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MECHANISM OF THE RECYCLIZATION OF 2-AMINO-5-BENZYLIDENE-1,3-THIAZOL-4(5H)-ONE INTO DERIVATIVES OF 2-AMINO-5-BENZYLIDENE-1,5-DIHYDRO-4H-IMIDAZOL-4-ONE

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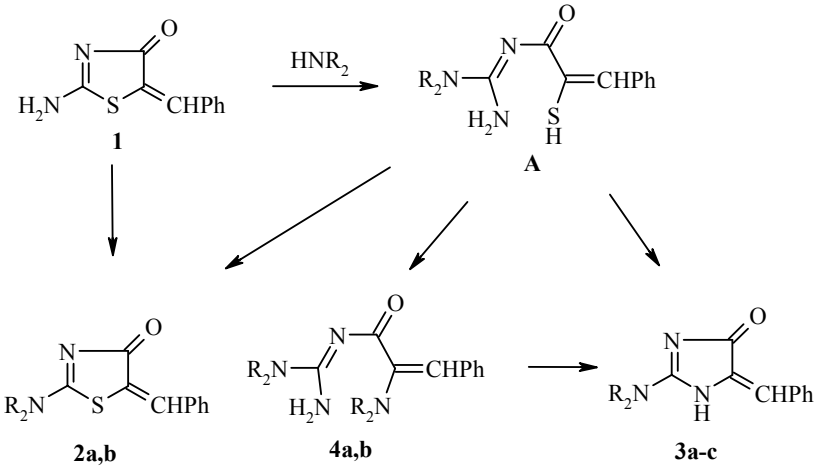
Mechanisms are given for reactions taking place upon heating 2-amino-5-benzylidene-1,3-thiazol-4(5H)-one in a medium consisting of a secondary amine.

Keywords: 2-amino-5-benzylidene-1,3-thiazol-4(5H)-one, derivatives of 2-amino-5-benzylidene-1,5-dihydro-4H-imidazol-4-one, diethylamine, morpholine, piperidine, aminolysis, recyclization.

In previous work [1], we showed that the aminolysis of 2-amino-5-benzylidene-1,3-thiazol-4(5H)-one (5-benzylidenepseudothiohydantoin, **1**) in piperidine or morpholine leads not only to the expected products of transanimation – 2-morpholino (**2a)** or 2-piperidino derivative **2b**, but also recyclization to give imidazole derivatives **3a** or **3b**.



a $R_2 = (CH_2)_2O(CH_2)_2$, **b** $R_2 = (CH_2)_5$, **c** R = Et

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Although the formation of compounds **2a**,**b** may occur without opening of the heterocycle, i.e., directly from the compound **1** by means of addition-elimination at the $C_{(2)}=N_{(2)}$ bond [2], the formation of **3a**,**b** is possible only as the result of ring opening and subsequent recyclization. In previous work [1], we proposed that the isolation of **2a** and **3a** or of **2b** and **3b** from the same reaction mixture is a consequence of a unique Dimroth rearrangement involving aminolytic ring opening a the $C_{(2)}–S_{(1)}$ bond and subsequent parallel recyclization of acyclic intermediate **A** to give the corresponding aminothiazolinone **2** and aminoimidazolinone **3**. Aminolysis of 5-benzylidene-pseudothiohydantoin **1** with opening of the $C_{(2)}–S_{(1)}$ bond in the ring is in accord with experimental findings on the alkaline hydrolysis [2], alcoholysis [3], and aminolysis [4] of derivatives of 2-amino-1,3-thiazol-4(5H)-one (pseudothiohydantoin).

However, our more extensive study of this reaction in the present work showed that the mechanism for the formation of compounds **3** is different. Indeed, acyclic products **4a** (in aminolysis by morpholine) and **4b** (in the aminolysis by piperidine) were isolated from the reaction mixtures. Products **4** proved extremely unstable and convert to imidazole derivatives **3a**,**b**, respectively, upon attempts to recrystallize these compounds from toluene or 2-propanol. Analysis of the experimental data showed that the noncrystalline compounds in virtually all reactions yielding **3a**,**b** are intermediate acrylamides **4a**,**b**, respectively. Thus, we propose that the major reaction pathway leading to aminoimidazolinones **3** consists of consecutive transformations **1** → **A** → **4** → **3**, i.e., may be a two-step aminolysis-recyclization process with substitution of the heteroatom. The reaction pathway **1** → **A** → **3** is extremely insignificant, if it occurs at all.

