REACTIONS OF 4-ACETYLSYDNONES WITH HYDRAZINE: FORMATION OF 2,4-DIHYDROPYROL-3-ONES

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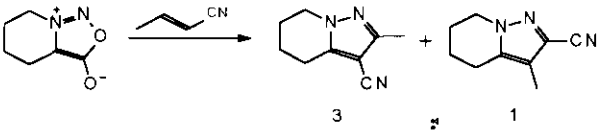
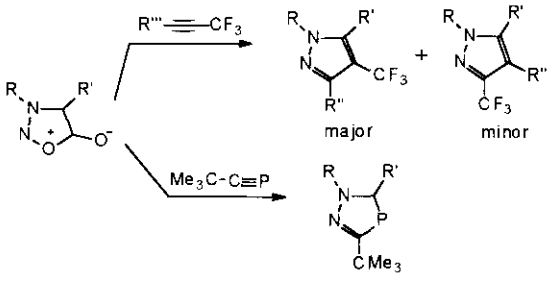
Abstract- Reactions of 4-acetylsydnones with hydrazine at room temperature yielded a series of 2,4-dihydropyrazol-3-ones. The cycloaddition *via* sydnone rings with loss of a nitrogen oxide ion is a new type of reaction for the application of sydnone in organic synthesis.

Much attention has been given to the preparation of sydnones because of their mesoionic character, biological activities, and the potential application in organic syntheses.[1] Among them, the preparation and the reaction of 4-acylsydnones have been studied to some extent.[2] Acylation of sydnones can be conducted by using the acid anhydride or acyl chloride in the presence of a Lewis acid.[2] Acylsydnones can be reduced to alcohol using sodium borohydride in a methanol solution.[3] The reaction of the 4-formylsydnones with hydrazine yielded a hydrazone or an azine, depending on the ratio of hydrazine used.[4] Reactions of the 4-acetylsydnones with hydroxylamine[5] and aminourea[6] gave the corresponding hydroxylimine and aminocarbonylhydrazones, respectively. The labile sydnone rings are able to undergo a 1,3-dipolar cycloaddition[7] with acrylonitrile[8], trifluoromethylacetylene[9] or *t*-butyl phosphaalkyne $[(CH_3)_3CCP]$[10] to form the pyrazole or 1,2,4-diazaphosphale, accompanied by the loss of a molecule of carbon dioxide (eq. 1, 2). Continuing our interest in the reaction of acetylsydnones, we carried out the reactions of acetylsydnones with hydrazine in ethanol solution at room temperature and isolated a series of 2,4-dihydropyrazol-3-ones as the major products (eq. 3). In this reaction, the cycloaddition takes place at C(1') and C(5) to form a five-membered pyrazolone with losing a nitrogen oxide molecule from the rupture of the sydnone ring. The unusual ring rupture process, with the formation of a new series of compounds, is worthy of reporting.

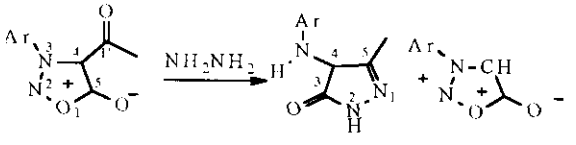
RESULTS AND DISCUSSION



eq. 1



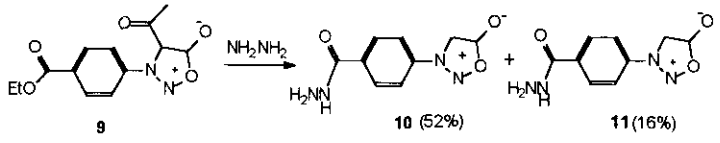
eq. 2



eq. 3

Ar : RC_6H_4—
R: H(**1**), 4-MeO(**2**); 4-Me(**3**);
2-Me(**4**); 4-Cl(**5**); 4-NO_2(**6**);
4-F(**7**), 2-F(**8**).

