Formation of Pyrimidine-5-carboxaldehydes, 1-Aminoethylene-2,2-dicarboxaldehyde and 2-Amino-4-anilino-1,3,5-triazine from Triformylmethane and Amidines

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Received November 3, 1993

Triformylmethane (**1**) reacted with benzamidine, guanidine and *S*-methylisothiourea to give the corresponding 2-substituted pyrimidines-5-carboxaldehydes. However, reactions of **1** with acetamidine (or formamidine) and phenylbiguanide gave the unexpected 1-aminoethylene-2,2-dicarboxaldehyde (**5**) and 2-amino-4-anilino-1,3,5-triazine (**9**), respectively.

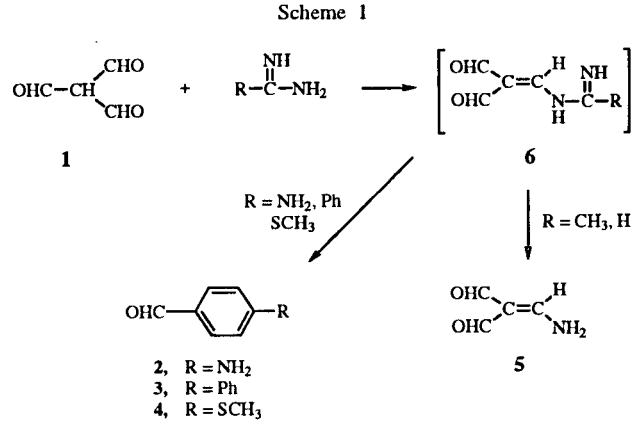
J. Heterocyclic Chem., **31**, 973 (1994).

In a previous paper [1], we described that the reactions of triformylmethane (**1**) with hydroxylamine, some hydrazines and amidines led to the formation of isoxazole-, pyrazole- and pyrimidinecarboxaldehydes, respectively. These reactions provided a convenient one-step synthesis of pyrazole-4-carboxaldehydes and pyrimidine-5-carboxaldehydes whose preparation is generally difficult. The above results prompted us to examine the condensation of **1** with various amidines and their analogues in order to obtain new pyrimidine-5-carboxaldehydes, and we found that the formation of pyrimidine ring compounds depends on amidines used. We also found that **1** reacted with phenylbiguanide to give a 1,3,5-triazine derivative. These results are reported here including relevant details of the previous paper.

Treatment of **1** with guanidine hydrochloride in boiling anhydrous ethanol for 20 hours in the presence of sodium ethoxide gave 2-aminopyrimidine-5-carboxaldehyde (**2**) in 49% yield. Similar reaction of **1** with benzamidine hydrochloride or *S*-methylisothiourea hydroiodide also afforded 2-phenylpyrimidine-5-carboxaldehyde (**3**) or 2-methylthiopyrimidine-5-carboxaldehyde (**4**) [2] in 60% and 33% yields, respectively (Scheme 1). The structures of **2**, **3** and **4** were supported by the analytical and spectral data. Especially in the ^{1}H-nmr spectra, the signals due to the formyl proton (δ 9.63-10.25 ppm, s, 1H) as well as the signals assignable to the C-4 and C-6 protons (δ 8.56-9.15 ppm, s, 2H) are quite characteristic. The ir spectra of **2**, **3** and **4** showed absorption band at 1678-1705 cm^{-1} attributable to the C=O group.

Reaction of **1** with acetamidine or formamidine under the same conditions did not afford the expected pyrimidinecarboxaldehyde, but 1-aminoethylene-2,2-dicarboxaldehyde (**5**) was obtained in 36% and 28% yields, respectively (Scheme 1). In this transformation, it is very likely that acetamidine and formamidine first reacted with **1** to provide 1,1-diformylethylene intermediates **6** (R = CH_3 and H), which are then hydrolyzed into **5**, in contrast to the corresponding intermediates **6** (R = NH_2, Ph and SCH_3) in the formation of pyrimidine-5-carboxaldehydes starting from guanidine, benzamidine and *S*-methylisothiourea.

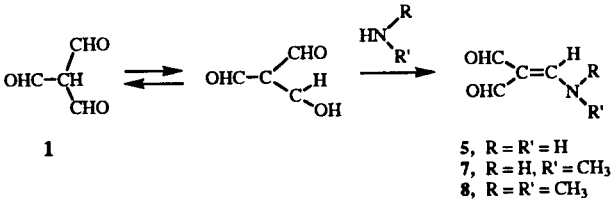
Scheme 1



To confirm its chemical structure, compound **5** was alternatively prepared by treatment of **1** with aqueous ammonia in methanol at room temperature. According to the same procedure, 1-(methylamino)ethylene-2,2-dicarboxaldehyde (**7**) and 1-(dimethylamino)ethylene-2,2-dicarboxaldehyde (**8**) were prepared by reacting **1** with methylamine and dimethylamine, respectively, in an aqueous methanolic solution. In these reactions triformylmethane behaves more as a hydroxyvinyl dicarboxaldehyde than as a tricarbonyl molecule. The easy formation of derivatives **5**, **7** and **8** from **1** is probably due to the electron attractive effect of the two formyl groups at the 1-position of 1,1-diformyl-2-hydroxyethylene as a tautomeric form of **1**. The formation of an enaminecarboxaldehyde when methyl diformylacetate reacts with amonia or methylamine [3], offers considerable similarity with these reactions.

