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Cascade reactions of captodative formyl(amino)alkenes with N,O-binucleophiles

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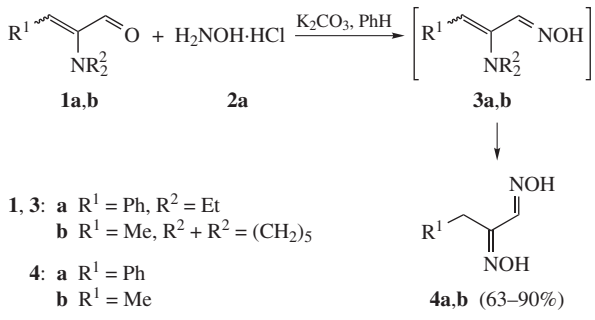
Captodative formyl(amino)alkenes react with N,O-binucleophiles in a cascade fashion to result mainly in dioximes (in the case of hydroxylamine) or oxazoline derivatives (in the case of 2-amino-2-methylpropanole).

Captodative carbonyl-bearing aminoalkenes are attractive and versatile polyfunctional building blocks in the synthesis of organic and bioorganic molecules.[1] Recently, we found an unexpected transformation of cross-conjugated formyl(amino)-alkenes under the action of nucleophiles. On the basis of these reactions, a general method for the one-pot synthesis of the derivatives of N,N-disubstituted α-amino acids[2–5] and α-amino- or α-hydroxy ketones[6] has been developed.

Because tertiary α-amino acids and their derivatives display significant biological activities,[7,8] the further development of

this synthetic methodology of the construction of an α-amino carbonyl moiety is of considerable current interest. The chemistry of captodative carbonyl-bearing aminoalkenes allows us to assume that they could be used as valuable precursors in the synthesis of heterocyclic systems. We report preliminary results of the reaction of formyl(amino)alkenes **1a–c** with N,O-binucleophiles.



Scheme 1

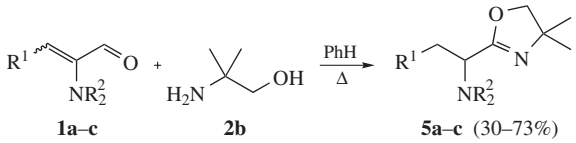
Initially, we performed the reaction with hydroxylamine since it provided a model reaction of initial substrates **1** with bidentate nucleophiles. We found that, like primary amines, the treatment of captodative formyl(amino)alkenes **1a**,**b** with two equivalents of hydroxylamine hydrochloride **2a** in the presence of K_2CO_3 proceeded exclusively at the formyl group; expected bis(oximes) **4a**,**b** were isolated in good yields under such conditions (Scheme 1).† Note that (i) according to ^{1}H NMR spectrum of the reaction mixture when the stoichiometry of **1**:**2a** was reduced from 1:2 to 1:1 the sole product observed was dioxime **4**, (ii) according to ^{1}H and ^{13}C NMR spectroscopy, dioximes **4** exist in two forms; because their relation depends on the solvent nature, it is reasonable to assume that we are dealing with the *syn*- and *anti*-forms of these oximes.

Bis(oxime) formation can be easily explained by the hydrolysis of oxime **3a**,**b** (as enamine) resulting at the first step which usually occurs very easily under strong basic conditions.[9] The following condensation of the oxo derivative with an excess of the nucleophile leads directly to dioximes **4a**,**b**.

We studied the effects of N,O-binucleophiles bearing a primary amino group. Ethanolamine and substituted ethanolamines were involved in the reaction with *gem*-formyl(amino)alkenes **1a–c**. These reactions lead always to complex mixtures of products even under mild conditions. The best results were obtained when 2-amino-2-methylpropanol **2b** was used as a binucleophile. In this case, corresponding oxazoline derivatives **5a–c** were isolated as major reaction products (Scheme 2).

We studied the nucleophilic reactions of captodative formyl(amino)alkenes from the mechanistic point of view and showed that the reactions of *gem*-formyl(amino)alkenes with soft nucleophiles occur as a non-trivial cascade of tautomeric transformations.[4,5] Evidently, the synthesis of oxazolines **5a–c**‡ is a multistep process, which occurs *via* the 1,2-addition. The following isomerization of intermediate adduct **6** into stable enamine **7** and further keto-enol tautomerization gives corresponding amide **8**. Their intramolecular cyclization leads to oxazoline derivative **5**. A similar synthesis of oxazolines from amides is well known.[10,11] An alternative sequence of transformations of captodative formyl(amino)alkenes involves the formation of azomethine **9** as an intermediate. Low-intensity signals of azomethine protons (7.2–8.2 ppm) are present in the ^{1}H NMR spectra of the reaction mixtures. Moreover, the reaction of non-substituted 3-phenylacrylaldehyde with ethanolamine leads to the formation of only an azomethine derivative.[12] The geometry of intermediate **9** is favourable for an O-nucleophilic attack on the new electrophilic centre. Therefore, it can be assumed that, under the reaction conditions, initially formed azomethine **9** undergoes intramolecular cyclization to give heterocyclic derivative **10**. The following double migration of the double bond leads finally to oxazoline derivatives **5a–c** (Scheme 3).