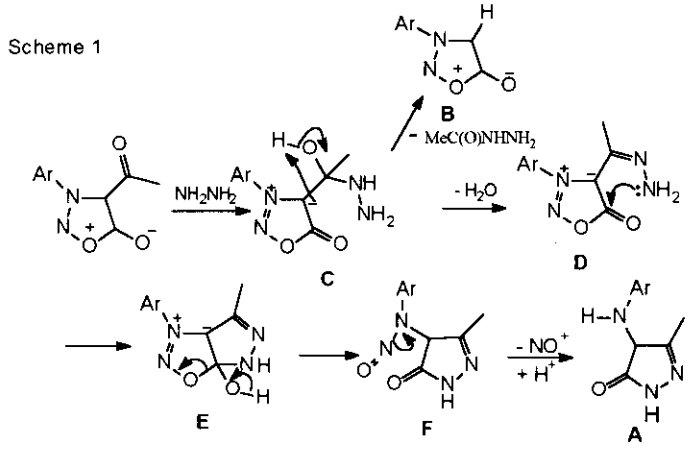
Hydrazine can serve as a reducing reagent to remove a bromine atom from 4-bromosydnone without interacting with the C(5)=O group.[11] In this study, a mixture of 4-acetylsydnone and an excess of hydrazine in ethanol was stirred at room temperature for 1 hour. After work-up, a five-membered pyrazolone (**A**) was obtained as a major product (eq. 3). Starting compound and deacetylated product (**B**) were obtained for the compounds containing an electron-withdrawing group, i.e. 4-acetyl-3-(4-nitrophenyl)sydnone (**6**). The ethoxyl group of the 4-acetyl-3-(4-ethoxycarbonylphenyl)sydnone (**9**) was substituted by hydrazine, suggesting that the ester group is more active toward hydrazine than the acetyl group (eq. 4). On the other hand, neither phenylhydrazine nor 2,4-dinitrophenylhydrazine underwent a similar reaction with acetylsydnone.



eq. 4

The formation of 2,4-dihydropyrazol-3-one (**A**) can be rationalized as Scheme 1. The reaction of 4-acetylsydnone with hydrazine yielded a hydrazone (**D**). A cyclization can be achieved *via* a nitrogen of the amino group of hydrazone (**D**) attacked the carbon atom of the C(5)=O group to form a bicycle intermediate (**E**) containing a hydroxyl group. The hydrogen of this hydroxyl group should possess an acidic nature, because that C(5) connects with two electronegative atoms (i.e., oxygen and nitrogen). Loss of a hydrogen from the hydroxyl group and formation of a carbonyl group with rupture of the original sydnone ring skeleton led to an intermediate (**F**), followed by the loss of a nitrogen oxide ion to form compound (**A**). Formation of an intermediate (**F**) is resemble to the condensations of hydrazine with β–keto ester to form a pyrazolone.[12] Sharp singlet resonances in the ^{1}H NMR spectrum at δ 1.90 are assigned to the methyl group attached on a sp^2 carbon; other sharp singlet resonances at ranging from

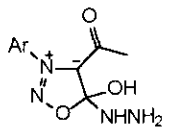
Scheme 1



δ 5.80 to δ 6.80 are due to a proton on a carbon next to two electronegative group (i.e., nitrogen and carbonyl group). Typically, the absorption of a carbonyl group of amides on a five-membered ring always appears at 1760 cm^{-1};[13] however, the carbonyl absorption compounds **A** appear at 1605 ~ 1620 cm^{-1}, which is resemble to that in a series of pyrazolone, which is reported at 1620 cm^{-1}.[14] Based on the spectral information, we can confirm the formation of the pyrazolone.

