The Hantzsch Pyrrole Synthesis: Non-conventional Variations and Applications of a Neglected Classical Reaction

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Abstract Pyrrole is one of the most important one-ring heterocycles because of its widespread presence in natural products and unnatural bioactive compounds and drugs in clinical use. The preparation of pyrroles by reaction between primary amines, β-dicarbonyl compounds, and α-halo ketones, known as the Hantzsch pyrrole synthesis, is reviewed here for the first time. In spite of its age and its named reaction status, this method has received little attention in the literature. Recent work involving the use of non-conventional conditions has rejuvenated this classical reaction and this is emphasized in this review. Some applications of the Hantzsch reaction in target-oriented synthesis are also discussed.

Key words pyrrole, green chemistry, solid-phase synthesis, sonochemistry, flow synthesis, photoredox catalysis, mechanochemical synthesis

1 Introduction

Pyrrole can be considered as one of the most important simple heterocycles. It is present in a variety of natural products including two pigments essential for life, namely heme and chlorophyll. It can also be found in a large number of bioactive secondary metabolites, many of which are of a marine origin1–3 and include the lamellarins, halitulin, and the marinopyrroles, which have attracted much recent attention because of their high activity against methicillin-resistant bacteria.4 A large number of bioactive non-natural pyrroles are also known, exhibiting properties such as antimycobacterial5 and antimalarial6 activities, inhibition of HIV virus fusion,7 and hepatoprotection,8 among many others. Some of these compounds have reached the pharmaceutical market, including the anti-inflammatory drugs zomepirac and tolmetin, the antihypercholesterolemic agent atorvastatin,9 and the anticancer drug sunitinib (Fig-
The Conventional Hantzsch Pyrrole Synthesis

Among the classical methods for pyrrole synthesis, the Hantzsch reaction is the least developed one. Indeed, in view of its named reaction status, it is surprising to realize how scant attention it has received. Thus, Hantzsch’s 1890 original note\(^1^3\) describes the synthesis of a single pyrrole derivative (Scheme 1). In a paper published in 1970, Roomi and MacDonald stated that they had only been able to find in the chemical literature eight additional examples published in the intervening 80-year period. Furthermore, these reactions proceeded in yields below 45% and allowed very little structural variation, which was limited to alkyl substituents at C-4 and C-5.

By tweaking the reaction conditions, the Roomi and MacDonald study extended slightly the scope of the Hantzsch reaction and allowed the preparation of compounds with substituents different from methyl at C-2 and esters other than ethyl at C-3. However, yields remained below 50% and the preparation of N-substituted pyrroles was still not possible.\(^1^4\) More recent examples of the Hantzsch pyrrole synthesis under traditional conditions still suffer from many limitations in scope.\(^1^5\)

![Scheme 1 The first reported example of the Hantzsch pyrrole synthesis](image)

Depending on the nature of the α-halo carbonyl substrate, the reaction can furnish 5-substituted/4,5-disubstituted pyroles (starting from α-halo ketones) or 4-substituted...
Substituted derivatives (starting from $\alpha$-halo aldehydes). Some representative pyrrole derivatives prepared by the Hantzsch method are summarized in Figure 2.

Figure 2 Some representative pyroles prepared by the Hantzsch reaction

The yields obtained in these conventional Hantzsch pyrrole syntheses are moderate and rarely surpass 60%. Compounds arising from competing side reactions have rarely been isolated, although in some literature examples, involving the use of $\alpha$-chlorocarbonyl starting materials, the Hantzsch reaction has been found to compete with a Feist–Benary furan synthesis, with no incorporation of the amine component into the product (Scheme 2, see also Scheme 26 below)).

A variation of the Hantzsch pyrrole synthesis using $\beta$-keto Weinreb amides as the dicarbonyl component has also been developed. By exploiting the reactivity of the Weinreb amide function, this method allows the presence of a very broad variety of ketone substituents at the C-3 position of the pyrrole products. Thus, the reaction between ethyl pyrrolidin-2-ylideneacetate and related substrates bearing alternative electron-withdrawing substituents $Z$ (compounds 1) and $N$-methoxy-$N$-methyl-$\alpha$-bromoacetamide (2) in the presence of LDA afforded the C-alkylation product 3. Its reaction with a variety of organometallic nucleophiles including Grignard reagents, organolithium derivatives, and DIBAL–H, gave initially the $N$-deprotonated intermediates 4. Their reaction with the nucleophile proceeded in fully chemoselective fashion in favor of the Weinreb amide and gave intermediates 5, which finally cyclized in situ to furnish the 2,3-dihydropyrrolizines 6 (Scheme 3). This method allowed a broad scope in the substituent coming from the organometallic reagent ($R^1 = H, alkyl, ethenyl, ethynyl, aryl, or masked function$).\(^{16}\)

