

A straightforward synthesis of pyrroles from ketones and acetylene: a one-pot version of the Trofimov reaction

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This work is dedicated to Prof. Vladimir I. Minkin on the occasion of his 70th birthday
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Abstract

Alkyl-, aryl- and hetaryl ketones after a one-pot oximation and treatment with acetylene are converted to 2-mono- and 2,3-disubstituted *NH*- and *N*-vinylpyrroles with alkyl-, aryl- and hetaryl substituents in good yields. The oximation is effected using a $\text{NH}_2\text{OH}\cdot\text{HCl}\text{-NaHCO}_3$ system at room temperature. The reaction with acetylene is carried out in the presence of the KOH/DMSO superbases at 100 °C under atmospheric pressure.

Keywords: Pyrroles, ketones, oximes, acetylene, superbases

Introduction

Important biological properties of pyrrole derivatives stimulate the incessant search for new and improved methods of the pyrrole nucleus. A progress in the substituted pyrrole synthesis is mostly associated with the modification of classical methods. Typically, a new version of the Paal-Knorr reaction with montmorillonite as a catalyst allows the expediency of the 2,5-disubstituted pyrroles synthesis to be considerably improved.¹ A recent novel synthesis of *N*-substituted pyrroles with rare amino, hydroxy, alkoxy and alkylthio functions at the pyrrole ring is based on the addition of acetylenic or allenic carbanions to isothiocyanates using butyllithium and other superbasic reagents under inert atmosphere at low temperature (-100 °C).² A number of modern pyrrole ring constructions employ catalysts composed of expensive platinum group metal derivatives.^{3,4} Some recently developed syntheses, though efficient, appear to be not of general character due to the utilization of exotic starting materials^{5,6} or special structures of the pyrroles formed.^{3,6,7}

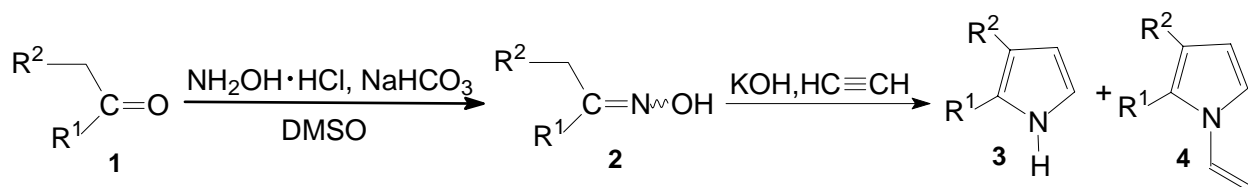
Results and Discussion

Notwithstanding the advances in the design of complex pyrrole derivatives, there is a lack in practical syntheses of “simple” pyrroles with alkyl, aryl and hetaryl substituents or annelated to common cyclic systems at desired positions, based on readily available starting materials and capable of scaling up to custom batches.

These requirements are fulfilled by the synthesis of pyrroles by the reaction of ketoximes with acetylenes in the MOH/DMSO (M = alkali metal) superbasic systems (the Trofimov reaction),^{8,9} which makes diverse 2-substituted, 2,3- and 2,5-disubstituted *NH*- and *N*-vinylpyrroles accessible. In a recent patent,¹⁰ some other solvents, including *N*-methylpyrrolidone (NMP), and alkali metal alkoxides (along with MOH) were claimed to be efficient in this reaction. However, our attempts to reproduce the best example of the patent (reaction of cyclohexanone oxime with acetylene in the *t*-BuOK/NMP system) showed the yield of 4,5,6,7-tetrahydroindole to be 17%, instead of 52% claimed, thus being in correspondence with the known regularities.⁹

Herein we describe a novel version of the Trofimov reaction, comprising a one-pot transformation of ketones (which are among the most readily available organic compounds) to *NH*- and *N*-vinylpyrroles. The version is devoid of a step of the intermediate ketoxime synthesis, which is always associated with losses of reactants, solvents and time, and in some cases (for example, with water-soluble ketoximes) poses various preparative difficulties. To avoid this cumbersome step, we have attempted a straightforward one-pot ketone-to-pyrrole transformation by the consecutive reaction of a ketone with hydroxylamine and acetylene in the KOH-DMSO system. Such an approach is by far not obvious due to the known oxidative properties of DMSO,¹¹ which might render the oximation stage impossible.

