Synthesis and Properties of *O*-Vinylamidoximes

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Abstract: *O*-Vinylamidoximes **2** are synthesized from amidoximes **1** and acetylene in superbase systems (KOH/DMSO, KOH/NMP, NaOH/CsF/NMP) in a preparative yield of up to 80%. They decompose explosively above 150 °C, being resistant to solvolysis in the KOH/DMSO system (100 °C, 3 h) and to polymerization (AIBN, UV). Trifluoroacetylation of *O*-vinylbenzamidoxime **2b** with $(CF_3CO)_2O$/pyridine gives 5-trifluoromethyl-3-phenyl-1,2,4-oxadiazole (**3**) in 49% yield.

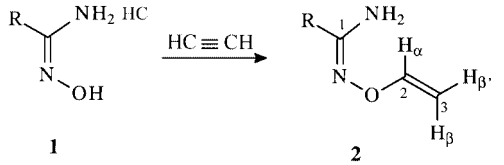
Key words: *O*-vinylamidoximes, amidoximes, acetylene, heterocycle, superbase, vinylation, trifluoroacetylation

The *O*-vinyloxime heteroconjugated system CH_2=CHON=, in spite of its high synthetic potential[1–7] and theoretical challenge[8,9] (are the double bonds p-conjugated through the two heteroatoms?), remains understudied due to the lack of corresponding preparative methods for their synthesis. It is known[1–5] that in the presence of superbases such as KOH/DMSO ketoximes with acetylene form *O*-vinylketoximes. As far as amidoximes are concerned, there are only scarce data on their nucleophilic addition to acetylenes in the literature.[10,11]

Meanwhile, *O*-vinylamidoximes have a promising synthetic potential, particularly for heterocyclic chemistry. Indeed their acid-catalyzed cyclization to yield 3-substituted-5-methyl-4,5-dihydro-1,2,4-oxadiazoles is capable of further aromatization. When catalyzed by optically active acids (e.g., camphorsulfonic acid), this cyclization may lead to the dihydrooxadiazoles enriched with one enantiomer, apparently useful as ligands in asymmetric catalysis. By analogy to the rearrangement of *O*-vinylketoximes to pyrroles,[1,2] *O*-vinylamidoximes are expected to open a new general access to imidazoles. Rearrangement of such a type admittedly was observed in the imidazole synthesis from amidoximes and propiolic esters.[10] Imidazole *N*-oxide derivatives are anticipated to be prepared through the oxime-nitrone rearrangement followed by cyclization. Also, as exemplified below in this paper, *O*-vinylamidoximes are prone to acylation (e.g., trifluoroacetylation) at the amino group to furnish, after [3,3] sigmatropic rearrangement of an intermediate, trifluoromethyl oxadiazoles easily, which are otherwise inaccessible by other ways.

Recently, in an attempt to obtain imidazole derivatives by analogy to pyrrole synthesis,[1–4] we have found[12] that acetamidoxime **1a** and benzamidoxime **1b** react unusually fast with acetylene (5–7 min, 75 °C) under pressure (12–14 atm) in the KOH/DMSO/DS superbase system to formo-vinylamidoximes **2a** and **2b** in 26% and 59% yields, respectively.

In this paper, we wish to report in detail on peculiarities of the amidoxime vinylation and a general facile synthetic route to *O*-vinylamidoximes **2** (Scheme 1). The effect of the reaction conditions on the yield of *O*-vinylamidoxime **2b** from benzamidoxime **1b** in *N*-methylpyrrolidone (NMP) can be seen from the Table.



R = Me (**a**), Ph (**b**), 2-F-C_6H_4 (**c**)

Scheme 1

Table Vinylation of Benzamidoxime **1b**[a]

M	Temp (°C)	Time (min)	HPLC Yield (%) of **2b**[b]
Na	73	~ 5–7	~1
Na	100	~ 5–7	11
Na (+CsF)[c]	100	~ 5–7	89 (74)
Na (+CsF)[c]	100	30	(73)
K	100	~ 5–7	84 (74)
K	100	30	71 (65)
K[d]	72	~ 5–7	(80)

[a] Initial acetylene pressure 15–16 atm, 50 mL of NMP, 23 mmol of oxime **1b**, 20 mmol of MOH.
[b] Isolated yields are given in parenthesis.
[c] Equimolar mixture of NaOH and CsF.
[d] In DMSO.

