Reactions of Triacetylmethane with Monosubstituted Hydrazines and Amidine Analogues. Syntheses of 4-Acetyl-3,5-dimethylpyrazole Amidinohydrazone and 1,3,5-Triazine Derivatives

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Triacetylmethane (**1**) reacts with amidinohydrazines in acidic medium to afford 4-acetyl-3,5-dimethylpyrazole amidinohydrazone derivatives **2**,**4**. However, a similar reaction of **1** with thiosemicarbazide or semicarbazide led mainly to 3,5-dimethylpyrazole (**6**). The great propensity of **1** to hydrolysis accounts for this last transformation, as well as for the fact that with guanidine it led to 2-amino-4,6-dimethylpyrimidine (**10**) and with *S*-methylisothiourea it provided the unexpected 2-amino-4-methyl-6-methylthio-1,3,5-triazine (**11**).

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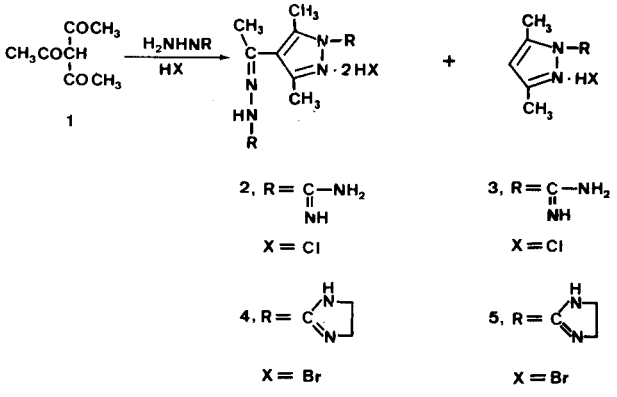
Amidinohydrazones of 5-acylpyrimidines and 4-acylpyrazoles are of interest in view of their structural analogy with methylglyoxal bis(guanylhydrazone) (MGBG) which is a good inhibitor of 5-adenosylmethionine decarboxylase and shows antitumor activities [3]. In the course of our synthetic studies of 5-acylpyrimidine amidinohydrazones, we have reported that several 5-acylpyrimidines underwent regiospecific ring transformation into 4-acylpyrazoles under the action of hydrazines in acidic medium [3-7]. This type of reaction gives access to new variously substituted 4-acylpyrazole amidinohydrazones [3,4,5] whose structures closely resemble that of MGBG. In continuation of our search for MGBG analogues, we investigated the reaction of triacetylmethane (**1**) with monosubstituted hydrazines, such as aminoguanidine, (2-imidazolinyl)hydrazine, thiosemicarbazide and semicarbazide. These reactions gave amidinohydrazones of 4-acetyl-3,5-dimethylpyrazoles **2**,**4** and related compounds **7**,**8**. On the contrary, the reactions of **1** with various amidines did not afford the expected 5-acetyl-4,6-dimethylpyrimidines. However, we found that **1** reacted with *S*-methylisothiourea to give a 1,3,5-triazine derivative **11**. This paper describes these results, including new synthesis of 4-acetyl-3,5-dimethylpyrazole amidinohydrazone and 1,3,5-triazine derivatives.

Treatment of **1** with aminoguanidine hydrogencarbonate in methanol in the presence of concentrated hydrochloric acid at room temperature for 19 hours gave 4-acetyl-1-amidino-3,5-dimethylpyrazole amidinohydrazone dihydrochloride (**2**) and 1-amidino-3,5-dimethylpyrazole hydrochloride (**3**) [8] in 59 and 17% yields, respectively. With (2-imidazolinyl)hydrazine hydrobromide in methanol in the presence of hydrobromic acid, **1** was transformed into a mixture of 4-acetyl-1-(2-imidazolinyl)-3,5-dimethylpyrazole (2-imidazolinyl)hydrazone dihydrobromide (**4**, 47% yield) and 1-(2-imidazolinyl)-3,5-dimethylpyrazole hydrobromide (**5**, 24% yield) (Scheme 1).

