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The Reactions of β-Amino Enones with Hydroxylamine

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Synopsis. The reactions of *N*-substituted β-amino enones with hydroxylamine give two isoxazole isomers. The ratio of these isomers changes with the electron-withdrawing effect of the *N*-substituents.

Previously, we reported the synthesis of β-amino enones, such as 1-substituted 3-amino-2-buten-1-ones, from 3,5-dimethylisoxazole *via* 5-substituted 3-methylisoxazoles by hydrogenolysis.[1] These β-amino enones are isoelectronic with the β-diketones. Although the β-diketones exhibit behavior similar to keto and enol tautomers, the β-amino enones exhibit mainly behavior similar to amino derivatives of enones. Therefore, the reactions of β-amino enones with nucleophiles are quite interesting. Grignard reactions with β-amino enones give β-alkylated enones.[2] Also Kashima *et al.* have reported the regioselective reaction of β-amino enones with *N*-monosubstituted ureas to give 1-substituted 2(1*H*)-pyrimidinones.[3]

In the literature, it has been reported that 3,5-unsubstituted isoxazoles can be prepared from the corresponding β-amino enones and hydroxylamine.[4] However, the regioselectivity of β-amino enones in the reaction with hydroxylamine has never been reported. The reactions of 1-substituted 3-amino-2-buten-1-ones with hydroxylamine to give 3,5-disubstituted isoxazoles are presented here.

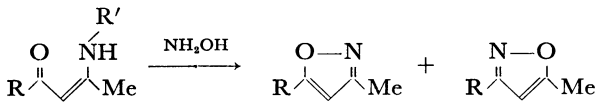
When a mixture of 5-amino-4-hexen-3-one (**4**) and hydroxylamine hydrochloride is refluxed in ethanol in the presence of potassium carbonate, two products, 3-ethyl-5-methyl- (**7a**) and 3-methyl-5-ethylisoxazole (**7b**) are expected. However, the only product was **7b** no trace of **7a** was detected in the NMR spectrum. These results suggest that the amino group of the hydroxylamine attacked the C-5 position of the amino enones as in Michael addition, and then the adducts were cyclized to isoxazoles by deamination and dehydration.

Here, the reactivity of the nucleophiles with the enones is considered to reflect the electron density at the reaction site. Fortunately, the electron densities of β-amino enones can be varied due to the electron-withdrawing effect of the acyl group on the nitrogen atom.[5] When 5-(methoxycarbonylamino)-4-hexen-3-one (**5**) and 5-(trichloroacetamido)-4-hexen-3-one (**6**) were treated with hydroxylamine under the same conditions, a mixture of **7a** and **7b** was obtained. The product ratio a/b from **6** is 3.0, while from **5** it is 0.5. From these results, it can be concluded that the product ratio a/b increases with an increase in the electron-withdrawing effect of the *N*-substituents (R′).

Furthermore, various β-trichloroacetamido enones, 5-(trichloroacetamido)-1-phenyl-4-hexen-3-one (**8**), 5-(trichloroacetamido)-2,2-dimethyl-4-hexen-3-one (**10**) and 3-trichloroacetamido-1-phenyl-2-buten-1-one (**13**), were treated with hydroxylamine to give the corresponding isoxazoles, **9**, **11**, and **14**, respectively. As shown in Table, the results suggest that as the substituents, R, become more bulky, the product ratio a/b decreases.

TABLE.

β-Amino-enoes	Isoxazoles	Yield	Ratio **a/b**
1	3	59	—
2	3	50	—
4	7	47	0
5	7	81	0.50
6	7	45	3.0
8	9	40	0.82
10	11	46	0
12	14	86	0
13	14	43	0



1 R=Me, R′=H
2 R=Me, R′=$COCCl_3$
4 R=Et, R′=H
5 R=Et, R′=COOMe
6 R=Et, R′=$COCCl_3$
8 R=CH_2CH_2Ph, R′=$COCCl_3$
10 R=*t*-Bu, R′=$COCCl_3$
12 R=Ph, R′=H
13 R=Ph, R′=$COCCl_3$

b

3 R=Me
7 R=Et
9 R=CH_2CH_2Ph
11 R=*t*-Bu
14 R=Ph

a

Experimental

Materials. Using known methods, 4-amino-3-penten-2-one (**1**),[6] 3-amino-1-phenyl-2-buten-1-one (**12**)[7] and 5-(methoxycarbonylamino)-4-hexen-3-one (**5**)[5] were prepared. *N*-Acylated derivatived were also prepared from the corresponding β-amino enones and acyl chloride in pyridine.[5]

5-Amino-4-hexen-3-one (4). By hydrogenolysis in ethanol in the presence of platinum, **4** was prepared from 3-methyl-5-ethylisoxazole, recrystallized from hexane, mp 62—63 °C; yield 69%; NMR ($CDCl_3$): δ 1.18 (t, 3H, J=4.0 Hz), 1.91 (s, 3H), 2.26 (q, 2H, J=4.0 Hz), 4.99 (s, 1H), 6.2 ppm (broad s, 1H).

