyrimidine ring system.[81]



16 **17** **18** **19**

Scheme 2.5 Synthesis of 2-amino pyrrole involving multi-component reaction

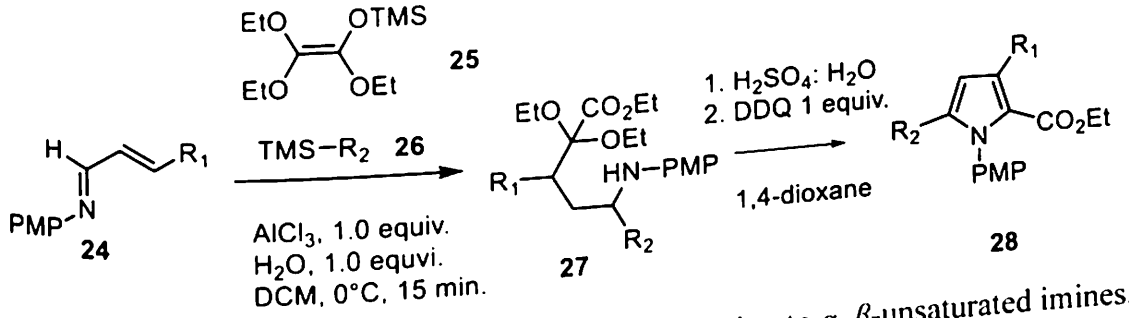
Arndtsen and co-workers reported a palladium-catalyzed reaction for the synthesis of pyrroles **23** by using alkynes **20**, acid chlorides **21** and imines **22**, in good yield shown in Scheme 2.6.[82] This one-step protocol gives a straightforward approach to prepare substituted pyrroles **23**.



20 **21** **22** **23**

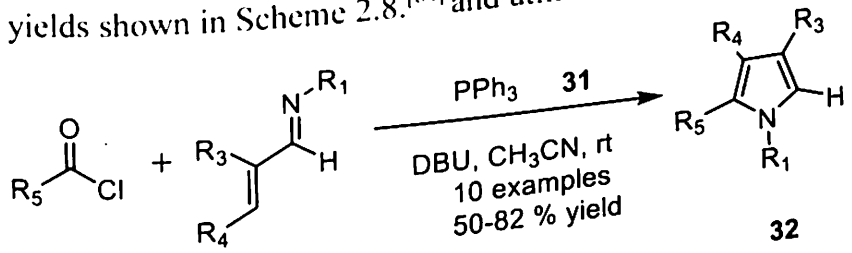
Scheme 2.6 Synthesis of pyrroles involving palladium catalyzed reaction

Shimizu and co-workers reported a regioselective synthesis of substituted pyrroles **28** through double nucleophilic addition reaction of α,α-dialkoxy ketene silyl acetals **25** with ketene dithioacetals or trimethylsilyl cyanide **26** to α, β-unsaturated imines **24** using acid mediated cyclization of **27** and oxidative sequence as shown in Scheme 2.7.[83]



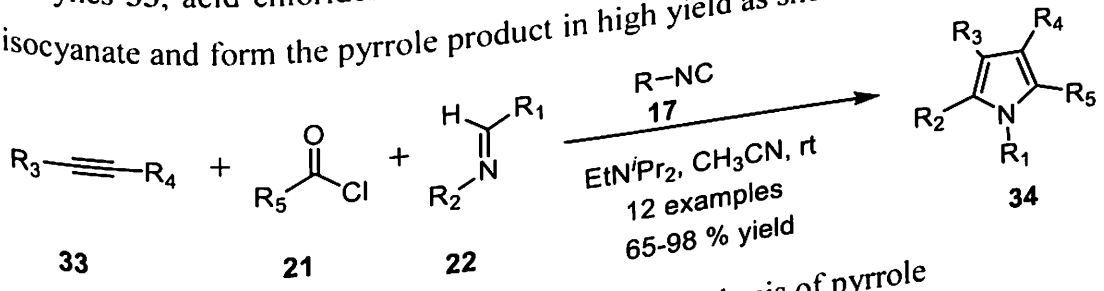
Scheme 2.7 Pyrrole synthesis using nucleophilic addition to α, β-unsaturated imines.

Lu and co-workers reported a one-step synthesis of pyrroles **32** from acid chlorides **29** and α, β-unsaturated imines **30** mediated by triphenylphosphine **31.** The desired product obtained in moderate to good yields shown in Scheme 2.8.[84] and utilized to the synthesis of lukianol A.



Scheme 2.8 PPh3-mediated synthesis of pyrrole

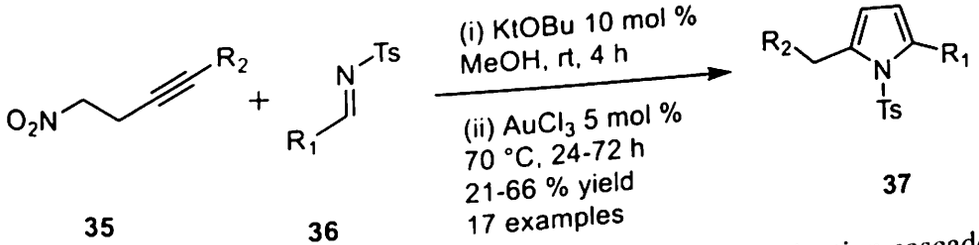
In 2010, Arndtsen and co-workers reported isocyanides **17** mediated a direct synthesis of pyrroles **34** from alkynes **33**, acid chlorides **21** and imines **22** undergo in situ coupling with alkynes to liberate isocyanate and form the pyrrole product in high yield as shown in Scheme 2.9.[66]



Scheme 2.9 Isocyanide-mediated synthesis of pyrrole

Dixon and co-workers reported an efficient one-pot direct synthesis of 2,5-disubstituted pyrroles **37** using 4-nitrobut-1-yne **35** and *p*-toluenesulfonyl protected imines **36** in the presence of base

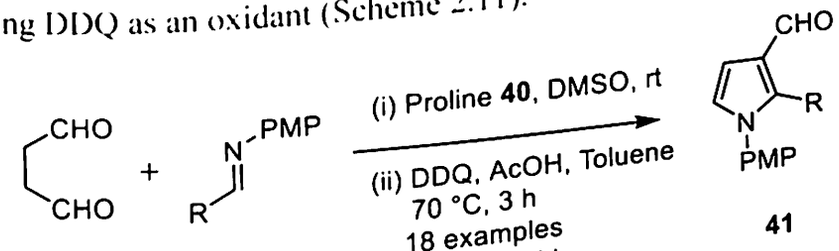
and Gold (III) catalysis through nitro-Mannich/hydroamination sequences as shown in Scheme 2.10.[85]



35 36 37

Scheme 2.10 Synthesis of pyrrole involving nitro-Mannich/hydroamination cascade sequence

Our group reported the two-pot synthesis of pyrrole-3-carboxaldehyde **41** under organocatalytic [3+2] annulations between succinaldehyde **38** and *N*-PMP imines **39** followed by oxidative aromatization using DDQ as an oxidant (Scheme 2.11).[86]



38 39 41

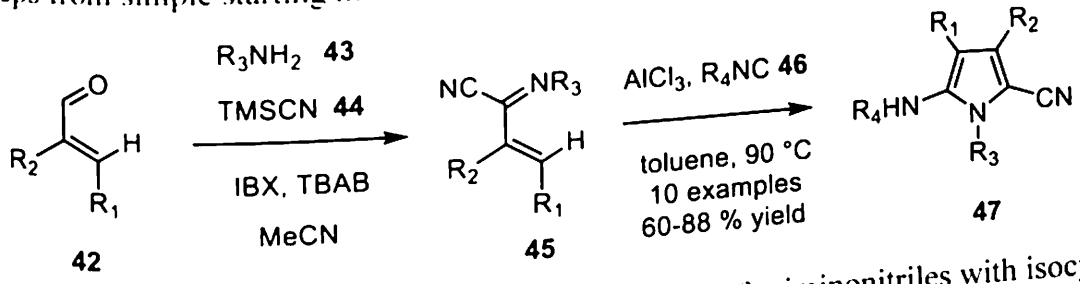
Scheme 2.11 Synthesis of pyrrole under [3+2] organocatalytic condition

Due to their extensive applications in several fields, a general method to synthesize pyrrole-3-methanol from simple building blocks and a minimal number of overall synthetic steps are highly desirable. Additionally, it is also motivating to develop a new method with a variation where 1, 4-dicarbonyl compounds serve as a source of three ring atoms and the other two atoms of the pyrrole moiety could be obtained from α-iminonitriles. In this direction, organocatalytic cascade reactions involving two or more selective transformations using single/multiple catalyzes, serve as powerful tools to conserve energy and minimize the number of synthetic operations.[87-95] However, the synthetic potential of α-iminonitriles, a corresponding highly functionalized ketimine synthon remained unmapped except few applications as the dienophile.[96-98] This may be because it was a hard-to-obtain entity until a simple method was developed by Masson and Zhu *et al.*[99] under very mild conditions. There are two methods available in the literature for pyrrole synthesis which directly involve α-iminonitriles.