Scheme 1



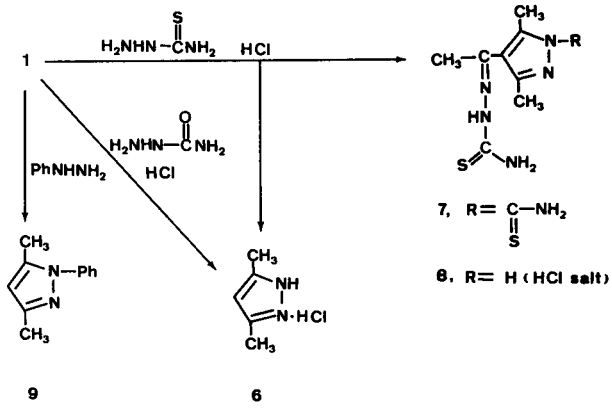
The structures of **2**, **3**, **4** and **5** were supported by their analytical and spectral data, especially the ^{1}H-nmr spectra of **2** and **4** showed signals attributable to protons of the three methyl groups (δ 2.15-2.65 ppm), while in the spectra of **3** and **5**, a signal due to the proton in 4-position of pyrazole ring was observed (δ 6.30 ppm for **3** and δ 6.45 ppm for **5**), besides signals due to protons of the two methyl groups (δ 2.20-2.55 ppm). The formation of **2** and **4** shows that **1** reacts with aminoguanidines in acidic medium to give the expected 4-acetylpyrazole derivatives. However, the above reactions lead also to the formation of pyrazoles **3** and **5** which implies that there was a loss of one acetyl group during the condensation process.

When a mixture of **1** and thiosemicarbazide in methanol containing concentrated hydrochloric acid was maintained at room temperature for 38 hours, 3,5-dimethylpyrazole hydrochloride (**6**) [9] was obtained as a main product (70% yield) together with 4-acetyl-3,5-dimethyl-1-thiocarbamoylpyrazole thiosemicarbazone (**7**, 18% yield) and 4-acetyl-3,5-dimethylpyrazole thiosemicarbazone hydrochloride (**8**, 7% yield). Under the same conditions, semicarbazide in reacting with **1** led exclusively to pyrazole **6** in quantitative yield (Scheme 2).

The formation of pyrazole **6** also shows that there was deacetylation in the course of the reaction and that the thiocarbamoyl or carbamoyl group at 1-position of the intermediates 3,5-dimethyl-1-thiocarbamoyl (or 1-carbamoyl)pyrazole thus formed was eliminated by hydrolysis. It is indeed known that 1-carbamoyl group in pyrazole rings is less stable than 1-amidino group [10].

In the reaction of **1** with aminoguanidine, a strong nucleophilic hydrazine, cyclization into pyrazole and formation of amidinohydrazone are facilitated. In fact, the deacetylated pyrazole **3** was formed in low yield and compound **2** was obtained as the main product. While, in the case of semicarbazide, a weak nucleophile, the condensation (or cyclization) might proceed with a certain difficulty, allowing the deacetylation of **1** and/or of a semicarbazone type intermediate. It is very likely that the deacetylation took place in the course of the condensation, but not after the achievement of pyrazole ring formation.

Scheme 2

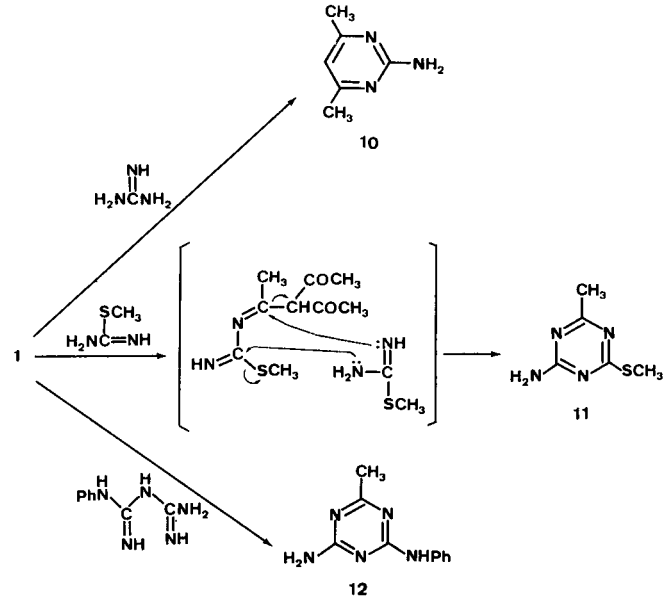


The reaction of **1** with phenylhydrazine (which is less nucleophile than amidinohydrazines) in methanol in the presence of hydrochloric acid, or in anhydrous ethanol containing a few drops of acetic acid at room temperature afforded 3,5-dimethyl-1-phenylpyrazole (**9**) [11] in quantitative yield, without formation of 4-acetyl-3,5-dimethyl-1-phenylpyrazole.