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The experimental procedure involved the vinylation of benzamidoxime **1b** in an autoclave in superbase system MOH/NMP (M = Na, K, Cs) followed by microcolumn reverse phase high performance liquid chromatography (RP HPLC) analysis of the reaction mixture. In some cases *O*-vinylbenzamidoxime **2b** was simultaneously isolated by preparative extraction with diethyl ether.

As the Table shows, NaOH catalyzes the reaction only slightly. At 73 °C, the target product **2b** is observed in the reaction mixture only in a trace amount. At the vinylation temperature of 100 °C, the product yield increases only up to 11%. Enhancement of the catalytic system basicity by the in situ generation of CsOH from the NaOH/CsF exchange at 100 °C leads to an excellent yield (89%) for just 5–7 min. With KOH as a catalyst at 100 °C, the yield is 84% for the same very short time. Such an instant vinylation is both peculiar and essential: at a longer duration (30 min) the yield of **2b** drops to 71%, obviously due to instability of both the starting amidoxime and the product.

The yield of *O*-vinylamidoximes is strongly temperature dependent (Figure). Thus, in the vinylation of **1b**, a temperature increase from 73 °C to 83 °C leads to a 6-fold yield gain (Figure, curve 1). The highest yield of **2b** (82–84%) is attained in the 90–100 °C range.

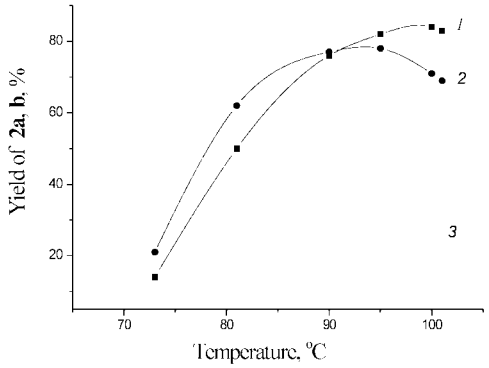


Figure Temperature dependence of theyield of *O*-vinylamidoxime (1. **2b**, KOH/NMP, 5–7 min; 2. **2b**, KOH/NMP, 30 min; 3. **2a**, KOH/DMSO, 5–7 min)

This subtle response of the yield of *O*-vinylamidoximes to the vinylation conditions is due to side reactions of deoximation and alkaline hydrolysis of amidoximes. Previously[5] we have shown that in the acetoxime vinylation, even trace amounts of water in alkali-NMP system do cause hydrolytic processes.

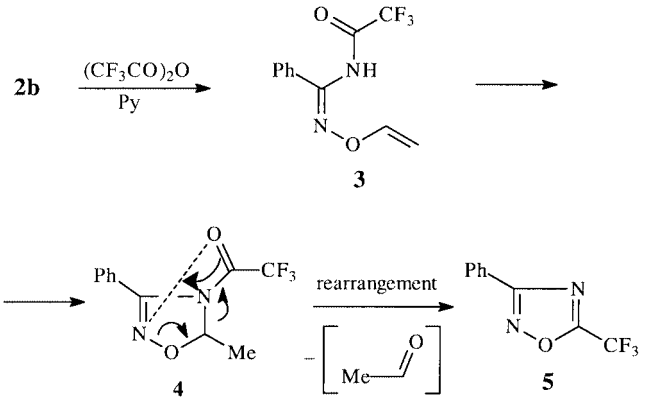
For the acetamidoxime **1a** vinylation in the KOH/DMSO system (Figure, curve 3) the highest yield of *O*-vinylacetamidoxime **2a** (46%) is obtained within 73–85 °C, thus indicating that the deoximation and hydrolysis are more pronounced in this case.

The vinylation of *o*-fluorobenzamidoxime **1c** in the KOH/DMSO system (74–77 °C, 5–7 min) is accompanied by resinification to give 21% yield of **2c**, seemingly owing to the fluorine solvolysis with the superbase.

O-Vinylamidoximes **2a** and **2b** are stable up to 150 °C, above this temperature they decompose with explosion. The products of explosive decomposition isolated from the solution in methanol are oligomers (20–26% yield, MM 400–450) with the element composition different from that of the initial monomers.

