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# The Synthesis of Pyrroles from Nitroolefins

**Abstract**

The synthesis of pyrroles occupies a key place in synthetic organic chemistry due to the numerous biological properties of pyrrole derivatives, in particular antimicrobial, antibacterial, antifungal, antimalarial, anticancer activities, etc. Therefore, pyrroles serve as building blocks in the creation of potential pharmaceuticals and also serve as the basis for the synthesis of boradipyrromethene dyes. One of the most well-known approaches to the synthesis of pyrroles is the reaction between nitroolefins, 1,3-dicarbonyl compounds, and amines, also known as the Grob-Camenisch reaction. This review is devoted to the historical chronology from the discovery of this transformation dating back to 1950s to the present, and covers the development of various modifications of the above reaction in the synthesis of pyrroles.

***Keywords*:** pyrrole; Grob–Camenisch reaction; nitroolefines

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## Синтез піролів з нітроолефінів

**Анотація**

Синтез піролів займає ключове місце в синтетичній органічній хімії завдяки численним біологічним властивостям похідних піролу, зокрема антимікробній, антибактеріальній, протигрибковій, антималярійній, протираковій тощо. Саме тому піроли слугують будівельними блоками у створенні потенційних фармацевтичних препаратів, а також є основою для синтезу барвників бордипірометенового ряду. Одним із найвідоміших підходів до синтезу піролів є реакція між нітроолефінами, 1,3-дикарбонільними сполуками та амінами, відома як реакція Гроба-Каменіша. Цей огляд висвітлює історичну хронологію від відкриття цього перетворення, датованого 1950-ми роками, до сьогодення та охоплює розробку різноманітних модифікацій вищезгаданої реакції в синтезі піролів.

***Ключові слова*:** пірол; реакція Гроба-Каменіша; нітроолефіни

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## ■ Introduction

Heterocyclic compounds are very important in the field of organic chemistry as they are widely spread in nature and commonly used as building blocks in pharmacology. Among heterocycles, pyrrole is of great interest due to its presence in a variety of medicines, such as atorvastatin [1], tolmetin [2], ketorolac [3] etc., and its application in the dye synthesis, for example, BODIPY [4]. Therefore, the pyrrole core synthesis methods play a key role in contemporary organic chemistry.

There are some well-known synthetic routes for the pyrrole synthesis. The first one is the Hantzsch reaction, including the transformation between ß-ketoesters, ammonia source, and


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haloketones [5]. Alternatively, the Knorr synthesis (the reaction between α-amino-ketones and 1,3-dicarbonyl compounds) [6] or the Paal-Knorr synthesis (the reaction between 1,4-diketones and different ammonia sources) [7] can be employed. Due to increased interest, other methods of the pyrrole synthesis were developed. One of them is based on the *aza*-Wittig reaction, involving the interaction between 1-aza-1,3-*bis*(triphenylphosphoranylidene)propane and 1,2-diketo-compounds [8], and another one includes the reaction between 3-formylchromones and amines under TMSCl-mediated conditions [9].

Nitroolefins are an efficient initial material for the synthesis of organic compounds. Their synthetic attractiveness refers to the simplicity of their preparation *via* the condensation between nitroalkanes and aldehydes, known as the Henry reaction [10]. In β-nitrostyrene, the conjugation of the double bond with the nitro group enables it to participate in the Michael addition [11], a reaction that plays a crucial role in the synthesis of heterocycles. For example, nitroolefins are widely used in the synthesis of aziridines, pyrrolidines, oxazoles, indoles, etc. [12].

Taking the aforementioned information into account, the aim of this review is to discuss the historical development and progress in the pyrrole synthesis methods from nitroolefin derivatives.

**Discovery of the Grob-Camenisch reaction**

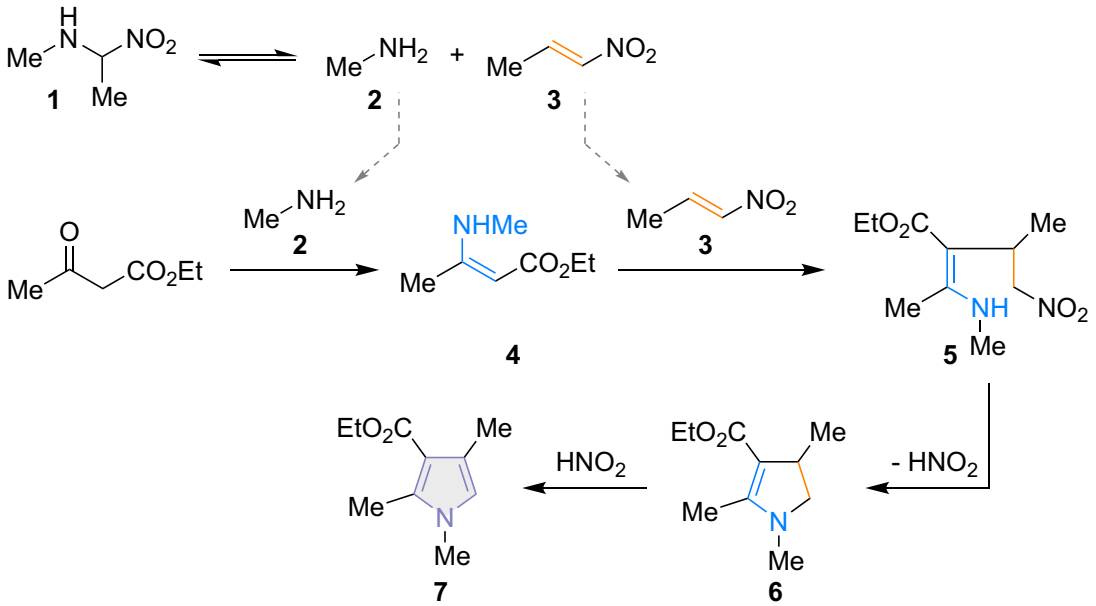
The first literary mention of the pyrroles synthesis from nitro compounds refers to the work of Grob and Kamenisch, dating back to 1953 [13]. Using 1-nitro-2-methylaminopropane and acetoacetic ester, the authors synthesized ethyl 1,2,4-trimethyl-2-pyrrolecarboxylate with a yield of 31%. They suggested the following mechanism (**Scheme 1**). In the solution, 1-nitro-2-methylaminopropane (**1**) exists in equilibrium with methylamine (**2**) and 1-nitropropene (**3**). After the addition of acetoacetic ester, the latter undergoes the condensation to form the corresponding enamine **4**, which further reacts with 1-nitropropene, resulting in Michael's product **5**. This product **5** cyclizes into dihydropyrrole **6**, eliminating a molecule of nitrous acid, which, in turn, oxidizes intermediate **6**, forming pyrrole **7**.