We should note that these experimental findings do not permit us to distinguish between the two possible mechanisms for the formation of **2** involving either direct formation from **1** (**1** → **2**) or formation through intermediate **A** (**1** → **A** → **2**).

Only aminoimidazolinone **3c** was isolated from the reaction mixture in the aminolysis with diethylamine as the medium. The corresponding aminothiazole **2** and intermediate **4** were not isolated in this case.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker AM-400 spectrometer at 400 MHz and a Bruker AM-200 spectrometer at 200 MHz in DMSO-d_6 with DMSO-d_6 as the internal standard. The IR spectra were taken on a Shimadzu FTIR-8400S. The electron impact mass spectra of **3a**,**b** were taken on a Finnigan MAT INCOS 50 spectrometer at 70 eV. Thin-layer chromatography was carried out on Silufol-254 plates with 1:2 acetone–hexane and 1:10 ethanol–chloroform as the eluents.

2-Amino-5-benzylidene-1,3-thiazol-4(5H)-one (1) was obtained according to Liberman [5].

5-Benzylidene-2-morpholino-1,5-dihydro-4H-imidazol-4-one (3a) and **5-Benzylidene-2-morpholino-1,3-thiazol-4(5H)-one (2a).** Compound **1** (2.00 g, 9.79 mmol) in morpholine (9.20 g, 9.20 ml, 106 mmol) was heated at reflux until the starting reagent fully dissolved (~5 min). The reaction mixture was left at about 20°C for 12 h. The precipitate formed was filtered off, washed with 1:1 petroleum ether–ethanol, and treated consecutively with boiling acetone and 2-propanol. The precipitate, which formed from the 2-propanol solution after 48 h, was recrystallized from 2-propanol to give 0.24 g (9%) **3a**, mp 220-221°C (mp 232°C for the *Z*-isomer [6]).

A precipitate formed from the combined filtrate after 30 min was recrystallized twice from toluene to give 0.14 g (5%) **2a**; mp 202-204°C (mp 202-204°C [7], mp 203-204°C [8]).

N-[Amino(morpholin-4-yl)methylene]-2-morpholin-4-yl-3-phenylacrylamide (4a). Compound **1** (2.00 g, 9.79 mmol) in morpholine (10.0 g, 10.0 ml, 115 mmol) was heated at reflux for 30 min and left stand for 24 h. The precipitate formed was filtered off, dried, and treated with hot acetone to give 0.674 g (20%) **4a**; mp 208-210°C. IR spectrum (neat), ν, cm^{-1}: 3420, 3182 (N–H), 1677 (C=O), 1592 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.00 (2H, d, *J* = 8.3, arom); 7.33 (2H, t, *J* = 7.4, arom); 7.19 (1H, t, *J* = 7.0,

arom); 6.32 (1H, s, =C<u>H</u>C_6H_5); 3.70 (4H, m, OCH_2 morpholino); 3.61 (4H, m, NCH_2 morpholino); 3.49 (4H, t, J = 4.5, OCH_2 morpholino); 2.66 (4H, t, J = 4.5, NCH_2 morpholino). Found, %: C 62.20; H 7.60; N 16.32. $C_{18}H_{24}N_4O_3$. Calculated, %: C 62.77; H 7.02; N 16.27.