Found: C, 63.78; H, 9.64; N, 12.22%. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38%.

4-(Trichloroacetamido)-3-penten-2-one (2). From **1** and trichloroacetyl chloride, **2** was prepared and recrystallized from hexane, mp 74.5—75.5 °C; yield 64%; IR (KBr): 1740, 1645, 1615, 1480 cm^{-1}: NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.43 (s, 3H), 5.59 (s, 1H), 13.5 ppm (broad s, 1H).

Found: C, 34.32; H, 3.23; N, 5.77%. Calcd for $C_7H_8NO_2Cl_3$: C, 34.39; H, 3.30; N, 5.73%.

5-(Trichloroacetamido)-4-hexen-3-one (6). From **4** and

trichloroacetyl chloride, **6** was prepared and recrystallized from hexane, mp 91—93 °C; yield 47%; IR (KBr): 3445, 1740, 1650, 1620, 1480 cm^{-1}; NMR ($CDCl_3$): δ 1.11 (t, 3H, J=6.8 Hz), 2.42 (s, 3H), 2.43 (q, 2H, J=6.8 Hz), 13.4 ppm (broad s, 1H).

Found: C, 37.33; H, 3.97; N, 5.56%. Calcd for $C_8H_{10}NO_2Cl_3$: C, 37.16; H, 3.90; N, 5.42%.

5-(Trichloroacetamido)-1-phenyl-4-hexen-3-one (8). From 5-amino-1-phenyl-4-hexen-3-one[1] and trichloroacetyl chloride, **8** was prepared, bp 170—176 °C/3 Torr; yield 77%; IR (liquid film): 3050, 1735, 1650, 1615, 1600, 1470 cm^{-1}; NMR ($CDCl_3$): δ 2.42 (s, 3H), 2.5—3.2 (m, 4H), 5.56 (s, 1H), 7.23 (s, 5H), 13.5 ppm (broad s, 1H).

Found: C, 50.79; H, 4.42; N, 4.18%. Calcd for $C_{14}H_{14}NO_2Cl_3$: C, 50.25; H, 4.22; N, 4.19%.

5-(Trichloroacetamido)-2,2-dimethyl-4-hexen-3-one (10). 3-Methyl-5-*t*-butylisoxazole was hydrogenated in ethanol in the presence of platinum to give 5-amino-2,2-dimethyl-4-hexen-3-one, which was recrystallized from hexane, mp 65—66.5 °C; yield; 95%; IR (KBr): 3300, 1620, 1595, 1530 cm^{-1}; NMR ($CDCl_3$): δ 1.15 (s, 9H), 1.98 (s, 3H), 5.2 (broad s, 1H), 5.23 (s, 1H), 9.7 ppm (broad s, 1H).

Found: C, 67.82; H, 10.76; N, 9.92%. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92%. 5-Amino-2,2-dimethyl-4-hexen-3-one was acylated using trichloroacetyl chloride to give **10**, bp 109—113 °C/3 Torr; yield 79%; IR (liquid film): 1740, 1650, 1605, 1470 cm^{-1}; NMR ($CDCl_3$): δ 1.20 (s, 9H), 2.47 (s, 3H), 5.79 (s, 1H), 13.6 ppm (broad s, 1H).

Found: C, 41.93; H, 5.00; N, 4.82%. Calcd for $C_{10}H_{14}NO_2Cl_3$: C, 41.91; H, 4.92; N, 4.89%.

3-(Trichloroacetamido)-1-phenyl-2-buten-1-one (13). From **12** and trichloroacetyl chloride, **13** was prepared and recrystallized from hexane, mp 118—119 °C; yield 63%; IR (KBr): 1730, 1625, 1600, 1470 cm^{-1}; NMR ($CDCl_3$): δ 2.57 (s, 3H), 6.30 (s, 1H), 7.3—8.1 (m, 5H), 10.4 ppm (broad s, 1H).

Found: C, 47.07; H, 3.32; N, 4.46%. Calcd for $C_{12}H_{10}NO_2Cl_3$: C, 47.01; H, 3.29; N, 4.57%.

The Reaction of β-Amino Enones with Hydroxylamine Hydrochloride. A mixture of β-amino enone (3.2 mmol), hydroxylamine hydrochloride (8.0 mmol) and anhydrous potassium carbonate (3.9 mmol) in ethanol (10 ml) was refluxed for 6 h (in the cases of *N*-acyl derivatives, the refluxing time was 20 h). To the mixture, ether was added, and the organic layer was separated. The organic layer was washed with dilute hydrochloric acid and water, and dried over anhydrous sodium sulfate. After the solvent was removed, the product ratios were measured by the NMR spectra of the residual mixture. The products were identified from authentic samples using the spectral data.[1]

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