

Norton P. Peet* and Shyam Sunder

Merrell Dow Research Institute, Indianapolis Center, 9550 Zionsville Road,
Indianapolis, IN 46268

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2-(1*H*-Pyrazol-1-yl)-4-(4-nitrophenyl)thiazoles **2a** and **2b**, resulting from the condensation of 2-hydrazino-4-(4-nitrophenyl)thiazole (**1**) and acetylacetone and dibenzoylmethane, respectively, were previously [4] misassigned as 3-(4-nitrophenyl)thiazolo[2,3-c][1,2,4]triazepines **3a** and **3b**. The assignments were corrected by authentic syntheses of **2a** and **2b** from 2-chloro-5-(4-nitrophenyl)thiazole (**6**) and 3,5-dimethyl-1*H*-pyrazole and 3,5-diphenyl-1*H*-pyrazole, respectively. In addition, the mass spectrum of **2a** is reported. An apparent ion-molecule reaction produces an ion of significant intensity at *m/e* 394.

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2-Hydrazinobenzothiazoles [1], 2-hydrazinothiazoles [2] and 1-hydrazinophthalazine [3] have all been recently reported to react with 1,3-dicarbonyl compounds to produce pyrazoles. Inconsistent with these reports is a recent article by Alaka, Patnaik and Rout [4] which describes the synthesis and mass spectra of 3-(4-nitrophenyl)thiazolo[2,3-c][1,2,4]triazepines **3a** and **3b** from 2-hydrazino-4-(4-nitrophenyl)thiazole (**1**) and the 1,3-diketones acetylacetone and dibenzoylmethane, respectively. Due to this discrepancy we reinvestigated this work and found it to be in error. The respective products of these reactions are instead, 2-(1*H*-pyrazol-1-yl)-4-(4-nitrophenyl)thiazoles **2a** and **2b**.

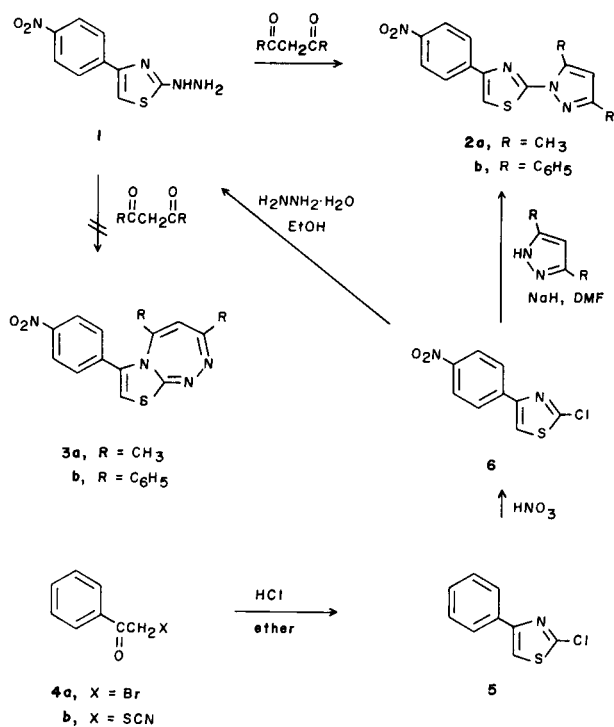
Structural revisions were based on alternate, unequivocal syntheses of **2a** and **2b**. Treatment of 2-chloro-5-(4-nitrophenyl)thiazole (**6**) with the sodium salt of 3,5-dimethyl-1*H*-pyrazole in dimethylformamide [5] provided pyrazolylthiazole **2a**, which was identical in all respects with the reaction product which we obtained from hydrazinobenzothiazole **1** and acetylacetone. In similar fashion, **6** and 3,5-diphenyl-1*H*-pyrazole gave **2b**, which was identical to the product from **1** and dibenzoylmethane. See Scheme 1.

Alaka, *et al.* [4] prepared **1** from α -bromo-4-nitroacetophenone, using the procedure of Bariana, Sachdev and Narang [6]. This procedure involves preparing the α -thiocyanatoacetophenone, and converting it to the 2-chlorothiazole with ethereal hydrogen chloride [7]. Since we obtained a mixture of products from this last procedure, we instead prepared 2-chlorothiazole **5** and converted **5** to **6** by nitration, using the procedure of Silberg, Benko and Panczel [10].

