JK Knowledge Initiative, 2(1): 22- 30, March 2018 ISSN: 2457-0974

Strategies for the preparation of pyrrole entities: A concise review

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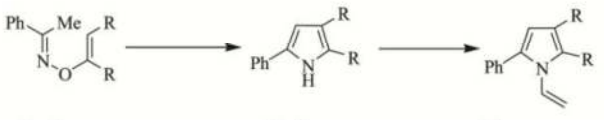
Abstract: Pyrroles is the special class of heterocyclic compounds with a broad spectrum of biological activities such as anti-inflammatory, antiproliferative, antihistaminic, anti-HIV, antifungal, antihelmintic and antiviral agents. Pyrrole is a five membered ring structure, with formula C_4H_4NH. The 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_4H_4NH. 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[1] in 1834. The discovery that pyrrole ring was an integral part of heme and of chlorophyll molecules[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[3] reported that when the base-catalyzed addition products [**1** and its *trans*-isomer, R = CO_2Me] of acetophenone oxime and dimethyl acetylenedicarboxylate were heated together, the pyrrole derivative (**3**) [R = CO_2Me] was obtained. Trofimov *et al*.[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[4] prepared compound **2** by heating acetophenone oxime, acetylene, and potassium hydroxide together in dimethyl sulfoxide solution, under conditions which can lead[5] to the formation of both 2-phenylpyrrole (**4**) and its 1-*N*-vinyl derivative (**5**, R = H).



(1, 2) **(3, 4)** **(5)**

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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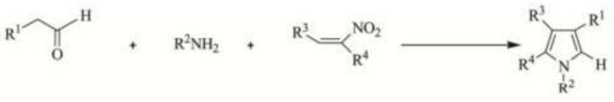
variety of pyrrole derivatives.[6] Recently, it was found that microwaves enhance the rate of this reaction. In this communication, Rao and Jothilingam[7] reported a novel one-pot synthesis of 2,5-di- and 1,2,5-trisubstituted pyrrole derivatives under microwave conditions (**7**) [Ar = C_6H_5, R = H; Ar = 4-ClC_6H_4, R = H; Ar = 4-BrC_6H_4, R = H; Ar = 4-$CH_3C_6H_4$, R = H; Ar = 4-$OCH_3C_6H_4$, R = H; Ar = 4-Cl,3-$CH_3C_6H_3$, R = H; Ar = C_6H_5, R = *n*-C_4H_9; Ar = C_6H_5, R = C_6H_5; Ar = C_6H_5, R = $CH_2C_6H_5$] from 2-butene-1,4-diones (**6**) [Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-Cl,3-$CH_3C_6H_3$] 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.

(**6**) (**7**)

Ranu and Dey[8] carried out one-pot, three-component condensation of a carbonyl compound (**8**), an amine (**9**) and a nitroalkene (**10**) leading to an efficient synthesis of alkyl-substituted pyrroles (**11**) [R^1 = C_8H_{17}, CH_3, CH_3CH_2; R^2 = $CH_3(CH_2)_3$, C_6H_{12}, $PhCH_2$, $PhCH(CH_3)_2$; R^3 = 4-$NO_2C_6H_4$, $C_7H_5O_2CH_3$, 4-ClC_6H_4, Ph; R^4 = CH_3, CH_3CH_2] in molten tetrabutylammonium bromide. Neither a catalyst nor an organic solvent was required for that reaction and the molten ammonium salt was recyclable.

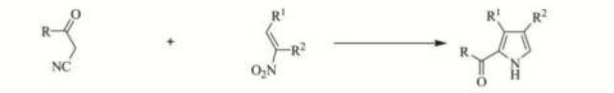


(**8**) (**9**) (**10**) (**11**)

They also performed synthesis of fused pyrroles by the coupling of cycloalkanones, amines 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.[9]