We will finally mention that Pal and co-workers have described a variation of the Hantzsch pyrrole synthesis involving a change in the regioselectivity of the reaction, although the method seems mostly restricted to 1,3-diketones and aromatic amines. Thus, the reaction between anilines, a 1,3-diketone, and phenacyl bromide in the presence of Yb(OTf)$_3$ as a Lewis acid catalyst leads to 4-substituted pyrroles (Scheme 4).\(^{17}\)

Although the mechanism of the Hantzsch pyrrole synthesis has not been studied in detail, it is commonly accepted that it starts by the formation of an enamino or enaminocarbonyl compound. This intermediate then reacts with the $\alpha$-
halo carbonyl component, leading to the C-alkylated intermediate 8, which furnishes the final product 9 by cyclocondensation with loss of a molecule of water (Scheme 5).

Abdel-Mohsen and co-workers, in 2015, applied the same method to the synthesis of 5-(N-substituted pyrrol-2-yl)-8-hydroxyquinolines 10, with potential biological interest (Scheme 7). The method was later extended in 2016 to the synthesis of tetrahydroindoles by use of cyclic 1,3-diketones as starting materials, although in this case the solvent was ethanol.

A mechanistic proposal is summarized in Scheme 8 for the case of the 5-(N-substituted pyrrol-2-yl)-8-hydroxyquinolines 10, and involves the initial reaction of the starting 5-(chloroacetyl)quinoline derivative with the organocatalyst to give the highly electrophilic intermediate 11. Its reaction with enamnine 12, formed from the primary

The Yb(OTf)₃-associated change in regioselectivity mentioned above can be ascribed to an increased reactivity of the carbonyl with respect to the alkyl halide due to efficient coordination of its oxygen atom with this potent Lewis acid.

To summarize, Hantzsch reactions performed in solution under conventional conditions often give modest yields and do not show a broad substituent scope. These limitations explain the limited use of this classical method and have stimulated in recent years the development of a number of non-conventional variations of the reaction.

3 Hantzsch Pyrrole Synthesis under Non-conventional Conditions

3.1 Hantzsch Pyrrole Synthesis in Green Solvents and in the Absence of Solvent

In 2012, Meshram and co-workers developed an organocatalytic approach to the Hantzsch pyrrole synthesis, using 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst and water as the reaction medium (Scheme 6). The authors examined mainly the structural variation of the primary amine component, and proved that a variety of alkyl or aryl substituents were tolerated, and also three different phenacyl bromides, but the only β-dicarbonyl component that they studied was pentane-2,4-dione.
amine and pentane-2,4-dione, gives 13, cyclocondensation of which is aided by deprotonation of the enamine nitrogen by DABCO.

Nageswar and co-workers have performed some examples of the Hantzsch pyrrole synthesis by using water as solvent and with the aid of β-cyclodextrin as a supramolecular catalyst. In this particular case, the authors examined only the structural variation of the primary amine component (Scheme 9).21

![Scheme 9](image)

The formation of a phenacyl bromide–cyclodextrin complex was proved by NMR experiments that suggested the mode of inclusion shown in Figure 3, as shown by the upfield shift of the H-3 and H-5 protons at the broader rim of the cyclodextrin. This mode of complexation is compatible with a subsequent alkylation of the dicarbonyl component to yield a 1,4-dicarbonyl intermediate that would then furnish the pyrrole by a Paal–Knorr reaction, as suggested by the authors (structure A), but also with the usual Hantzsch mechanism involving the alkylation of an enaminone (structure B).

![Figure 3](image)

Das and co-workers have performed a three-component Hantzsch synthesis from primary amines, pentane-2,4-dione, and 3-(bromoacetyl)coumarin derivatives 15 in a mixture of water and polyethylene glycol (PEG-400) in the presence of Alum (AlK(SO₄)₂·12H₂O), an ecofriendly catalyst that requires an aqueous medium. The reaction leads to the synthesis of pyrrole derivatives 16 containing the pharmaco-logical important coumarin moiety. The role of polyethylene glycol is to provide a micellar environment, and the Al³⁺ in alum acts as a Lewis acid, as shown in structure 17.