The further development of the reaction involving nitroolefins, 1,3-dicarbonyl compounds, and amines focused on identifying alternative synthetic approaches to increase pyrrole yields and expand the range of substrates that could be used. Currently, several variants of this reaction are known, including two-, three-, and four-component Grob-Camenisch-type reactions.

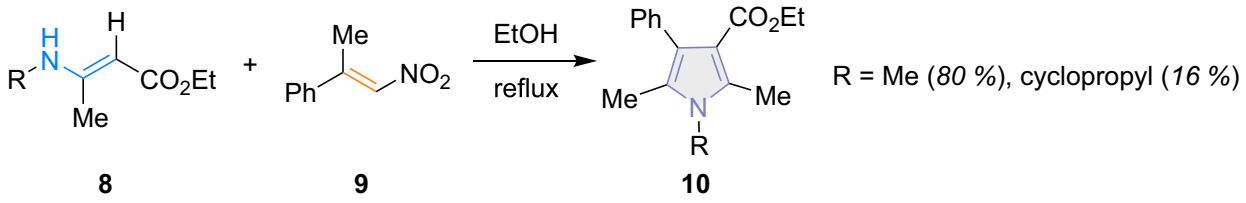
**A two-component Grob-Camenisch-type reaction**

The two-component Grob-Camenisch-type synthesis of pyrroles involves the reaction of β-enaminoesters or ketones with nitrostyrenes. First reported in 1981, this method utilized enamines **8**, derived from acetoacetic ester and (*E*)-(2-nitroprop-1-en-1-yl)benzene (**9**) [14]. Refluxing the reaction mixture in ethanol for four to six hours allows the pyrroles **10** to be obtained with yields ranging from 16% to 80% (**Scheme 2**).

The authors also found that using *N*-unsubstituted enamine **11** in the reaction with nitro




**Scheme 1**. The synthesis of pyrrole by Grob–Camenisch




**8** **9** **10**

**Scheme 2**. The synthesis of pyrroles from methyl- and cyclopropyl-derived enaminoesters

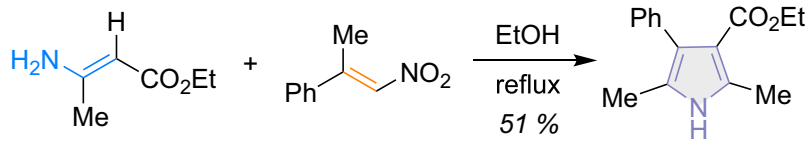
compound **9** by refluxing in ethanol for 14 hours could produce pyrrole **12** with a yield of 51% (**Scheme 3**).

Enaminoketones can also be used in a Grob-Camenisch-type reaction. However, harsher conditions are required, delivering the products with lower yields compared to standard substrates. Specifically, the reaction of enamine **13** with nitrostyrene **10** in a melt at 150°C produces pyrrole **14** with a yield of only 26% (**Scheme 4**) [14].

Further studies of the pyrrole synthesis from nitrostyrenes and ß-enaminoesters or ß-enaminoketones showed that enaminones **15** reacted with nitrostyrene or *p*-tolylnitrostyrene (**16**) under solvent-free conditions, yielding pyrroles in 70–90% yield (**Scheme 5**) [15]. The mechanism proposed involves the Michael-type addition of ß-enaminones to nitroolefins, forming intermediate **17**, which cyclizes to pyrroline **18** with the elimination of nitrous acid. The subsequent oxidation results in the production of the final pyrrole **19**.

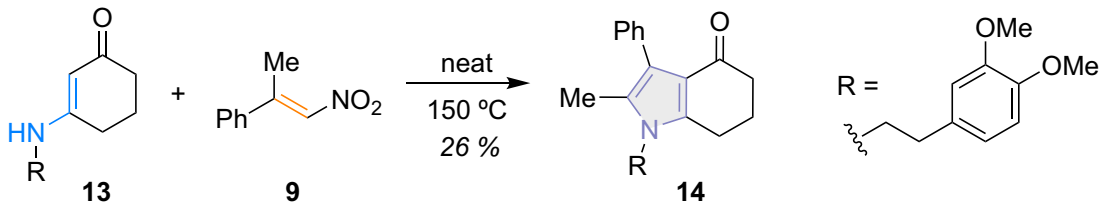
The scope and diversity of pyrroles synthesized from ß-enaminones or esters and nitroolefins can be enhanced by using solvents or catalysts. For instance, the reaction of *N*-phenyl-substituted enamine **20** with substituted nitropropene **21** in methanol at 120°C yields pentasubstituted pyrroles **22** (**Scheme 6**) [16].