2.2.2 Utilization of iminonitriles for Pyrrole Synthesis

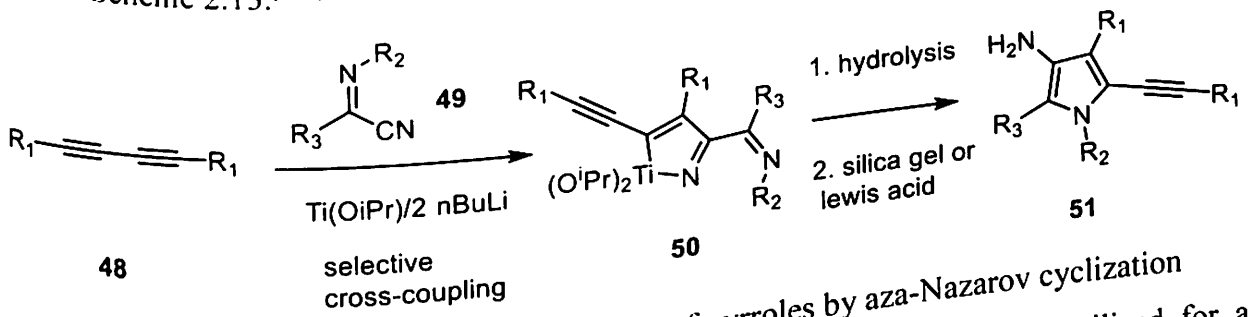
Jieping Zhu and co-workers reported [4+1] cycloaddition of α,β-unsaturated imidoyl cyanide (2-cyano-1-azadienes) **45** with isocyanides **46** in the presence of a catalytic amount of $AlCl_3$ afforded

polysubstituted 2-amino-5-cyanopyrroles **47** in good to excellent yields. In combination with the IBX/TBAB-mediated oxidative Strecker reaction, this important heterocycle is readily synthesized in two steps from simple starting materials shown in Scheme 2.12.[100]



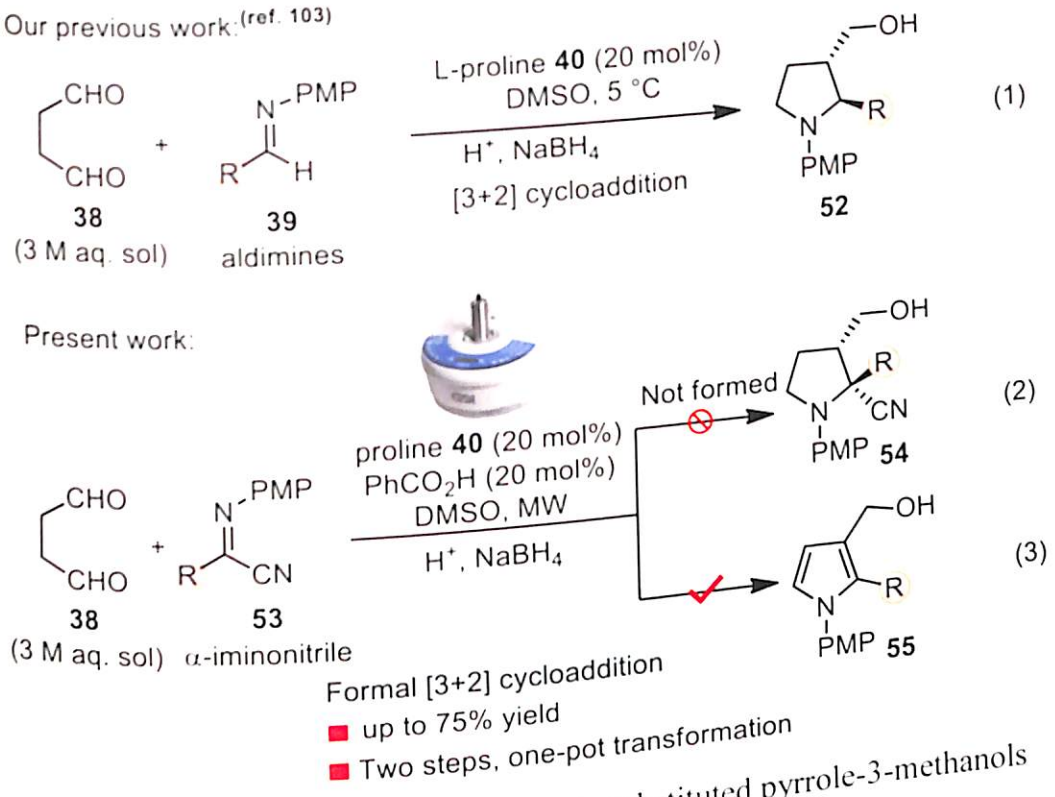
Scheme 2.12 Synthesis of pyrroles by [4+1] cycloaddition of α-iminonitriles with isocyanides

Yuanhong Liu and coworkers reported an efficient synthesis of functionalized 3-amino pyrrole **51** using a titanium-mediated regioselective cross-coupling reaction of 1,3-butadiynes **48** with α-iminonitriles **49** were efficiently constructed upon treatment of the crude hydrolysis products **50** with silica gel or Lewis acid. The reaction likely proceeds via a novel imino-aza-Nazarov type cyclization of the diimines produced by hydrolysis of the *in situ* generated azatitanacycles **50** shown in Scheme 2.13.[101]



Scheme 2.13 Titanium-mediated synthesis of pyrroles by aza-Nazarov cyclization

Besides being an activated ketimine (C=N), α-iminonitriles have not been utilized for any organocatalytic transformations, as far as we know. Therefore, our main objective was to explore the synthetic effectiveness of this important entity in organocatalytic transformations. Herein, we disclose the aminocatalytic synthesis of substituted pyrrole-3-methanols **55** from succinaldehyde **38** and α-iminonitriles **53** through direct Mannich reaction-cyclization and dehydrocynation sequence followed by *in situ* reductions with $NaBH_4$ in one pot two-steps operation as shown in Scheme 2.14.[102]

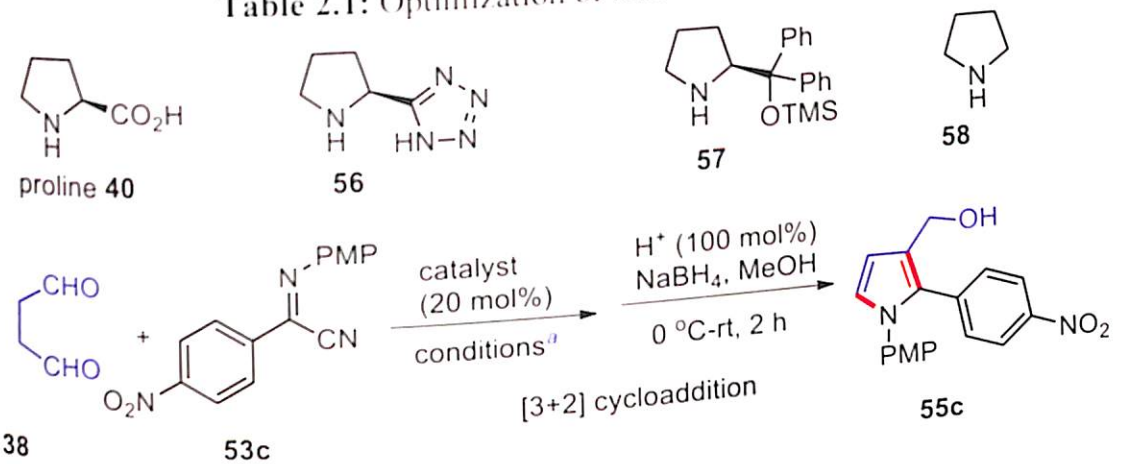


Scheme 2.14 One pot synthesis towards substituted pyrrole-3-methanols

2.3 Results and discussion

As a part of our continued interest for the organocatalytic approaches towards medium-sized N-heterocycles,[104-105] we recently reported a formal [3+2] cycloaddition reaction for the asymmetric synthesis of pyrrolidines **52** by a cascade Mannich/cyclization and *in situ* reduction sequence between succinaldehyde **38** and aldimines **39** (eq 1, Scheme 2.14).[103] We further anticipated that a [3+2] formal cycloaddition with α-iminonitrile **53** in place of aldimine **39**, in a similar cascade reaction, to afford pyrrolidine **54** decorated with quaternary chiral center (eq 2, Scheme 2.14). Needless to mention that pyrrolidines having quaternary stereocenters are existing as a main structural core in many active pharmaceuticals and natural products.[106-109] With this premise in mind and our previous study in this direction, we initiated our work by using *N*-PMP-α-iminonitrile **53c** (PMP = *p*-$OMeC_6H_4$) as a model substrate for [3+2] formal cycloaddition with aqueous succinaldehyde **38** for pyrrolidine **54** and the results are summarized in Table 2.1. However, we obtained pyrrole-3-alcohol **55** as a major outcome of the reaction (eq 3, Scheme 2.14).