When treated with thiourea in the presence of an alkali, **1** did not allow the formation of the expected pyrimidine-5-carboxaldehyde, but led to a mixture of unidentified products.

Scheme 2

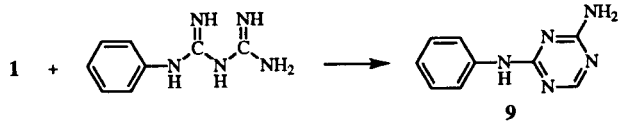


1

5, R = R' = H
7, R = H, R' = CH_3
8, R = R' = CH_3

On the other hand, phenylbiguanide reacting with **1** gave 2-amino-4-anilino-1,3,5-triazine (**9**) in 31% yield, instead of the expected pyrimidine-5-carboxaldehyde derivative. The triazine **9** was identical with that obtained by the action of ethyl formate on phenylbiguanide hydrochloride in the presence of a base according to an already described procedure [4]. The formation of **9** starting from **1** suggests that **1** acts as a formyl group provider which condenses on the two imino groups of phenylbiguanide. Such direct formation of triazine, starting from β,β-tricarbonyl derivative has already been observed in the case of triacetylmethane reacting with phenylbiguanide [5].

Scheme 3



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EXPERIMENTAL

Melting points were determined using a Köfler 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 direct inlet system. Infrared spectra were obtained on a Perkin-Elmer model 1710 spectrometer.

2-Substituted Pyrimidine-5-carboxaldehydes (**2**, **3** and **4**).

A mixture of guanidine hydrochloride (0.23 g, 2.4 mmoles) and **1** [6] (0.2 g, 2.0 mmoles) in an ethanolic sodium ethoxide solution (0.05 g of sodium in 25 ml of anhydrous ethanol) was stirred at room temperature for 1 hour, and then refluxed for 20 hours. After removal of the solvent under reduced pressure, the residue was treated with water (20 ml). The mixture was made acidic by addition of hydrochloric acid, and then alkalized with sodium hydrogencarbonate. The resultant solution was extracted with ethyl acetate and the extract was washed with water, dried (magnesium sulfate) and concentrated to yield **2** which was purified by recrystallization.

In the same manner by using benzamidine hydrochloride or *S*-methylisothiourea hydroiodide in place of guanidine hydrochloride, **3** or **4** was obtained.

Compound **2**, was obtained in 49% yield (0.12 g) mp 208-210° (benzene/ethanol); ^{1}H-nmr (DMSO-d_6): δ 7.53 (br, s, 2H, NH_2), 8.56 (s, 2H, C_4- and C_6-H), 9.63 (s, 1H, CHO); ms: m/z 123 (M^+); ir (potassium bromide): 3287, 3181 (NH_2), 1678 (CO) cm^{-1}.

Anal. Calcd. for $C_5H_5N_3O$: C, 48.78; H, 4.09; N, 34.13. Found: C, 48.85; H, 3.83; N, 34.44.

Compound **3** was obtained in 60% yield (0.22 g) mp 131-132° (cyclohexane); ^{1}H-nmr (DMSO-d_6): δ 7.2-7.6 (m, 3H, Ph), 8.1-8.5 (m, 2H, Ph), 9.15 (s, 2H, C_4- and C_6-H), 10.25 (s, 1H, CHO); ms: m/z 184 (M^+); ir (potassium bromide): 1705 (CO) cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.65; H, 4.56; N, 15.45.

Compound **4** was obtained in 33% yield (0.1 g) mp 83-84° (cyclohexane) (lit [2] mp 84°); ^{1}H-nmr (DMSO-d_6): δ 2.60 (s, 3H, CH_3), 9.05 (s, 2H, C_4- and C_6-H), 10.05 (s, 1H, CHO); ir (potassium bromide): 1698, 1682 (CO) cm^{-1}.

1-Aminoethylene-2,2-dicarboxaldehyde (**5**).

a) A mixture of acetamidine hydrochloride (0.23 g, 2.4 mmoles) and **1** (0.2 g, 2.0 mmoles) in an ethanolic sodium ethoxide solution (0.05 g of sodium in 25 ml anhydrous ethanol) was stirred at room temperature for 1 hour, and then refluxed for 20 hours. After evaporation of the solvent, the residue was treated with water (20 ml). The mixture was made acidic (*p*H 1) by addition of hydrochloric acid, and extracted with ethyl acetate. The extract was dried (magnesium sulfate) and concentrated to yield compound **5** which was practically pure (0.072 g, 36%). Recrystallization from benzene gave an analytical sample., mp 124-125°; ^{1}H-nmr (DMSO-d_6) δ 7.57-7.93 (2 q, becomes d after deuterium oxide exchange, 1H, =CH), 9.27 (s, 1H, CHO), 9.63 (d, 1H, CHO); ms: m/z: 99 (35, M^+); ir (potassium bromide): 1682, 1631 (CO) cm^{-1}.

