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Synthesis of *O*-2-(acyl)vinylketoximes and their unusual rearrangements into 2- and 3-acyl-substituted pyrroles

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ABSTRACT

O-2-(Acyl)vinylketoximes (freshly prepared from ketoximes and acylacetylenes in the presence of Ph_3P as catalyst in up to 83% yields) rearrange upon heating (125–150 °C) to give 2- or 3-acylpyrroles, wherein the positions of the acyl substituents do not correspond to known *O*-vinyloxime rearrangements; the chemo- and regioselectivity of the rearrangements depend on the reaction conditions. The described rearrangement enables syntheses of previously inaccessible substituted 2- or 3-acylpyrroles.

The discovery of new antibiotics, pheromones, toxins, cell fission inhibitors, and immunomodulating agents bearing the pyrrole motif has stimulated growing interest in the chemistry of functionalized pyrroles.[1] The application of tailor-made functionalized pyrroles has provided breakthroughs in the fields of organic semi-conductors, light-emitting diodes, solar batteries, and nanocomposites.[2] Although a number of protocols for the syntheses of functionally substituted pyrroles have been documented,[3] many are multi-step and require difficult to access and expensive reagents. Therefore, progress towards the synthesis of functionalized pyrroles from routinely available starting materials remains a challenging goal in organic chemistry.

It is known that *O*-vinyloximes, prepared by the vinylation of ketoximes with acetylene,[4] rearrange to pyrroles (the Trofimov reaction)[5] under heating in the presence of the superbase system KOH–DMSO[6] (or non-catalytically).[7] The key step of the reaction involves a [3,3]-sigmatropic rearrangement of an *N*-alkenylhydroxylamine *O*-vinyl ether (the tautomeric form of the *O*-vinyloxime) to an iminoaldehyde which then cyclizes into the pyrrole (after dehydration of the intermediate hydroxypyrroline and prototropic rearrangement of the 3*H*-pyrroles so formed). The same sequence of transformations has been postulated for *O*-vinyloximes bearing an acyl (ester) moiety, which gives 3-acylsubstituted pyrroles on heating.[8]

Herein, we report an unexpected pathway for the transformation of *O*-2-(acyl)vinylketoximes **3a–c**, the representatives of a new family of functionalized *O*-vinyloximes, which were synthesized by the reaction of ketoximes **1a–c** with 1-(2-furyl)-3-phenyl-2-propyn-1-one (**2**) and 10 mol% of triphenylphosphine in CH_2Cl_2 at room temperature over 7 h in yields of up to 83% (Scheme 1).[9]

By analogy with the commonly accepted mechanism,[5–8] one might expect the formation of 3-acylpyrroles (3-benzoyl- or 3-furoylpyrroles) **4** via [3,3]-sigmatropic rearrangements of oximes **3a–c** (Scheme 2).

In reality, *O*-vinyloximes **3a–c** rearranged on heating (125–130 °C, 2 h) to give 2-benzoylpyrroles **5a–c** (Scheme 3)[10] in 12–14% unoptimized yields; pyrroles **4** were not detected at all in the reaction mixtures (^{1}H NMR).

Heating *O*-vinyloxime **3a** in *p*-xylene (138 °C, 4 h) furnished a mixture of the isomeric pyrroles **5a** and **6a** in a ratio of ≈1:2 (total yield 25%, Scheme 4). Separation of pyrroles **5a** and **6a** was difficult and, therefore, the structure of compound **6a**[11] was assigned (unambiguously) by NMR correlation spectroscopy.

When oxime **3a** was heated at a higher temperature (145–150 °C, 10 min) without solvent, 2-benzoyl-5-phenyl-3-furylpyrrole (**5a**) and 2,4-diphenyl-3-furoylpyrrole **7**[12] were isolated from the reaction mixture in a ratio of ≈1:1, the total yield of the products being 25% (Scheme 4). In this case, only a very short reaction time (10 min) was required, whereas extended heating led to resinification. The different outcomes of the reaction (Scheme 4) may be explained by the essentially different reaction conditions. Indeed, the 'solvent-free' reaction resulting in pyrrole **7** occurs in the presence of the strongly polar oxime **3a** which facilitates another mechanism of pyrrole formation triggered by the elimination of an enol (see below, Scheme 7). Interestingly, pyrrole **7** was also detected (^{1}H NMR) in the reaction mixture in a negligible amount (~5%) when oxime **3a** was heated at 125–130 °C.