O-Vinylbenzamidoxime **2b** turned out to be resistant to the superbase KOH/DMSO system (100 °C, 3 h). The recovered **2b** was just slightly contaminated (< 5%) by the products of its polymerization, hydrolysis and deoximation (benzamide). Attempts to polymerize **2b** polymerization were unsuccessful: the monomer was completely recovered after both boiling in benzene (6 h) in the presence of azoisobutyronitrile (AIBN) and UV-irradiation (4 h).

O-Vinylamidoximes readily react with trifluoroacetic anhydride in the presence of pyridine at room temperature in diethyl ether. Thus from **2b**, 5-trifluoromethyl-3-phenyl-1,2,4-oxadiazole (**5**) is obtained in 49% yield (non-optimized). Unlike the trifluoroacetylation of *O*-vinylketoximes,[6,7] *O*-vinylamidoximes appear to get attacked by trifluoroacetyl cation first at the amide group nitrogen atom to give the intermediate **3**, which seemingly cyclizes to oxazoline **4**, further rearranging to **5** (Scheme 2). Apparently, a driving force of the rearrangement is the aromatization energy gain.



Scheme 2

The intermediate **3** was identified in the reaction mixture by ^{1}H NMR spectroscopy. The structure of oxadiazole **5** follows from its ^{1}H, ^{13}C and ^{15}N NMR spectra and the patterns of the electron impact-induced fragmentation.

^{1}H (400.13 MHz), ^{13}C (100.69 MHz) and ^{15}N (40.55 MHz) NMR spectra were run on a Bruker DPX 400 spectrometer in $CDCl_3$ with HMDS as internal standard. IR spectra were recorded on a Bruker IFS 25 instrument. Mass spectra were run on an LKB 2091 CLC-MS spectrometer, ionization energy 60 eV, capillary column 38 m long, SB-5 phase, isothermal conditions, column temperature 40 °C, ion source temperature 200 °C. Chromatographic analysis was performed using RP HPLC[13] on a Milikhrom A-02 microcolumn liquid chromatograph (l = 75 mm, d = 2 mm, Nucleosil 100-5 C18 AB, 5000–6000 theoretical plates, chrysene peak as reference). Eluents were: (A) aqueous buffer K_2HPO_4 or NaOAc solutions (1–

0.5 mM, pH 2.5–7.0); (B) MeCN or MeOH; isocratic or gradient elution at a rate of eluent discharge 0.15–0.2 mL/min, column temperature 35 °C, simultaneous photometric detection at 210, 226 and 260 nm, volume of the sample introduced into the column: 2–5 μL.

The amidoximes **1** were prepared by a known procedure.[14] Commercial grade DMSO, NMP (Merck, < 0.2% H_2O), NaOH (< 2% H_2O), KOH (~ 15% H_2O) and CsF (ABCR, 99 +%) were used in the experiments.

Vinylation of Acetamidoxime 1a; *N'*-(Vinyloxy)ethanimidamide (2a); Typical Procedure

A steel 1 L rotating autoclave was charged with **1a** (1.85 g, 25 mmol), KOH (2.25 g, 34.6 mmol) and DMSO (50 mL). The mixture was saturated with acetylene up to 15–16 atm and heated for 30 min to 79 °C (during this process the maximum acetylene pressure in the autoclave approached ~ 35 atm). Then the heating was immediately ceased and the autoclave furnace was opened (the reaction time at the above temperature was ~ 5–7 min). After cooling to r.t., the mixture was discharged, neutralized with solid CO_2, diluted with H_2O to 100 mL and extracted with Et_2O (4 × 20 mL). The collected Et_2O extracts were washed with H_2O (3 × 10 mL), dried ($MgSO_4$) and filtered. The filtrate was passed through an Al_2O_3 column (30 × 3). Evaporation of the solvent at reduced pressure gave 1.16 g of **2a**; yield: 46%; colorless oil; n_D^{20} 1.5682.

IR (neat, cm^{-1}): 3475s, 3340s (ν NH_2), 3085s (ν $=CH_2$), 1655vs (ν C=N), 1630s, 1615s (ν C=C), 1190s (δ C–O), 1170m (ν C–N), 960m (δ CH=CH), 835m cm^{-1} (δ $=CH_2$).

