SYNTHESIS OF PYRROLE AND SUBSTITUTED PYRROLES (REVIEW)

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ABSTRACT

Pyrrole is widely known as a biologically active scaffold which possesses a diverse nature of activities. The combination of different pharmacophores in a pyrrole ring system has led to the formation of more active compounds. Pyrrole containing analogs are considered as a potential source of biologically active compounds that contains a significant set of advantageous properties and can be found in many natural products.

The present review highlights the synthetic methods of representatives of nitrogen heterocycles such as pyrrole, substituted pyrroles and other related compounds. The aim of this review is to indicate and summarise the different methods for the synthesis of nitrogen containing heterocycles from the group of pyrrole and pyrrole related structures.

Keywords: pyrrole, synthesis, pharmacological activity.

INTRODUCTION

Pyrrole is a five membered heterocyclic compound, corresponding to the C₄H₄NH general formula [1]. It is a colorless volatile liquid, unstable in the presence of air, where it easily darkens. Thus a preliminary distillation before use is necessary [2].

Pyrrole is included in the group of aromatic compounds, and its hydrogenated is difficult. The Diels-Alder reactions or usual olefin reactions are not characteristic for this ring. Due to the fact, that it can easy polymerize, most of the electrophilic reaction, used in benzene chemistry, are not applicable to pyrroles. On the other hand, the substituted pyrrole derivatives have been included in various transformations [3].

REACTION OF PYRROLE WITH ELECTROPHILES

In general pyrroles most commonly react with electrophiles at α-position, due to the highest stability of the obtained intermediate protonation (Scheme 1).

From the group of electrophilic addition, pyrroles are easily nitrated, halogenated and sulfonated, where normally polyhalogenated derivatives are obtained, but monohalogenation may also occur (Scheme 2) [6]. When the pyrrole nitrogen is silated, a halogenation on 3rd position is also possible, thus this is considered as a useful procedure for functionalization of the less active 3rd position [4].

Origin of pyrrole

In 1834 F.F. Runge has detected pyrrole for the first time as a constituent of coal tar [5]. Later in 1857 it has

Scheme 1. Mechanism of the reaction of pyrrole with electrophiles.
been isolated for the first time from bone pyrolysate. Its name comes from the Greek pyrrhos - based on the reaction used for its detection [6]. Pyrrole itself is not naturally occurring, but many of its derivatives are found in a variety of cofactors and natural products. Pyrroles are components of more complex macrocycles, including vitamin B$_{12}$, bile pigments like bilirubin and biliverdin, and the porphyrins of heme, chlorophyll, chlorins, bacteriochlorins, and porphyrinogens [7, 8]. Pyrrole is a constituent of tobacco smoke and not as an ingredient [9].

**Pharmacological activity of pyrrole and its derivatives**

Pyrrole and its derivatives play an important role in pharmaceutical and natural chemistry. Commonly they are widely used as an intermediate in the synthesis of pharmaceuticals, medicines, agrochemicals, dyes, photographic chemicals, perfumes and other organic compounds. For example, chlorophyll, heme are derivatives which are made by four pyrrole ring formation of porphyrin ring system (Fig. 1). In addition they are used as catalysts for polymerization process, corrosion inhibitors, preservatives, solvents for resins and terpenes, standard in a chromatographic analysis and they are also used in organic synthesis in the pharmaceutical industry. It is an important constituent in the structure of a number of pharmaceutical products and new active agents with variety of pharmacological effects like: atorvastatine - antihyperlipidemic, aloracetam for treatment of Alzheimers’ disease, elopiprazole - antipsychotic, lorpiprazole - anxiolytic, tolmetin - anti-inflammatory activity (Fig. 2) [10].
CLASSICAL APPROACHES FOR PYRROLE SYNTHESIS

Industrial preparation

In industry pyrrole is produced by treatment of furan with ammonia in the presence of solid acid catalysts, like SiO$_2$ and Al$_2$O$_3$ (Scheme 3) [6].

Pyrrole can also be obtained by catalytic dehydrogenation of pyrrolidine (Scheme 4).

Paal-Knorr pyrrole synthesis

The most prominent and applied method for synthesis of pyrroles, furans and thiophenes, and their derivatives is the well known Paal-Knorr synthesis, based on a reaction of a 1,4-dicarbonyl compound with ammonia or a primary amine to form pyrrole and substituted pyrrole, respectively (Scheme 5) [11, 12].

Mechanism of Paal-Knorr pyrrole synthesis

In 1991 V. Amarnath et al. [13] suggest the mechanism of Paal-Knorr reaction based on the attack of the amine to the protonated carbonyl, forming hemiaminal. Further the amine attacks the other carbonyl and forms 2,5-dihydroxytetrahydropyrrrole derivative, which is further dehydrated to form the corresponding substituted pyrrole [14]. The proposed mechanism is presented on Scheme 6. The reaction is typically run under protic or Lewis acidic conditions, with a primary amine. The usage of ammonium hydroxide or ammonium acetate (as reported by Paal) gives the N-unsubstituted pyrrole [14].

