Strategies for the preparation of pyrrole entities: A concise review

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Abstract: Pyrroles is the special class of heterocyclic compounds with a broad spectrum of biological activities such as anti-inflammatory, antiproliferative, antihistaminic, anti-HIV, antifungal, antihelmintic and antiviral agents. Pyrrole is a five membered ring structure, with formula C\textsubscript{4}H\textsubscript{4}NH. The heterocyclic pyrroles are the ideal building blocks for different biologically efficient molecules including porphyrins and bile pigments. Therefore researchers are synthesizing these heterocycles through multi-stepped or single stepped pathways as target structures for biological studies. In this review, different synthetic protocols/methodologies are shown in which different entry molecules are converted into pyrrole derivatives, which are important from medicinal and pharmaceutical points of view.

Key words: Synthesis, Pyrrole, Multicomponent, Paal-Knorr reaction

Introduction

Pyrrole is a heterocyclic aromatic organic compound, a five membered ring with formula C\textsubscript{4}H\textsubscript{4}NH. It is a colorless volatile liquid that darkens readily upon exposure to air. The existence of pyrrole in coal tar, bone oil, and in general, in products obtained by the dry distillation of proteins was first surmised by Runge\textsuperscript{1} in 1834. The discovery that pyrrole ring was an integral part of heme and of chlorophyll molecules\textsuperscript{2} not only created intense interest in the chemistry of pyrrole and its derivatives, but also resulted in the majority of investigations conducted during the latter part of the nineteenth century and the early years of the twentieth century being dominated by this relationship of pyrrole with naturally occurring compounds.

A number of years ago, Sheradsky\textsuperscript{3} reported that when the base-catalyzed addition products [1 and its \textit{trans}-isomer, R = CO\textsubscript{2}Me] of acetophenone oxime and dimethyl acetylenedicarboxylate were heated together, the pyrrole derivative (3) [R = CO\textsubscript{2}Me] was obtained. Trofimov \textit{et al.}\textsuperscript{4} have since reported that when the o-vinyl derivative (2) [R = H] of acetophenone oxime was heated with potassium hydroxide in dimethyl sulfoxide solution, 2-phenylpyrrole (4) [R = H] was obtained in high yield. The Russian workers\textsuperscript{4} prepared compound 2 by heating acetophenone oxime,

\[
\begin{align*}
(1, 2) & \quad \rightarrow \quad (3, 4) \quad \rightarrow \quad (5) \\
\end{align*}
\]

acetylene, and potassium hydroxide together in dimethyl sulfoxide solution, under conditions which can lead\textsuperscript{5} to the formation of both 2-phenylpyrrole (4) and its 1-\textit{N}-vinyl derivative (5, R = H).

Generally, pyrroles are synthesized by the condensation of 1, 4-dicarbonyl compounds with primary amines. This condensation, known as the Paal-Knorr reaction, has a wide scope, permitting the synthesis of a wide

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variety of pyrrole derivatives. Recently, it was found that microwaves enhance the rate of this reaction. In this communication, Rao and Jothilingam reported a novel one-pot synthesis of 2,5-di- and 1,2,5-trisubstituted pyrrole derivatives under microwave conditions (7) [Ar = C₆H₅, R = H; Ar = 4-ClC₆H₄, R = H; Ar = 4-BrC₆H₄, R = H; Ar = 4-CH₃C₆H₄, R = H; Ar = 4-OCH₃C₆H₄, R = H; Ar = 4-Cl,3-CH₃C₆H₃, R = H; Ar = C₆H₅, R = n-C₆H₁₃; Ar = C₆H₅, R = C₆H₅; Ar = C₆H₅, R = CH₂C₆H₅] from 2-butene-1,4-diones (6) [Ar = C₆H₅, 4-ClC₆H₄, 4-BrC₆H₄, 4-CH₃C₆H₄, 4-OCH₃C₆H₄, 4-Cl,3-CH₃C₆H₃] through domino pathways via palladium-assisted transfer hydrogenation followed by a Paal-Knorr reaction using ammonium formate and its analogs.

The advantage of this reaction is the utility of PEG-200 as a solvent, which replaces use of high dielectric constant solvents such as water and DMF. PEG-200 is miscible with water, thereby simplifying the work-up. Furthermore, it is inexpensive and readily available in bulk quantities. But the drawback is that PEG-400 can’t be used possibly due to low solubility of ammonium formate.