^{1}H NMR: δ = 6.72 (dd, 1 H, -α, $^3J_{\alpha\text{-}\beta}$ = 14.0 Hz, $^3J_{\alpha\text{-}\beta'}$ = 6.8 Hz), 4.62 (br s, 2 H, NH_2), 4.55 (dd, 1 H, H-β, $^3J_{\alpha\text{-}\beta}$ = 14.0 Hz, $^2J_{\beta\text{-}\beta'}$ = 1.6 Hz), 4.01 (dd, 1 H, H-β′, $^3J_{\alpha\text{-}\beta'}$ = 6.8 Hz, $^2J_{\beta\text{-}\beta'}$ = 1.6 Hz), 1.85 (s, 3 H, CH_3).

^{13} NMR (100.69 MHz): δ = 153.44 ($^1J_{1\text{-Me}}$ 52.6 Hz, C-1), 153.23 ($^1J_{2\text{-}3}$ 80.2 Hz, C-2), 85.70 ($^1J_{2\text{-}3}$ 80.2 Hz, C-3), 16.55 (CH_3).

Anal. Calcd for $C_4H_8N_2O$: C, 47.99; H, 8.05; N, 27.98. Found: C, 47.88; H, 8.33; N, 28,01.

***N'*-(Vinyloxy)benzenecarboximidamide (2b)**

Following the typical procedure for the preparation of **2a**, compound **1b** (3.13 g, 23 mmol) was reacted with acetylene (initial acetylene pressure 16 atm) for ~ 5–7 min in the presence of KOH (1.35 g, 20.7 mmol) in DMSO (50 mL) at 72 °C; yield: 2.99 g (80%); colorless oil; n_D^{20} 1.5806.

IR (neat, cm^{-1}): 3490s, 3390s (ν NH_2), 1645vs (ν C=N), 1620m (δ NH_2), 1600s (ν C=C), 1185s (ν C–O), 960m (δ CH=CH), 845m (δ $=CH_2$).

^{1}H NMR: δ = 6.88 (dd, 1 H, H-α, $^3J_{\alpha\text{-}\beta}$ = 14.0 Hz, $^3J_{\alpha\text{-}\beta'}$ = 6.8 Hz), 4.95 (br s, 2 H, NH_2), 4.66 (dd, 1 H, H-β, $^3J_{\alpha\text{-}\beta}$ = 14.0 Hz, $^2J_{\beta\text{-}\beta'}$ = 1.6 Hz), 4.13 (dd, 1 H, H-β′, $^3J_{\alpha\text{-}\beta'}$ = 6.8 Hz, $^2J_{\beta\text{-}\beta'}$ = 1.6 Hz).

^{13}C NMR: δ = 154.37 ($^1J_{1\text{-}ipso}$ = 65.7 Hz, C-1), 153.23 ($^1J_{2\text{-}3}$ = 80.2 Hz, C-2), 133.08 ($^1J_{1\text{-}ipso}$ = 65.7 Hz, C_{ipso}), 130.70 ($^1J_{para\text{-}meta}$ 55.4 Hz, C_{para}), 129.07 ($^1J_{meta\text{-}ortho}$ 56.4 Hz, C_{meta}), 126.91 ($^1J_{ortho\text{-}ipso}$ 58.8 Hz, C_{ortho}), 87.36 ($^1J_{2\text{-}3}$ = 80.2 Hz, C-3).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.86; H, 6.28; N, 27.10.

2-Fluoro-*N'*-(vinyloxy)benzenecarboximidamide (2c)

Prepared following the typical procedure and using the same conditions as for **2b**;

Yield: 21%; colorless oil; n_D^{20} 1.5818.

^{1}H NMR: δ = 7.65–7.00 (m, 4 H_{arom}), 6.80 (dd, 1 H, H-α, $^3J_{\alpha\text{-}\beta}$ = 14.0 Hz, $^3J_{\alpha\text{-}\beta'}$ = 6.8 Hz), 5.19 (br s, 2 H, NH_2), 4.60 (dd, 1 H, H-β, $^3J_{\alpha\text{-}\beta}$ = 14.0 Hz, $^2J_{\beta\text{-}\beta'}$ = 1.6 Hz), 4.05 (dd, 1 H, H-β′, $^3J_{\alpha\text{-}\beta'}$ = 6.8 Hz, $^2J_{\beta\text{-}\beta'}$ = 1.6 Hz).

