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Expedient one-pot synthesis of pyrroles from ketones, hydroxylamine, and 1,2-dichloroethane

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ABSTRACT

2- and 2,3-Substituted pyrroles are readily synthesized in a one-pot procedure from ketones, hydroxylamine hydrochloride, and 1,2-dichloroethane in the KOH/DMSO system (120 °C, 2–4 h), the yields of pyrroles ranging 11–85%. Aliphatic, cycloaliphatic, aromatic, and heteroaromatic ketones tolerate the reaction conditions.

1. Introduction

Pyrroles are known to be widely important heterocycles, key structural units of chlorophyll and hemoglobin ensuring the photosynthesis in plants and oxygen exchange in animals. A great variety of natural compounds includes the pyrrole scaffold fulfilling a number of diverse major biological functions. No wonder that many potent drugs actually represent various pyrrole derivatives. A lot of pyrroles have been recently shown to be COX-2 isoenzyme inhibitors,[1] DNA minor groove recognition reagent DB884,[2] bioantioxidants.[3] Different pyrroles are known to possess anti-inflammatory, antiviral, antiproliferative, antibacterial, antidepressant, antipsychotic, antihyperglycemic activities.[4] Today among the most salable modern drugs is the pyrrole hypolipidemic Atorvastatin.[5] A rapidly growing attention is attracted by the functionalized aryl pyrroles exhibiting anti-tuberculosis activity, some of them already under clinical trials. The pyrrole derivative BM212 [1,5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl)methylpyrrole] and its congeners were found to possess strong inhibitory activity against both *Mycobacterium tuberculosis* and some non-tuberculosis mycobacteria. Particularly important that these pyrroles inhibit drug-resistant mycobacteria and also are active against intracellular bacilli of the human histiocytic lymphoma cell.[6] Most recently, enormous efforts have been focused on the functionalized pyrroles displaying the properties of anti-HIV-1 drugs as reverse transcriptase and protease inhibitors,[7] already being tested in clinic.

Owing to their highly important role in human life in the last decade, many methodologies for pyrrole synthesis have been developed. This includes cycloaddition reactions,[8] multicomponent reactions,[9] dehydrogenative cyclization reactions,[10] coupling of enamides with alkynes,[11] and oxidative cyclization of *N*-allylimines,[12] various reactions of oximes[13] and *N*-oxyenamines,[14] the list far from being exhausted. Despite these avalanche-like developing syntheses of pyrroles, as a rule functionalized, it is always felt the lack of robust methods for preparation of pyrroles with such fundamental substituents as alkyl, aryl, and hetaryl as well as the fused pyrrolic systems. For instance, one of the latest synthesis of 2-phenylpyrrole (55% yield) is based on intramolecular cyclization of 1-amino-1-phenyl-3-butyn-2-ol in the presence of 10 mol % binuclear ruthenium complex {[Cp*RuCl(μ2-SMe)2RuCp*(OH_2)]OSO_2CF_3}.[15] Until recently, just a few syntheses of 2-(2-thienyl) pyrroles are known, which are multistep, low yield, and based on inaccessible starting materials.[16]

Among the current most dynamically elaborating methods of the pyrrole synthesis are those based on the rearrangement of available *O*-vinyl ketoximes, which are readily synthesized by addition of ketoximes to acetylenes in the presence of superbases,[17] Au/Ag[18], or Eu(III) catalysts.[19] A breakthrough along this line has been Ir/Ag catalyzed isomerization of allyl ketoximes to their

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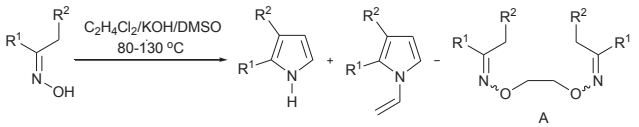
1-propenyl isomers, which further cyclize to pyrroles.[20] In last minute paper, it has been reported that two molecules of *O*-acylketoximes are transformed (CuBr, DMSO, 140 °C, 2 h) to tetrasubstituted symmetrical pyrroles.[21]

We have assumed that *O*-vinyl ketoximes and, consequently, pyrroles therefrom can be synthesized in a one-pot manner directly from ketones, hydroxylamine, and 1,2-dichloroethane in superbase media, e.g., KOH/DMSO.

Previously, a somewhat similar route to pyrroles was attempted using preliminarily prepared ketoximes, which were subjected to the reaction with dihaloethanes.

However, these reactions were accompanied by numerous expected side processes, particularly such as nucleophilic substitution of the chlorine atom in the intermediate β-chloroethyl ketoxime **B** by oximate, hydroxide, or pyrrolate anions or further chloroethylation of *NH*-pyrroles followed by the formation of *N*-vinylpyrroles. Just the formation of ketoxime diethers **A** (up to 33%) appeared to be the major hurdle in these earlier attempts to synthesize pyrroles from ketoximes and dihaloethanes (Scheme 1).[22]



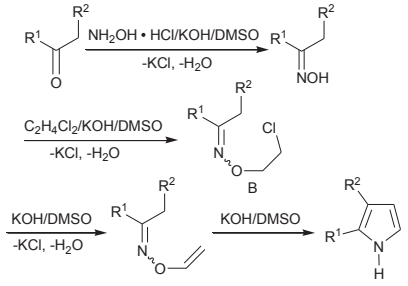
Scheme 1. Previous work.