We next examined the reaction of **1** with some amidine analogues. Treatment of **1** with guanidine in anhydrous ethanol under reflux for 2 hours gave 2-amino-4,6-dimethylpyrimidine (**10**) [12] in 18% yield without formation of the expected 4-acetylpyrimidine derivative. Similar reaction of **1** with benzamidine did not afford any crystalline product, but resulted in decomposition of the starting materials. However, heating of **1** with *S*-methylisothiourea in anhydrous ethanol provided 2-amino-4-methyl-6-methylthio-1,3,5-triazine (**11**) [13] in 44% yield.

We suggest a possible mechanism for the formation of **11** (Scheme 3), which involves triple condensation between one molecule of **1** and two molecules of *S*-methylisothiourea, probably *via* biguanide type intermediate. Similar reaction involving formamide and *S*-methylisothiourea has been reported [14] to yield 2-amino-4-methylthio-1,3,5-triazine. The formation of **11** from **1** and *S*-methylisothiourea indicates that **1** acts as one carbon source for triazine ring formation. Indeed, we found that **1** reacted with phenylbiguanide in anhydrous ethanol to give 2-amino-4-anilino-6-methyl-1,3,5-triazine (**12**) which has been prepared from phenylbiguanide and acid derivatives [15].

Scheme 3



The reaction of **1** with thiourea in the presence of an alkali only gave a trace of *N*-acetylthiourea without any other condensation product.

The above results show that the condensation of **1** with amidine analogues into pyrimidines is difficult under alkaline conditions which strongly favour the cleavage of **1** and/or condensation intermediates in the reaction. Generally the condensation of amidines to form pyrimidine rings do not take place in acidic medium. This is in contrast with the reaction of **1** with amidinohydrazines which proceeds in acidic medium to give the expected pyrazole derivatives. It is noteworthy that triacetylmethane **1**, depending on the nature of the nucleophile used, can behave like a β,β'-tricarbonyl, a β-dicarbonyl or a monocarbonyl compound.

EXPERIMENTAL

Melting points were determined using a Kofler bench apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded on a Hitachi-Perkin Elmer 60 MHz spectrometer or a Varian 390 90 MHz spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Ribermag R10-10 apparatus using a direct inlet system. Infrared spectra were obtained on a Perkin-Elmer model 1710 spectrophotometer.

4-Acetyl-1-amidino-3,5-dimethylpyrazole Amidinohydrazone Dihydrochloride (**2**) and 1-Amidino-3,5-dimethylpyrazole Hydrochloride (**3**).

A solution of **1** (1.4 g, 0.01 mole) in methanol (25 ml) was added to a cold solution (in an ice bath) of aminoguanidine hydrogencarbonate (3.3 g, 0.024 mole) and concentrated hydrochloric acid (4 ml) in water (6 ml). The mixture was stirred at room temperature for 19 hours. After evaporation of the solvent to dryness under reduced pressure, the residue was treated with ethanol and the insoluble solid (aminoguanidine hydrochloride) was filtered off. The ethanolic filtrate was evaporated under reduced pressure to yield a crystalline solid whose ^{1}H-nmr spectrum showed the presence of two compounds **2** and **3**. Recrystallization from anhydrous ethanol gave **2** (1.8 g, 54%), mp >270°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.30 (br s, 6H, $2CH_3$), 2.60 (s, 3H, CH_3), 7.85 (br s, 4H, exch), 9.55 (br s, 3H, exch), 13.5-14.0 (br, 2H, exch); ms: m/z 236 (14, M^+), 221 (11), 194 (41), 179 (50), 122 (28), 99 (14), 58 (46), 44 (100), 43 (98).

Anal. Calcd. for $C_9H_{16}N_8 \cdot 2HCl \cdot 1.5\ H_2O$: C, 32.15; H, 6.29; N, 33.32; Cl, 21.08. Found: C, 32.16; H, 6.27; N, 33.15; Cl, 21.17.

The ethanolic solution after recrystallization of **2** was concentrated under reduced pressure and the oily residue was chromatographed on silica gel column with a mixture of chloroform and methanol (10:3, v/v) as eluent. The first eluate (220 ml) was concentrated to give a crystalline solid (0.3 g, 17%) whose ^{1}H-nmr spectrum was identical with that of the authentic sample of **3**, mp 150°, prepared from acetylacetone and aminoguadine [8]; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.20 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.30 (s, 1H, H-4), 9.35 (br, exch); ms: m/z 138 (30, M^+), 96 (80), 95 (100), 81 (21), 65 (8), 54 (20).