Table 2.1: Optimization of reaction conditions[a]



Entry	Catalyst	Solvent	Temperature	Time	Yield[b] (%)
1	**40**	DMSO	rt	48 h	nr
2	**40**	DMSO	80 °C	24 h	nr
3	**40**	DMSO	MW, 50 °C	30 min	42
4	**40**	DMSO	MW, 60 °C	40 min	55
5	**40**	DMSO	MW, 70 °C	40 min	60
6[c]	**40**	**DMSO**	**MW, 70 °C**	**40 min**	**75**
7[c]	**40**	DMSO	MW, 80 °C	60 min	51
8[c]	**40**	Toluene	MW, 70 °C	40 min	nr
9[c]	**40**	DMF	MW, 70 oC	40 min	52
10[c]	**40**	CH3CN	MW, 70 °C	40 min	40
11[d]	**56**	DMSO	MW, 70 °C	40 min	45
12[e]	**57**	DMSO	MW, 70 °C	40 min	30
13[f]	**58**	DMSO	MW, 70 °C	40 min	40
14	-	DMSO	MW, 70 °C	40 min	n.r.

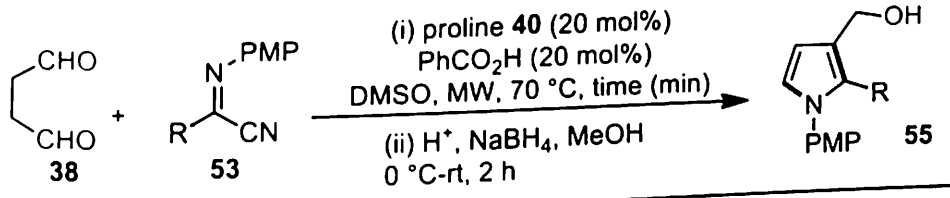
[a]Unless otherwise indicated, the reaction was carried out with (i) Imino-nitrile 53c (0.3 mmol), 38 (3 M aq. sol, 0.9 mmol), catalyst 40 (20 mol %), solvent (3.0 mL); (ii) AcOH (100 mol %), $NaBH_4$, 0 °C to rt, 2 h. [b]Isolated yields after two steps. [c]With additive $PhCO_2H$ (20 mol %). [d]Catalyst 56 (20 mol %), additive $PhCO_2H$ (20 mol %). [e]Catalyst 57 (20 mol %), additive $PhCO_2H$ (20 mol %). [f]Catalyst 58 (20 mol %), additive $PhCO_2H$ (20 mol %).

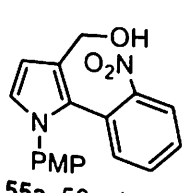
Unfortunately, no reaction was observed under previously established conditions at rt (entry 1, Table 2.1), and at conventional heating up to 80 °C (entry 2, Table 2.1). However, pyrrole-methanol **55c** was obtained in 42% yield, instead of the pyrrolidine **54c** when the reaction was carried out under microwave heating at 50 °C for 30 min, followed by in situ reductions with $NaBH_4$ (entry 3, Table 2.1). Further increase in yield was observed when the reaction was carried out by changing the temperature and time (entries 4-5, Table 2.1). Interestingly, a significant increase in yield (75%) was observed when the reaction was carried out at 70 °C for 40 min with $PhCO_2H$ (20mol %) as an additive (entry 6, Table 2.1). The increasing reactivity of imino-nitrile **53** in presence of acid additive might be responsible for the increment in the observed yield. However, further attempts to increase the reaction yield was failed such as; by increasing the reaction temperature and time (entry 7, Table 2.1), by altering solvent (entries 8-10, Table 2.1), and catalysts (entries 11-13, Table 2.1). Moreover, no reaction was observed when a control experiment was carried out under microwave irradiation without amine catalyst (entry 14, Table 2.1). Therefore, we preferred to perform this one-pot two-steps sequence to N-PMP-pyrrole-3-methanols **55** with optimized conditions (entry 6, Table 2.1).

Next, the scope of this method was examined with a variety of preformed N-PMP-α-iminonitrile **53** under optimized conditions and summarized in Table 2.2. The reactions proceeded well in almost all cases when α-iminonitriles **53** were substituted with electron withdrawing groups (EWG) (e.g. $-NO_2$, –F, –Cl, –Br and –CN) at the ortho-, meta-, or para- position of the phenyl group to furnish corresponding pyrroles **55a–55q** (Table 2.2) with good yields. However, the reactions were rather slow in case of α-iminonitriles **53** substituted at ortho-position and required a little longer reaction time. Gratifyingly, pyrrole-3-methanols **55r-55v** (Table 2.2) were also obtained in good yields when preformed α-iminonitriles **53** from corresponding hetero-aromatic aldehydes were employed under standardized conditions except for longer reaction time (60 min). A similar result was obtained with pyrrole-3-methanol **55w** (Table 2.2) when α-iminonitrile **53** derived from naphthaldehyde was employed. This reaction has limitation to electron deficient α-iminonitrile **53**, as reaction failed to give pyrrole-3-methanols **55x** (Table 2.2) when iminonitrile derived from electronically rich aryl aldehydes was employed.

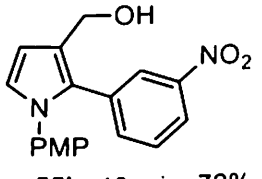
On the basis of the aforementioned results and our previous studies, a plausible mechanism is proposed to justify the formation of pyrrole-3-methanols **55** over pyrrolidines **54** through this transformation as shown in Scheme 2.15.