Ranu and Dey carried out one-pot, three-component condensation of a carboxyl compound (8), an amine (9) and a nitroalkane (10) leading to an efficient synthesis of alkyl-substituted pyrroles (11) [R¹ = C₈H₁₇, CH₃, CH₃CH₂; R² = CH₃(CH₂)₃, C₆H₁₂, PhCH₂, PhCH(CH₃)₂; R³ = 4-NO₂C₆H₄, C₇H₇O₂CH₂, 4-ClC₆H₄, Ph; R⁴ = CH₃, CH₃CH₂] in molten tetrabutylammonium bromide. Neither a catalyst nor an organic solvent was required for that reaction and the molten ammonium salt was recyclable.

They also performed synthesis of fused pyrroles by the coupling of cycloalkanones, amnes and nitroalkenes.

Nitroolefins or β-acetoxy-nitro compounds (13a-i) react with α-isocyanoesters (12a-i) in the presence of an organic base to give pyrroles (14a-i) in good yield.

The pyrroles produced by the present approach could be ideal building blocks for porphyrins and bile pigments since they are unsubstituted in the 5-position and the 2-position can be protected by an easily removable group such as an ester. The substituents in the 3- and 4- position originate from the nitroolefin component and can be readily varied in view of the exceptionally rich chemistry of the nitro group. In addition, the condensation to give pyrroles could also be extended to aliphatic nitro olefins. The major drawback is the difficulty in handling and storing small, very base sensitive nitro-olefins.

Nakamura et al. reported a straightforward one-pot synthesis of 1-(dimethylamino)-1H-pyrroles (20-23) through [3 + 2] coupling of a ketone hydrazone (15-18) and a vinyl stannane. The keys to the development of this process are the
carbometalation reaction of zincated hydrazone (19) with a vinyl stannane and efficient aerobic oxidation of the resulting functionalized gem-Zn/Sn dimetallic species under mild reaction conditions.

Wang et al.\textsuperscript{12} synthesized 2,4- and 2,3,4-substituted pyroles (27) in two or three steps from commercially available ketones (26) and allyl hydroxylamine. An iridium-catalyzed isomerization reaction was developed to convert α-allyl oximes to α-vinyl oximes, which undergo a facile [3,3] rearrangement to form 1,4-imino aldehyde Paal-Knorr intermediates that cyclized to afford the corresponding pyroles.

This is an interesting alternative approach to the synthesis of pyroles because it uses the Paal-Knorr sequence without requiring the synthesis of 1,4-dicarbonyl compounds. The overall method provides a simple, selective, and functional group tolerant synthesis of substituted pyroles.

Major advantages of the methodology is application of non-toxic iron salts as catalysts with high reaction efficiency, good to excellent yields, and use of a wide variation of substituents. Noticeably, pyroles synthesized by this approach contain a characteristic 3-carboxamide group. The pyrrole-3-carboxamide has been found to be a key subunit in therapeutically active compounds, the well-known cholesterol reducing drug Lipitor\textsuperscript{®}. Thus, present scheme could provide an efficient access to such kinds of compounds.

Dergner and Opatz\textsuperscript{13} prepared 2,3,4,5-tetrasubstituted pyroles (30a-q) with high regioselectivity by a formal cycloadditions of α-(alkylideneamino) nitriles (28) [R\textsuperscript{1}, R\textsuperscript{2} as defined below] and nitroolefins (29) [R\textsuperscript{3}, R\textsuperscript{4} as defined below] followed by elimination of HCN and HNO\textsubscript{2}. The reaction allowed the convergent construction of the pyrrole ring in four steps from a nitroalkane and three aldehydes.

Since the pronucleophiles 28 can be obtained from two aldehydes and the electrophiles 29 can be prepared by condensation of an aldehyde and a nitroalkane, this method represents a highly modular synthesis of the pyrrole ring that is amenable to the combinatorial variation of all four substituents. While many reported pyrrole syntheses yield only acceptor-substituted products, this protocol also permits the preparation of products devoid of an electron-
withdrawing substituent. On the other hand, compounds of this type can be sensitive to aerial oxidation and their longer exposure to halogenated solvents such as CDCl₃ should also be avoided to prevent the formation of intensely colored oxidation products.

Settambolo et al.¹⁴ reported synthesis of (3R)-3-(Pyrrrol-1-yl) but-1-cnc (35), (3R)-4-methyl-3-(pyrrol-1-yl) pent-1-ene (36), (3R)-3-(pyrrol-1-yl) hex-1-ene (37) in high enantiomeric excess (>92%) were prepared starting from D-α-amino acids (31). The crucial steps in the synthesis, reduction (DIBAII) of the corresponding pyrrolyl esters (33) to the corresponding pyrrolylaldehyde (34) followed by Wittig olefination proceeded without compromising the stereochemical integrity.