The authors observed that catalytic amounts of bases (e.g., sodium acetate or piperidine) and polar aprotic solvents (e.g., DMSO or acetonitrile)



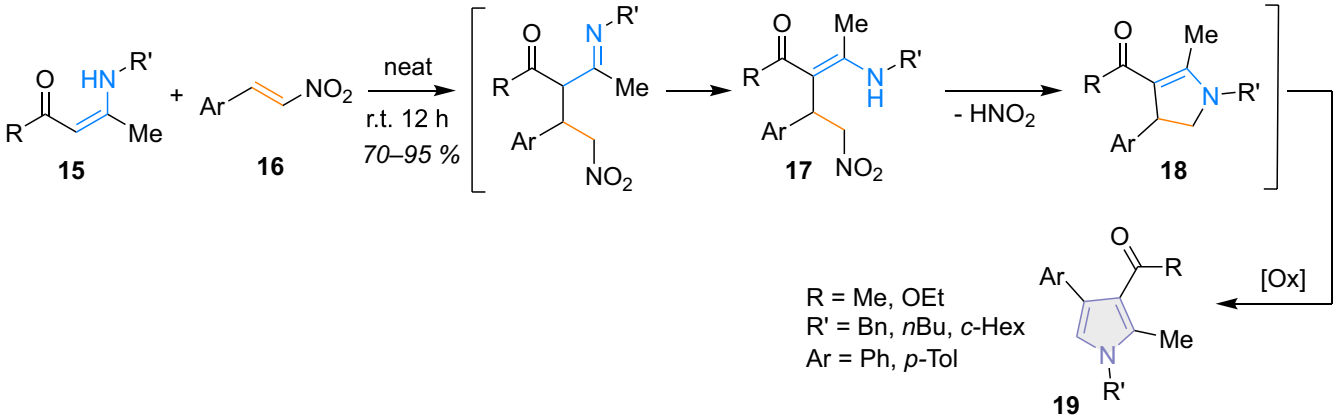

**11** **9** **12**

**Scheme 3**. The synthesis of pyrrole from *N*-unsubstituted enaminoester




**13** **9** **14**

**Scheme 4**. The synthesis of pyrrole from enaminone based on dimedone




**15** **16** **17** **18** **19**

**Scheme 5**. The reaction mechanism of the pyrrole formation in the reaction between enamines and nitrostyrenes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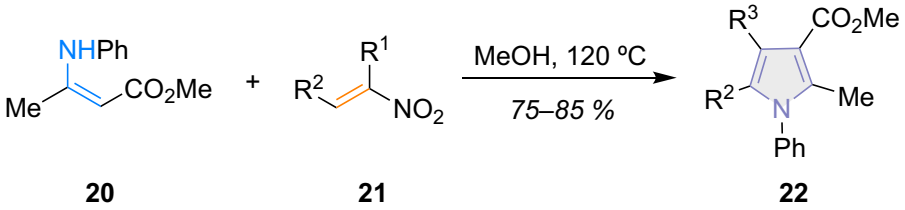



**20** **21** **22**

$R^1$ = H, Me
$R^2$ = Ph, 4-Me-$C_6H_4$, 3-Me-$C_6H_4$, 4-OMe-$C_6H_4$, 4-Me-$C_6H_4$, 4-$NMe_2$-$C_6H_4$, 4-F-$C_6H_4$, 2-furfuryl

**Scheme 6**. The synthesis of *N*-substituted pyrroles **22**

significantly decreased pyrrole yields. Electron-donating substituents on the aryl groups of nitrostyrenes and ß-enaminoesters substantially improve yields compared to electron-withdrawing ones. It is noteworthy that the use of [2-nitroprop-1-en-1-yl]furan made it possible to synthesize pyrrole with a furyl group in position 3, yielding 79% of the product. Additionally, the application of nitrostyrene as a reagent facilitates the production of α-CH pyrrole with good yields.

Catalytic reactions provide an effective preparative method for synthesizing pyrroles from ß-enaminoesters and nitroolefins. For instance, using iodine as a catalyst allows the formation of *N*-substituted pyrroles from nitrostyrene and ß-enaminoesters derived from the acetoacetic ester. It is noteworthy that nitrostyrenes bearing electron-donating substituents result in pyrroles with significantly higher efficiency, whereas *N*-alkyl-substituted 3-aminobut-2-enoates lead to slightly lower yields due to competing side reactions [17].

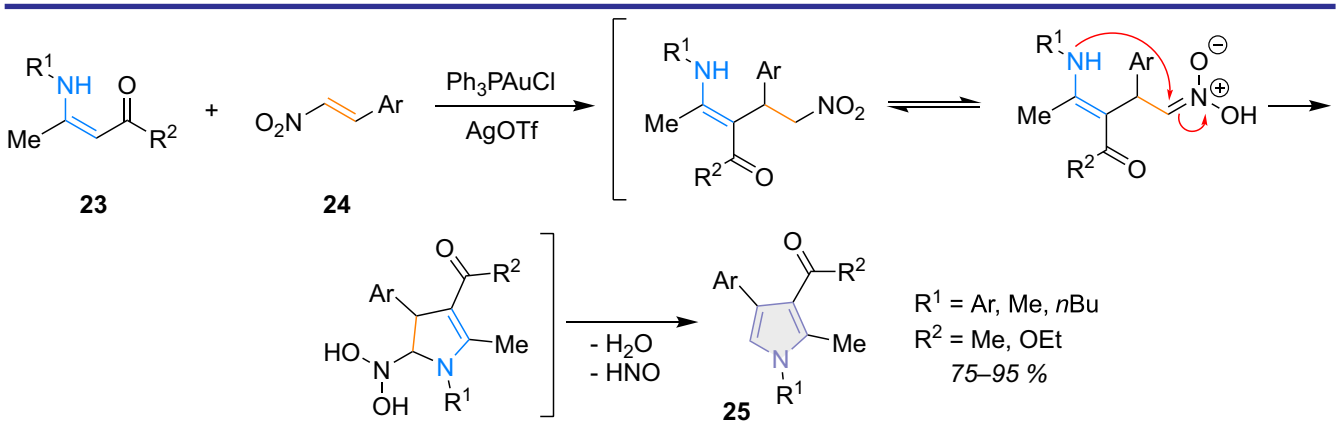
The $Ph_3PAuCl$ catalyst combined with AgOTf significantly enhances the pyrrole synthesis *via* a two-component reaction. Reactions of *N*-substituted enamines **23** obtained from acetoacetic ester or acetylacetone with substituted nitrostyrenes **24** lead to pyrroles **25** with yields exceeding 80% (**Scheme 7**) [18]. It is noteworthy that the nature of substituents in aryl groups has minimal impact on pyrrole yields, and *N*-alkyl-substituted enamines react without side reactions, also giving pyrroles in high yields.