SYNTHESIS OF 1,4-DIKETONES

A number of methods used for synthesis of the necessary for cyclisation 1,4-diketones has been reported:

One-pot method for synthesis of γ-diketones or γ-keto esters by conjugated addition of primary nitroalkans to α,β-unsaturated ketones or esters (Scheme 7) [15].

Pd-catalyzed addition [16] and cross-coupling [17] for obtaining a 1,4-diketones in good yield, as presented on Scheme 8 and Scheme 9, respectively:
The last method enables convenient preparation of functionalized 1,4-diketones and allows obtaining a stereoselective products [17].

Various 1,4-diketones have been synthesized in moderate to good yields through a Michael addition type reaction between aryl chlorides and chalcones in the presence of samarium metal in N,N-dimethylformamide as solvent (Scheme 10) [18].

The merger of photoredox catalysis and primary amine catalysis enables a direct construction of all-carbon quaternary stereocenters via α-photoalkylation of β-ketocarbonyls with high efficacy and enantioselectivities (Scheme 11) [19].

**MODIFIED APPROACHES FOR PAAL-KNORR PYRROLE SYNTHESIS**

**Modifications in Paal-Knorr pyrrole synthesis**

The classical Paal-Knorr approach has been currently modified and optimized by a number of changes in the initial reagents and/or reaction conditions as presented on Scheme 12.

A high increase of yields and an improvement of reaction rates have been accomplished by inclusion of bismuth nitrate (A) [20], organic-inorganic hybrid (B) [21], silica-supported bismuth(III) chloride (BiCl₃/ SiO₂) (G) [22] and metal triflates as a possibility to run the reaction in a solvent free media (E) [23]. In addition...
A one-pot ecofriendly catalyst has been also suggested by Rahmatpour et al. [24]. Currently the green chemistry is highly recommended for synthesis of new and available products.

In the last years a number of modifications in Paal-Knorr pyrrole synthesis have been additionally performed and reported. Wang et al. have reported synthesis of substituted pyrroles using ionic liquids as solvent. The reaction is characterized with an avoidance of using toxic catalysts and simplicity in the isolation procedure [25]. Also, Zhang et al. have described the synthesis of N-substituted pyrroles in good to excellent yields from various substituted 1,4-diketones with primary amines catalyzed by MgI$_2$ etherate (Scheme 13) [28].

Veitch et al. have developed a method for synthesis of pyrrole analogues by cyclocondensation of 1,4-dicarbonyl compounds with magnesium nitride (Scheme 14) [29]. Phan et al. have synthesized pyrrole analogues from benzyl amine with 2,5-hexanediol.

Handy and associates report a method consisting in application of inexpensive, non-toxic and recyclable deep eutectic solvents (the combination of either urea or glycerol with choline chloride) as effective solvents/catalysts for Paal-Knorr reactions to form pyrroles of furans. The reaction conditions are quite mild and do not require additional Bronsted or Lewis acid catalyst (Scheme 12) [27].
edione using efficient heterogeneous catalyst - a highly porous metal-organic framework (IRMOF-3) as shown below (Scheme 15) [30]:

On the other hand, currently number of different methods has also been developed for synthesis of pyrrole and its derivatives.

**Other methods for pyrrole synthesis**

An operationally simple and economical condensation of 2,5-dimethoxytetrahydrofuran with various primary aromatic amides in the presence of one equivalent of thionyl chloride [31] or amines and sulfonamides in water in the presence of catalytic amount of iron(III) chloride [32] led to formation of N-substituted pyroles under mild reaction conditions in good yields (Scheme 16).

An interesting approach for polysubstituted pyrrole synthesis is through reaction of 1-sulfonyl-1,2,3-triazoles with allenes in the presence of a nickel(0) catalyst as described in Miura et al. [33] (Scheme 17A). This compound has been considered also from other authors as an initial component for synthesis of mono-, di- and tri-substituted pyroles by rhodium (II)-catalyzed...
cycloaddition with isoxazoles (Scheme 17B) [34] or transannulation with vinyl ether (Scheme 17C) [35] or with alkenyl alkyl ethers (Scheme 17D) [36].

A highly efficient reaction of 1,4-dihalo-1,3dienes has been described for formation of pyrroles and heteroaryl pyrroles under Cu-catalysis (Scheme 18) [37] and copper catalyzed double alkenylation of amides (Scheme 19) [38].
New approaches for obtaining substituted NH pyrroles have been developed based on vinyl azides annulation with esters and/or aldehydes, as presented on Scheme 20, ensuring good yields obtained under mild, neutral and very simple conditions [39 - 43] (Scheme 21A, Scheme 21B and Scheme 21C).

Various polysubstituted pyrroles are easily accessible from acetylenes and alkynes interacting with the corresponding N-containing substances in one-step (Scheme 22A) [44] and in highly regioselective manner (Scheme 22B) [45], (Scheme 23) [46].
Recently other authors have obtained substituted pyrroles in good yields, using gold-catalyzed reactions of 2H-azirines with ynamides [47], and cyclization of α-amino ketones with alkynes [48], (Scheme 24A and Scheme 24B).