Table 2.2: substrate scope with respect to various iminonitriles **53**

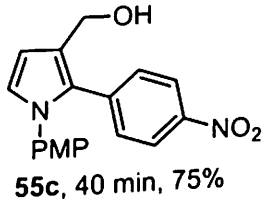




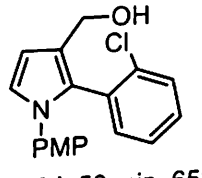
55a, 50 min, 69%



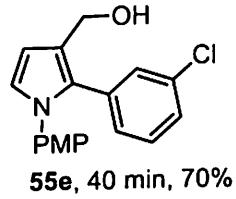
55b, 40 min, 72%



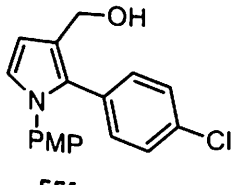
55c, 40 min, 75%



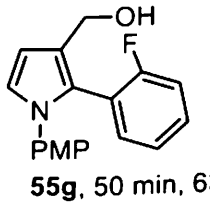
55d, 50 min, 65%



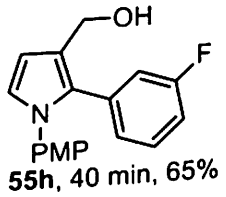
55e, 40 min, 70%



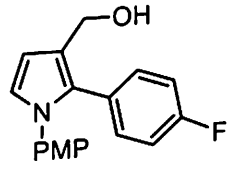
55f, 40 min, 72%



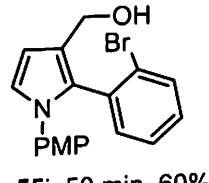
55g, 50 min, 63%



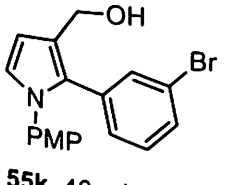
55h, 40 min, 65%



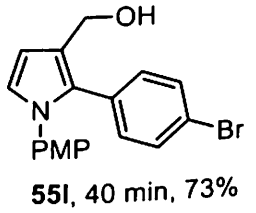
55i, 40 min, 73%



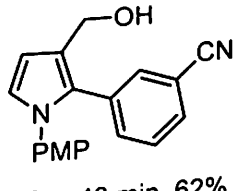
55j, 50 min, 60%



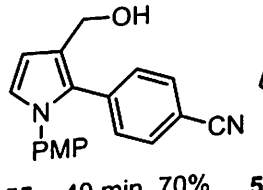
55k, 40 min, 65%



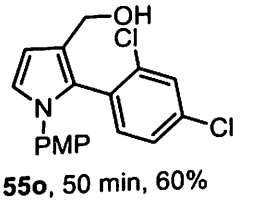
55l, 40 min, 73%



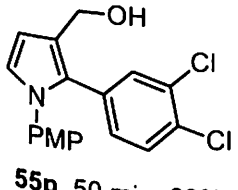
55m, 40 min, 62%



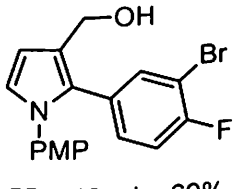
55n, 40 min, 70%



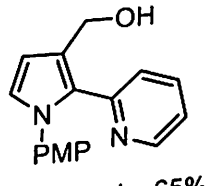
55o, 50 min, 60%



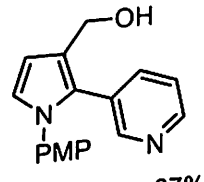
55p, 50 min, 63%



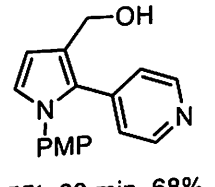
55q, 40 min, 69%



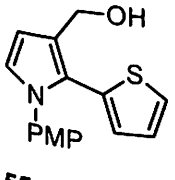
55r, 60 min, 65%



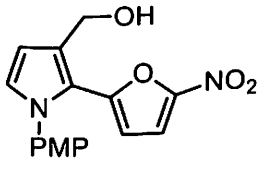
55s, 60 min, 67%



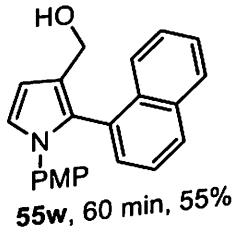
55t, 60 min, 68%



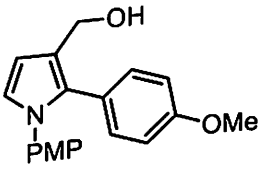
55u, 60 min, 60%



55v, 60 min, 67%



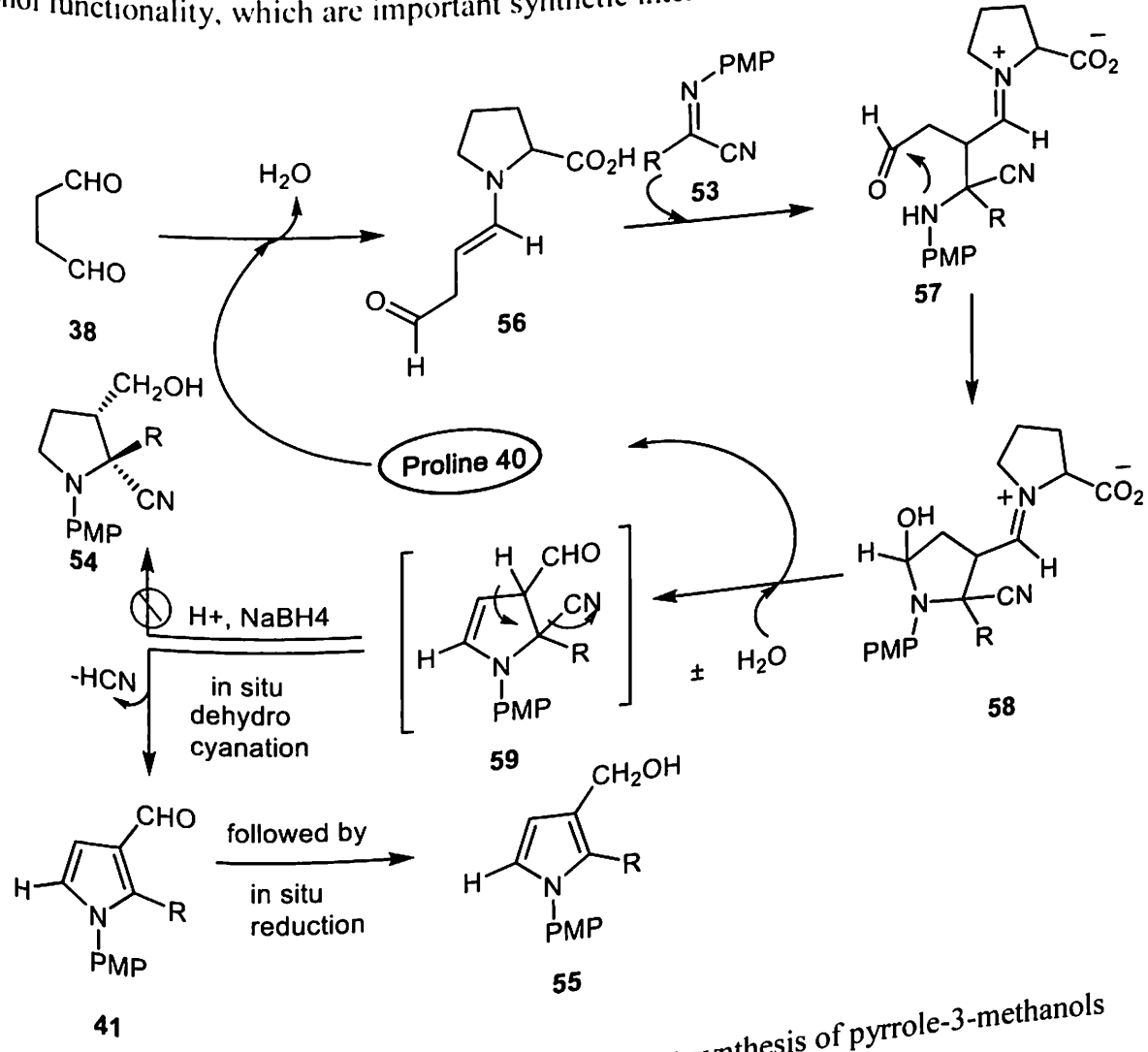
55w, 60 min, 55%



55x, n.r.

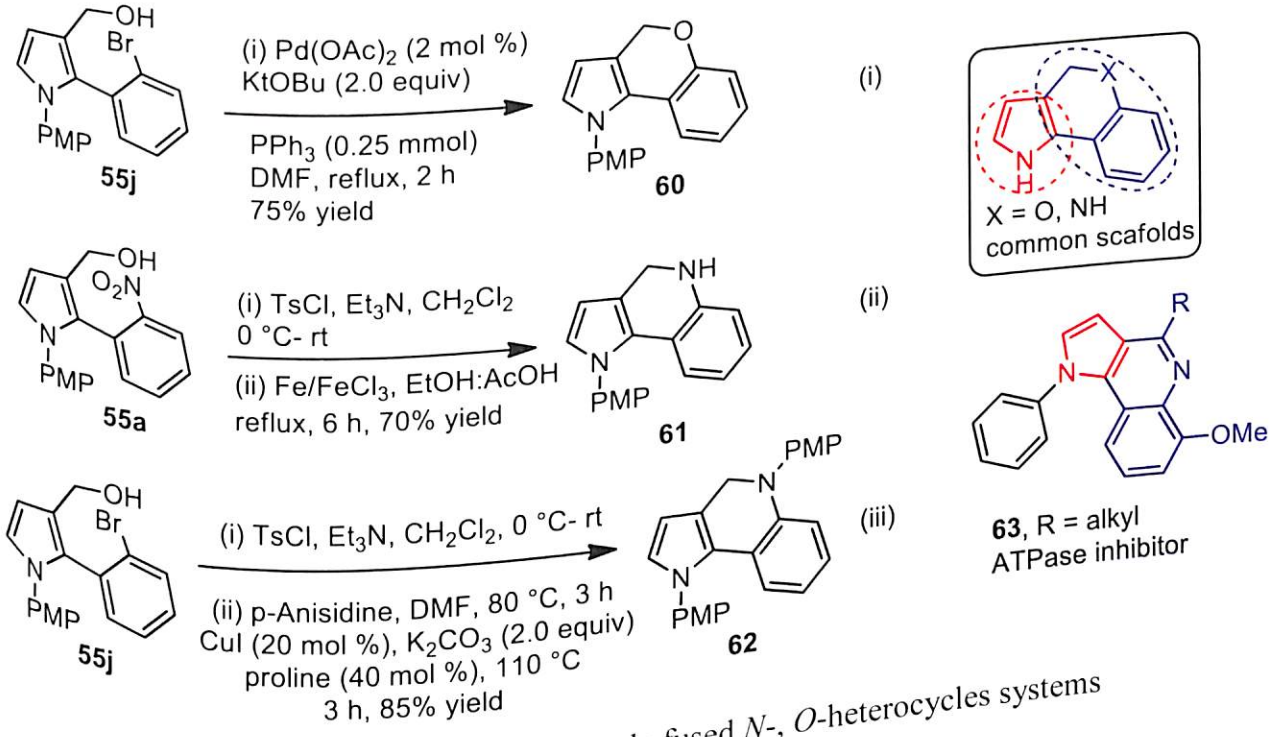
[a]Unless otherwise indicated, the reaction was carried out with (i) Imino-nitrile **53** (0.3 mmol), **38** (3 M aq. sol, 0.9 mmol), proline **40** (20 mol %), $PhCO_2H$ (20 mol %), DMSO (3.0 mL), [b]Time required for completion of the first step. [c]Isolated yields of **55**.