The PEG-400 catalyst demonstrated a high effectiveness for synthesizing isoxazole derivatives bearing a pyrrole moiety in position 4 [19]. The reaction of ethyl 3-((3-methyl-5-((*E*)-styryl)-isoxazol-4-yl)amino)but-2-enoate derivatives (**26**) with nitrostyrenes **27** gave the corresponding pyrroles **28** with yields from 70 to 90% (**Scheme 8**).

A solid-phase method for the pyrrole synthesis was also developed [20]. Initially, Rink Amide resin (**29**) is acetoacetylated with diketene to form amide **30**, which is subsequently converted to polymer-bound enaminone **31** upon the treatment with primary amines. Further reaction of polymer-bound **31** with nitroolefins in a DMF/EtOH solvent mixture at 60°C yielded pyrroles **32**, which upon the treatment with trifluoroacetic acid produced final amides **33**. In this method, the pyrrole yield exceeds 80% when using both aliphatic and aromatic amines, as well as aliphatic nitroolefins (**Scheme 9**).

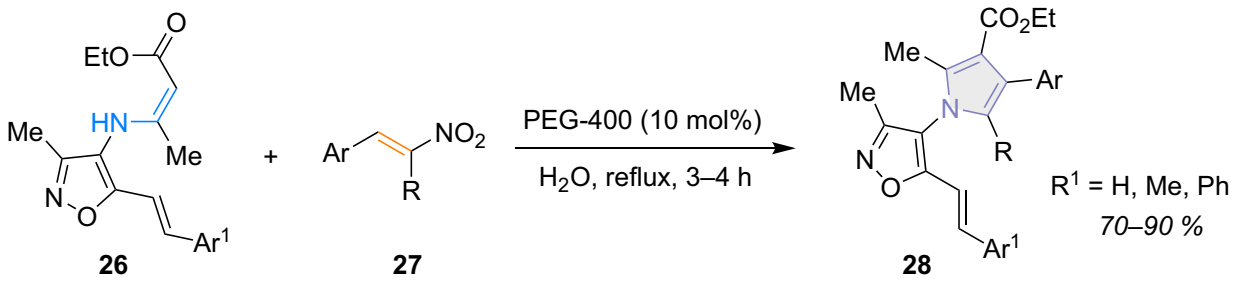
**A three-component Grob-Camenisch-type reaction**

The three-component Grob-Camenisch synthesis of pyrroles involves the reaction of amines, 1,3-dicarbonyl compounds, and nitrostyrenes,

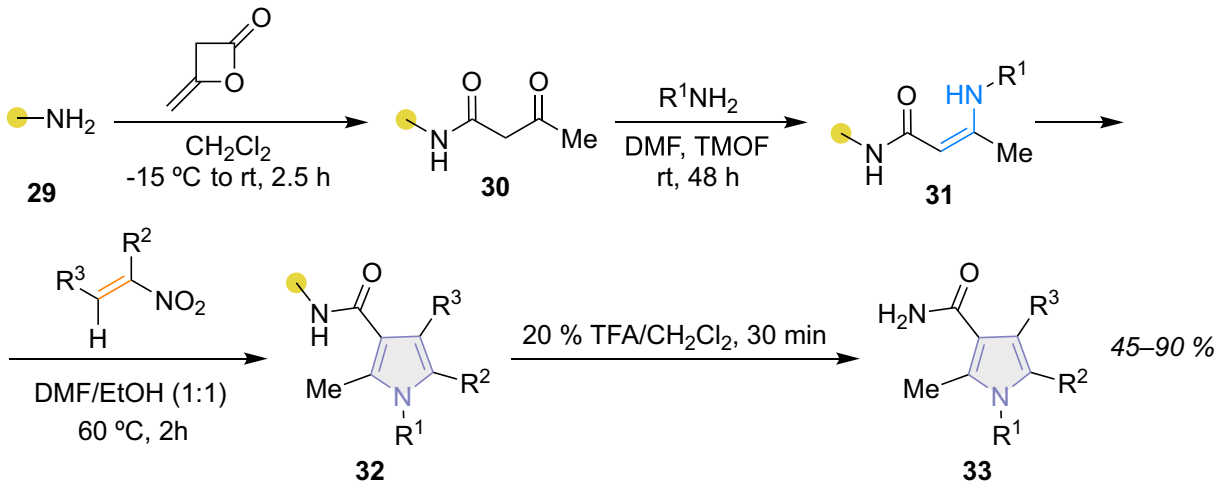



**23** **24** **25**

**Scheme 7**. The reaction mechanism of the pyrrole formation in the reaction between enamines and nitrostyrenes catalyzed with $Ph_3PAuCl$




**Scheme 8**. The synthesis of pyrroles **28**




**Scheme 9**. The solid-phase synthesis of pyrroles from nitroolefins

which make it possible to prepare pyrroles with catalytic activity. For instance, research [21] demonstrates that lactic acid serves as an effective medium for synthesizing tetrasubstituted pyrroles from acetylacetone and substituted anilines, achieving yields of approximately 70–90%. The study indicates that neither electron-withdrawing nor electron-donating substituents on the aniline significantly influence pyrrole yields.

Iron-based catalysts, such as $FeCl_3$, are widely employed in the catalytic synthesis of pyrroles from nitroolefins and 1,3-dicarbonyl compounds. For instance, $FeCl_3$ facilitates a three-component reaction, yielding pyrroles at 70–80% using 1,3-dicarbonyl compounds like acetoacetic ester, acetylacetone, or ethylbenzyl acetate [22]. As a Lewis acid, $FeCl_3$ promotes the formation of ß-enaminoester **34**, which undergoes the Michael-type addition to nitrostyrene, followed by the cyclization of the resulting adduct **35** into pyrrole *via* the nitro group conversion to its aci-nitro form (**Scheme 10**).

Interestingly, iron(III) chloride makes it possible to synthesize pyrroles from nitrostyrene bearing ethynyl substituents in the *ortho*-position, obtaining the target products with a yield of about 50% [23]. Additionally, the catalyst facilitates the pyrrole synthesis from peptides with a free amino group [24].