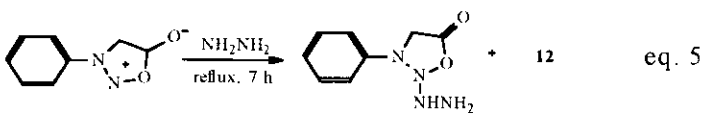
Deacetylated product (**B**) was obtained from the intermediate (**C**), which obtained from the reaction of acetylsydnone with hydrazine, in which C(1') contains a hydroxyl group and a hydrazino group. A hydrogen migrates from the hydroxyl group to the C(4) position, followed by the loss of an acetylhydrazine.

The alternative mechanism was postulated as that a hydrazine attacks the carbon of the C=O group to form intermediate (**G**). In order to investigate the possibility of a hydrazine reacting with C(5)=O group, the mixture of 3-phenylsydnone and hydrazine was treated under same conditions. After a period of 24 h, no product was isolated. However, under reflux, this reaction resulted in an unusual adduct (**13**), i.e.,



G

hydrazine is bound with N(2) and proton is trapped by C(4) (eq. 5). This reaction behavior is consistent with the charge distribution obtained from calculation, the N(2) bears a positive charge and the C(4) bears a negative charge.[15] The N(2) atom underwent an electrophilic reaction toward the nitrogen of hydrazine, and the C(4) picked up a proton to form compound (**13**). This result demonstrates the peculiar nature of the carbonyl group of the sydnone ring.



12 13 (49%) eq. 5

NMR spectroscopy is the most power method to determine the electron density around a specific nucleus.[16,17] The chemical shift of C(4)-H is very sensitive to the substituents on the phenyl ring and ranges from 6.23 (4-MeO-, σ = -0.27) to 6.83 ppm (4-Cl-, σ = 0.23). The correlation line for C(4)-H with Hammett constant (σ) corresponds to a slope (ρ = 1.23; r = 0.980) for groups varying from 4-methoxyl to 4-chloro group. Surprisingly, a large substituent chemical shift was observed for the hydrogens being two atoms away from the benzene ring. This might be due to the lone pair electrons of the nitrogen between two rings responsible for the resonance effect. The chemical shifts of the proton of the methyl group at the C(5) position are rather constant. The chemical shifts of the proton on the nitrogen are absent which might be due to the collapse with signal of the moisture in the DMSO-d_6, and appear at about 3.3 ppm.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 250 MHz at ambient temperature with DMSO-d_6 as the solvent. The concentrations for the determining the chemical shift were about 3 mg in 0.3 mL solution. Mass spectra were obtained on a JEOL DX-300 double focusing mass spectrometer. Samples were introduced *via* a direct insertion probe. The ionization energy was 70 eV. Microanalyses were performed on a Heraeus CHN-O-Rapid analyzer. 3-Arylsydnones and 3-aryl-4-acetylsydnones were prepared according to the

literature.[2]

Reaction of 3-aryl-4-acetylsydnone and hydrazine: typical procedure

A mixture of 4-acetyl-3-phenylsydnone (**1**) (0.204 g, 1.0 mmol) and hydrazine (80%, 2.0 mL, 33 mmol) in ethanol (99.5%, 2.0 mL) was stirred at 30 ℃ for 1 h. The white deacetylated product (**1B**) (31 mg, 19%) was obtained from filtration. The light yellow needles were obtained from re-filtration of the filtrate which was stand at 30℃ for 3 days. The yellow product, recrystallized from ethanol, was identified as 4-phenylamino-5-methyl-2,4-dihydropyrazol-3-one (**1A**) (109 mg, 58%), mp 235-236℃ (decomp), ^{1}H NMR δ 1.95 (s, 3H, C(5)-CH_3), 6.46 (d, 2H, J = 8.3 Hz, Ar-H), 6.50 (d, 1H, J = 7.4 Hz, Ar-H), 6.59 (s, 1H, C(4)-H), 7.01 (dd, 2H, J = 7.4, 8.3 Hz, Ar-H); IR 3394 (ν_{N-H}), 1611 ($\nu_{C=O}$) cm^{-1}; MS (m/z, %) 189 (M$^+$, 100); Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.32; H, 5.81; N, 22.31. Compound (**1B**) was verified by comparing mp and the spectra of an authentic sample.[11] Same process was used for reacting compounds (**2-9**) with hydrazine. The physical properties and their spectral data were summarized as following.