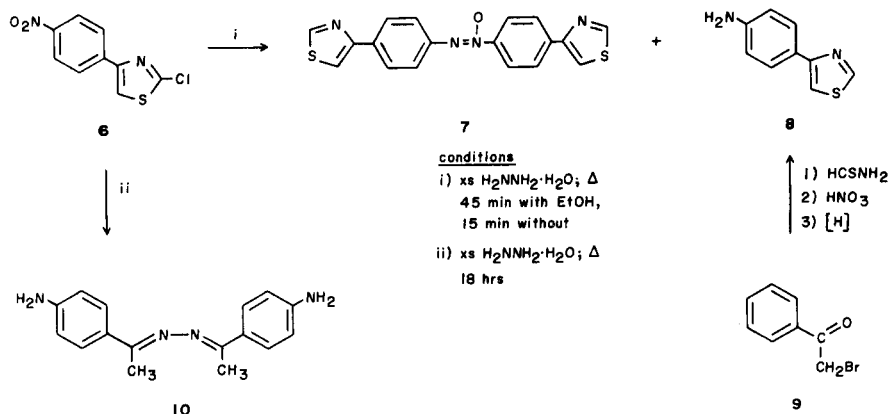
When the reaction of chlorothiazole **6** with hydrazine hydrate was not attenuated with ethanol, we obtained products of over-reduction as shown in Scheme 2. Treatment of **6** with excess hydrazine monohydrate in ethanol for 45 minutes, followed by distillation of the ethanol and 15 minutes of additional reflux gave a product mixture from which azoxy compound **7** and aminophenylthiazole **8** were obtained by flash chromatography. With both of these products, nitro group reduction and effective hydrogenolysis of the chloro group has occurred. However, displacement of the chloro group by hydrazine must be the first step of the hydrogenolysis. Thiazole **8** has previously been prepared [11] from α -bromoacetophenone by cyclization with thioformamide, followed by nitration and reduction of the nitro group, as shown in Scheme 2.

When **6** was treated with excess, neat hydrazine monohydrate at reflux for 18 hours, *p*-aminoacetophenone azine (**10**) resulted. Presumably, thiazole **8** is a precursor to **10**, and the thiazole ring is ruptured by the extended exposure to hydrazine monohydrate.

Scheme 1



Scheme 2



An interesting observation in the electron impact mass spectrum of compound **2a** was a molecular ion peak at m/e 394, in addition to the expected molecular ion peak at m/e 300. Since this observation was made with samples of **2a** generated by both routes, we thought it unlikely that an impurity of this molecular weight was present. Although ion-molecule reactions are uncommon [12], we suggest that m/e 394 results from a combination of ion **11** and molecule **13**, generated from a γ -hydrogen rearrangement (analogous to a McLafferty rearrangement) [13] of ion **11**, as shown in Scheme 3 [14]. A competing, related fragmentation process for **11** is probably one in which the same carbon-nitrogen bond is cleaved (without hydrogen transfer) to give radical **14** and ion **15**, which is observed at m/e 95 [14].

Additional data was gathered which supported the ion-molecule origin of the ion peak at m/e 394. Hplc analysis [15] of samples of **2a** generated by both routes showed a single component. When we systematically lowered the concentration of sample in the ion source while recording electron impact mass spectra, we observed a decrease in

intensity and finally the disappearance of the ion at m/e 394. Compound **2a**, unfortunately, did not display a fast atom bombardment (FAB) positive ion spectrum. Future studies will focus on this interesting ion-molecule reaction.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 710B, 727B and 1310 spectrophotometers, nmr spectra with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan gc/ms Model 4023 (electron impact and chemical ionization) mass spectrometer. Combustion analyses for C, H and N were performed by Merrell Dow Analytical Laboratories, Cincinnati, Ohio.

Materials.

α -Isothiocyanatoacetophenone (**4b**), mp 73-74°, and 2-chloro-4-phenylthiazole (**5**), mp 52-54° (lit [6] mp 50-51°) were prepared using the method of Bariana, Sachdev and Narang [6]. 2-Chloro-4-(4-nitrophenyl)thiazole (**6**), mp 136-137° (lit [10] mp 137.5°) was prepared using the procedure of Silberg, Benko and Panczel [10].

2-Hydrazino-4-(4-nitrophenyl)thiazole (**1**).