An alternative to $FeCl_3$ is the use of $Fe_3O_4$ nanoparticles, in particular $Fe_3O_4$@$SiO_2$-CPTMS-guanidine-$SO_3H$, which contain a terminal sulfo group [24]. This catalyst allows the synthesis of tetrasubstituted pyrroles from acetoacetic ester, acetylacetone, and *para*-chloro- or *para*-bromoanilines with yields of approximately 90% (**Scheme 11**). The sulfo group is supposed to catalyze the reaction similarly to $FeCl_3$.

Cerium(III) chloride serves as an alternative catalyst to $FeCl_3$, effective in the microwave-assisted synthesis using nitromethane as a solvent [26]. This method allows the synthesis of tetrasubstituted pyrroles from acetoacetic ester or acetylacetone, nitrostyrenes, and anilines, with yields of about 80%. However, when *para*-chloronitrostyrene is used, the yield decreases to about 50%.

An alternative to $CeCl_3$ is cerium(IV) ammonium nitrate (CAN), which catalyzes the reaction of nitrostyrene **38**, acetoacetic ester (**36**),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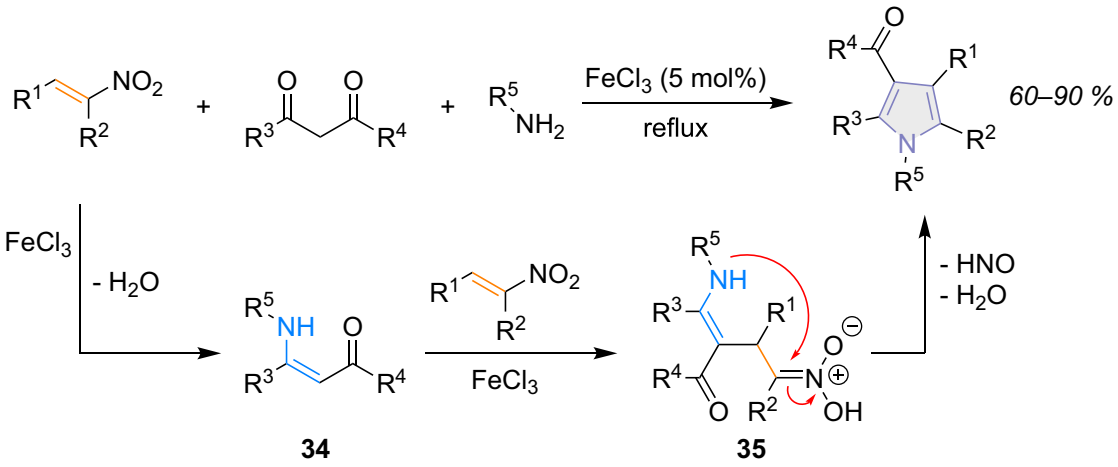
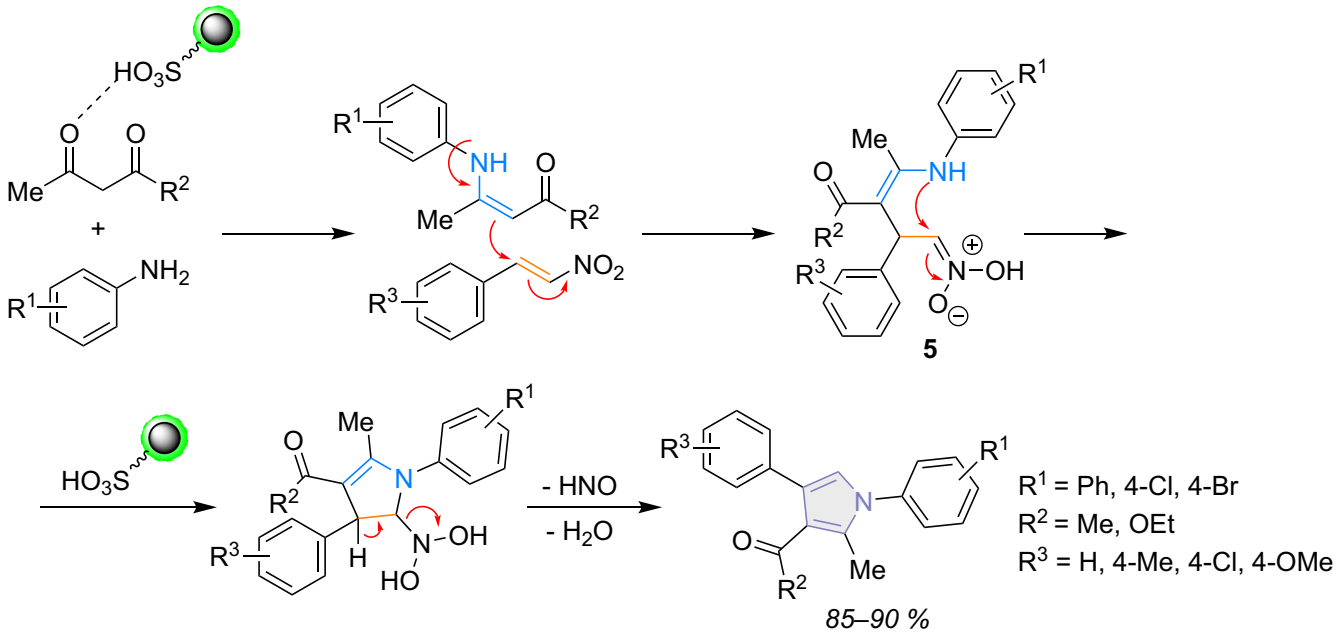



$R^1$ = Ph, 4-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-OMe-$C_6H_4$, 4-Cl-$C_6H_4$, Br-$C_6H_4$, 2-thiophenyl, 2-naphtyl
$R^2$ = H, Me
$R^3$ = Me, Ph
$R^4$ = Me, OEt
$R^5$ = 4-Me-$C_6H_4$, 4-Me-$C_6H_4$, 4-OMe-$C_6H_4$, 4-F-$C_6H_4$, 4-Cl-$C_6H_4$, Br-$C_6H_4$, 2-naphtyl