The direct Mannich reaction of enamine intermediate **56** with iminonitrile **53** to yield an intermediate **57**, which subsequently converted to enamine intermediate **59** through intramolecular cyclization, dehydration, and simultaneous regeneration of catalyst **40**. As expected, *in situ* $NaBH_4$ reductions of intermediate **59** under acidic conditions should have delivered pyrrolidine **54**, however, we obtained functionalized pyrrole **55** exclusively. Here, we assume that the dehydrocyanation step from dihydropyrrole **59** is very fast under microwave heating conditions due to the aromatic nature of resultant pyrrole **41**, as **59** could not be isolated. A similar observation of *in situ* microwave-assisted dehydrocyanation of 3,4-dihydro-2H-pyrrole-2-carbonitriles to substituted pyrroles was recently presented by Opatz and co-workers,[110] which further supports our hypothesis. The present one-pot protocol furnishes pyrrole-3-methanols **55** enclosing an alcohol functionality, which are important synthetic intermediates for further functionalization.



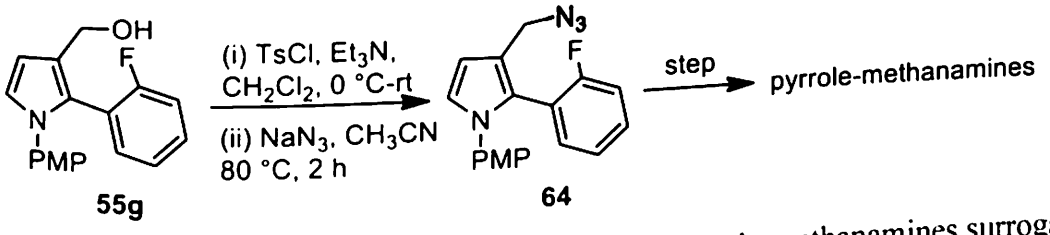
Scheme 2.15 Proposed Mechanism for one-pot synthesis of pyrrole-3-methanols

Therefore, we initially explored the synthetic potential of these compounds. In this direction, a quick synthesis of polycyclic pyrrolo-dihydrochromene **60** was achieved from compound **55j** through Pd-catalyzed intramolecular C-O coupling reaction under optimal conditions (eq i, Scheme 2.16). Next, pyrrolo-dihydroquinoline compounds **61** and **62** were synthesized using two different approaches. Firstly, alcohol group of compound **55a** was converted to –OTs under standard condition and reduction of $-NO_2$ group was performed with Fe/$FeCl_3$ in EtOH: AcOH (2:1) with the crude material without purification. The intramolecular cyclization of the *in situ* generated amine from the reduction of $-NO_2$ furnished corresponding tricyclic pyrrolo-dihydroquinoline **61** with good yield (eq ii, Scheme 2.16). Next, compound **55j** was tosylated first as earlier and used without purification for nucleophilic substitution, Cu-catalyzed intramolecular C-N coupling with p-anisidine under a standard condition in DMF at high temperature to furnish N-PMP-pyrrolo-dihydroquinoline **62** with 85% yield (eq iii, Scheme 2.16).[111-114] These polycyclic N-heterocycles and their structurally similar fused skeletons are present in many biologically important compounds.[115-121] For example, a structurally similar compound phenylpyrrolo[3,2-c]quinolines **63**, was established as a novel class of inhibitors of the gastric (H+/K+)-ATPase.[122]Therefore, the ease of access to fused pyrroles by this approach is also worthy to note.



Scheme 2.16 Synthesis of pyrrole fused *N*-, *O*-heterocycles systems

Next, azido–derivative **64** was obtained in good yield from **55g** through the nucleophilic substitution of the corresponding tosylate compound with NaN_3 at elevated temperature. Compound **64** can act as a suitable surrogate for several bioactive pyrrole-3-methanamines as well as for click-reaction with various alkynes (Scheme 2.17).



Scheme 2.17 Synthesis of azido-derivative **64** as a pyrrole-methanamines surrogate

2.4 Conclusions:

In summary, we have described a new method for the synthesis of pyrrole-3-methanols **53**from N-PMP-α-iminonitriles **53** and succinaldehyde **38** under microwave irradiation. The overall one-pot process proceeds through amine-catalyzed direct Mannich/intramolecular cyclization, dehydrocyanation, and *in situ* reduction as [3+2] annulation under mild condition. Synthetic application of this method was further shown for the synthesis of biologically important polycyclic *N*-heterocycles.

2.5 General Experimental Methods:

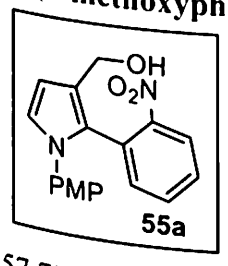
General Remarks: Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated plates (0.25 mm). The column chromatography was performed on silica gel (100-200) using a mixture of hexane/EtOAc. Chemical yields refer to pure isolated substances. ^{1}H-NMR spectra were recorded on a BRUKER-AV400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$= δ 7.26 for ^{1}H, and 77.00 for ^{13}C-NMR). Data are reported as follows: chemical shift, multiciplity(s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. ^{13}C-NMR spectra were recorded on a BRUKER-AV400 (75 MHz) spectrometer with complete proton decoupling. High-resolution mass spectra were recorded using the quadrupole electrospray ionization (ESI) technique.

2.6 Typical procedure for the synthesis of pyrrole-3-methanols (55)

Succinaldehyde **38** (0.3 mL, 0.9 mmol, 3M solution) was added to a mixture of preformed N-PMP-iminonitrile **53** (0.3 mmol) and proline **40** (7.0 mg, 0.06 mmol) in DMSO (3.0 mL), $PhCO_2H$ (7.3 mg, 0.06 mmol) and irradiated under microwave condition at 70 °C until the α-iminonitrile **53** was consumed as monitored by TLC. Once the imine consumed, reaction was taken to 0 °C and cold MeOH (2.0 mL), CH_3CO_2H (100 mol%, 18 μL) was added. To this solution $NaBH_4$ was added cautiously, and stirred for additional 2 h. The reaction was subsequently quenched with aqueous $NaHCO_3$ (20 % sol, 5.0 mL). The aqueous solution was extracted with EtOAc (2 × 8.0 mL) and combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuo after filtration. The residue was purified by silica gel column chromatography; eluting with hexane:EtOAc to afford pyrrole-3-methanols **55** with 50-75% yields.

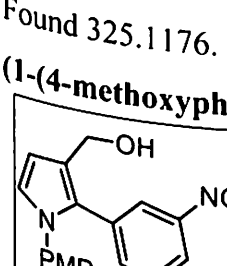
2.7 Analytical data of (55a-55w)

(1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1H-pyrrol-3-yl)methanol (55a). (66 mg, 69% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.39 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 2.6 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.37, 57.77, 109.50, 114.16 (2C), 123.42, 123.60, 124.34, 126.60, 126.68 (2C), 126.86, 128.82, 132.32, 132.48, 134.08, 149.66, 158.33; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}N_2O_4$ 325.1178; Found 325.1176.

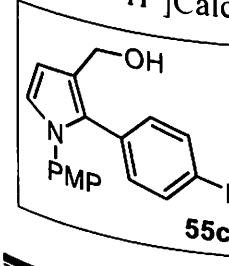


55a

(1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-pyrrol-3-yl)methanol (55b). (69 mg, 72% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.56 (s, 2H), 6.45 (d, J = 2.3 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 8.8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.41, 57.82, 109.94, 114.38 (2C), 121.44, 123.81, 124.26, 124.59, 126.99 (2C), 128.87, 129.35, 132.63, 133.32, 135.79, 147.96, 158.52; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}N_2O_4$ 325.1178; Found 325.1181.



55b

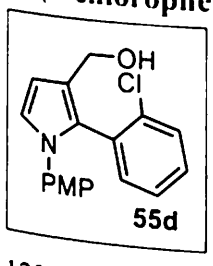


55c

(1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrol-3-yl)methanol (55c). (72 mg, 75% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.55 (s, 2H), 6.45 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 2.1 Hz, 1H), 7.00 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 8.07 (d, J

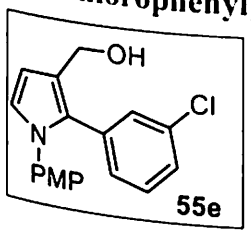
= 8.5 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.36, 57.69, 110.40, 114.36 (2C), 123.21 (2C), 124.60, 124.99, 126.78 (2C), 129.46, 130.12 (2C), 132.67, 138.18, 145.89, 158.47; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}N_2O_4$ 325.1178; Found 325.1182.