5-Benzylidene-2-morpholino-1,5-dihydro-4H-imidazol-4-one (3a). A. Compound **1** (1.00 g, 4.90 mmol) in morpholine (4.60 g, 4.60 ml, 52.8 mmol) was heated for ~10 min until the starting reagent dissolved completely. After 48 h, the precipitate formed was filtered off, washed with acetone, and recrystallized from 2-propanol to give compound **3a** (0.132 g, 10.5%); mp 210°C (for the *Z*-isomer, mp 232°C [6]). IR spectrum (neat), ν, cm^{-1}: 3437, 3113 (N–H), 1706 (C=O), 1643 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.24 (1H, s, NH); 7.96 (2H, d, J = 6.8, arom); 7.30 (2H, t, J = 7.3, arom); 7.18 (1H, t, J = 7.9, arom); 6.30 (1H, s, =C<u>H</u>$_6H_5$); 3.70 (4H, m, OCH_2 morpholino); 3.62 (4H, m, NCH_2 morpholino). Mass spectrum, *m/z* (I_{rel}, %): 259 [M^++2] (1.4), 258]M^++1] (17), 257 [M^+] (100). Found, %: C 65.35; H 5.83; N 16.47. $C_{14}H_{15}N_3O_2$. Calculated, %: C 65.35; H 5.88; N 16.33.

B. Compound **4a** (1.18 g, 3.43 mmol) in 2-propanol was heated at reflux until completed dissolved and then heated at reflux for an additional 10-15 min. The precipitate formed upon cooling was recrystallized from toluene to give compound **4a** (0.449 g, 51.3%); mp 200°C (for the *Z*-isomer, mp 232°C [6]).

5-Benzylidene-2-piperidino-1,5-dihydro-4H-imidazol-4-one (3b) and **5-Benzylidene-2-piperidino-1,3-thiazol-4(5H)-one (2b).** Compound **1** (1.00 g, 4.90 mmol) in piperidine (9.57 g, 11.1 ml, 112 mmol) was heated at reflux for ~10 min until dissolved and then left for 24 h at ~20°C. The precipitate formed was filtered off, washed with 10:1 petroleum ether–ethanol, and recrystallized from toluene to give compound **3b** (0.250 g, 20%); mp 208-210°C (for the *Z*-isomer, mp 198°C [6]).

A precipitate of **2b** formed after letting the combined filtrate stand for several days. This precipitate was recrystallized consecutively from toluene and ethanol to give compound **2b** (0.253 g, 19%); mp 202-204°C (mp 202-204°C [7], mp 209-211°C [8]).

N-[Amino(piperidin-1-yl)methylene]-2-piperidin-1-yl-3-phenylacrylamide (4b). Compound **1** (1.00 g, 4.90 mmol) in piperidine (6.02 g, 7.00 ml, 70.7 mmol) was heated at reflux for ~20 min until the starting reagent completely dissolved. After 24 h, the precipitate formed was filtered off, washed with petroleum ether, dried, and treated with hot acetone to give compound **4b** (0.337 g, 20%); mp 204-205°C. IR spectrum (neat), ν, cm^{-1}: 3433, 3181 (N–H), 1675 (C=O), 1579 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.91 (2H, d, J = 6.7, arom); 7.28 (2H, t, J = 6.7, arom); 7.14 (1H, t, J = 7.3, arom); 6.25 (1H, s, =C<u>H</u>C_6H_5); 3.58 (4H, m, NC<u>H</u>$_2$ piperidino); 2.69 (4H, m, NC<u>H</u>$_2$ piperidino); 1.61 (6H, m, $(CH_2)_3$ piperidino); 1.45 (6H, m, $(CH_2)_3$ piperidino). Found, %: 71.36; H 8.44; N 16.60. $C_{20}H_{28}N_4O$. Calculated, %: C 70.56; H 8.29; N 16.46.