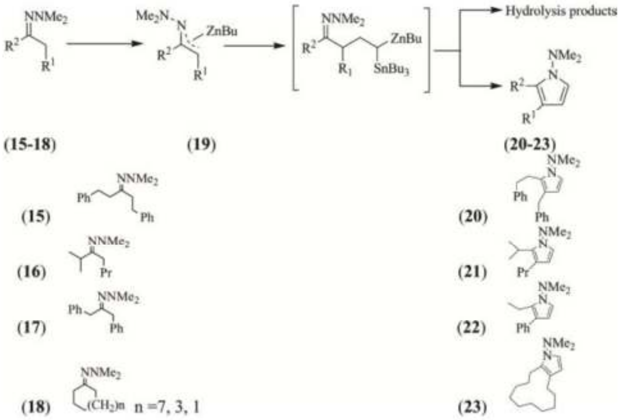
The pyrroles produced by the present approach could be ideal building blocks for porphyrins and bile pigments since they are unsubstituted in the 5-position and the 2-position can be protected by an easily removable group such as an ester. The substituents in the 3- and 4- position originate from the 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.



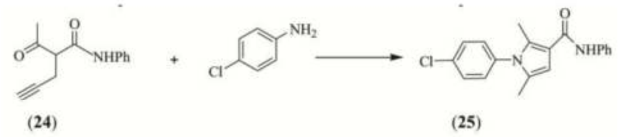
(**12a-i**) (**13a-i**) (**14a-i**)

	R	**R^1**	**R^2**		**R**	**R^1**	**R^2**
(a)	*t*-BuO	4-$MeOC_6H_4$	Me	**(f)**	*t*-BuO	Me	CH_2CH_3
(b)	EtO	4-$PhCH_2OC_6H_4$	Me	**(g)**	*t*-BuO	CH_2CH_3	Me
(c)	*t*-BuO	H	Me	**(h)**	*t*-BuO	Me	$(CH_2)_2CO_2Me$
(d)	MeO	H	Me	**(i)**	Me_2N	Me	CH_2CH_3
(e)	*t*-BuO	CH_2CH_3	CH_2CH_3				

Nakamura *et al.*[10] reported a straightforward one-pot synthesis of 1-(dimethylamino)-1*H*-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.



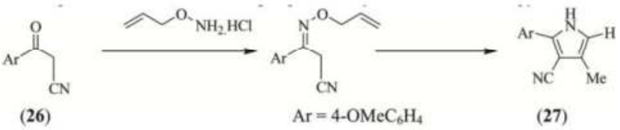
Wang *et al.*[11] developed a highly efficient iron-catalyzed approach to polysubstituted pyrroles (**25**) through the [4C+1N] cyclization of 4-acetylenic ketones (**24**) with primary amines, leading to the synthesis of a variety of tetra- and fully-substituted pyrroles as well as fused pyrrole derivatives in good to excellent yields.



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, pyrroles 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®. Thus, present scheme could provide an efficient access to such kinds of compounds.

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

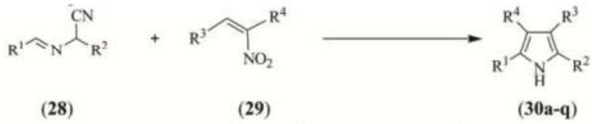
This is an interesting alternative approach to the synthesis of pyrroles because it uses the Paal-Knorr sequence without requiring the synthesis of 1,4-dicarbonyl compounds. The overall method provides a simple, selective, and functional group tolerant synthesis of substituted pyrroles.



Bergner and Opatz[13] prepared 2,3,4,5-tetrasubstituted pyrroles (**30a-q**) with high regioselectivity by a formal cycloadditions of α-(alkylideneamino) nitriles (**28**) [R^1, R^2 as defined below] and nitroolefins (**29**) [R^3, R^4 as defined below] followed by elimination of HCN and HNO_2. The reaction allowed the convergent construction of the pyrrole ring in four steps from a nitroalkane and three aldehydes.