Other preparation of pyrrole derivatives has been reported, consisting of condensation of propargyl amines with ethyl vinyl ether under microwave irradiation in good yields (Scheme 25) [49].

Another microwave-promoted formation of 2-acylpyrroles in good yields is iminyl radical cyclizations, terminated by trapping with TEMPO, affording functionalized adducts without using toxic and hazardous reagents and using alkynes as radical acceptors (Scheme 26) [50].

Currently Zheng et al. and Gao et al. have synthesized polysubstituted pyrroles by formation of C-C and C-N bonds from N-homo allylicamines with arylboronic acids and phenyl acetaldehydes with primary amines as shown in Scheme 27A and Scheme 27B [51, 52].

Another method is synthesis of pyrrole derivatives by an one-pot hetero-Diels-Alder/ring contraction affords N-arylpyrroles from 1,3-dienylboronic esters with nitrosoarenes in excellent yields (Scheme 28) [53].

Recently Bayat et al. have described new fused heterocyclic derivatives of pyrrole containing acetonitrile or cyanoacetonitrile moiety at 3-position by an one-pot multicomponent reaction in good yields, Scheme 29 [54].
Bunrit et al. have described a new method for synthesis of 2-substituted pyrroles in overall good yields with only water and ethene as side-products using Pd, Ru and Fe catalyst, (Scheme 30), [55].

Scheme 27A. Synthesis of polysubstituted pyrroles from N-homo allylicamines with aryloboronic acids.

Scheme 27B. Synthesis of polysubstituted pyrroles from phenyl acetaldehydes with primary amines.

Scheme 28. Synthesis of N-arylpyrroles from 1,3-dienylboronic esters with nitrosoarenes.

Scheme 29. Synthesis of heterocyclic derivatives of pyrrole by one-pot multicomponent reaction.

Scheme 30. Synthesis of 2-substituted pyrroles using Pd, Ru and Fe catalyst.

SYNTHESIS OF SUBSTITUTED PYRROLES

Substituted pyrroles in excellent yields have formulated by highly regioselective N-substitution of pyrrole with alkyl halides, sulfonyl chlorides, and benzoyl...
chloride ion ionic liquids [Bmim][PF6] or [Bmim][BF4] as shown in Scheme 31 [56].

1-Vinylpyrroles have synthesized by the N,N-dimethylformamide/oxalyl chloride reagent system to give the corresponding 1-vinylpyrrole-2-carbaldehydes in good yields in short reaction times (Scheme 32) [57].

2-alkyl-1H-indoles and 2-substituted or 2,3-disubstituted 5-alkyl-1H-pyrroles have been synthesized in good yields by the 1H-indoles and electron-deficient 1H-pyrroles, palladium/norbornene-cocatalyzed regioselective alkylation with primary alkyl bromides at the C-H bond adjacent to the NH group (Scheme 33) [58].

The transient acid iodide intermediates undergo nucleophilic attack from a variety of relatively weak nucleophiles - including Friedel-Crafts acylation of N-methylpyrroles N-acylation of sulfonamides, and acylation reactions of hindered phenol derivatives (Scheme 34) [59].

CONCLUSIONS

The current review presents the synthetic methods for obtaining pyrrole, substituted pyrroles and other related compounds in high to excellent yields under mild, neutral and very simple reaction conditions and/or presence of different catalysts like microwave-promoted irradiation, introduction of a number of metals and metal complexes as a reaction catalyst such as Pd, Ru, Li, Fe, etc. A green chemistry reaction conditions and one-pot synthetic approaches are also discussed, based on application of media-free reactions and usage of environmentally friendly recyclable catalysts.

REFERENCES

12. L. Knorr, Synthese von Furfuranderivaten aus dem Diacetbernsteinäureester [Synthesis of furan derivatives from the [diethyl] ester of 2,3-diacetyl-succinic acid], Berichte der deutschen chemischen Gesellschaft, 17, 1884, 2863-2870.
28. X. Zhang, G. Weng, Y. Zhang, P. Li, Unique chemoselective Paal-Knorr reaction catalyzed by MgI2 etherate under solvent-free conditions, Tetrahedron, 71, 2015, 2595-2602.
34. X. Lei, L. Li, Y.-P. He, Y. Tang, Rhodium(II)-Catalyzed Formal [3 + 2] Cycloaddition of N-Sulfonyl-1,2,3-triazoles with Isoxazoles: Entry to Polysubstituted 3-Aminopyrroles, Org. Lett., 17, 2015, 5224-5227.
49. H. Chachignon, N. Scalacci, E. Petricci, D. Castag-
nolo, Synthesis of 1,2,3-Substituted Pyrroles from Propargylamines via a One-Pot Tandem Enyne Cross Metathesis-Cyclization Reaction, J. Org. Chem., 80, 2015, 5287-5295.
52. Y. Gao, C. Hu, J. P. Wan, C. Wen, Metal-free cascade reactions of aldehydes and primary amines for the synthesis of 1,3,4-trisubstituted pyrroles, Tetrahedron Letters, 57, 2016, 4854-4857.