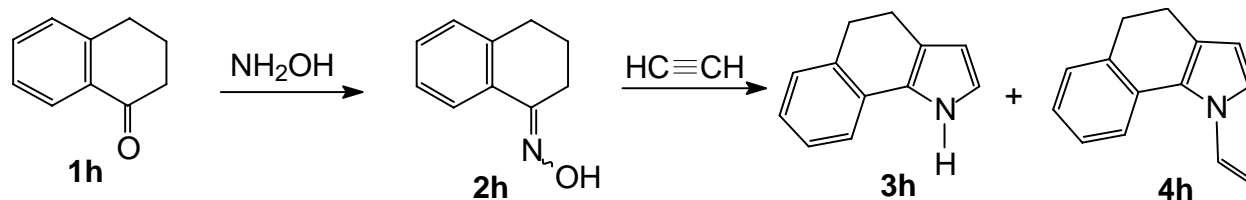
To investigate the scope and the limitations of this new version of the Trofimov reaction, a number of ketones **1a-h** with substituents of diverse nature were tested (results are given in the Table) (Scheme 1).



$R^1 = \text{Me}, R^2 = \text{H}$ (**a**); $R^1 = \text{Et}, R^2 = \text{H}$ (**b**); $R^1 = t\text{-Bu}, R^2 = \text{H}$ (**c**); $R^1\text{-}R^2 = \text{-(CH}_2\text{)}_4\text{-}$ (**d**), $R^1 = \text{Ph}, R^2 = \text{H}$ (**e**); $R^1 = 2\text{-Thienyl}, R^2 = \text{H}$ (**f**); $R^1 = 2\text{-Furyl}, R^2 = \text{H}$ (**g**)

Scheme 1

It was found that the new one-pot version of the pyrrole synthesis can be successfully extended to ketones of the hydronaphthalene series. For example, from 1-tetralone (**1h**), 4,5-dihydrobenzo[*g*]indoles (**3h**) and (**4h**) were readily prepared (Scheme 2).

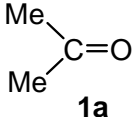
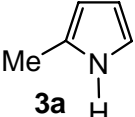
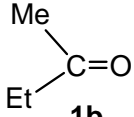
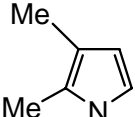
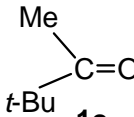
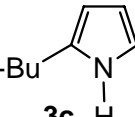
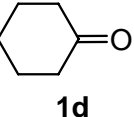
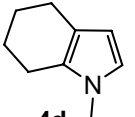
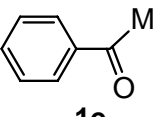
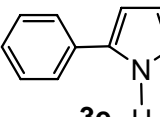
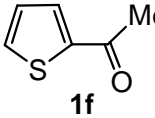
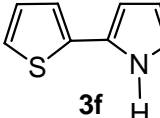
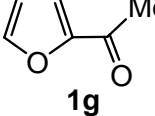
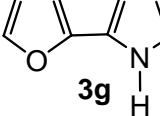
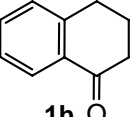
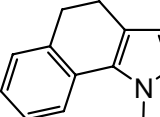


Scheme 2

The procedure is carried out under mild conditions (100 °C), its implementation being simple, safe and feasible to any laboratory: acetylene was fed into the reaction mixture under atmospheric pressure.

Utilizing NaHCO_3 in this process as a base, instead of alkali (KOH or NaOH), prevents possible condensations and methylenation¹² of starting ketones which are feasible in the KOH/DMSO system. Prior to the introduction of KOH (which, along with DMSO, catalyzes the interaction of oximes with acetylene),^{8,9} the reaction mixture has to be heated (100 °C) and blown out with acetylene for the removal of CO_2 .

Table 1. One-pot synthesis of pyrroles from ketones and acetylene (5 mmol of ketone, 5 mmol of H₂NOH·HCl, 5 mmol of NaHCO₃, 7.5 mmol of KOH·0.5H₂O, 100 °C, 5 h,^a atmospheric pressure, acetylene flow rate 15 cm³/min)

| Ketone | Pyrrole | Content in the crude product, % | Yield (GLC or ¹ H NMR), % |
|--|--|---------------------------------|--------------------------------------|
|  1a |  3a | 31 ^b | 12 |
|  1b |  3b | 80 ^c | 65 |
|  1c |  3c | 85 ^d | 72 |
|  1d |  4d | 87 ^e | 71 |
|  1e |  3e | 60 ^f | 60 |
|  1f |  3f | 47 ^g | 46 |
|  1g |  3g | 56 ^h | 45 |
|  1h |  3h | 70 ⁱ | 72 |

^a Acetylene feeding time. ^b Other components: ketoxime **2a** – 4%, *N*-vinylpyrrole **4a** – 38%.