**Scheme 10**. The reaction mechanism of the three-component synthesis of pyrroles from nitroolefins catalyzed with $FeCl_3$




$R^1$ = Ph, 4-Cl, 4-Br
$R^2$ = Me, OEt
$R^3$ = H, 4-Me, 4-Cl, 4-OMe

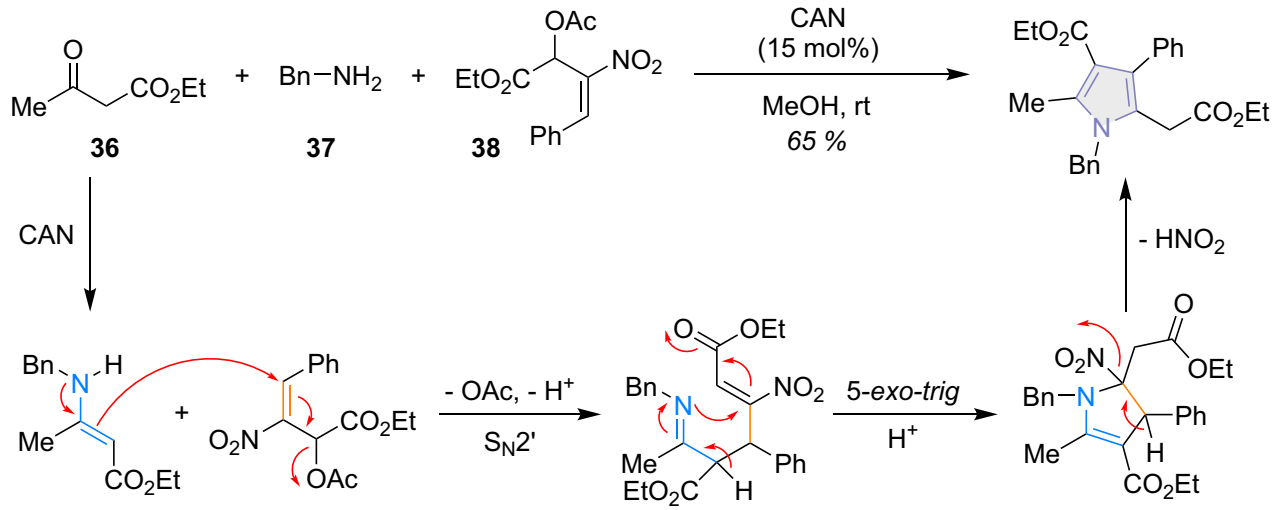
**Scheme 11**. The reaction mechanism of the three-component synthesis of pyrroles from nitroolefins catalyzed with $Fe_3O_4$@$SiO_2$-CPTMS-guanidine-$SO_3H$

and benzylamine (**37**) at room temperature in methanol [27]. This method produces pyrroles with yields ranging from 50 to 75% (**Scheme 12**).

In addition to other metal-containing catalysts, $Ph_3PAuCl$ combined with AgOTf [28] and zirconyl dichloride complexes [29] makes it possible to use acetoacetic ester and various ß-diketoamides as 1,3-dicarbonyl compounds, yielding pyrroles at approximately 70%.

Furthermore, diacetoxyiodobenzene serves as an effective non-metal catalyst for the pyrrole synthesis, producing pyrroles from acetoacetic ester and acetylacetone with yields of about 70%, unaffected by substituents on nitrostyrene or aniline [30, 31].

The combination of oxone and iodobenzene makes it possible to synthesize pyrroles from nitrostyrenes, acetylacetone, or acetoacetic ester, and anilines, yielding 80–90% of the desired product. Notably, neither electron-donating nor electron-withdrawing substituents on nitrostyrene or aniline impact the pyrrole yield [31].




**Scheme 12**. The reaction mechanism of the three-component synthesis of pyrroles from nitroolefin **38**

Ionic liquids, such as *N*-methyl-2-pyrrolidonium methyl sulfonate, serve as effective catalysts for the three-component synthesis of pyrrole involving nitroolefins, amines, and 1,3-dicarbonyl compounds. Notably, the yields of pyrroles from substituted nitrostyrenes and anilines, ranging from 70 to 90%, show no correlation with the substituent effects. However, using aliphatic nitroolefins and amines decreases yields to 30% [32].

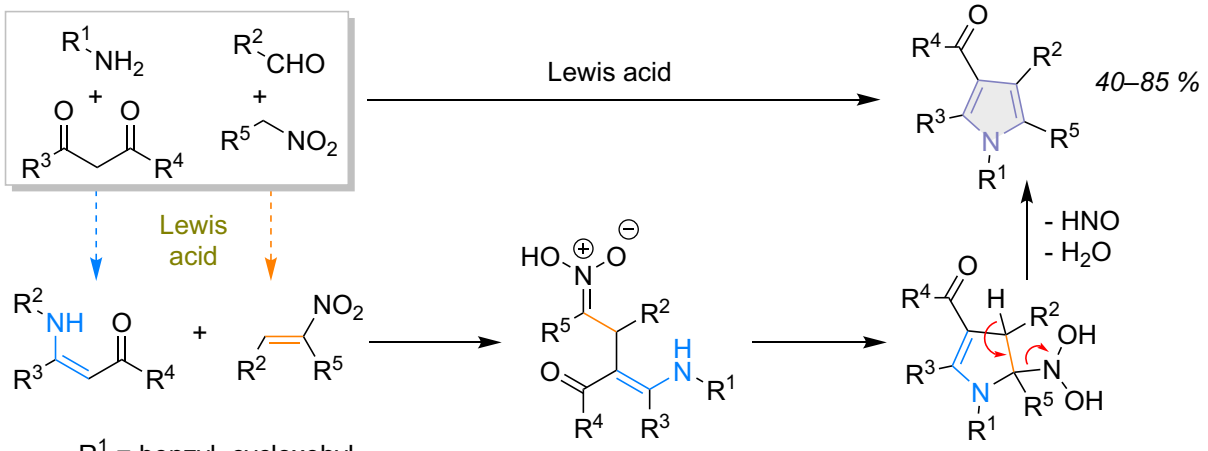
**A four-component Grob-Camenisch-type reaction**

Another convenient option for the synthesis of pyrroles is a four-component reaction involving aldehydes, nitroalkanes, 1,3-dicarbonyl compounds, and amines. Currently, only catalytic variants of this transformation have been developed using $FeCl_3$ [32], palladium [34], and tungsten-based complexes [35], CuO nanoparticles [36], ionic liquids [37, 38], iodine [39], clay [40], $NiCl_2 \cdot 6H_2O$ [41], as well as organic acids – lactic and gluconic [42] (**Scheme 13**).