Anal. Calcd for $C_9H_9FN_2O$: C, 59.99; H, 5.03; F, 10.54; N, 15.10. Found: C, 60.06; H, 5.28; F 10.51; N, 15.10.

5-Trifluoromethyl-3-phenyl-1,2,4-oxadiazole (5)

To a stirred mixture of **2b** (0.80 g, 5 mmol), pyridine (0.79 g, 10 mmol) and Et_2O (10 mL) was added trifluoroacetic anhydride (2.10 g, 10 mmol) during 40 min at r.t. The mixture was stirred for 1.5 h more and neutralized with aq $NaHCO_3$ solution. The Et_2O layer was separated, the aqueous layer was extracted with Et_2O and the combined Et_2O extracts combined were dried ($MgSO_4$). After distilling off the solvent, the product was purified by column chromatography (Al_2O_3, hexane) to give 0.52 g (49%) of **5** in 49% yield; light-yellow crystals; mp 62–64 °C.

^{1}H NMR: δ = 8.08 (m, 2 H, H_{ortho}), 7.56 (m, 1 H, H_{para}), 7.50 (m, 2 H, H_{meta}).

^{13}C NMR: δ = 169.51 (C-3), 166.15 (C-5), 116.35 (CF_3), 132.54 (C_{para}), 129.42 (C_{ortho}), 128.03 (C_{meta}), 125.27 (C_{ipso}).

^{15}N NMR (40.55 MHz): δ (with respect to NH_3) = 361.3 (N-2), 245.90 (N-4). Its ^{15}N chemical shifts correspond to the structure of 1,2,4-oxadiazole.[15]

MS: *m*/*z* (%) = 215 (M^+, 12%), 214 [$(M - H)^+$, 100] 145[$(M - H - CF_3)^+$, 34] 119, (59), 91 (52), 103 (PhCN, 15%), 77 (Ph, 45), 69 (CF_3, 90).

Anal. Calcd for $C_9H_5F_3N_2O$: C, 50.48; H, 2.35; F, 26.62; N, 13.08. Found: C, 50.16; H, 2.33; F 26.52; N, 13.09.

Evaluation of Thermal Stability of *O*-Vinylamidoximes 2a,b

A sample of *O*-vinylamidoxime **2a,b** (0.35 g) sealed in a 1.5-mL glass ampoule was placed in a brass case with a capillary opening to discharge excess pressure and heated (bath, silicone oil) by raising the temperature at the rate of 4 °C/min. After explosion, the heating was stopped and the case was allowed to reach r.t. A mixture of finely dispersed glass fragments and a dark-brown powdery product was collected and treated with MeOH (5 mL) and decanted. This was repeated twice to completely recover the product. After evaporation of MeOH and drying, the product (well soluble in MeOH, EtOH and moderately soluble in $CHCl_3$, DMSO) was obtained and further analyzed.

O-Vinylacetamidoxime **2a** exploded at 152 °C to give 0.09 g (26%) of oligomers (Mol. mass 400).

IR (film, cm^{-1}): 3176s (ν $CONH_2$), 2880–2960s (ν CH_3,CH_2), 2220w (ν C≡N), 1669vs (ν C=N), 1420s (δ H–C=), 1106m (ν C–O). Broadened bands, high background. Absorption bands were assigned according to Ref.[16]

Anal. Found: C, 64.4; H, 7.1; N, 14.3.

O-Vinylbenzamidoxime **2b** exploded at 153 °C to give 0.07 g (20%) of oligomers (Mol. mass 450).

IR(film, cm^{-1}): 3161vs (ν $CONH_2$), 3064s (ν CH), 2924s (ν C_2), 2228w (ν C≡N), 1666vs (ν C=N), 1650s, 1606s, 1580s (ν C=C), 1468w (δ CH_2), 1416w (δ H–C=), 1106 m (ν C–O), 775s, 751s, 710s, 693s (δ, benzene ring). Broadened bands, high background, assigned according to Ref.[16]

Anal. Found: C, 66.7; H, 6.2; N, 17.3.

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