4-Acetyl-1-(2-imidazolinyl)-3,5-dimethylpyrazole (2-Imidazolinyl)-hydrazone Dihydrobromide (**4**) and 1-(2-Imidazolinyl)-3,5-dimethylpyrazole Hydrobromide (**5**).

A solution of **1** (1.4 g, 0.01 mole) in methanol (20 ml) was added to a cold solution of (2-imidazolinyl)hydrazine hydrobromide (3.6 g, 0.02 mole) and hydrobromic acid (48%, 2 ml) in methanol (100 ml). The mixture was kept at room temperature for 48 hours. After evaporation of the solvent to dryness under reduced pressure, the residue was treated with small amount of ethanol. The insoluble solid (4 g), whose ^{1}H-nmr spectrum showed the presence of two compounds **4** and **5** was recrystallized from methanol to yield **5** (0.6 g, 24%), mp >270°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.25 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.00 (s, 4H, $2CH_2$), 6.45 (s, 1H, H-5), 10.0-11.0 (br, exch); ms: m/z 164 (95, M^+), 149 (15), 136 (10), 109 (73), 69 (100), 55 (73), 44 (100).

Anal. Calcd. for $C_8H_{12}N_4 \cdot HBr$: C, 39.19; H, 5.34; N, 22.86; Br, 32.60. Found: C, 39.28; H, 5.23; N, 22.76; Br, 32.47.

The methanolic solution after recrystallization of **5** was concentrated under reduced pressure. The residue was treated with a small amount of cold ethanol and the insoluble crystalline solid was recrystallized from ethanol to yield **4** (2.1 g, 47%), mp >270°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 3.35 (s, 4H, $2CH_2$) 4.00 (s, 4H, $2CH_2$), 8.30 (s, 2H, exch), 10.0-11.0 (br, exch); ms: m/z 288 (76, M^+), 273 (75), 259 (18), 203 (14), 190 (16), 125 (18), 98 (25), 69 (52), 55 (68), 44 (100).

Anal. Calcd. for $C_{13}H_{20}N_8 \cdot 2HBr$: C, 34.68; H, 4.92; N, 24.89; Br, 35.49. Found: C, 34.76; H, 5.19; N, 24.55; Br, 35.30.

Reaction of **1** with Thiosemicarbazide.

A mixture of **1** (1.85 g, 0.013 mole), thiosemicarbazide (2.4 g, 0.026 mole) and concentrated hydrochloric acid (2 ml) in methanol (180 ml) was stirred at room temperature for 38 hours. A white precipitate was collected by filtration and washed with methanol and ether. Recrystallization from methanol gave 4-acetyl-3,5-dimethyl-1-thiocarbamoylpyrazole thiosemicarbazone (**7**) (0.65 g, 18%), mp >270°; ^{1}H-nmr (dimethyl sulfoxide-d_6-deuterium oxide): δ 2.25 (s, 6H, $2CH_3$), 2.72 (s, 3H, CH_3); ms: m/z 270 (12, M^+), 211 (100), 195 (57), 136 (28), 121 (43), 59 (82).

Anal. Calcd. for $C_9H_{14}N_6S_2$: C, 39.98; H, 5.21; N, 31.08; S, 23.71. Found: C, 40.06; H, 5.30; N, 30.35; S, 24.04.

The methanolic solution after the crystallization of **7** was concentrated under reduced pressure. The residue was treated with ether to give a white precipitate which was recrystallized from ethanol/ether to yield 4-acetyl-3,5-dimethylpyrazole thiosemicarbazone hydrochloride (**8**) (0.25 g, 8%), mp >270°; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.30 (s, 3H, CH_3), 2.45 (s, 6H, $2CH_3$), 9.5 (br, 5H, exch); ms: m/z 211 (66, M^+), 196 (35), 149 (16), 136 (12), 123 (32), 59 (100), 55 (45).

Anal. Calcd. for $C_8H_{13}N_5S \cdot HCl$: C, 38.79; H, 5.70; N, 28.27; S, 12.94; Cl, 14.31. Found: C, 38.73; H, 5.68; N, 28.32; S, 13.11; Cl, 14.28.

The reaction solution after isolation of the insoluble fraction was evaporated under reduced pressure. The residue was stirred in ether for 1 hour and the solid was collected by filtration and recrystallized from ethanol/ether to give 3,5-dimethylpyrazole hydrochloride (**6**) (1.2 g, 70%), mp 166° (free base, mp 107°), which was identified by comparison of its ^{1}H-nmr spectrum with that of the authentic sample prepared from acetylacetone and hydrazine (lit [9] free base, mp 107-108°); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.10 (s, 6H, $2CH_3$), 5.70 (s, 1H, H-4), 12.1 (br, 1H, exch).