(2-(2-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55d). (60 mg, 65% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 6.47 (s, 1H), 6.74 (d, *J* = 8.3 Hz, 2H), 6.92 (s, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 7.21 (dd, *J* = 13.0, 6.8 Hz, 3H), 7.35 (d, *J* = 7.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.33, 58.15, 108.76, 113.90 (2C), 122.74, 123.67, 126.24 (2C), 126.42, 128.62, 129.48, 129.49, 131.20, 133.20, 133.59, 135.49, 158.04; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}ClNO_2$ 314.0948; Found 314.0947.



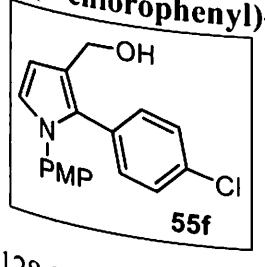
55d

(2-(3-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55e). (65 mg, 70% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H),4.55 (s, 2H), 6.44 (d, *J* = 1.3 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 1.5 Hz, 1H), 7.01 (d, *J* = 8.5 Hz, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 14.0 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.37, 57.88, 109.57, 114.14 (2C), 123.20, 123.53, 126.77 (2C), 126.88, 128.31, 129.14, 129.95, 130.26, 133.03, 133.38, 133.78, 158.21; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}ClNO_2$ 314.0948; Found 314.0946.



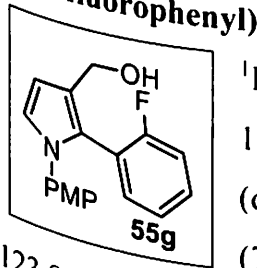
55e

(2-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55f). (67 mg, 72% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.54 (s, 2H), 6.43 (d, *J* = 2.8 Hz, 1H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 2.8 Hz, 1H), 7.00 (d, *J* = 8.9 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.40,58.01, 109.56, 114.13 (2C), 122.79, 123.38, 126.82 (2C), 128.27 (2C), 129.94, 130.65, 131.33 (2C), 132.80, 133.06, 158.15; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}ClNO_2$ 314.0948; Found 314.0950.



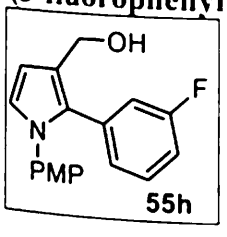
55f

(2-(2-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55g). (55 mg, 63% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.52 (s, 2H), 6.51 (d, *J* = 2.5 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 7.00-7.06 (m, 3H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 5.7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.32, 58.04, 109.20, 113.94 (2C), 115.49, 115.72, 123.44, 123.84, 124.13, 125.16, 126.23 (2C), 129.58, 129.98, 133.31, 158.11, 161.42; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}FNO_2$ 298.1243; Found 298.1240.



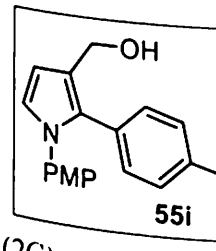
55g

(2-(3-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55h). (57 mg, 65% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.56 (s, 2H), 6.44 (d, *J* = 2.6 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.86-6.97 (m, 4H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.36, 57.90, 109.55, 113.81, 114.10 (2C), 116.94, 123.02, 123.50, 125.85, 126.73 (2C), 129.37, 130.45, 133.03, 133.63, 158.15, 161.30; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}FNO_2$ 298.1243; Found 298.1241.



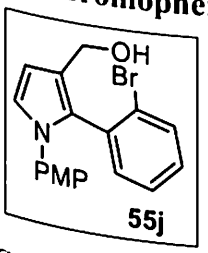
55h

(2-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55i). (64 mg, 73% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.53 (s, 2H), 6.43 (d, *J* = 2.5 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.91-6.99 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.36, 58.01, 109.35, 114.07 (2C), 114.92, 115.14, 122.53, 122.98, 126.83 (2C), 127.57, 130.90, 131.81, 131.89, 133.18, 158.13, 163.02; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}FNO_2$ 298.1243; Found 298.1245.



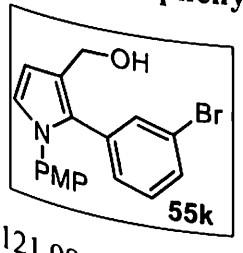
55i

(2-(2-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55j). (63 mg, 60% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 6.46 (d, *J* = 2.9 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 2.9 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.15 (ddd, *J* = 8.1, 5.6, 3.6 Hz, 1H), 7.21–7.25 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.32, 58.19, 108.63, 113.87 (2C), 122.51, 123.38, 126.34 (2C), 126.98, 129.70 130.43, 132.57, 133.13, 133.35, 133.70, 158.04; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}BrNO_2$358.0442; Found 358.0446.



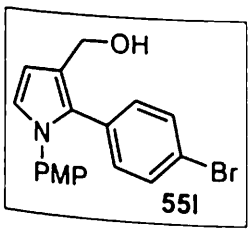
55j

(2-(3-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55k). (69 mg, 65% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.55 (s, 2H), 6.43 (d, *J* = 2.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 2.8 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.03 (s, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.37 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.43, 57.93, 109.57, 114.14 (2C), 121.98, 123.10, 123.59, 126.80 (2C), 128.76, 129.45, 129.82, 130.19, 132.81, 132.96, 133.58, 158.20; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}BrNO_2$ 358.0442; Found 358.0445.



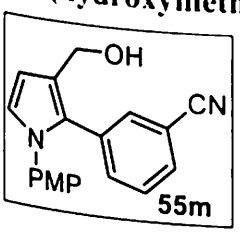
55k

(2-(4-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55l). (77 mg, 73% yield);



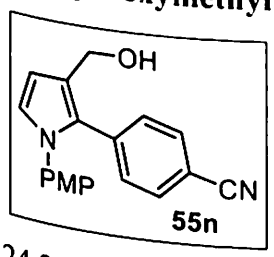
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.53 (s, 2H), 6.41 (d, J = 1.9 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 2.1 Hz, 1H), 6.98 (dd, J = 11.9, 8.5 Hz, 5H), 7.43 (d, J = 6.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.46, 57.92, 109.56, 114.26 (2C), 115.89, 116.11, 123.09, 123.51, 126.91 (2C), 129.20, 129.51, 130.72, 130.79, 132.87, 134.91, 158.37; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}BrNO_2$ 358.0442; Found 358.0444.

3-(3-(hydroxymethyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)benzonitrile (55m). (56 mg, 62%



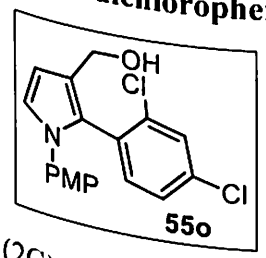
yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.96 (s, 2H), 6.46 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 2.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 7.34–7.38 (m, 2H), 7.43 (s, 1H), 7.52 (d, J = 7.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.43, 59.72, 109.69, 112.33, 114.34 (2C), 118.53, 118.55, 124.17, 126.88 (2C), 128.99, 130.55, 130.59, 132.40, 132.67, 133.39, 134.36, 158.50; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{19}H_{16}N_2O_2$ 305.1290; Found 305.1294.

4-(3-(hydroxymethyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)benzonitrile (55n). (63 mg, 70%



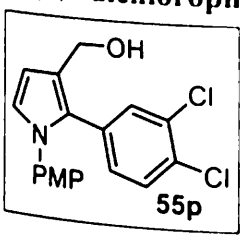
yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.58 (s, 2H), 6.48 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 2.5 Hz, 1H), 7.03 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.44, 57.88, 110.23, 114.37 (2C), 118.89, 124.21, 124.66, 126.84 (2C), 129.91, 130.25 (2C), 131.75 (2C), 132.09, 132.81, 136.23, 158.51; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{19}H_{16}N_2O_2$ 305.1290; Found 305.1293.

(2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55o). (62 mg, 60%



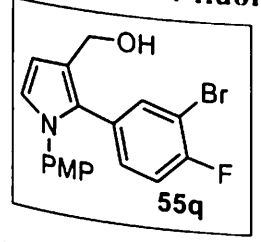
yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.26 (d, J = 11.4 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 6.76 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 2.8 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 7.19 (s, 2H), 7.35 (d, J = 0.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.32, 58.19, 108.63, 113.87 (2C), 122.51, 123.38, 126.34, 126.38 (2C), 126.98, 129.70, 130.43, 132.57, 133.13, 133.35, 133.70, 158.04;HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{15}Cl_2NO_2$ 348.0558; Found 348. 0552.