The structures of the pyrroles were established by 2D NMR spectroscopy (COSY, NOESY, HSQC, HMBC). In ^{1}H and ^{13}C NMR spectra, the values of the chemical shifts corresponded to those of substituted pyrroles.[13] The position of the substituents in the pyrrole ring was determined using 2D HMBC and NOESY spectra (Scheme 5). The values of the direct C–H spin–spin coupling constants of the pyrrole ring ($^1J_{CH}$ = 165.1 Hz for **5a** and **6a** and

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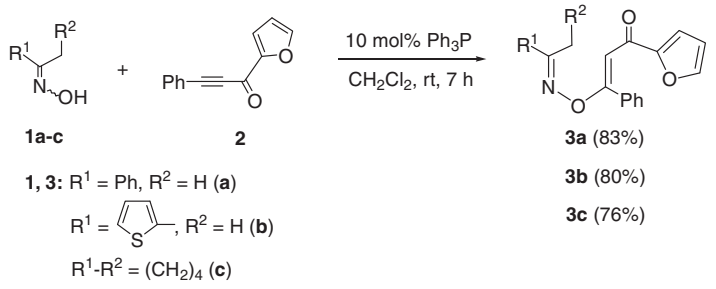
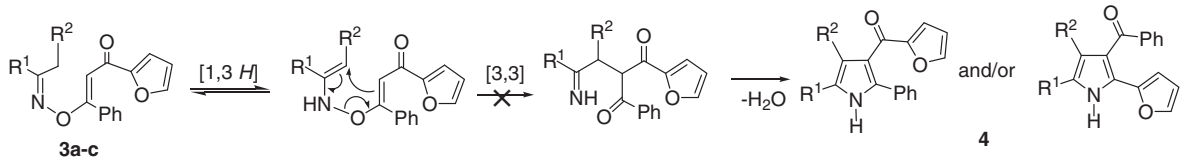
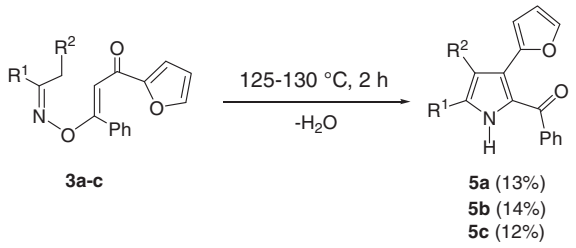


Scheme 1. Synthesis of *O*-2-(acyl)vinylketoximes **3a**–**c**.



Scheme 2. Expected direction of rearrangement of *O*-2-(acyl)vinylketoximes **3a**–**c** to pyrroles **4**.



Scheme 3. Synthesis of 2-benzoylpyrroles **5a**–**c**.

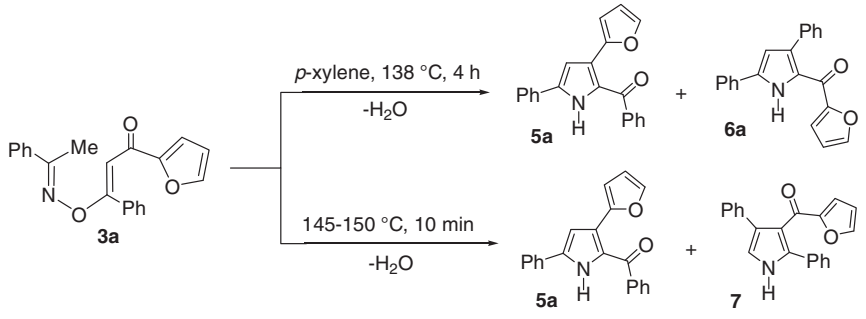
$^1J_{CH}$ = 185.8 Hz for **7**) were in good agreement with those of β- and α-unsubstituted pyrroles, respectively.[14]

The formation of pyrroles **5a–c** is likely to proceed by the rearrangement of oximes **3a–c** into diketones **A**, intramolecular condensation of the latter leading to pyrroles **5a–c** (Scheme 6). This process can be accomplished with the participation of either of the two carbonyl moieties due to free rotation of the 1,3-dicarbonyl fragment around the C(sp^3)–N bond resulting in pyrrole **6a**.

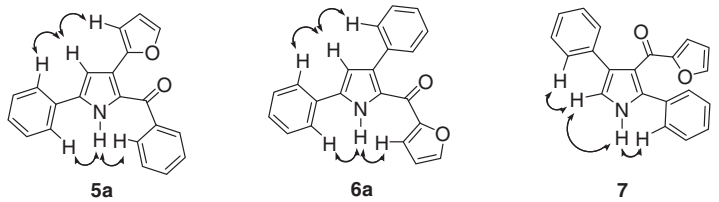
The formation of 3-acyl-substituted pyrrole **7** can be rationalized by the elimination of enol **9** (a tautomer of 1,3-diketone **10**) from oxime **3a** to give azirine **8**. These two intermediates interact at high temperature (145–150 °C) affording aziranyl-1,3-diketone **11**. The latter further rearranges into hydroxypyrroline **12**, which dehydrates and aromatizes to deliver pyrrole **7** (Scheme 7).

The formation of pyrroles from azirines and 1,3-dicarbonyl compounds has been previously described.[15] Generally, such reactions proceed at high temperatures as well as in the presence of either strong bases or metal-complex catalysts.