Anal. Calcd. for $C_4H_5NO_2$: C, 48.40; H, 5.05; N, 14.14. Found: C, 48.31; H, 5.36; N, 13.91.

In the same manner using formamidine acetate (0.24 g, 2.4 mmoles) in place of acetamidine hydrochloride, **5** was obtained (0.055 g, 28%).

b) To a solution of **1** (0.4 g, 4 mmoles) in methanol (40 ml) was added 2.5 ml of aqueous ammonia (28%). The mixture was kept at room temperature for 1 hour. After removal of the solvent under reduced pressure at room temperature, the residue was treated with a small amount of benzene to give **5** (0.346 g, 87%) which was practically pure without further purification.

1-(Methylamino)ethylene-2,2-dicarboxaldehyde (**7**).

To a solution of **1** (0.37 g, 3.7 mmoles) in methanol (38 ml) was added 3.8 ml (50 mmoles) of aqueous solution of methylamine (40%). After distillation of the solvent, under reduced pressure at room temperature, the residue was chromatographed on a silica gel column with ethyl acetate to give **7**, which was purified by recrystallization from cyclohexane (0.312 g, 73%) mp 110°; ^{1}H-nmr (DMSO-d_6): δ 3.1-3.2 (d, becomes s after deuterium oxide exchange, 3H, CH_3), 7.8 (d, becomes s after deuterium oxide exchange, 1H, =CH-), 9.23 (s, 1H, CHO), 9.5 (s, 1H, CHO), 10.5 (br, 1H, ech, NH); ms: m/z: 113 (M^+); ir (potassium bromide) 1687, 1610 (CO) cm^{-1}.

Anal. Calcd. for $C_5H_7NO_2$: C, 53.09; H, 6.20; N, 12.39. Found: C, 53.4; H, 6.22; N, 12.09.

1-(Dimethylamino)ethylene-2,2-dicarboxaldehyde (**8**).

Compound **8** was obtained according to the same technique and using the same proportions of **1** and of dimethylamine, as described for the preparation of **7**. Purification by chromatography on a silica gel column with methanol gave **8** (57% yield), mp 41-42°, which was previously described (lit [7] mp 39-41.5°); ^{1}H-nmr (DMSO-d_6) δ 3.3 (s, 3H, CH_3), 3.4 (s, 3H, CH_3), 7.65 (s, 1H, =CH-), 9.4 (s, 2H, 2 CHO); ms m/z: 127 (M^+); ir (potassium bromide): 1605 (CO) cm^{-1}.

2-Amino-4-anilino-1,3,5-triazine (**9**).

To an ethanolic sodium ethoxide solution (0.05 g of sodium in 20 ml of anhydrous ethanol) were added phenylbiguanide hydrochloride (0.5 g, 2.2 mmoles) and **1** (0.2 g, 2 mmoles). The mixture was maintained at room temperature for 1 hour and then refluxed for 20 hours. After removal of the solvent, the residue was treated with water (20 ml) to give a crystalline solid which was collected by filtration, washed with water and dried. Purification by chromatography on a silica gel column with ethyl acetate provided **9** (0.13 g, 31%), mp 235-236°, which was identical with an authentic sample (lit [4] mp 235-236°); ^{1}H-nmr (DMSO-d_6): δ 6.8-7.3 (m, 3H and 2H exch, H-3',4',5' and NH_2), 7.6-7.8 (m, 2H, H-2',6'), 8.1 (s, 1H, C6-H), 9.4 (s, 1H, exch, NH); ms: m/z: 187 (M^+); ir (potassium bromide): 3093 (NH_2) cm^{-1}.

REFERENCES AND NOTES

[1] K. Takagi, A. Bajnati, and M. Hubert-Habart, *Bull. Soc. Chim. France*, **127**, 660 (1990).

[2] The pyrimidine **4** has been prepared from 5-bromo-2-methylthiopyrimidine-4-carboxylic acid *via* four steps. J. Arukwe and K. Undheim, *Acta Chem. Scand.*, **B40**, 588 (1986).

[3] L. F. Tietze, A. Bergmann, and K. Bruggeman, *Tetrahedron Letters*, **24**, 3579 (1983).

[4] C. G. Overberger, and S. L. Shapiro, *J. Am. Chem. Soc.*, **76**, 93 (1954).

[5] K. Takagi, A. Bajnati, and M. Hubert-Habart, *J. Heterocyclic Chem.*, **27**, 1565 (1990).

[6] Z. Arnold, and J. Zemlicka *Collect Czech. Chem. Commun.*, **25**, 1318 (1960).

[7] Z. Arnold, *Collect Czech. Chem. Commun.*, **26**, 3051 (1961).