The reaction mechanism includes the catalyzed formation of a β-enaminone from a nitroolefin, followed by the Michael addition to form an intermediate. This intermediate undergoes elimination of a hyponitrous acid molecule, resulting in the formation of pyrrole.

**The synthesis of *N*-unsubstituted α-CH pyrroles**

The synthesis of N-H α-CH pyrroles is of significant interest in the Grob cyclization, as these compounds serve as precursors for luminescent BODIPY borofluoride complexes and porphyrins. The earliest reported attempt to synthesize such




$R^1$ = benzyl, cycloxehyl
$R^2$ = Ph, 4-Me-$C_6H_4$, 4-OMe-$C_6H_4$, 4-F-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-CN-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 2-thiophenyl, 2- furfuryl, 2-naphtyl
$R^3$ =Ph, Me
$R^4$ = OMe, OEt
$R^5$ = H, Me

**Scheme 13**. The reaction mechanism of the four-component synthesis of pyrroles from nitroolefins catalyzed by Lewis acids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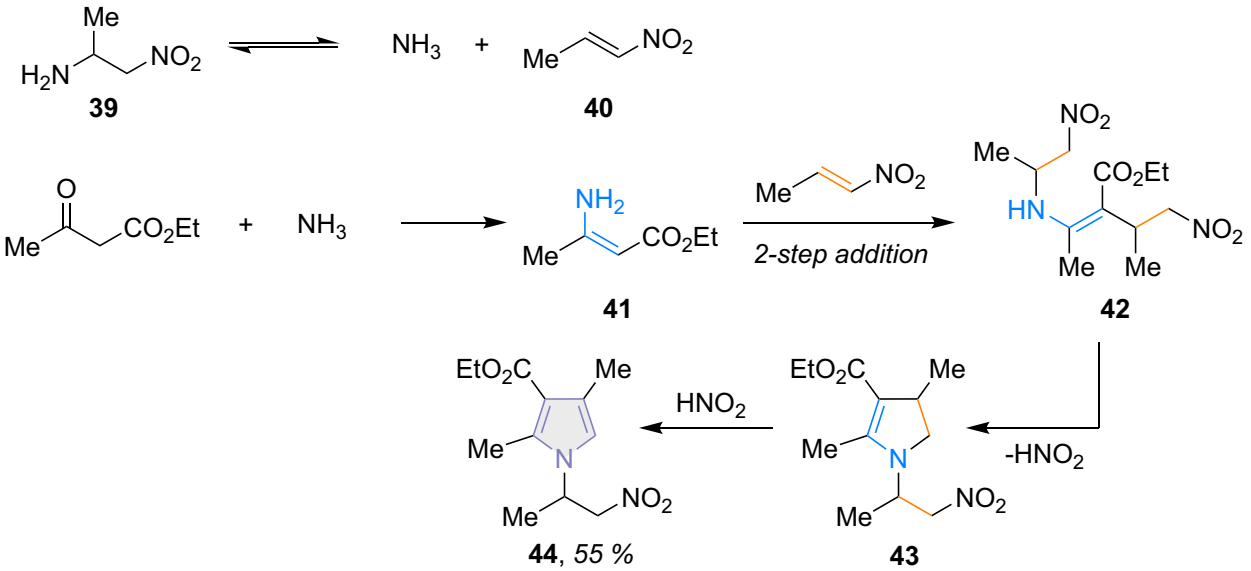
pyrroles was by Grob [13] where 1-nitropropan-2-amine **39** and acetoacetic ester were used. However, instead of the expected N-H pyrrole, an *N*-substituted derivative **44** was obtained. This outcome was attributed to intermediate **41** possessing two nucleophilic centers: a carbon atom and a nitrogen one. Hence, two Michael additions occur, leading to intermediate **42**, which undergoes further cyclization, thus yielding *N*-isopropyl derivative **44** instead of the expected N-H one (**Scheme 14**).

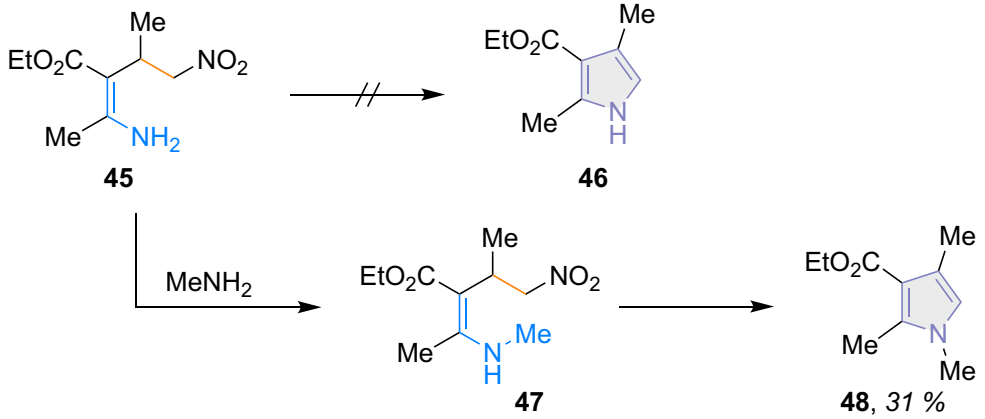
In order to synthesize the corresponding N-H α-CH pyrrole, Grob first isolated intermediate **45**, which failed to transform into pyrrole **46** under different conditions (**Scheme 15**). The author attributed this to the conjugation of the nitrogen atom lone pair in intermediate **45** with the ethoxycarbonyl group reducing its nucleophilicity. However, interestingly, upon the treatment of **45** with methylamine, pyrrole **48** could be isolated, assuming that the transamination occurred with the formation of **47**, which then cyclized to **48**. From this observation, it could be suspected that the presence of even weak electron-donating groups favors the pyrrole synthesis by the Grob cyclization.