From 4-acetyl-3-(4-methoxyphenyl)sydnone (2): 4-(4-methoxyphenylamino)-5-methyl-2,4-dihydropyrazol-3-one (2A), recrystallized from ethanol to give colorless needles; yield 71%; mp 149-151℃ (decomp); ^{1}H NMR δ 1.93 (s, 3H, C(5)-CH_3), 3.60 (s, 3H, Ar-OCH_3), 6.23 (s, 1H, C(4)-H), 6.39 (d, 2H, J = 9.0 Hz, Ar-H), 6.65 (d, 2H, J = 9.0 Hz, Ar-H); IR 3394 (ν_{N-H}), 1617 ($\nu_{C=O}$) cm^{-1}; MS (m/z, %) 219 (M$^+$, 100); Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.20; H, 6.05; N, 19.34.

From 4-acetyl-4-(4-methylphenyl)sydnone (3): 4-(4-methylphenylamino)-5-methyl-2,4-dihydropyrazol-3-one (3A), recrystallized from ethanol to give colorless needles; yield 79%, mp 198-199℃ (decomp); ^{1}H NMR δ 1.93 (s, 3H, C(5)-CH_3), 2.12 (s, 3H, Ar-CH_3), 6.37 (d, 2H, J = 8.2 Hz, Ar-H), 6.39 (s, 1H, C(4)-H), 6.83 (d, 2H, J = 8.2 Hz, Ar-H); IR 3394 (ν_{N-H}), 1620 ($\nu_{C=O}$) cm^{-1}; MS (m/z, %) 203 (M$^+$, 77), 91 (100); HRMS Calcd for $C_{11}H_{13}N_3O$: 203.1060. Found: 203.1062.

From 4-acetyl-3-(2-methylphenyl)sydnone (4): 4-(2-methylphenylamino)-5-methyl-2,4-dihydropyrazol-3-one (4A), recrystallized from ethanol to give colorless crystals; yield 84%, mp 116-118℃ (decomp); ^{1}H NMR δ 1.93 (s, 3H, C(5)-CH_3), 2.17 (s, 3H, Ar-CH_3), 5.82 (s, 1H C(4)-H), 6.18 (d, 1H, J = 7.8 Hz, Ar-H), 6.46 (t, 1H, J = 7.2 Hz, Ar-H), 6.83-6.96 (m, 2H, Ar-H); IR 3418 (ν_{N-H}), 1611 ($\nu_{C=O}$)cm^{-1}; MS (m/z, %) 203 (M$^+$, 100); Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.00; H, 6.45; N, 20.67. Found: C, 64.89; H, 6.45; N, 20.60.

From 4-acetyl-3-(4-chlorophenyl)sydnone (5): 4-(4-chlorophenylamino)-5-methyl-2,4-dihydro-

pyrazol-3-one (5A), recrystallized from ethanol to give yellow needles; yield 67%; mp 173-173℃ (decomp); ^{1}H NMR δ 1.94 (s, 3H, C(5)-CH_3), 6.45 (d, 2H, J = 8.8 Hz, Ar-H), 6.83 (s, 1H,C(4)-H), 7.04 (d, 2H, J = 8.8 Hz, Ar-H); IR 3406 (ν_{N-H}), 1605 ($\nu_{C=O}$); MS (m/z, %), 223 (M^+, 100); HRMS Calcd for $C_{10}H_{10}N_3OCl$: 223.0514. Found: 223.0507.