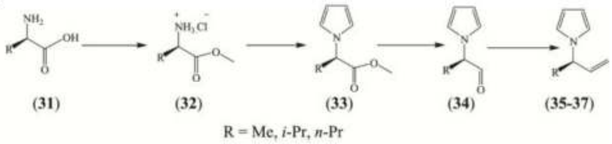
Since the pronucleophiles **28** can be obtained from two aldehydes and the electrophiles **29** can be prepared by condensation of an aldehyde and a nitroalkane, this method represents a highly modular synthesis of the pyrrole ring that is amenable to the combinatorial variation of all four substituents. While many reported pyrrole syntheses yield only acceptor-substituted products, this protocol also permits the preparation of products devoid of an electronwithdrawing substituent. On the other hand, compounds of this type can be sensitive to aerial oxidation and their longer exposure to halogenated solvents such as $CDCl_3$ should also be avoided to prevent the formation of intensely colored oxidation products.

Settambolo *et al*.[14] reported synthesis of (3*R*)-3-(Pyrrol-1-yl) but-1-ene (**35**), (3*R*)-4-methyl-3-(pyrrol-1-yl) pent-1-ene (**36**), (3*R*)-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 (DIBAH) of the corresponding pyrrolyl esters (**33**) to the corresponding pyrrolylaldehydes (**34**) followed by Wittig olefination proceeded without compromising the stereochemical integrity.

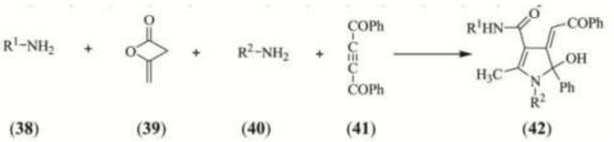


	R¹	R²	R³	R⁴
(a)	2-Naph	Me	4-ClC_6H_4	Me
(b)	2-Naph	Me	4-ClC_6H_4	Me
(c)	2-Naph	Me	3,4-$(MeO)_2C_6H_3$	Me
(d)	2-Naph	Me	Me	Et
(e)	2-Naph	Me	Me	*n*-Pent
(f)	2-Naph	Me	4-CNC_6H_4	Et
(g)	2-Naph	Me	Ph	Ph
(h)	2-Naph	Bn	4-ClC_6H_4	Me
(i)	3,4-$(MeO)_2C_6H_3$	Bn	4-ClC_6H_4	Me
(j)	3,4-$(MeO)_2$ C_6H_3	Ph	4-CNC_6H_4	Et
(k)	3,4-$(MeO)_2C_6H_3$	Ph	Ph	Ph
(l)	2-Naph	Me	-$(CH_2)_4$-	
(m)	2-Naph	Bn	-$(CH_2)_4$-	
(n)	3,4-$(MeO)_2C_6H_3$	Bn	-$(CH_2)_4$-	
(o)	3,4-$(MeO)_2C_6H_3$	Bn	-$(CH_2)_4$-	
(p)	3,4-$(MeO)_2C_6H_3$	Ph	-$(CH_2)_4$-	
(q)	3,4-$(MeO)_2C_6H_3$	Ph	-$(CH_2)_4$-	

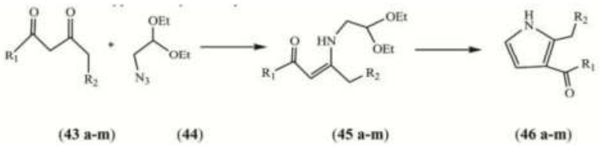
This synthetic scheme uses inexpensive reagents and provides pure products after simple purification processes. Suitable experimental conditions to minimize the racemization process during both the ester reductions and the Wittig methylenations were set up which makes the protocol a general enantiomeric route to (3S)- or (3R)-3-(pyrrol-1-yl) alk-1-enes.



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 dibenzoylacetylene **(41)** leading to 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives (**42**) [R¹ = *n*-Pr, *i*-Bu, *i*-Pr, *i*-Bu, *i*-Bu, *n*-Pr, *t*-Bu, *t*-Bu, R² = *i*-Bu, *n*-Pr, *i*-Bu, *i*-Pr, *i*-Bu, *n*-Pr, *i*-Pr, *n*-Pr].