(2-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55p). (65 mg, 63% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.54 (s, 2H), 6.42 (d, *J* = 2.7 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J*= 2.7 Hz, 1H), 6.93 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.33 (d, *J* = 1.7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.43, 57.93, 109.57, 114.14 (2C), 121.98, 123.10, 123.59, 126.80 (2C), 128.76, 129.45, 129.82, 130.19, 132.88, 132.96, 133.58, 158.20; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{15}Cl_2NO_2$348.0558; Found 348.0556.



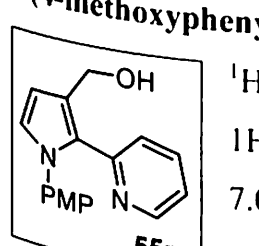
55p

(2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)methanol (55q). (77 mg, 69% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.41 (s, 1H), 4.56 (s, 1H), 6.47 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.87 (t, *J* = 2.8 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 2H), 7.07 (dd, *J* = 14.7, 7.7 Hz, 1H), 7.30–7.39 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.44, 57.98, 109.58, 110.90, 114.20 (2C), 120.84, 121.94, 123.60, 126.84 (2C), 128.79, 129.27, 129.35, 129.84, 132.88, 133.30, 158.18; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{15}BrFNO_2$ 376.0348; Found 376.0344.



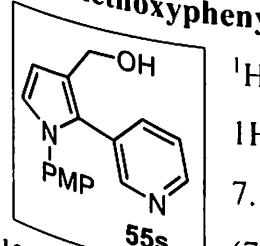
55q

(1-(4-methoxyphenyl)-2-(pyridin-2-yl)-1*H*-pyrrol-3-yl)methanol (55r). (54 mg, 65% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 4H), 4.50 (s, 2H), 6.35 (d, *J* = 2.6 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.05 (dd, *J* = 7.3, 5.0 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.39 (td, *J* = 8.3, 1.6 Hz, 1H), 8.56 (d, *J* = 4.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.48, 58.05, 110.54, 114.42 (2C), 120.44, 123.20, 124.96, 126.94 (2C), 128.66, 130.35, 133.50, 135.94, 148.41, 150.70, 158.62; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{17}H_{16}N_2O_2$ 281.1290; Found 281.1293.



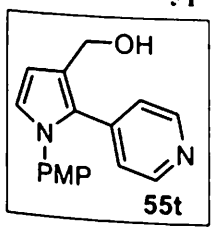
55r

(1-(4-methoxyphenyl)-2-(pyridin-3-yl)-1*H*-pyrrol-3-yl)methanol (55s). (55 mg, 67% yield); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 4.55 (s, 2H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 2.5 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 7.18 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 8.41 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.41, 57.78, 109.87, 114.33 (2C), 122.97, 123.84, 124.10, 127.02 (2C), 127.89, 128.20, 132.78, 137.35, 147.53, 150.41, 158.44; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{17}H_{16}N_2O_2$ 281.1290; Found 281.1292.



55s

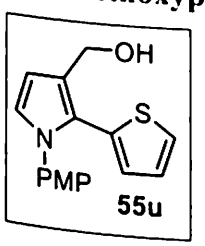
(1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrol-4-yl)methanol (55t). (56 mg, 68% yield);



55t

^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 1H), 3.80 (s, 3H), 4.57 (s, 2H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 2.6 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 4.5 Hz, 2H), 8.44 (bs, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.44, 57.67, 109.54, 114.41 (2C), 124.25, 125.06, 125.30, 126.06, 126.83 (2C), 128.53, 132.67, 138.48, 140.11, 148.29, 158.58; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{17}H_{16}N_2O_2$ 281.1290; Found 281.1294.

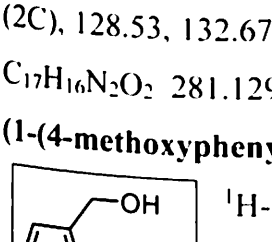
(1-(4-methoxyphenyl)-2-(thiophen-2-yl)-1*H*-pyrrol-3-yl)methanol (55u). (50 mg, 60% yield);



55u

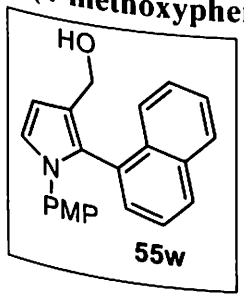
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.61 (s, 2H), 6.41 (d, *J* = 2.5 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 4H), 6.4 (t, 3.8 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 5.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.40, 58.11, 109.38, 113.97 (2C), 123.63, 123.98, 125.17, 126.22, 126.76, 127.40 (2C), 128.05, 132.45, 132.96, 158.62 ; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{16}H_{15}SNO_2$ 286.0901; Found 281.0905.

(1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl)-1*H*-pyrrol-3-yl)methanol (55v). (63 mg, 67% yield); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.84 (s, 2H), 5.63 (d, *J* = 3.9 Hz, 1H), 6.44 (d, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 2.7 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 3.9 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 2H), ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.59, 58.32, 108.43, 111.17, 113.85, 114.52 (2C), 120.14, 127.26, 127.93 (2C), 128.59, 132.12, 139.28, 150.23, 159.74; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{16}H_{14}N_2O_5$ 315.0981; Found 315.0985.



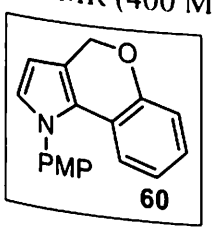
55v

(1-(4-methoxyphenyl)-2-(naphthalen-1-yl)-1*H*-pyrrol-3-yl)methanol (55w). (54 mg, 55% yield); ^{1}H-NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 3H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 6.55 (d, *J*= 2.9 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 2.9 Hz, 1H), 7.33 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.36–7.40 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.22, 58.22, 108.80, 113.75 (2C), 114.07, 122.65, 124.05, 125.07, 125.80, 125.85, 125.90 (2C), 126.29, 128.13, 128.44, 129.52, 129.99, 133.36, 133.41, 133.44, 157.71; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{22}H_{19}NO_2$ 330.1494; Found 330.1498.



55w

2.8 Experimental procedure for the synthesis of 1-(4-methoxyphenyl)-1,4-dihydrochromeno [4, 3-*b*]pyrrole (60). In a two-necked round bottom flask fitted with condenser, substrate **55j** (0.05g, 0.14 mmol), KO^{t}Bu (31 mg, 0.28 mmol), and $Pd(OAc)_2$ (1.0 mg, 2 mol %), PPh_3 (7.3 mg, 20 mol %), was taken in dry DMF (3 mL) and degassed for 10 minutes with N_2 and reaction mixture was heated at 110°C for 3 h. The reaction mixture was allowed to cool tort and quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was evaporated under vacuo and purified through silica gel column chromatography by eluting with hexane/EtOAc (90:10). The product **60** was obtained as colorless oil (24 mg, 63% isolated yield) as shown in (**Scheme 2.16**).

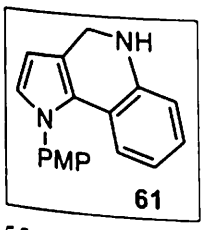


60

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 7.8, 1.7 Hz, 1H), 7.53 (dd, J = 8.0, 1.1 Hz, 1H), 7.37 (td, J = 7.4, 0.9 Hz, 1H), 7.23–7.26 (m, 2H), 7.12–7.17 (m, 1H), 6.89–6.94 (m, 3H), 6.84–6.86 (m, 1H), 6.18 (s, 1H), 3.82 (s, 3H); ^{13}C-NMR (75MHz, $CDCl_3$) δ 55.41, 57.82, 109.94, 114.38 (2C), 121.44, 123.81, 124.26, 124.59,126.99 (2C), 128.87, 129.35, 132.63, 133.32, 135.79, 147.96, 158.52; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{15}NO_2$ 278.1181; Found 278.1184.

2.9 Experimental procedure for the synthesis of 1-(4-methoxyphenyl)-4,5-dihydro-1H-pyrrolo[3,2-*c*]quinoline (61). To a stirred solution of compound **55a** (97 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (3.0 equiv, 0.9 mmol) at rt. Reaction was taken to 0 °C and TsCl (68 mg, 0.36 mmol) in CH_2Cl_2 (2.0 mL) was added drop wise and then stirred at rt for additional 4 h. Progress of the reaction was monitored by TLC. Reaction was stirred with NH_4Cl (20% sol. 5.0 mL) and extracted with additional CH_2Cl_2 (5.0 mL). The combined organic layer was washed with brine solution and concentrated under vacuo to give crude solid mass. This was used further without purification at this stage. To this crude mass was added ethanol and acetic acid (3mL, 2:1 ratio respectively), Fe powder (125 mg, 7.5 equiv, 2.2 mmol), and $FeCl_3$ (9.5 mg, 0.2 equiv, 0.06 mmol) while stirring. The reaction mixture was refluxed for 6 hours and monitored by TLC. After completion of the reaction, ethanol was evaporated under reduced pressure. The reaction mixture was filtered through celite and washed with the CH_2Cl_2 (10 mL). The organic layer was stirred with $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (10 mL). The combined organic layer was washed with brine solution, dried over $Na_2SO_4$and concentrated under reduced pressure. The

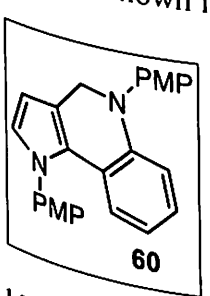
crude residue was purified by silica-gel column chromatography (EtOAc/hexanes) to afford **61** as brownish pasty liquid (48 mg, 58% yield) as shown in (**Scheme 2.16**).