In the subsequent study, Gómez-Sánchez [43] investigated the synthesis of N-H α-CH pyrroles using nitro compounds, with a focus on the formation of anomalous Michael products from nitrostyrene and acetylacetone. By employing non-catalytic amounts of sodium methoxide with acetylacetone and nitrostyrene **49**, the authors obtained anomalous Michael products **50** (**Scheme 16**). The latter product, upon the treatment with saturated methanolic ammonia solution at 0°C, gives rise to pyrrole **51 (Scheme 16)**.

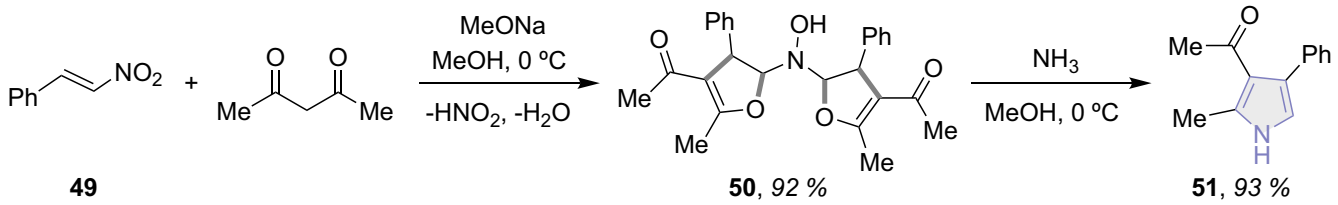
Based on this observation, the authors developed a one-pot procedure of the pyrrole synthesis, including the treatment of nitrostyrene **49** with acetylacetone, acetoacetic ester, or methyl acetoacetate in methanol with a non-catalytic




**Scheme 14.** The synthesis of pyrrole by Grob-Camenisch

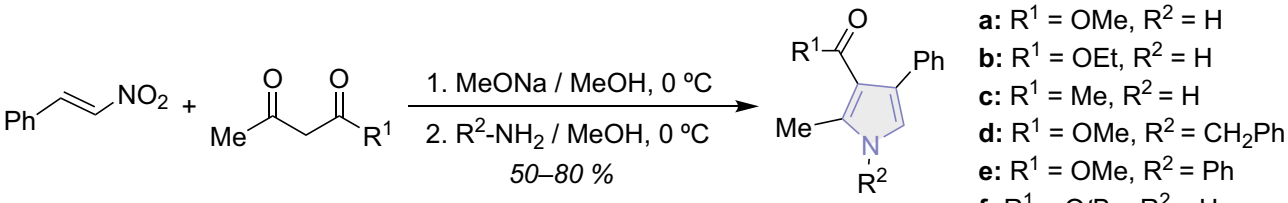



**Scheme 15**. Transformations of intermediate **45**




**49** **50**, *92 %* **51**, *93 %*

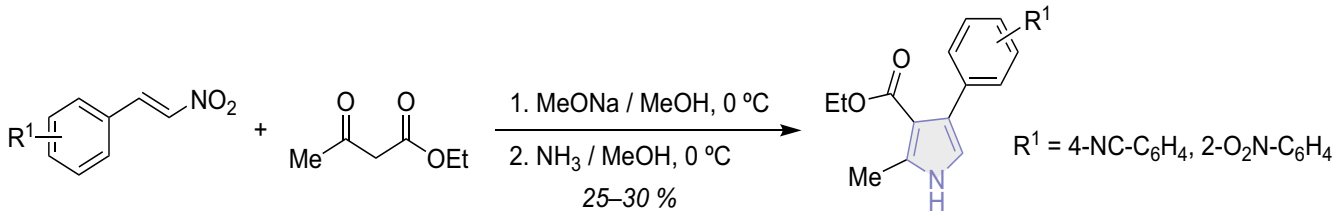
**Scheme 16**. The synthesis of anomalous Michael's product **50** and pyrrole **51**




**49** **52**

**a:** $R^1$ = OMe, $R^2$ = H
**b:** $R^1$ = OEt, $R^2$ = H
**c:** $R^1$ = Me, $R^2$ = H
**d:** $R^1$ = OMe, $R^2$ = $CH_2Ph$
**e:** $R^1$ = OMe, $R^2$ = Ph
**f:** $R^1$ = O*t*Bu, $R^2$ = H

**Scheme 17**. The one-pot pyrrole synthesis by Gómez-Sánchez




**49** **52**

$R^1$ = 4-NC-$C_6H_4$, 2-$O_2N$-$C_6H_4$

**Scheme 18**. The synthesis of other pyrrole derivatives by the Gómez-Sánchez-like procedure

amount of sodium methoxide at 0°C for 1 hour with further addition of an ammonia source, such as aniline, benzylamine or saturated methanolic ammonia solution. This synthetic procedure allowed obtaining pyrroles **52** with yields of up to 80% (**Scheme 17**).

Two additional literature references describe similar methods for synthesizing N-H α-CH pyrroles, involving the initial formation of the Michael addition product between nitrostyrenes **53** and acetoacetic ester, followed by the treatment with ammonia (**Scheme 18**). Using this approach, pyrroles **54** were obtained, though in low yields, from 25 to 30% [44, 45].

## Conclusions

The Grob-Camenisch synthesis of pyrroles is highly valued for its straightforward methods and procedures, as evidenced by numerous publications. The main advantage of this reaction is the possibility of obtaining tetra- and three-substituted pyrrole derivatives. This reaction also allows the synthesis of pyrroles in multi-gram amounts. It is noteworthy that for this method, it is possible to use catalysts of different types (Lewis and Brønsted acids, nanoparticles, etc.), which broadens the synthetic possibilities of the pyrrole synthesis.

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