Also, difficult-to-separate mixtures of *NH*- and *N*-vinylpyrroles (in poor yields) were always formed.

Thus, it seems worthwhile to check whether the straightforward employment of ketones in combination with hydroxylamine allows to suppress the above side reactions.

2. Results and discussion

In this paper, we concisely report how this assumption has come true. Indeed, after systematic optimization of each operation presented in this reaction sequence, we have succeeded in developing of the efficient straightforward synthesis of 2- and 2,3-substituted pyrroles in good to high yields (Scheme 2).



Scheme 2. The formation of pyrroles from ketones and dichloroethane.

Eventually, we have in hand a direct transformation of diverse (aliphatic, cycloaliphatic, aromatic, condensed aromatic, and heteroaromatic) ketones **1a**–**l** to substituted pyrroles **2a**–**l** via a simple single-reactor procedure (Table 1).

Experimentally, the synthesis is carried out as follows. A mixture of a ketone, $NH_4OH \cdot HCl$, and KOH in the 1.2:1.2:1.2 M ratio in DMSO is stirred at 70 °C for 0.5 h. Then to the ketoxime obtained, KOH (3 equiv) is added and to a vigorously stirred suspension, dichloroethane (2 to 4-fold molar excess relative to the starting ketone depending on its structure) in DMSO is gradually fed dropwise at 120 °C for 2–4 h until the *N*-vinylpyrrole becomes detectable by GLC. The *NH*-pyrroles are isolated after aqueous work-up followed by extraction procedures (see Experimental section). Unreacted ketones (conversion 20–100%, Table 1) are recovered as ketoximes, which can be further used directly for the synthesis of the same pyrroles. The isolated yields of pyrroles **2** have been calculated based on the starting ketones. The yields of the recovered ketoximes (actually, unconsumed ketones) are also given in Table 1. Since this is a multistep transformation for the regioselective synthesis of highly substituted compounds, the overall yields of 11–85% may be considered as acceptable.

As seen from Table 1, the yields of pyrroles **2a**–**l** differ considerably, that is, anticipated for such a complex and multistep process. The major cause of this is that *NH*-pyrroles have different rates of their further *N*-vinylation. As mentioned above, we stop the reaction just after GLC detection of trace *N*-vinylpyrroles. Therefore, if the rate of *N*-vinylation is high, the reaction is interrupted at low conversion of the corresponding ketoxime that leads to a low yield of *NH*-pyrrole. Thus, higher yields of pyrroles **2b** and **2f** as compared with others may result from lower vinylation rates of the corresponding *NH*-pyrroles. In the former case, the vinylation should be sterically hindered by bulky *N*-butyl substituent in the α-position of the pyrrole ring, while in the latter case, nucleophilicity of the corresponding pyrrolate anion is diminished due to electron-withdrawing effect of *para*-chlorophenyl substituent. This should lower *N*-vinylation rate.

The major alterations, which allow to suppress the above side reactions are as follows: (i) the direct employment of ketones instead of ready ketoximes; (ii) the strictly controlled (GLC) dosing of 1,2-dichloroethane to prevent formation of *N*-vinylpyrroles and other undesirable products instead of its threefold excess used in the previous attempts;[22b] (iii) significant decrease of KOH loading (3 equiv vs 7–12 equiv used previously); (iv) shortening of the reaction time (mainly 2–2.5 h vs 4–11 h); (v) change of the order of the reactants mixing (continuous dropwise feeding of 1,2-dichloroethane to the ready ketone/$NH_4OH \cdot HCl$/KOH/DMSO suspension vs portion-wise adding of KOH and dichloroethane during the reaction course).

An advantage of the method is its scalability: most of the pyrroles have been prepared here in more than 1 g scale that allows recrystallization or distillation rather than laborious column chromatography to be applied for their purification. However, column chromatography (silica gel, $CHCl_3$) is certainly also valid for isolation and purification of the target pyrroles as exemplified by the preparation of pyrroles **2h**, **2j**.

In contrast, the methodology developed ensures the synthesis of *NH*-pyrroles containing even no traces of *N*-vinylpyrroles (GLC).

Notably, some works are known where dichloroethane has been used as a solvent but not as a reactant in the synthesis of pyrroles or in the reaction of the pyrrole ring modification.[13]

As commonly accepted, the pyrrole formation from *O*-vinyl ketoximes proceeds via 3,3-sigmatropic rearrangement (Scheme 3) catalyzed either by superbases[23] or transition-metal complexes[18] or can be realized as formally non-catalytic process (heating at 100 °C in DMSO).[24]

Apparently, the parallel vinylation of ketoximes with vinyl chloride and acetylene, the products of deeper dehydrochlorination of dichloroethane, can contribute to *O*-vinyl ketoximes formation as well. Obviously, the method here devised, being essential modification of the pyrrole synthesis from ketoximes and acetylene,[11] will attract more specialists interested in the pyrrole chemistry, since it does not require the special equipment and safety measures[25] common for the work with free acetylene.

One of the synthesized pyrrolic compounds (Table 1), namely 4,5,6,7-tetrahydroindole **2c**, now available due to this method, has recently been successfully used for the synthesis of 2-substituted