5-Benzylidene-2-piperidino-1,5-dihydro-4H-imidazol-4-one (3b). A. Compound **1** (2.00 g, 9.79 mmol) in piperidine (6.88 g, 8.0 ml, 80.8 mmol) was heated at reflux for ~15 min until the starting reagent was completely dissolved. The precipitate formed after several hours was filtered off, washed with acetone, and recrystallized from toluene to give compound **3b** (1.43 g, 57%); mp 200-202°C (for the *Z*-isomer mp 198°C [6]). IR spectrum (neat), ν, cm^{-1}: 3441, 3117 (N–H), 1702 (C=O), 1651 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.06 (1H, s, NH); 7.98 (2H, d, J = 7.9, arom); 7.30 (2H, t, J = 7.3, arom); 7.18 (1H, t, J = 7.3, arom); 6.23 (1H, s, =C<u>H</u>C_6H_5); 3.61 (4H, m, NCH_2); 1.66 (6H, m, $(CH_2)_3$ piperidino). Mass spectrum, *m/z* (I_{rel}, %): 257 [M^++2] (1.0), 256 [M^++1] (16), 255 [M^+] (89). Found, %: C 70.71; H, 6.60; N 16.38. $C_{15}H_{17}N_3O$. Calculated, %: C 70.56; H 6.71; N 16.46.

B. Compound **4b** (0.633 g, 1.86 mmol) in toluene was heated at reflux until completely dissolved. Heating at reflux was continued for an additional 10-15 min. After 24 h, the precipitate was filtered off to give compound **4b** (0.109 g, 23%); mp 200°C (for the *Z*-isomer, mp 198°C [6]).

5-Benzylidene-2-diethylamino-1,5-dihydro-4H-imidazol-4-one (3c). Compound **1** (1.00 g, 4.90 mmol) in diethylamine (10.58 g, 15.0 ml, 144.7 mmol) was heated at reflux for ~5 h until the starting reagent was completely dissolved. Diethylamine was distilled off in a weak vacuum at ~20°C. The residue, which solidified after standing for several days, was stirred for 30 min with benzene (30 ml) at ~20°C.

The benzene solution was decanted from the oily residue through a paper filter and benzene was distilled off in a weak vacuum until dryness. The solidified residue in 2-propanol (25 ml) was heated at reflux. The precipitate was filtered off after 24 h to give compound **3c** (0.108 g, 9%); mp 165°C. IR spectrum, ν, cm^{-1}: 3382, 3122 (N–H), 1699 (C=O), 1650 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.17 (1H, s, NH); 8.00 (2H, d, *J* = 5.9, arom); 7.30 (2H, t, *J* = 6.9, arom); 7.17 (1H, t, *J* = 6.4, arom); 6.21 (1H, s, =C<u>H</u>C_6H_5); 3.51 (4H, m, NC<u>H_2</u>CH_3); 1.19 (6H, m, NCHC<u>H_3</u>). Found, %: C 69.08; H 7.18; N 17.35. $C_{14}H_{17}N_3O$. Calculated, %: C 69.11; H 7.04; N 17.27.

REFERENCES

1. S. M. Ramsh and N. L. Medvedskii, *Zh. Obshch. Khim.*, **77**, 877 (2007).
2. S. M. Ramsh, A. G. Ivanenko, V. A. Shpilevyi, N. L. Medvedskii, and P. M. Kushakova, *Khim. Geterotsikl. Soedin.*, 1089 (2005). [*Chem. Heterocycl. Comp.*, **41**, 921 (2005)].
3. M. T. Omar and M. A. Kasem, *J. Heterocycl. Chem.*, **18**, 1413 (1981).
4. O. S. Eltsov, V. S. Mokrushin, N. P. Belskaya, and N. M. Kozlova, *Izv. Akad. Nauk, Ser. Khim.*, 440 (2003).
5. D. Liberman, J. Himbert, and L. Hengl, *Bull. Soc. Chim. Fr.*, 1120 (1948); *Chem. Abstr.*, **43**, 3819 (1949).
6. A. I. Khodair, H. I. El-Subbagh, and A. M. Al-Obaid, *Phosphorus, Sulfur, and Silicon*, **140**, 159 (1998).
7. A. R. A. Raouf, M. T. Omar, S. M. A. Omran, and K. E. El-Bayoumy, *Acta Chim. (Budapest)*, **83**, 359 (1974).
8. P. Kutschy, M. Dzurilla, P. Kristian, and K. Kutschyova, *Collect. Czechosl. Chem. Commun.*, **46**, 436 (1981).