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\begin{align*}
R^1 \quad R^2 \quad R^3 \quad R^4 & \quad R^5 \\
(a) & 2-Naph \quad Me \quad 4-C\text{Cl}_2\text{C}_6\text{H}_4 \quad H \\
(b) & 2-Naph \quad Me \quad 4-C\text{Cl}_2\text{C}_6\text{H}_4 \quad Me \\
(c) & 2-Naph \quad Me \quad 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Me \\
(d) & 2-Naph \quad Me \quad Me \quad Et \\
(e) & 2-Naph \quad Me \quad Me \quad n\text{-Pent} \\
(f) & 2-Naph \quad Me \quad 4-C\text{NC}_6\text{H}_4 \quad Et \\
(g) & 2-Naph \quad Me \quad Ph \quad Ph \\
(h) & 2-Naph \quad Bn \quad 4-C\text{Cl}_2\text{C}_6\text{H}_4 \quad Me \\
(i) & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Bn \quad 4-C\text{Cl}_2\text{C}_6\text{H}_4 \quad Me \\
(j) & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Ph \quad 4-C\text{NC}_6\text{H}_4 \quad Et \\
(k) & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Ph \quad Ph \\
(l) & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad <\text{Cl}>_2\text{Er} \\
m & 2-Naph \quad Bn \quad <\text{CH}>_3 \\
n & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Bn \quad <\text{CH}>_3 \\
o & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Ph \quad <\text{CH}>_3 \\
p & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Ph \quad <\text{CH}>_3 \\
q & 3,4-(\text{MeO})_2\text{C}_6\text{H}_4 \quad Ph \quad <\text{CH}>_3 \\
\end{align*}
\]

Alizadeh et al.¹⁵ carried out one-pot four-component reaction between two amines (38, 40) [R¹, R² as defined below] and diketene (39) in the presence of dibenzoylacetone (41) leading to 4,5-dihydro-1H-pyrrol-3-carboxamide derivatives (42) [R¹ = n-Pr, i-Bu, i-Pr, i-Bu, i-Bu, n-Pr, i-Bu, i-Bu, R² = i-Bu, n-Pr, i-Pr, i-Bu, i-Bu, n-Pr, i-Pr, n-Pr].

Bellur and Langer¹⁶ synthesized a variety of pyroles. Staudinger-aza-wittig reaction of 2-azido-1, 1-diethoxyethane (44) with 1, 3-dicarbonyl compounds (43a-m) afforded N-(2, 2-diethoxyethyl)-3-aminoalk-2-en-1 ones (45 a-m), which were subsequently transformed into functionalized pyroles (46 a-m). This approach being multi-component/one-pot and involves the synthesis of resultant pyroles in potential yields.

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\begin{align*}
R^1 \quad R^2 \quad R^3 \quad R^4 & \quad R^5 \\
(a) & \text{OMe} \quad H \quad H \quad \text{H} \\
(b) & \text{OMe} \quad H \quad H \quad \text{H} \\
(c) & \text{OMe} \quad H \quad H \quad \text{H} \\
(d) & \text{OMe} \quad H \quad H \quad \text{H} \\
(e) & \text{OMe} \quad H \quad H \quad \text{H} \\
(f) & \text{OMe} \quad H \quad H \quad \text{H} \\
(g) & \text{OMe} \quad H \quad H \quad \text{H} \\
(h) & \text{OMe} \quad H \quad H \quad \text{H} \\
(i) & \text{OMe} \quad H \quad H \quad \text{H} \\
(j) & \text{OMe} \quad H \quad H \quad \text{H} \\
(k) & \text{OMe} \quad H \quad H \quad \text{H} \\
(l) & \text{OMe} \quad H \quad H \quad \text{H} \\
m & \text{OMe} \quad H \quad H \quad \text{H} \\
n & \text{OMe} \quad H \quad H \quad \text{H} \\
o & \text{OMe} \quad H \quad H \quad \text{H} \\
p & \text{OMe} \quad H \quad H \quad \text{H} \\
q & \text{OMe} \quad H \quad H \quad \text{H} \\
\end{align*}
\]

de Silva et al.¹⁷ described an efficient one-pot synthesis of substituted pyroles (9a-n). α-Diazo carbonyl compounds (47) were treated with a catalytic quantity of Rh(II) acetate in the presence of butyl vinyl ether to produce the corresponding 3-carbonyldihydrofurans (48). The reaction of the
dihydrofuran intermediates with the excess of primary amines in presence of glacial acetic acid; afford the substituted pyroles (49a-n) in moderate to good yields.

\[ \text{R} = \text{Ph, 4-NO}_2\text{C}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, \text{Ph, Ph, Me, Me; R}^1 = \text{H, H, H, Ph, Me, Me, Et;} \]

\[ \text{R}^2 = \text{COOME, H; R}^3 = \text{Me, Et} \]

This method involves the gold as catalyst which later on produced pyrroles in very sufficient amounts. Since this gold catalyzed reaction is atom-economic, remarkably mild with regard to reaction conditions.