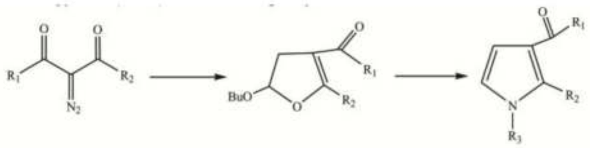


Bellur and Langer[16] synthesized a variety of pyrroles. Staudinger-aza-wittig reaction of 2-azido-1, 1-diethoxyethane (**44**) with 1, 3-dicarbonyl compounds (**43a-m**) afforded N-(2, 2-diethoxyethyl)-3-aminoalk-2-en-1-ones (**45 a-m**), which were subsequently transformed into functionalized pyrroles (**46 a-m**). This approach being multi-component/ one-pot and involves the synthesis of resultant pyrroles in potential yields.



R¹	R²	R¹	R²
(a) OMe	H	**(h)** OEt	*n*-Oct
(b) OEt	H	**(i)** OEt	*n*-Non
(c) $O(CH_2)_2OMe$	H	**(j)** OEt	*n*-Dec
(d) $OCH_2CH{=}CH_2$	H	**(k)** OEt	$(CH_2)_6Cl$
(e) OMe	Me	**(l)** Me	H
(f) OEt	Et	**(m)** Ph	H
(g) OEt	*n*-Hex		

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



(47) **(48)** **(49 a-n)**

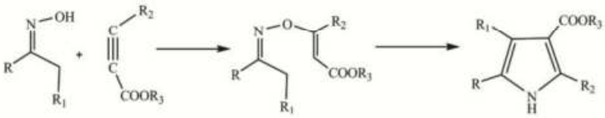
	R^1	R^2	R^3		R^1	R^2	R^3
(a)	OEt	Me	Benzyl	**(h)**	Me	Me	Cyclohexyl
(b)	OEt	Me	Decyl	**(i)**	Me	Me	Isopropyl
(c)	OEt	Me	Cyclohexyl	**(j)**	Me	Me	Butyl
(d)	OEt	Me	Isopropyl	**(k)**	H	H	Benzyl
(e)	OEt	Me	Butyl	**(l)**	H	H	Butyl
(f)	Me	Me	Decyl	**(m)**	H	H	Propyl
(g)	Me	Me	Benzyl	**(n)**	H	H	H

Ngwerume and Camp[18] reported gold catalyzed synthesis of highly substituted pyrroles (**53**) in an efficient and regiocontrolled process. First, O-vinyl oximes (**52**) were synthesized by the reaction of oximes (**50**) with electron deficient alkynes (**51**) using the nucleophilic catalyst DABCO. The second phase of the work was directed towards the catalytic rearrangement of O-vinyl oxime to pyrrole (**53**).

R = Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, Ph, Ph, Me, Me; $\mathbf{R^1}$ = H, H, H, Ph, Me, Me, Et;

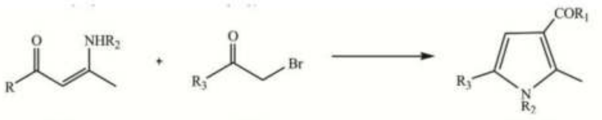
$\mathbf{R^2}$ = COOMe, H; $\mathbf{R^3}$ = Me, Et

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.



(50) **(51)** **(52)** **(53)**

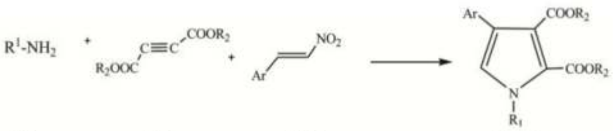
Yavari *et al.*[19] synthesized tetra substituted pyrrole derivatives (**56a-l**) by the reaction of enaminone (**54**) with haloketones (**55**), under solvent free conditions.