^c Other components: *N*-vinylpyrrole **4b** – 20%. ^d Other components: *N*-vinylpyrrole **4c** – 15%.

^e Other components: pyrrole **3d** – 3%. ^f Other components: ketoxime **2e** – 30%, *N*-vinylpyrrole **4e** – 10%.

^g Other components: ketoxime **2f** – 47%, *N*-vinylpyrrole **4f** – 6%. ^h Other components: ketone **1g** – 12%, oxime **2g** – 7%, *N*-vinylpyrrole **4g** – 25%.

ⁱ Other components: *N*-vinylpyrrole **4h** – 30%.

As seen from Table 1, the conditions chosen (unoptimized) allow the selective preparation of *N*-vinyl-4,5,6,7-tetrahydroindole (**4d**) (71% yield). Under the same conditions, 2-phenylpyrrole (**3e**), 2-thienylpyrrole (**3f**) and 4,5-dihydrobenzo[*g*]indole (**3h**) were also synthesized selectively (60, 46 and 72% yield, respectively). Acetone (**1a**) forms 2-methyl-*NH*- and *N*-vinylpyrroles in low yield, presumably, due to a higher reactivity of the intermediate acetoxime **2a** in side autocondensation processes in the superbasic media.¹³

Analysis of the reaction mixtures by GLC and ¹H NMR (Table 1) show that under the conditions studied, conversion of aryl- and heteroarylketoximes in the reaction is incomplete. It is known that to reach their full conversion in the reaction with acetylene [for example, in the case of 2-acetylfuran oxime (**2g**) or 2-acetylthiophene oxime (**2f**)], one needs to increase the reaction temperature to 130-140 °C and use longer reaction times (6-8 h).¹⁴ Obviously, optimization of the conditions (variation of temperature, reaction time, nature and amount of base) for each ketone will allow to improve the yield of target pyrroles and *N*-vinylpyrroles and increase the reaction selectivity for each of them.

In conclusion, a novel version of the Trofimov reaction allowing to accomplish a one-pot synthesis of *NH*-pyrroles and *N*-vinylpyrroles directly from ketones and acetylene was developed. Among important advantages of this version are simplicity, technological feasibility (atmospheric pressure of acetylene) and readily available ketones instead of ketoximes. Getting rid of the oximation step and related drawbacks, as well as avoiding inevitable losses occurring during the isolation of the oximes, which lower the total yield of the target pyrroles, increase the preparative efficiency of this method and makes it more attractive to a broad range of researchers involved in pyrrole chemistry.

Experimental Section

General Procedures. NH₂OH·HCl (5 mmol) was dissolved in DMSO (10 mL) in a 25-mL flask equipped with a stirrer, and then NaHCO₃ (5 mmol) and ketone (5 mmol) were added. The intense evolution of CO₂ was observed. The mixture was allowed to stand for 3-4 h at room temperature until the reaction completion. Then the mixture was heated to 100 °C, and acetylene was fed upon stirring for 0.5 h. After addition of KOH·0.5H₂O (7.5 mmol), acetylene feeding was continued at the same temperature for 5 h at a rate of ~15 cm³/min. Then the mixture was cooled, diluted with water to ~30 mL and extracted with ether (5x5 mL). The extracts were washed with water (3x5 mL) and dried over K₂CO₃. After removal of the ether, the residue (crude product) was analyzed by GLC or ¹H NMR (Table). For the isolation of the pure pyrroles the column chromatography (Al₂O₃) was used. First, *N*-vinylpyrrole was eluted with hexane and then, *NH*-pyrrole was eluted with the system hexane-ether (3:1). All the characteristics including ¹H and ¹³C NMR-data of the pyrroles **3a-h** were corresponded to those of the literature.⁹ ¹H and ¹³C NMR spectra were recorded on a Bruker DPX 400 (400.13 and 100.61 MHz, respectively)

instrument in CDCl₃, using HMDS as an internal standard. IR spectra were recorded on a Bruker IFS 25 instrument.

Acknowledgements

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