![Scheme 10](image)

Zhao and co-workers discovered that irradiation at 500 W of α-bromoacetophenones, ethyl acetoacetate, and primary amines in a pressurized microwave vial afforded 5-arylpyrroles 18 in good yields, without the need for any solvent or catalyst (Scheme 11). In terms of scope, the reaction tolerated well the presence of electron-withdrawing or electron-releasing groups in the α-bromoacetophenone component and the use of alkyl-, aryl-, and (hetero)aryl methylamines. Modifications of the β-dicarbonyl component were not investigated.23

![Scheme 11](image)

When starting from a pre-formed enaminone, microwave irradiation proved unnecessary. Thus, Yavari and co-workers found that by simply stirring compounds 19 and α-bromo ketones 20 under solvent-free conditions at room temperature, they could isolate the corresponding 5-substituted pyrroles 21 in good to excellent yields (Scheme 12).24
3.2 Hantzsch Pyrrole Synthesis under Solid-Phase Conditions

Jung and co-workers reported, in 1998, a solid-support- ed three-component Hantzsch reaction, involving the use of an acetoacetylated Rink resin 22. This material was prepared by treatment of commercial polystyrene Rink amide resin with a variety of acetoacetylating reagents such as diketene at −15 °C to room temperature, 2,2,6-trimethyl-1,3-dioxin-4-one at 110 °C, or N-hydroxysuccinimidyl acetooacetate at room temperature (Scheme 13). As shown in Scheme 14, the Rink resin thus modified was first treated with primary amines, presumably to afford the corresponding β-enaminoamides 23. This step was followed by reaction with α-halo carbonyl compounds to give pyrroles 24, which were finally liberated from the solid support by acid hydrolysis. Due to the structure of the resin-contained dicarbonyl component, the method was restricted to the preparation of pyrrole-3-carboxamide derivatives, which were isolated in excellent purities, but unfortunately the authors failed to report the reaction yields.25

3.3 Sonochemical Hantzsch Pyrrole Synthesis

Shahvelayati and co-workers described an efficient Hantzsch pyrrole synthesis performed in the absence of solvents, under irradiation with an ultrasonic cleaner with a frequency of 60 kHz and an intensity of 285 W, and catalyzed by ZnO nanoparticles (Scheme 15).26 The catalyst was prepared by treatment of zinc acetate with sodium hydroxide in an ionic liquid, followed by irradiation with ultrasound for 1.5 hours (Scheme 16). It was observed that particles with a smaller crystallite size were obtained in the ionic liquid than in water. It is relevant for the mechanism of the reaction to note that the ZnO-NPs thus obtained have both Lewis acid sites (Zn²⁺) and Lewis basic sites (O²⁻). These catalysts were re-used up to three times, with no significant loss in yield.

The reaction was proposed to follow the usual Hantzsch mechanism, with the Zn²⁺ sites acting as Lewis acids interacting with the carbonyls in the 1,3-dicarbonyl compound and the α-bromo ketone and thus facilitating the formation of the intermediate enamino ester and its alkylation to give 25. On the other hand, the O²⁻ sites may deprotonate the NH in intermediate 25 and thus facilitate the final cyclocondensation step, with concomitant assistance by coordination of its carbonyl with a Lewis acidic site (Scheme 17).
3.4 Hantzsch Pyrrole Synthesis under Flow Conditions

As summarized in Scheme 18, Cosford and Herath described a one-pot synthesis of pyrrole-3-carboxylic acid derivatives based on the Hantzsch reaction that involves the continuous flow of tert-butyl acetoacetate, primary amines, and α-bromo ketones at 200 °C during 8 minutes.

The generation of HBr during the alkylation step was exploited to achieve the in situ hydrolysis of the tert-butyl ester groups. The subsequent coupling of the carboxylic substituent to diverse amines was also described and gave pyrrole-3-carboxamide derivatives, including two cannabinoid receptor subtype 1 (CB1) inverse agonists. If desired, the pyrrole derivatives could be isolated in ester form by adding one equivalent of base to trap HBr.

3.5 Hantzsch Pyrrole Synthesis under Photoredox Catalysis

Wu and co-workers developed a photochemical version of the Hantzsch pyrrole synthesis when they discovered that the irradiation with visible light (λ = 450 nm) of a DMSO solution of enaminones and α-bromo ketones at room temperature, in the presence of a catalytic amount of Ir(ppy)₃ as a photosensitizer, afforded 2,5-diaryl-substituted pyrroles in good to excellent yields (Scheme 19). Furthermore, an increase in yield to quantitative levels was achieved by addition of triethylamine to the reaction medium.
The mechanism proposed to explain this transformation is summarized in Scheme 20. Irradiation of the photosensitizer leads to its excited form Ir(ppy)$_3^*$, which, following single electron-transfer oxidation by the starting α-bromo ketone 26, is transformed into Ir(ppy)$_3^{+}$. The reduced 26, upon debromination, generates radical 27, which adds to the enaminone 28 to furnish another radical, 29. This species transfers one electron to Ir(ppy)$_3^{+}$, closing the catalytic cycle, and affords imine 30, which finally furnishes the final pyrrole products by intramolecular cyclocondensation with loss of a molecule of water.