From 4-acetyl-3-(4-nitrophenyl)sydnone (**6**): Compound (**6**) was recovered (yield 36%) and 3-nitrophenyl-sydnone (**6B**) was obtained in yield 39%. Both compounds were confirmed by comparing the mp and spectra with the authentic compounds.[17]

From 4-acetyl-3-(4-fluorophenyl)sydnone (7): 4-(4-fluorophenylamino-5-methyl-2,4-dihydropyrazol-3-one (7A), recrystallized from ethanol to give yellow needles; yield 15%; mp 241-242℃ (decomp); ^{1}H NMR δ 1.94 (s, 3H, C(5)-CH_3), 6.39-6.48 (m, 2H, Ar-H) 6.63 (s, 1H, C(4)-H), 6.85 (t, 2H, J = 6.9 Hz, Ar-H); IR 3400 (ν_{N-H}), 1617 ($\nu_{C=O}$); MS (m/z, %) 207 (M^+, 100); Anal. Calcd for $C_{10}H_{10}N_3OF$: C, 57.97; H, 4.86; N, 20.28. Found: C, 57.95; H, 4.97; N, 20.20. Compound (**7B**), colorless crystals from ethanol, yield 39%, was identified by comparing the mp and spectra with authentic sample.[18]

From 4-acetyl-3-(2-fluorophenyl)sydnone (8): 4-(2-fluorophenylamino)-5-methyl-2,4-dihydro-pyrazol-3-one (8A), recrystallized from ethanol to give light green needles; yield 10%, mp 228-230℃ (decomp); ^{1}H NMR δ 1.95 (s, 3H, C(5)-CH_3), 6.32 (t, 1H, J = 8.6 Hz, Ar-H), 6.45 (s, 1H, C(4)-H), 6.50-6.56 (m, 1H, Ar-H), 6.84 (t, 1H, J = 7.7 Hz, Ar-H), 7.00 (dd, 1H, J = 8.2, 12.2 Hz, Ar-H); IR 3400 (ν_{N-H}), 1623 ($\nu_{C=O}$); MS (m/z, %) 207 (M^+, 100); Anal. Calcd for $C_{10}H_{10}N_3OF$: C, 57.97; H, 4.86; N, 20.28. Found: C, 57.94; H, 4.99; N, 20.30. 3-(2-Fluorophenyl)sydnone (**8B**), colorless crystals, yield 43%, was identified by comparing the mp and spectra of authentic sample.[19]

From 4-acetyl-3-(4-ethoxycarbonylphenyl)sydnone (**9**): 4-acetyl-3-(4-hydrazinocarbonyl)sydnone (**10**), yield 52%; 3-(4-hydrazinocarbonyl)sydnone (**11**), yield 16%, both compounds were identified by comparing the mp and spectra of the authentic samples.[20]

Reaction of 3-phenylsydnone (12) and hydrazine: A mixture of 3-phenylsydnone(0.324 g, 2.0 mmol) and hydrazine (80%, 4.0 mL, 65 mmol) in ethanol (99.5%, 4.0 mL) was refluxed for 7 h. After removing the solvent, the residues was dissolved in ethanol (99.5%, 4.0 mL) and then was absorbed by silica gel (40-230 mesh) for column chromatographical separation with n-hexane and ethyl acetate (1:1 v/v) as an eluent to give white needles of compound (**12**) (0.12 g, 37% recovery) and yellow solid of 2-hydrazino-3-phenyl-1,2,3-oxadiazolidin-5-one (**13**)(0.19 g, 49%); mp 98.0-99.0℃; ^{1}H NMR δ 4.26 (s, 2H, NH_2); 4.63 (s, 2H, CH_2); 7.39-7.63 (m, 5H, Ar-H); 9.36 (s, 1H, NH); IR 3298 (ν_{N-H}), 1659 ($\nu_{C=O}$); MS (m/z,

%) 194 (M^+, 1), 106 (100); Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.34; H, 5.25; N, 28.75.

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