A solution of 2.41 g (10.0 mmoles) of **6** in 12.0 ml of hydrazine monohydrate and 50 ml of ethanol was heated at reflux for 2 hours. Upon cooling, orange-red crystals formed. The solid was collected and dried to give 1.85 g (78%) of **1**, mp 198-199° (dec) [lit mp 200-202° dec [8,9]]; ir (Nujol): 3340, 3310 and 3200 (NH), 1600 cm^{-1} .

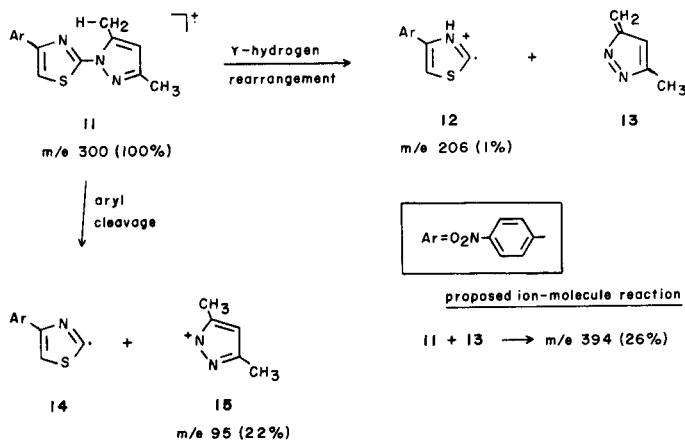
2-(3,5-Dimethyl-1H-pyrazol-1-yl)-4-(4-nitrophenyl)thiazole (**2a**).

To a mixture of 0.360 g (15.0 mmoles) of dry sodium hydride and 50 ml of dimethylformamide was added 0.961 g (10.0 mmoles) of 3,5-dimethyl-1H-pyrazole (Aldrich). After a few minutes of stirring, 2.41 g (10.0 mmoles) of **6** was added and the mixture was heated in an oil bath at 130-140° for 18 hours. The mixture was cooled, diluted with water and the resulting solid was collected and dried to give 2.20 g (73%) of **2a**, mp 202-204° (2-methoxyethanol); ir (Nujol): 1600 ($\text{C}=\text{N}$) cm^{-1} ; nmr (dimethylsulfoxide- d_6): δ 8.32 (d, $J = 9.7$ Hz, 2H, both H *ortho* to NO_2), 8.23 (s, 1H, thiazole H), 8.21 (d, $J = 9.7$ Hz, 2H, both H *meta* to NO_2), 6.25 (s, 1H, pyrazole H), 2.74 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ms: see Scheme 3.

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{O}_2\text{S}$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.68; H, 3.94; N, 18.70.

The melting point, the tlc retention time, and the ir, nmr and mass spectra for this material were identical to those of **2a** generated from **1** and acetylacetone (in 85% yield) using the procedure of Alaka, Patnaik

Scheme 3



and Rout [4].

2-(3,5-Diphenyl-1*H*-pyrazol-1-yl)-4-(4-nitrophenyl)thiazole (**2b**).

To a mixture of 0.370 g (15.0 mmoles) of dry sodium hydride and 50 ml of dimethylformamide was added 2.20 g (10.0 mmoles) of 3,5-diphenyl-1*H*-pyrazole (Fairfield). After 5 minutes of stirring, 2.41 g (10.0 mmoles) of **6** was added and the mixture was heated in an oil bath at 140° for 22 hours. The mixture was cooled, diluted with water and extracted with methylene chloride. The organic layer was dried (sodium sulfate) and concentrated, and the residue was triturated with ether. The resulting solid was combined with an insoluble solid from the aqueous phase to yield 1.65 g (39%) of **2b**, mp 249-250° (dimethylformamide-water); ir (Nujol): 1600 (C=N) cm⁻¹; nmr (dimethylsulfoxide-d₆): δ 8.32 (s, 1H, thiazole H), 8.21 (d, J = 9.7 Hz, 2H, both H *ortho* to NO₂), 7.99 (d, J = 9.7 Hz, 2H, both H *meta* to NO₂), 8.30 (d, J = 10 Hz, 2H, phenyl), 7.75-7.66 (m, 2H, phenyl), 7.60-7.40 (m, 6H, phenyl) 6.67 (s, 1H, pyrazole H); ms: (70 eV, electron impact) m/e 424 (molecular ion).

Anal. Calcd. for C₂₄H₁₈N₄O₂S: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.92; H, 3.83; N, 13.23.

The melting point and the ir, nmr and mass spectra for this material were identical to those of **2b** generated from **1** and dibenzoylmethane (in 78% yield) using the procedure of Alaka, Patnaik and Rout [4].