### 3.6 Hantzsch Pyrrole Synthesis under Mechanochemical Conditions

Due to our interest in the use of cerium(IV) ammonium nitrate (CAN) as a Lewis acid catalyst, we investigated the Hantzsch reaction in ethanol between β-dicarbonyl compounds, primary amines, and α-iodo ketones in the presence of CAN and silver nitrate, which was necessary in order to prevent reductive dehalogenation of the starting α-iodo ketones by the HI liberated in the alkylation step. In 2013, we discovered that the reaction could be also performed in a solvent-free fashion, under high-speed vibration milling conditions (HSVM) in a mixer mill working at 20 Hz with the use of a single zirconium oxide ball 20 mm in diameter. Furthermore, the mechanochemical version of the Hantzsch pyrrole synthesis could be telescoped with the synthesis of the starting α-iodo ketone from the corresponding ketone and N-iodosuccinimide (NIS). This solvent-free method afforded considerably higher yields of pyrroles than previous versions of the Hantzsch reaction, in spite of comprising an additional step, and was far broader in scope (Scheme 21).

The generality of the mechanochemical method was proved by its application to the preparation of fused pyrrole systems derived from the indole 34, homoindole 35, benzo[gl]indole 36, and indeno[1,2-b]pyrrole 37 frameworks, which had not been previously possible using the Hantzsch reaction, from β-dicarbonyl compounds 31, primary amines 32, and cyclic ketones 33 (Scheme 22). Again, the mechanochemical method proved to have considerable advantages in terms of yield over a similar solution-phase protocol.

![Scheme 21 - Hantzsch pyrrole synthesis under high-speed vibration milling](image1)

**Scheme 21** Hantzsch pyrrole synthesis under high-speed vibration milling

Bearing in mind the importance of symmetrical compounds formed by two identical pharmacophores connected by a spacer chain in the drug discovery field, we studied the pseudo-five-component reactions between diamines, α-iodo ketones (prepared in situ from aryl ketones, 2 equiv) and β-dicarbonyl compounds (2 equiv). We found that the mechanochemical method allowed the efficient construction of two pyrrole systems at the ends of a central chain in a single synthetic operation, furnishing compounds 38 (Scheme 23). One example of the construction of three pyrrole rings was also achieved.

In the same context, we also studied the Hantzsch reactions of some symmetrical aromatic compounds containing two acetyl groups and successfully employed them as substrates for pseudo-five-component reactions leading to additional symmetrical systems 39 capped by two pyrrole rings (Scheme 24).
4 Applications of the Hantzsch Pyrrole Synthesis

The anticancer drug pemetrexed (LY231514, Alimta®) and related compounds provide a good example of the application of the Hantzsch reaction to the synthesis of complex heterocyclic systems containing a pyrrole fragment. A synthesis of pemetrexed starts from 2,6-diaminopyrimidin-4(3H)-one and an α-bromoaldehyde, which is the suitable kind of reaction partner to obtain a β-substituted pyrrole moiety. The Hantzsch reaction was achieved by exposure of these starting materials to sodium acetate and afforded compound after saponification of the ester group. A final conjugation with diethyl glutamate and a second saponification afforded pemetrexed disodium (Scheme 25).

Pemetrexed regioisomeric structures bearing the side chain at the position adjacent to the pyrrole nitrogen (e.g., compound) are also accessible by Hantzsch chemistry, replacing the α-halo aldehyde by an α-halo ketone derivative. In this case, two starting materials were assayed, corresponding to X = Cl and X = Br. In the first case, a 1:1 mixture of products was obtained, corresponding to a furan derivative arising from a competing Feist–Benary reaction, and the desired pyrrole derivative. On the other hand, when X = Br the reaction showed full selectivity in favor of the Hantzsch product (Scheme 26).

The anti-inflammatory agent, an analogue of zomepirac, was synthesized from diethyl 3-oxopentanedioate, methylamine, and α-chloroacetone. It is interesting to note that in this case the Hantzsch reaction gave the unexpected 4-substituted regioisomer. This result was ascribed to the fact that, upon mixing diethyl acetonedicarboxylate and methylamine, a precipitate was formed that was identified as a salt of the enolate anion. Thus, the authors proposed that the reaction follows the mechanism summarized in Scheme 27, involving the reaction of this anion with the carbonyl group of α-chloroacetone, followed by an alkylation-cyclocondensation reaction sequence with methylamine to give pyrrole derivative. Further functional group manipulation furnished the target compound.