Unfortunately, an unambigous choice between these two alternative sequences is difficult for the present time.



Scheme 2

† The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer at room temperature. IR spectra were measured on a Specord 75 IR spectrometer. MS and GC/MS analyses (EI, 70 eV) were performed on a Hewlett-Packard HP 5971A instrument.

Dioxime **4a**. 2-(Diethylamino)-3-phenylacrylaldehyde **1a** (1.0 g, 5 mmol), hydroxylamine hydrochloride **2a** (0.7 g, 10 mmol) and K_2CO_3 (0.7 g, 5 mmol) in benzene (15 ml) were refluxed for 2 h. After filtration and evaporation of the solvent, product **4a** was isolated (0.8 g, 90%); mp 163 °C (THF) (lit.,[13] mp 163 °C; lit.,[14] 160–161.5 °C). ^{1}H NMR (1.2:1 mixture of two isomers) δ: (major isomer): 3.87 (s, 2H), 7.10–7.35 (m, 5H), 7.70 (s, 1H), 11.52 (s, 1H), 11.74 (s, 1H); (minor isomer): 3.72 (s, 2H), 7.10–7.35 (m, 5H), 8.27 (s, 1H), 11.38 (s, 1H), 11.81 (s, 1H). ^{13}C NMR, δ: (major isomer): 29.20 (CH_2), 126.07, 128.31, 128.62, 137.16 (Ph), 147.02 (CH=N), 153.78 (C=N); (minor isomer): 35.72 (CH_2), 126.19, 128.27, 128.70, 138.35 (Ph), 139.65 (CH=N), 150.48 (C=N). IR (ν/cm^{-1}): 3280 (OH), 1628 (C=N), 945 (N–O). MS (EI), *m*/*z*: 178 (43, [M]$^+$), 161 (13), 144 (38), 117 (76), 91 (100).

Dioxime **4b**. 2-Piperidino-2-butenal **1b** (2.3 g, 15 mmol), hydroxylamine hydrochloride **2a** (2.1 g, 30 mmol) and K_2CO_3 (2.1 g, 15 mmol) in benzene (20 ml) were stirred at room temperature for 5 days and treated with water. Ether extracts were dried ($MgSO_4$). The solvent was evaporated to give 1.1 g (63%) of dioxime **4b**, which was purified by vacuum sublimation; mp 126–127 °C (lit.,[14] mp 127–128 °C). ^{1}H NMR (10:1 mixture of two isomers) δ: (major isomer): 1.03 (t, 3H, *J* 7.5 Hz), 2.50 (q, 2H, *J* 7.5 Hz), 7.60 (s, 1H), 11.50 (br. s, 2H); (minor isomer): 1.09 (t, 3H, *J* 7.5 Hz), 2.42 (q, 2H, *J* 7.5 Hz), 8.27 (s, 1H), 11.50 (br. s, 2H). ^{13}C NMR, δ: (major isomer): 10.61 (Me), 16.83 (CH_2), 146.71 (CH=N), 156.76 (C=N); (minor isomer): 11.87 (Me), 23.27 (CH_2), 139.68 (CH=N), 152.14 (C=N). IR (ν/cm^{-1}): 3310 (OH), 1630 (C=N), 945 (N–O). MS (EI), *m*/*z*: 116 (9, [M]$^+$), 99 (75), 44 (100).

