$C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.98; H, 10.60.

Registry No. **2a**, 2594-21-0; **2b**, 22139-32-8; **2c**, 36598-10-4; **2d**, 6030-54-2; **2e**, 70288-80-1; **2f**, 70288-77-6; **2g**, 86688-70-2; **3a**, 76469-96-0; **3b**, 86688-71-3; **3c**, 86688-72-4; **3d**, 86688-73-5; **3e**, 86688-74-6; **3f**, 86688-75-7; **3g**, 86688-76-8; **4a**, 4461-87-4; **4b**, 1599-47-9; **4c**, 10022-28-3; **4d**, 54286-89-4; **4e**, 25176-55-0; **4f**, 4220-66-0; **4g**, 86688-77-9; **5a**, 86688-78-0; **5b**, 5817-68-5; **5c**, 39076-02-3; **6a**, 54583-19-6; **6b**, 933-40-4; **6c**, 3453-99-4; **8**, 76649-94-0; **9**, 86709-30-0; **10**, 10395-51-4.

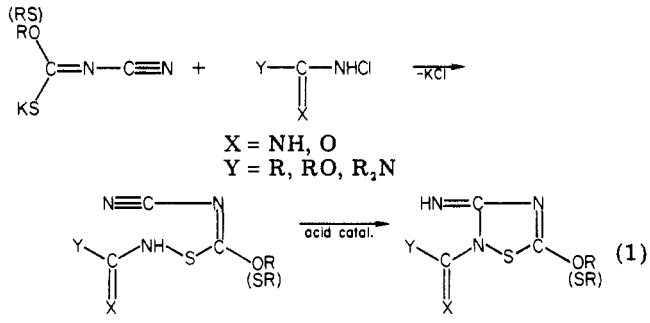
Facile Synthesis of 5-Acyl-4-amino-2-ethoxythiazoles from an [Ethoxy(thiocarbonyl)]cyanamide Salt and α-Halo Ketones

Toshio Fuchigami* and Tsutomu Nonaka

Department of Electronic Chemistry, Graduate School at Nagatsuta, Tokyo Institute of Technology, Midori-ku, Yokohama 227, Japan

Received January 25, 1983

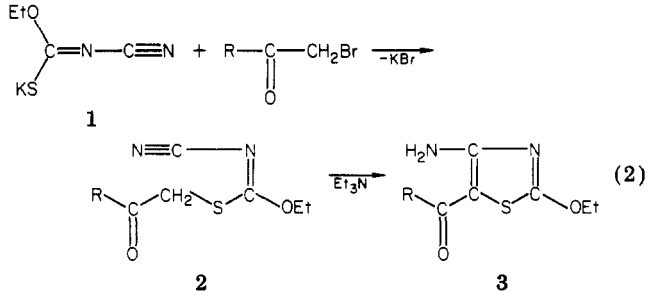
In the course of our synthetic studies[1-4] of heterocyclic compounds using cyanamide derivatives, we found that Δ^4-1,2,4-thiadiazoline derivatives were easily prepared by the reaction of potassium [alkoxy(thiocarbonyl)]cyanamide and potassium methyl *N*-cyanodithiocarbonimidate with *N*-halo compounds (eq 1). We have now extended this



(1)

process to provide a facile synthesis of 5-acyl-4-amino-2-ethoxythiazoles using potassium [ethoxy(thiocarbonyl)]-cyanamide (1) and α-halo ketones instead of *N*-halo compounds. Although several types 2-aminothiazoles are known, relatively few synthetic studies on 4-aminothiazoles have been reported.

α-Bromoacetophenone readily reacted with **1** to provide an open-chain intermediate **2a** (eq 2) that showed two



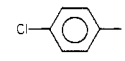
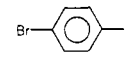
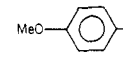
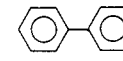
1

2 3

(2)

strong IR absorptions of a nitrile group around 2200 cm^{-1}.

Table I. Synthesis of 5-Acyl-4-amino-2-ethoxythiazoles (3)[a]

compd	R	yield, %	mp, °C	recrystn solvent
3a	Ph	97	87–88	MeOH
3b		100	121–122	MeOH
3c		95	129–130	MeOH
3d		99	87–88	MeOH(aq)
3e		100	157–158	C_6H_6
3f	Me	90	121–122	MeOH

[a] Satisfactory analyses (±0.3 for C, H, and N) consistent ^{1}H NMR spectra (Et, NH_2, Ar signals) were reported for all compounds.

Although **2a** did not cyclize on heating in acetone or ethanol, it was converted into 4-amino-5-benzoyl-2-ethoxythiazole (**3a**) in high yield by treatment with triethylamine at room temperature. We found that the initial condensation and subsequent cyclization could be run in sequence in acetone at room temperature without isolating the intermediate **2**. Several 4-aminothiazoles were thus prepared from α-bromo ketones in excellent yields, as shown in Table I.

In a similar manner, bis(4-amino-2-ethoxy-5-thiazolyl) ketone (**3g**) was easily synthesized in a good yield from 2 equiv of **1** and 1,3-dichloro-2-propanone.