Formation of **6** from **1** and Semicarbazide.

A mixture of **1** (1.4 g, 0.01 mole), semicarbazide hydrochloride (2.3 g, 0.02 mole) and concentrated hydrochloric acid (1 ml) in methanol (180 ml) was stirred at room temperature for 48 hours. After removal of the solvent, the residue was treated with a small amount of absolute ethanol. The insoluble fraction was filtered off and ethanolic filtrate was evaporated under reduced pressure. The residue was treated in ether to yield **6** as a crystalline solid (1.3 g, 98%). Recrystallization from ethanol/ether gave a pure sample, mp 166°, which was identical with **6** previously obtained from **1** and thiosemicarbazide.

Formation of **9** from **1** and Phenylhydrazine.

A solution of **1** (1.42 g, 0.01 mole) in methanol (25 ml) was added to a cold solution of phenylhydrazine (2.2 g, 0.02 mole) and concentrated hydrochloric acid (2 ml) in water (15 ml). The mixture was stirred at room temperature for 20 hours. After removal of the solvent, the residue was dissolved in water. The resultant solution was neutralized with sodium hydrogencarbonate and extracted with ethyl acetate. The extract was washed with water, dried (magnesium sulfate) and evaporated to yield **9** as an oily product (1.6 g, 93%) whose ^{1}H-nmr spectrum was identical with that of the authentic sample [11].

When a mixture of **1** (1.42 g, 0.01 mole) and phenylhydrazine (2.2 g, 0.02 mole) in anhydrous ethanol (40 ml) containing acetic acid (2 drops) was treated in the same manner, pyrazole **9** also obtained in quantitative yield.

Formation of **10** from **1** and Guanidine.

To an ethanolic sodium ethoxide solution (0.46 g of sodium in 50 ml of anhydrous ethanol) were added guanidine hydrochloride (2.3 g, 0.024 mole) and **1** (2.8 g, 0.02 mole). The mixture was stirred at room temperature for 2 hours and then refluxed for 2 hours. After removal of the solvent, water was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with water, dried (magnesium sulfate) and concentrated to yield a crystalline solid. Recrystallization from cyclohexane/ethyl acetate gave **10** (0.45 g, 18%), mp 151-152°, whose ^{1}H-nmr spectrum was identical with that of the authentic sample [12]. If the same mixture is kept at room temperature for 24 hours, the reaction did not take place.

2-Amino-4-methyl-6-methylthio-1,3,5-triazine (**11**).

To an ethanolic sodium ethoxide solution (0.8 g, of sodium in 100 ml of anhydrous ethanol) were added *S*-methylisothiourea hydroiodide (7.6 g, 0.035 mole) and **1** (4.2 g, 0.03 mole) dissolved in anhydrous ethanol (20 ml) with cooling in an ice bath. The mixture was maintained at room temperature for 2 hours and then refluxed for 2 hours. After removal of the solvent, the residue was treated with cold water and the mixture was extracted with ethyl acetate. The extract was washed with water, dried (magnesium sulfate) and concentrated to dryness to yield a crystalline solid. Recrystallization from cyclohexane/benzene gave **11** (1.2 g, 44%), mp 160° (lit [13] mp 165°); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.20 (s, 3H, CH_3), 2.40 (s, 3H, SCH_3), 7.35 (s, 2H, exch NH_2); ms: m/z 156 (100, M^+), 110 (86), 69 (62), 42 (82).

When the same reaction was carried out using triethylamine in the place of sodium, triazine **11** was obtained in 34% yield.

2-Amino-4-anilino-6-methyl-1,3,5-triazine (**12**).

A mixture of **1** (1.42 g, 0.01 mole) and phenylbiguanide hydrochloride (2.5 g, 0.012 mole) in an ethanolic sodium ethoxide solution (0.23 g of sodium in 50 ml of anhydrous ethanol) was heated under reflux for 7 hours. After removal of the solvent, the residue was treated with water to yield a crystalline solid. Recrystallization from ethanol gave **12** (1.1 g, 55%), mp 178-179° (lit [15] mp 178°); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.20 (s, 3H, CH_3), 6.90 (s, 2H, exch NH_2), 6.8-8.0 (m, 5H, Ph-H), 9.35 (s, 1H, exch NH); ms: m/z 201 (100, M^+), 159 (16), 118 (21), 91 (13), 84 (9), 77 (30).

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