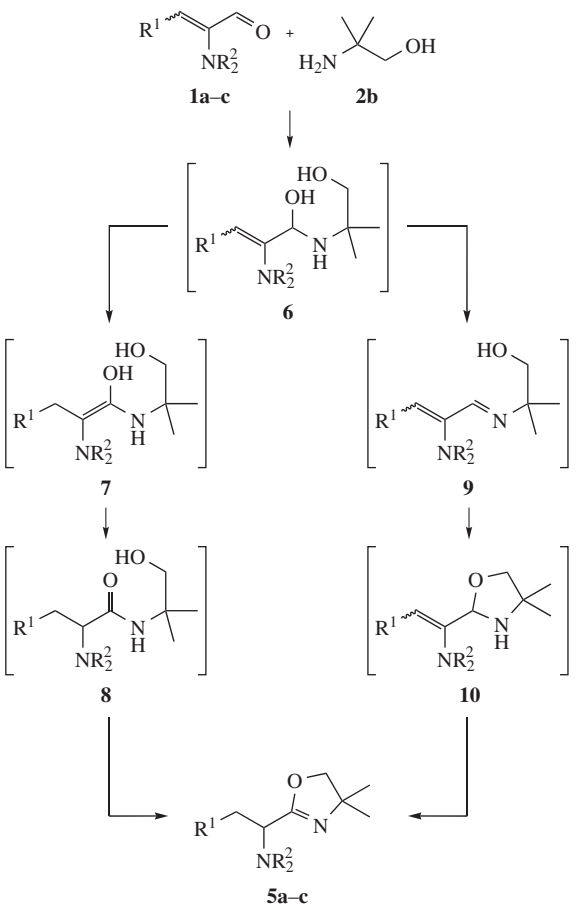
‡ *Typical experimental procedure for the preparation of* N-*[1-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2-phenylethyl]*-N,N-*diethylamine* **5a**. The mixture of 2-(diethylamino)-3-phenylacrylaldehyde **1b** (2.0 g, 10 mmol) and 2-amino-2-methylpropanol **2b** (0.90 g, 10 mmol) in benzene was refluxed for 2 h. The solvent was evaporated, and pure compound **5a** (1.4 g, 51%) was obtained by vacuum distillation.

^{1}H NMR ($CDCl_3$) δ: 1.02 (t, 6H, *J* 7.3 Hz), 1.05, 1.20 (2s, 6H), 2.50–2.80 (m, 4H), 2.90–3.10 (m, 2H), 3.67 (dd, 1H, *J* 9.1 and 6.3 Hz), 3.81 (s, 2H), 7.10–7.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 13.61 (Me), 28.52 (C*Me*$_2$), 36.77 (CH_2), 44.41 (NCH_2), 60.22 (CHN), 66.91 (*C*Me$_2$), 78.55 (CH_2O), 126.20, 128.15, 129.54, 139.02 (Ph), 164.32 (C=N). IR (ν/cm^{-1}): 1647 (C=N). MS, *m*/*z* (%): 203 (58), 183 (100), 91 (65). Found (%): C, 74.75; H, 9.37; N, 10.18. Calc. for $C_{17}H_{26}N_2O$ (%): C, 74.41; H, 9.55; N, 10.21.

Oxazoline derivatives **5b**,**c** were prepared by the above procedure and purified by preparative GLC.

1-[1-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)propyl]piperidine **5b**. ^{1}H NMR ($CDCl_3$) δ: 0.89 (t, 3H, *J* 7.3 Hz), 1.26, 1.29 (2s, 6H), 1.35–1.60 (m, 6H), 1.65–1.80 (m, 2H), 2.40–2.60 (m, 4H), 3.07 (dd, 1H, *J* 7.3 and 5.8 Hz), 3.90 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 11.11 (Me), 23.21 (CH_2), 24.95, 26.66 [$N(CH_2)_2$], 28.25 (C*Me*$_2$), 51.33 (NCH_2), 65.25 (CHN), 67.10 (*C*Me$_2$), 78.66 (CH_2O), 164.65 (C=N). IR (ν/cm^{-1}): 1634 (C=N). MS, *m*/*z* (%): 224 (<1, M$^+$), 195 (5), 141 (21), 126 (100). Found (%): C, 70.06; H, 10.89; N, 12.62. Calc. for $C_{13}H_{24}N_2O$ (%): C, 69.60; H, 10.78; N, 12.49.

1-[1-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)propyl]morpholine **5c**. ^{1}H NMR ($CDCl_3$) δ: 0.91 (t, 3H, *J* 7.3 Hz), 1.28, 1.29 (2s, 6H), 1.65–1.80 (m, 2H), 2.50–2.65 (m, 4H), 3.08 (dd, 1H, *J* 8.8 and 6.2 Hz), 3.65–3.75 (m, 4H), 3.92 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 10.87 (Me), 22.74 (CH_2), 28.91 (C*Me*$_2$), 50.52 (NCH_2), 63.17 (*C*Me$_2$), 67.23 (CHN), 67.52 [$(CH_2)_2O$], 78.77 (CH_2O), 163.95 (C=N). IR (ν/cm^{-1}): 1653 (C=N). MS, *m*/*z* (%): 197 (2), 141 (27), 126 (100). Found (%): C, 63.19; H, 9.80; N, 12.17. Calc. for $C_{12}H_{22}N_2O_2$ (%): C, 63.69; H, 9.80; N, 12.38.



Scheme 3

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