(54) **(55)** **(56 a-l)**

	R^1	R^2	R^3		R^1	R^2	R^3
(a)	OEt	*n*-Bu	4-BrC_6H_4	**(g)**	OEt	Bn	CO_2Et
(b)	OEt	*n*-Bu	CO_2Et	**(h)**	OEt	Bn	4-$MeOC_6H_4$
(c)	OEt	*n*-Bu	4-$MeOC_6H_4$	**(i)**	OEt	Bn	4-BrC_6H_4
(d)	OEt	*c*-Hexyl	CO_2Et	**(j)**	Me	Bn	CO_2Et
(e)	OEt	*c*-Hexyl	4-$MeOC_6H_4$	**(k)**	Me	Bn	4-$MeOC_6H_4$
(f)	OEt	*c*-Hexyl	4-BrC_6H_4	**(l)**	Me	Bn	4-BrC_6H_4

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

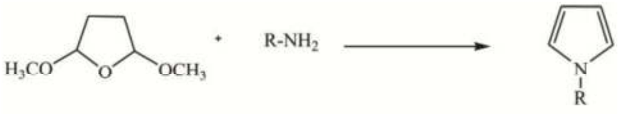


(57) **(58)** **(59)** **(60 a-p)**

	R^1	Ar		R^1	Ar
(a)	Bn	Ph	**(i)**	CH_3CH-Ph	2-BrC_6H_4
(b)	Bn	Ph	**(j)**	CH_3CH-Ph	4-ClC_6H_4
(c)	Bn	4-BrC_6H_4	**(k)**	CH_3CH-Ph	4-$MeOC_6H_4$
(d)	Bn	4-ClC_6H_4	**(l)**	CH_3CH-Ph	4-MeC_6H_4
(e)	Bn	4-$MeOC_6H_4$	**(m)**	CH_2=$CHCH_2$	Ph
(f)	Bn	4-MeC_6H_4	**(n)**	CH_2=$CHCH_2$	Ph
(g)	Bn	3-$NO_2C_6H_4$	**(o)**	Ph	Ph
(h)	CH_3CH-Ph	Ph	**(p)**	4-$MeOC_6H_4$	Ph

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 Michel addition/ cyclization process.[20] This reaction protocol being one-pot three component, fast, efficient mild and metal-free synthesis of substituted pyrrole heterocycles.

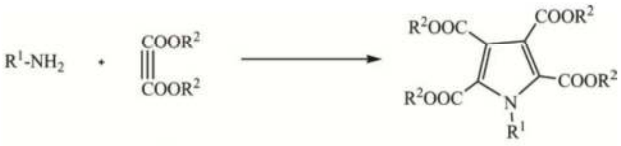
Bandyopadhyay *et al.*[21] carried out the simple ultrasound-assisted eco-friendly practical method for the synthesis of N-substituted pyrroles (**66**) [R=Ph, 4-OMeC_6H_4, Py, naphthyl, tri-naphthyl, adamantly, crysenyl, pyrenyl, 1,10-phenanthrolinyl, phenanthrenyl by reacting 2,5-dimethoxytetrahydrofuran (**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.



(64) **(65)** **(66)**

The classes of compounds synthesized by using bismuth nitrate as a catalyst are acting drugs for peptic ulcer, esophageal reflux diseases, and antibacterial infections.

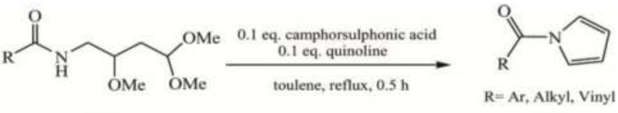
Zhang *et al.* [22] studied copper catalyzed [10 ml% of $Cu(OAC)_2$] reaction of amines (**67**) [R=4-MeC_6H_4, 4-MeOC_6H_4, 3-MeOC_6H_4, 4-*i*-PrC_6H_4, 4-ClC_6H_4, 3-Br, 4-FC_6H_3, 4-FC_6H_4, 4-BrC_6H_4, 4-COOEtC_6H_4, 2,4,6-$Me_3C_6H_2$, Benzyl-4-Me, Bn, Benzyl-4-F, *n*-Bu] with but-2-ynedioates (**68**) [R^2= Et, Me] to furnish pyrrole-2,3,4,5-tetracarboxylates (**69**) [R^1, R^2 as defined above] in moderate to good yields. The reaction proceeded in the presence of dioxygen with the formation of three bonds during the process.