Yavari et al. synthesized tetra substituted pyrrole derivatives (56a-l) by the reaction of enamino (54) with haloketones (55), under solvent free conditions.

This reaction being the modification of Hantzsch's protocol, produce high yields of products and involve solvent free conditions.

The three-component reaction of primary amines (57) [R\(^1\) as defined below], dialkyl acetylenedicarboxylate (58) [R\(^2\) = Me, Et] and β-nitrostyrene derivatives (59) in the presence of iron (III) chloride afforded 1,2,3,4-tetra-substituted pyrroles (60 a-p) in high yields. These reactions could precede via domino Michael addition/ cyclization process. This reaction protocol being one-pot three component, fast, efficient mild and metal-free synthesis of substituted pyrrole heterocycles.

Bandyopadhyay et al. carried out the simple ultrasound-assisted eco-friendly
practical method for the synthesis of N-substituted pyrroles (66) [R=Ph, 4-OMeC₆H₄, Py, naphthyl, tri-naphthyl, adamantly, crysensyl, pyrenyl, 1,10-phenanthroinyl, phenanthrenyl by reacting 2,5-dimethoxytetrahydrofuran (64) with various amines (65) [R as defined above] in the presence of catalytic amounts (5 mol%) of bismuth nitrate pentahydrate under solvent free conditions. They also screened these new N-substituted compounds for in vitro cytotoxicity against a panel of mammalian cancer cell lines, which showed potential toxicity without being toxic to normal cancer lines.

This reactions which is catalyzed by Cu(OAc)₂ are highly atom-economical and environmentally benign which makes it ideal in many ways for further modifications and derivatizations.

Maehara et al. developed a method for the preparation of N-acylpyrroles (71) involving the condensation of carboxylic acids with 2, 4, 4-trimethoxybutan-1-amine (70), followed by acid mediated cyclization to form the pyrrole ring. The preparation procedure is highly tolerant to various functional groups.

Zhang et al. developed a highly regioselective synthesis of pyrroles (75) via ruthenium catalyzed three-component reaction. A variety of ketones (72), amines (73) and substituted diols (74) were supposed to react in presence of Ruthenium catalyst, potassium salt of t-butanol and t-amyl alcohol. The yields were obtained in good amounts. The utility of using the Ruthenium catalyst is its highly tolerance to various functional groups. The Ruthenium catalyst also allows for metathesis reactions to be performed at low temperatures, as well as for the formation of tetra substituted olefins via cross metathesis.

Kucukdisli et al. developed the synthesis of disubstituted pyrroles (77) by placing a solution of cyanopyrrole (76) in dichloromethane into a MW reaction vessel. The solvent was removed in vacuo and the
vessel was flushed with argon, closed with a cap to yield the desired product.

This reaction involves the microwave heating which involves the internal heat source. Microwave absorption is able to heat the target compounds without heating the entire oil bath, hence saved time and energy. Due to the Microwave assistance, the reaction got completed in few minutes. This reaction took 6 h to get completed under conventional refluxing procedure.

Reddy et al. 26 published a MW-activated synthetic protocol for a series of polystituted pyroles (80). Added to a solution of 1 mmol of substituted phenacyl bromide (78) were 1 mmol substituted amino unsaturated ketone (79) and 10 mol% of BF₃OEt₃ in dichloromethane and the mixture was irradiated with MWs for 10-16 min at 130 °C (250 W).

Adib et al. 27 showed the reaction of 4-nitro-1, 3-diarylbutan-1-ones (81) and ammonium acetate (82) in the presence of morpholine and sulphur provides the corresponding 2,4-diarylpyrroles (83) in excellent yields.

Morpholine is used to create all volatile environment and also due to its slow decomposition at high temperatures and pressures. Further its low cost and polarity leads to its common use as a solvent for chemical reaction. That is why the reaction shown above is solvent free.

Ayaz M Dar et al. 28 revealed a convenient procedure for the synthesis of steroidal dihydro-1H-pyrole (87-89) from steroidal oximes (84-86) under refluxing conditions.

Ayaz M Dar et al. 29 revealed a procedure for the convenient and an efficient synthesis of steroidal pyrimidines (93-95) from corresponding steroidal thiosemicarbazones (90-92) and (2-methyl) diethyl malonate in absolute ethanol under refluxing conditions.

**Conclusion**

These protocols provide convenient strategies to synthesize these pyrrole derivatives or to annelate different heterocyclic nuclei with widespread bioactive pyroles thereby extending the categories of
heterocyclic systems. These strategies also provide valuable information for the further design of more active biological agents through various modifications and derivatizations.

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