The structures of **3** were confirmed by elemental analyses and mass, ^{1}H NMR, and IR spectral data. In the IR spectra, the absorption of the carbonyl group of **3** appears around 1620 cm^{-1}, which is a much lower frequency than that of ordinary ketones and probably reflects intramolecular hydrogen bonding between the carbonyl and amino groups.[5]

The cyclization of **2** seems to proceed via a carbanion intermediate, which is stabilized by the carbonyl group and sulfur atom.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a Hitachi R24B spectrometer with Me_4Si as an internal standard. IR spectra were obtained on a Hitachi 295 infrared spectrometer. Electron-impact mass spectra were determined at 75 eV on a JEOL JMS-D100 mass spectrometer by direct introduction via solid probe.

Typical Procedure for the Preparation of Thiazoles. Preparation of 4-Amino-5-benzoyl-2-ethoxythiazole (3a). To a stirred solution of 0.84 g (5 mmol) of potassium [ethoxy(thiocarbonyl)]cyanamide salt **1**[6] in 8 mL of acetone was gradually added a solution of 1.00 g (5 mmol) of phenacyl bromide in 2 mL of acetone at room temperature. After about 1 h of stirring, 0.3 mL of triethylamine was added to the reaction mixture. After an additional 1 h of stirring, the reaction mixture was evaporated to dryness under reduced pressure. The residue was mixed with water, and insoluble material was collected by filtration: yield 1.20 g (97%); mp 87–88 °C. Recrystallization from methanol provided 0.90 g (73%) of pure **3a** as a white solid: mp 87–88 °C; IR (KBr) 1610 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7 Hz, CH_3), 4.40 (q, 2 H, J = 7 Hz, CH_2), 7.10 (s, 2 H, NH_2), 7.53 (m, 5 H, C_6H_5); MS, m/e 248 (M^+).

Preparation of Bis(4-amino-2-ethoxy-5-thiazolyl) Ketone (3g). In a similar manner as for the preparation of **3a**, the reaction was carried out by using 0.84 g (5 mmol) of **1**, 0.32 g (2.5 mmol)

(1) Fuchigami, T.; Odo, K. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 310.
(2) Fuchigami, T.; Odo, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3165.
(3) Fuchigami, T.; Nonaka, T.; Odo, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3170.
(4) Fuchigami, T.; Nonaka, T. *Chem. Lett.* **1979**, 829.
(5) The ^{1}H NMR signal of NH_2 group of **3** did not disappear completely right after D_2O was added to the solution of **3**.
(6) Suyama, T.; Odo, K. *J. Synth. Org. Chem. Jpn.* **1971**, *29*, 65.

0022-3263/83/1948-3340$01.50/0

of 1,3-dichloro-2-propanone, and 0.3 mL of triethylamine in 10 mL of acetone. After the reaction mixture had been evaporated, the remaining residue was mixed with water. The insoluble oily material was separated from water, and the oil was solidified with acetone, giving crude **3g**: 0.58 g (74%); mp 196–197 °C. Recrystallization from DMF–methanol provided 0.42 g (55%) of **3g** as a yellow solid: mp 196–197 °C; IR (KBr) 3400, 3300 (NH) and 1620 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.40 (t, 6 H, J = 7 Hz, CH_3), 4.40 (q, 4 H, J = 7 Hz, CH_2), 7.67 (s, 4 H, NH_2); MS, m/e 314 (M^+).

Registry No. 1, 29422-34-2; **2a**, 86690-06-4; **3a**, 86690-07-5; **3b**, 86690-08-6; **3c**, 86690-09-7; **3d**, 86690-10-0; **3e**, 86690-11-1; **3f**, 86690-12-2; **3g**, 86695-78-5; $PhCOCH_2Br$, 70-11-1; 4-$ClC_6H_4COCH_2Br$, 536-38-9; 4-$BrC_6H_4COCH_2Br$, 99-73-0; 4-$MeOC_6H_4COCH_2Br$, 2632-13-5; 4-$PhC_6H_4COCH_2Br$, 135-73-9; $MeCOCH_2Br$, 598-31-2; 1,3-dichloro-2-propane, 534-07-6.

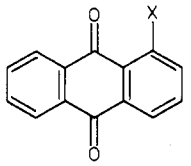
Synthesis and Rearrangements of Dihydro-1,4-oxazepine and Dihydro-1,4-thiazepine Derivatives

A. Paul Krapcho* and Kenneth J. Shaw

Vermont Regional Cancer Center and Department of Chemistry, The University of Vermont, Burlington, Vermont 05405

Received February 2, 1983

In a drug development program dealing with a study of the structure–activity relationship of substituted anthraquinones (anthracene-9,10-diones) as antineoplastic agents, we wished to prepare 1-(2-aminoethoxy)anthraquinone (**1a**) and the corresponding sulfur analogue **1b** for evaluation of their antitumor activity.[1] Our efforts in this research have uncovered some interesting heterocylic chemistry which we report.