61

^{1}H- NMR (400 MHz, $CDCl_3$) δ 7.09–7.14 (m, 1H), 7.05 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 3.1 Hz, 1H), 6.87 (dd, J = 7.9, 1.6 Hz, 1H), 6.76 (d, J = 9.0 Hz, 2H), 6.67 (s, 1H), 6.62–6.66 (m, 2H), 6.62 (d, J = 3.1 Hz, 1H), 3.82 (d, J = 19.7 Hz, 1H), 3.75 (s, 3H), 3.69 (d, J = 12.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 55.34, 59.93, 109.37, 113.76, 114.03 (2C), 115.35, 118.14, 120.42, 124.43, 125.40, 125.80 (2C), 129.92, 132.45, 138.30, 145.84, 158.28; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{16}N_2O$ 277.1341; Found 277.1345.

2.10 Experimental procedure for the synthesis of 1,5-bis(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrrolo[3,2-*c*]quinoline (62). To a stirred solution of compound **55a** (90 mg, 0.28 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (3.0 equiv, 0.83 mmol) at rt. Reaction was taken to 0 °C and TsCl (63 mg, 0.33 mmol) in CH_2Cl_2 (2.0 mL) was added drop wise and then stirred at rt for additional 4 h. Progress of the reaction was monitored by TLC. Reaction was stirred with NH_4Cl (20% sol, 5 mL) and extracted with additional CH_2Cl_2 (5.0 mL). The combined organic layer was washed with brine solution and concentrated under vacuo to give crude solid mass. This was used further without purification at this stage. To this crude mass in DMF (3 mL) was added *p*-anisidine (34 mg, 0.27 mmol, 1.0 equiv) and heated at 80 °C for 2 h. Next, to this reaction mixture, K_2CO_3 (76 mg, 0.55 mmol, 2.0 equiv.), CuI (10 mg, 20 mol %), proline as ligand (13 mg, 40 mol %) were added and further heated at 110 °C for additional 3 h under an N_2 atmosphere. Progress of this reaction was monitored by TLC. The reaction was cooled to rt and quenched with water (8.0 mL) and extracted with EtOAc (3 × 8.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuo. The crude mass was purified using silica-gel column chromatography by eluting with hexane/EtOAc to afford **62** as yellow pasty liquid (93 mg, 87% yield) as shown in (Scheme 2.16).

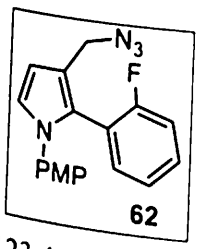


60

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.8, 1.7 Hz, 1H), 7.56 (dd, J = 7.9, 1.2 Hz, 1H), 7.28–7.33 (m, 1H), 7.23 (d, J = 9.0 Hz, 2H), 7.08–7.14 (m, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.90 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 1.8 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.47 (d, J = 8.9 Hz, 2H), 6.25 (dd, J = 2.8, 1.8 Hz, 1H), 5.80 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 157.62, 151.97, 142.23, 141.30, 134.14, 132.93, 128.44, 128.15, 127.80, 126.79, 123.57, 121.93 (2C),

119.96, 118.18, 114.77 (2C), 114.55 (2C), 114.25 (2C), 109.20, 56.26, 55.70, 55.52; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{25}H_{22}N_2O_2$ 383.1759; Found 383.1762.

3-(azidomethyl)-2-(2-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (64). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 4.63 (s, 2H), 6.46 (d, *J* = 2.5 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 9.3 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.20 – 7.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.32, 56.04, 109.20, 113.94 (2C), 115.49, 115.72, 123.44, 123.84, 124.13, 125.16, 126.23 (2C), 129.58, 132.98, 133.31, 158.11, 161.42; IR (KBr)/cm^{-1} 2965, 2052, 1612, 1512, 1466, 1319, 1134, 1034, 964; HRMS (ESI-TOF) *m/z* [M + H$^+$]Calcd for $C_{18}H_{15}FN_4O$ 322.1308; Found 322.1312.



62

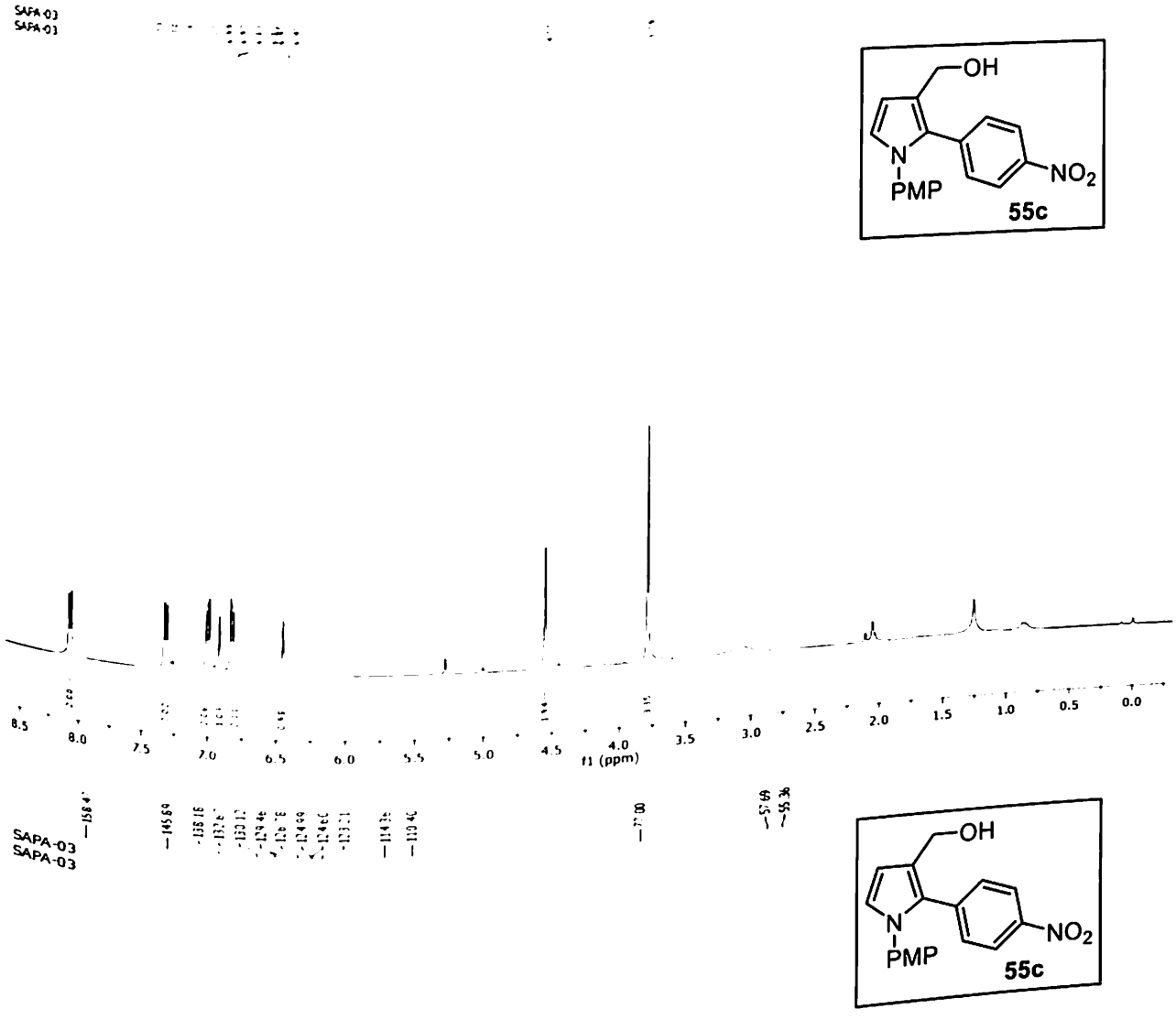


Figure 2.2 ^{1}H and ^{13}C NMR spectra of (**55c**)

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