4,4'-(Azoxidi-4,1-phenylene)bis(thiazole) (**7**) and 4-(4-Aminophenyl)thiazole (**8**).

A solution of 2.41 g (10.0 mmoles) of **6** in 30 ml of hydrazine monohydrate and 15 ml of ethanol was heated at reflux for 45 minutes. The condenser was removed and the solution was heated at reflux for an additional 15 minutes, during which time the ethanol was removed by distillation. The solution was cooled and partitioned between water and methylene chloride. The organic phase was dried (sodium sulfate) and concentrated to leave 1.40 g of solid. Trituration with ethanol gave a solid which was collected to yield 180 mg of **7**, mp 242° (dec); ir (Nujol): 3100 and 3050 (CH), 1600 cm⁻¹; nmr (dimethylsulfoxide-d₆): δ 9.35-9.26 (m, 2H, both thiazole C2-H), 8.50-8.15 (m, 10H, remaining protons); ms: (70 eV, chemical ionization, methane) 365 (M⁺ + 1), 393 (M⁺ + 29), 405 (M⁺ + 41).

Anal. Calcd. for C₁₈H₁₂N₄O₂S: C, 59.32; H, 3.32; N, 15.37. Found: C, 58.95; H, 3.45; N, 15.75.

The filtrate from the trituration was concentrated and the residue (1.02 g) was applied to a column of Baker flash chromatography silica gel (500 ml dry volume) and eluted with hexane/ethyl acetate (1/1 volume). A 500-ml forerun was discarded and 12 fractions (75 ml each) were collected. Fractions 5-11 were combined and concentrated to leave 520 mg of solid. Recrystallization from ethanol gave 40 mg of additional **7**. The filtrate was concentrated and the solid was recrystallized from toluene to give 290 mg of **8** as brown prisms, mp 92-94° (lit [11] mp 99°); ir (Nujol): 3450-3050 (NH₂), 1640, 1610 cm⁻¹; nmr (dimethylsulfoxide-d₆): δ 9.10-8.97 (m, 1H, C2-H), 7.80-7.47 (m, 3H, C5-H, and 2 phenyl H), 6.77-6.47 (m, 2H, 2 phenyl H), 5.26 (br s, 2H, NH₂, deuterium oxide-exchangeable); ms: (70 eV, chemical ionization, methane) 177 (M⁺ + 1), 205 (M⁺ + 29), 217 (M⁺ + 41).

1-(4-Aminophenyl)ethanone [1-(4-Aminophenyl)ethylidene]hydrazone (**10**).

A solution of 2.41 g (10.0 mmoles) of **6** in 50 ml of hydrazine monohydrate was heated at reflux for 18 hours. The clear yellow solution was partially concentrated, diluted with water and extracted with methylene chloride. The organic layer was dried (sodium sulfate) and concentrated to leave 0.78 g of material which was recrystallized from ethanol to give

10 as a yellow crystalline solid, mp 145-147°; nmr (dimethylsulfoxide-d₆): δ 7.63 (d, J = 8.8 Hz, 4H, all H *meta* to NH₂), 6.58 (d, J = 8.8 Hz, 4H, all H *ortho* to NH₂), 5.50 (s, 4H, both NH₂), 2.24 (s, 6H, both CH₃); ms: (70 eV, chemical ionization, methane) 267 (M⁺ + 1), 295 (M⁺ + 29), 307 (M⁺ + 41).

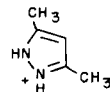
Anal. Calcd. for C₁₆H₁₈N₄·½H₂O: C, 69.79; H, 6.95; N, 20.35. Found: C, 70.08; H, 6.89; N, 20.50.

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- [13] A similar fragmentation has been observed with ethyl 4-methylthiazole-2-carboxylate. See H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, CA, 1967, pp 635-636.
- [14] The chemical ionization mass spectrum of **2a** also shows a pair of molecular ions at 301 (M⁺ + 1), with adducts at 329 (M⁺ + 29) and 341 (M⁺ + 41); and at 395 (M⁺ + 1), with an adduct at 423 (M⁺ + 29). The base peak in this spectrum is 97, which may be the following ion:



- [15] The following hplc conditions were used: column - Partisil 10 micron ODS; detection - ultraviolet at 234 nm; mobile phase - acetonitrile/aqueous 0.05 M perchloric acid and 0.05 M sodium perchlorate; flow rate - 1.5 ml/minute.