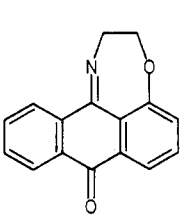


1a, X = $OCH_2CH_2NH_2$
b, X = $SCH_2CH_2NH_2$
c, X = Cl
d, X = $OCH_2CH_2N(CH_3)_2$
e, X = $NHCH_2CH_2OH$
f, X = F
g, X = $OCH_2CH_2N{=}CHC_6H_5$
h, X = $OCH_2CH_2NH_2 \cdot HCl$

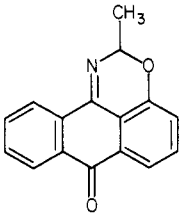
It had previously been reported by Cheng and coworkers[1] that treatment of 1-chloroanthraquinone (**1c**) with the potassium salt of 2-(dimethylamino)ethanol yielded **1d** (60%, isolated as the hydrochloride salt). Our initial attempt to prepare **1a** was to react **1c** with 1 equiv of the sodium salt of 2-aminoethanol in Me_2SO as solvent (65 °C, 15 h). However, this reaction led to **1e** (8%) along with starting anthraquinone **1c** (56%). Compound **1e** could also be prepared in a 73% yield by treatment of **1c** with 5 equiv of 2-aminoethanol in Me_2SO at 70 °C for 20 h. Since displacements by amines are known to proceed more readily with 1-fluoroanthraquinone (**1f**)[2] than **1c** the preparation of **1e** could most readily be accomplished by treatment of **1f** with excess 2-aminoethanol at 25 °C for 16 h (68% yield).

To preclude reaction at the nitrogen atom, we converted 2-aminoethanol to the corresponding imine[3] by treatment with benzaldehyde in a benzene solution with azeotropic removal of water. Addition of **1f** to the sodium salt of this imine (treatment with NaH in THF) followed by stirring at room temperature for 1.5 h leads to **1g** (90%). The imine **1g** could be readily converted into the hydrochloride salt **1h** (96%) by hydrolysis in dilute HCl. The free amine could be obtained by treatment of **1h** with aqueous sodium bicarbonate.

Some interesting chemistry was uncovered during the purification of the imine **1g**. Column chromatography of the crude reaction mixture on silica gel led to a new product which was identified as the dihydro-1,4-oxazepine derivative **2** (68%) by ^1H and ^{13}C NMR analysis. The conversion of pure **1g** to the dihydro-1,4-oxazepine **2** (93%) could be most readily accomplished by merely passing a solution of the imine in CH_2Cl_2 through a column of silica gel. The dihydro-1,4-oxazepine derivative **2** arises from initial hydrolysis of the imine linkage to the amine **1a** and subsequent intramolecular condensation of **1a** on the silica gel.



2



3

An unexpected rearrangement was discovered when **1a** was refluxed in toluene. After 20 h of refluxing, in addition to the expected dihydro-1,4-oxazepine derivative **2** (56%), a significant amount of the rearranged 1,3-oxazine derivative **3** (36%) was formed. It was then found that merely refluxing the amine **1a** or the imine **1g** in glacial acetic acid for 1 h also led to **3** (68% and 67% yields, respectively). In addition to the 1,3-oxazine **3**, both reactions produce 1-hydroxyanthraquinone in approximately 20% yields. This latter product arises from hydrolysis of the oxazine **3** since on heating **3** for 24–48 h in glacial acetic acid a nearly quantitative yield of 1-hydroxyanthraquinone was obtained (TLC assay).

The sulfur analogue **1b** was prepared by treatment of 2-aminoethanethiol hydrochloride in a basic medium of dioxane–water–ethanol with **1f**. The thio amine **1b** was isolated and characterized as its Schiff base **4** which formed upon crystallization of **1b** from acetone. When **1b** was refluxed in toluene (20 h) followed by silica gel chromatography, the thiazepine derivative **5** was isolated in a 56% yield. The crude base **1b** on being refluxed in glacial acetic acid for 1 h led to 7*H*-dibenzo[*de*,*h*]quinolin-7-one (**6**, 66%), the product of a formal loss of H_2S. This result contrasts markedly with the transformation undergone by the oxazepine derivative **2**.

It has previously been reported that treatment of **1c** with *o*-aminothiophenol followed by treatment of the product with refluxing acetic acid leads to the thiazepine derivative **7**. However, this thiazepine **7** on being refluxed in diethyl phthalate leads to **8**, the product of a formal extrusion of sulfur.[4]

(1) Zee Cheng, R. K.-Y.; Podrebarac, E. G.; Menon, C. S.; Cheng, C. C. *J. Med. Chem.* **1979**, *22*, 501.
(2) (a) Solodar, W. E.; Simon, M. S. *J. Org. Chem.* **1962**, *27*, 689. (b) Shein, S. M.; Shternshis, M. V. *J. Org. Chem. USSR (Engl. Transl.)* **1971**, *7*, 1278 and references cited therein.
(3) Bergman, E. D.; Zimkin, E.; Pinchas, S. *Recl. Trav. Chim. Pays-Bas* **1952**, *71*, 168.

0022-3263/83/1948-3341$01.50/0