(67) **(68)** **(69)**

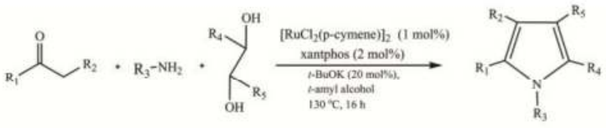
This reactions which is catalyzed by $Cu(OAC)_2$ are highly atom-economical and environmentally benign which makes it ideal in many ways for further modifications and derivatizations.

Maehara *et al.* [23] 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.



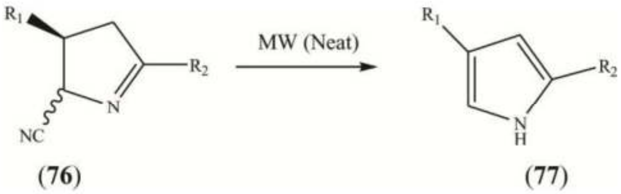
(70) **(71)**

Zhang *et al.* [24] 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.



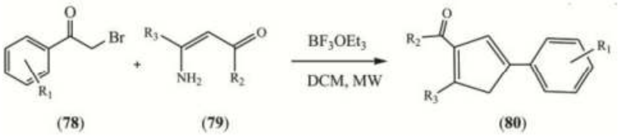
(72) **(73)** **(74)** **(75)**

Kucukdisli *et al.* [25] developed the synthesis of disubstituted pyrroles (**77**) by placing a solution of cyanopyrrolene (**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.

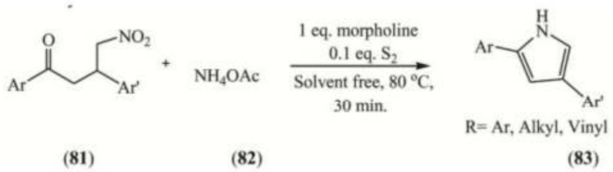


This reaction involves the microwave heating which involves the internal heat source. Microwave absorption is able to heat the target compounds without heating the entire oil bath, hence saved time and energy. Due to the Microwave assistance, the reaction got completed in few minutes. This reaction took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

Reddy *et al.* [26] published a MW-activated synthetic protocol for a series of polysubstituted pyrroles (**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 BF_3OEt_3 in dichloromethane and the mixture was irradiated with MWs for 10-16 min at 130 °C (250 W).

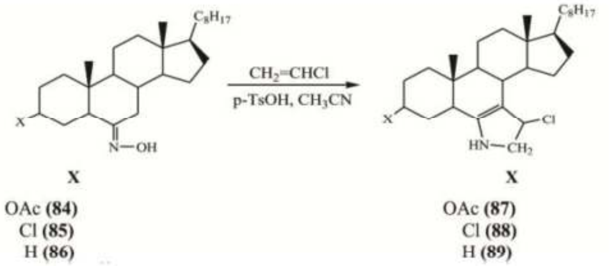


Adib *et al.* [27] showed the reaction of 4-nitro-1, 3-diarylbutan-1-ones (**81**) and ammonium acetate (**82**) in the presence of morpholine and sulphur provides the corresponding 2,4-diarylpyrroles (**83**) in excellent yields.

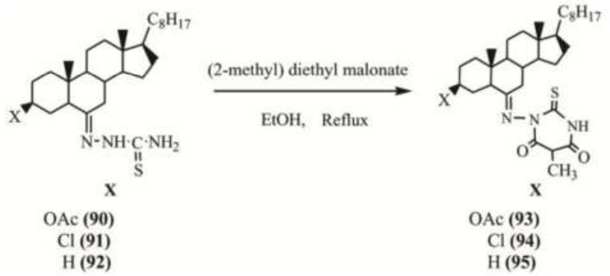


Morpholine is used to create all volatile environment and also due to its slow decomposition at high temperatures and pressures. Further its low cost and polarity leads to its common use as a solvent for chemical reaction. That is why the reaction shown above is solvent free.

Ayaz M Dar *et al.* [28] revealed a convenient procedure for the synthesis of steroidal dihydro-1H-pyrrole (**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 pyrroles 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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