The Hantzsch pyrrole synthesis has been applied to the synthesis of radiolabeled pyrroles. Since pyrrole-2,3,5-tricarboxylic acid is a metabolite of melatonin, a radiolabeled version of this compound was deemed to be useful as a biomarker to monitor the effectiveness of drug candidates against hyperpigmentation. In this context, the synthesis of [13C4,15N]pyrrole-2,3,5-tricarboxylic acid was carried out...
using a route that had as the key step the Hantzsch pyrrole synthesis from [1,2,3,4-13C4]ethyl acetoacetate, 15NH4OH, and chloroacetaldehyde.37 The pyrrole derivative 49 thus obtained had all the radiolabels in place and was transformed into 50 by additional functional group manipulation (Scheme 28).

Atorvastatin is the best-known member of the statins, the main group of cholesterol-lowering drugs. This drug was marketed in 1997 as its calcium salt under the trade name Lipitor® and spent almost a decade at the top of the list of largest-selling branded pharmaceuticals, being thus regarded as the best-selling drug in history.

Thus, atorvastatin can be arguably regarded as the most important unnatural pyrrole derivative ever made. This compound has received much attention from synthetic chemists, and the target of all this work is normally the atorvastatin lactone, which is readily transformed into the drug molecule by hydrolysis followed by salt formation.38 In the literature, the construction of the atorvastatin pyrrole core is normally based on the Paal–Knorr pyrrole synthesis or 1,3-dipolar cycloadditions. We noticed that our mecha-

Scheme 25 Synthesis of the anticancer drug pemetrexed based on a Hantzsch pyrrole synthesis

Scheme 26 Synthesis of a homologue of the pemetrexed C-2 regioisomer

Scheme 27 Synthesis of a 4-methylpyrrole derivative by an anomalous Hantzsch reaction and its proposed mechanistic explanation

nochemical pyrrole synthesis was well suited to achieve a very short, convergent route to the atorvastatin lactone, although we acknowledged the fact that the target is a penta-substituted pyrrole with a branched substituent at C-2 and an amide group at C-3 would bring our method to its limits. In the event, the reaction between β-ketoamide 51 and the commercially available amine 52, corresponding to the atorvastatin side chain, was problematic and it did not take place at all, under our usual CAN catalysis. In view of the success of initial model reactions starting from 51, this result was attributed to the presence of the acetal protection, which is susceptible to hydrolysis by CAN. After some optimization work, we discovered that ytterbium triflate was a suitable catalyst for the desired process, although the reaction was slow at room temperature. The enaminoamide 53 thus obtained was transformed into pyrrole 55 upon treatment with α-iodo ketone 54 under mecanochemical Hantzsch reaction. Treatment with acid led to the deprotection of the terminal tert-butyl ester, with concomitant cyclization of the resulting hydroxy acid to give atorvastatin lactone 56 (Scheme 29).39

We will finally discuss one example of the application of Hantzsch pyroles as starting materials for the synthesis of more complex heterocycles. The generation of diversity-oriented libraries by combination of a multicomponent reaction with a complexity-generating event is known as the build-couple-pair strategy and was initially proposed by Schreiber and Nielsen as a new strategy for the exploration of chemical space in search for bioactive compounds.40 The mildness of the mecanochemical Hantzsch reaction allowed its compatibility with the presence in the starting materials of functional groups (e.g., acetals) that are amenable to a subsequent cyclization reaction. Thus, when the mecanochemical Hantzsch reaction was performed starting from 2-aminoacetaldehyde dimethyl acetal 57, β-dicarboxyl compounds, and acyclic and cyclic α-iodo ketones, the corresponding pyroles and fused pyroles 58 were obtained uneventfully.
We then discovered that their treatment with catalytic amounts of trimethylsilyl triflate allowed very mild and efficient Pommeranz–Fritzsch-type cyclizations that gave polycyclic compounds 59, corresponding to six different frameworks, in high yields (Scheme 30).

5 Conclusions

The Hantzsch pyrrole synthesis, one of the classical methods for the construction of simple heterocycles, has been long neglected in spite of its named reaction status. In recent years, the use of a number of non-conventional approaches has improved its outcome and broadened its scope. We hope that this review will stimulate the use of this important reaction by the synthetic community.

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