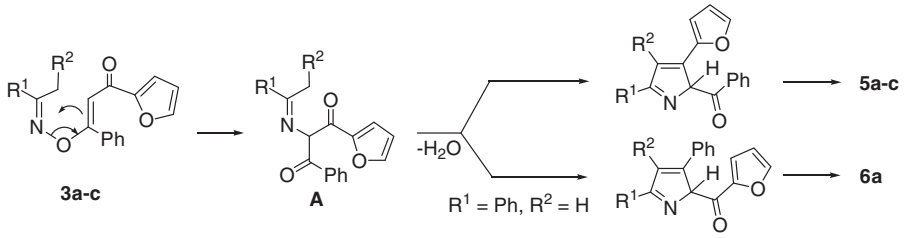
Indirect evidence for the scheme proposed for the formation of pyrrole **7** is the presence of signals at δ 6.7 and δ 16.1 in the ^{1}H NMR spectrum of the reaction mixture, which were assigned to CH= and OH protons of enol **9**.[16]



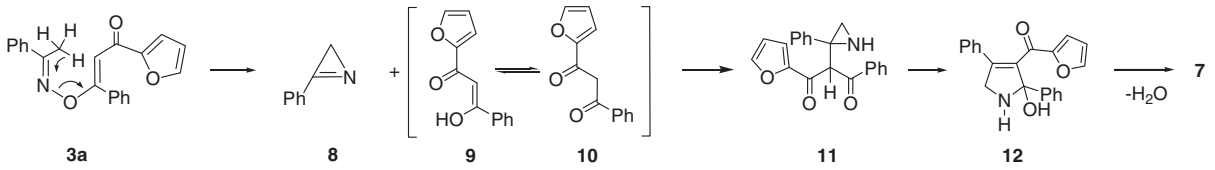
Scheme 4. Synthesis of 2-acylpyrroles (**5a**, **6a**) and 3-acylpyrrole (**7**) from *O*-vinyloxime (**3a**).



Scheme 5. NOESY data for pyrroles **5a**, **6a,** and **7**.



Scheme 6. Tentative mechanism of pyrroles **5a–c** and **6a** formation.



Scheme 7. Tentative mechanism of pyrrole **7** formation.

We have tried to optimize the yields of the pyrroles by thermolysis of oxime **3a** under milder conditions: reflux in benzene (10 h), heating in DMSO (80–85 °C, 10 h), reflux in toluene in the presence of 5 wt % CuBr or 1 wt % $CuOTf_2$ (4 h). However, the reaction mixtures contained mainly enols, acetophenone, and unidentified oligomers, in none of the cases were any pyrroles detected (^{1}H NMR).

In conclusion, unusual rearrangements of *O*-2-(acyl)vinylketoximes lead to 2- or 3-acylsubstituted pyrroles. The positions of the acyl and aryl (hetaryl) substituents on the pyrrole ring are variable depending on the reaction conditions, that is, the reaction can be chemo- and regio-controlled. Despite the modest yields of the pyrroles, these syntheses could find applications (when optimized) for the preparation of unusually functionalized pyrroles, as new and valuable building blocks for advanced technologies, pharmaceuticals, and materials.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.101.

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9. General procedure for the synthesis of *O*-vinyloximes **3a–c**: A mixture of ketoxime **1a–c** (2 mmol), 1-(2-furyl)-3-phenyl-2-propyn-1-one (**2**) (392 mg, 2 mmol), and Ph_3P (52 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 7 h under Ar and then the solution was evaporated. The crystalline products were ground in Et_2O (5 mL) and allowed to stand at −12 → −8 °C overnight. The residue was filtered, dried under vacuum, and recrystallized from hexane.
10. General procedure for the synthesis of pyrroles **5a–c**: *O*-2-(Acyl)vinylketoximes **3a–c** (0.5 mmol) were placed into a vial and heated in an oil bath at 125–130 °C for 2 h. After cooling, the reaction mixture was diluted with Et_2O (5 mL) and separated on Al_2O_3 using Et_2O–hexane (1:3) as eluent.
11. ^{1}H NMR data for (3,5-diphenyl-1*H*-pyrrol-2-yl)(2-furyl)methanone (**6a**): δ_H (400.1 MHz, $CDCl_3$) 6.48 (dd, 1*H*, H^4_{furyl}, ^3J = 3.2 Hz, ^3J = 1.7 Hz), 7.15 (d, 1*H*, $H^4_{pyrrole}$, ^4J = 2.9 Hz), 7.16 (dd, 1*H*, H^3_{furyl}, ^3J = 1.7 Hz, ^4J = 0.8 Hz), 7.35–7.69 (m, 11*H*, Aryl, H^5_{furyl}), 8.73 (br s, 1*H*, NH).
12. Synthesis of (2,4-diphenyl-1*H*-pyrrol-3-yl)(2-furyl)methanone (**7**): *O*-2-(acyl)vinylketoxime **3a** (0.5 mmol) was placed into a vial and heated in an oil bath at 145–150 °C for 10 min without solvent. After cooling, the reaction mixture was diluted with Et_2O (5 mL) and separated on Al_2O_3 using Et_2O–hexane (1:3) as eluent.
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