ORIGINAL ARTICLE

Unexpected products from the reaction of different compounds with hydrazine hydrate or aryl thiosemicarbazides

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Expected products; 2,5-Dihydroxyacetophenone; 1-(1,4-Dihydroxynaphthalen-2-yl)ethanone; 2-(2,5-Dimethoxybenzylidene)propanedioate; Ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propanoate

Abstract The reaction of 2,5-dihydroxyacetophenone I or 1-(1,4-dihydroxynaphthalen-2-yl)ethanone II with various 4-aryl thiosemicarbazides did not yield the expected 4-aryl-1-[1-(2,5-dihydroxyphenyl)ethylidene]thiosemicarbazides III nor 4-aryl-1-[1-(1,4-dihydroxy-naphthalen-2-yl)ethylidene]thiosemicarbazides IV, respectively. However, unexpected products were formed namely, N1,N2-bis[1-(2,5-dihydroxyphenyl)ethylidene]hydrazine V or N1,N2-bis[1-(1,4-dihydroxynaphthalen-2-yl)ethylidene]hydrazine VI, respectively. Also, an unexpected product N1,N2-bis(2,5-dimethoxybenzylidene)hydrazine XI was obtained when heating under reflux diethyl 2-(2,5-dimethoxybenzylidene)propanedioate VII or ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propanoate VIII with 99% hydrazide hydrate in ethanol. The mechanisms of these reactions were proposed.

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1. Introduction

Thiosemicarbazone derivatives of aldehydes and ketones are known to be prepared by condensation of equimolar amounts of aldehyde or ketone with the appropriately substituted thiosemicarbazide under variable reaction conditions (Jouad et al., 2001; Bharti et al., 2002; Tenório et al., 2005; Bal et al., 2005; Chaaban et al., 2006; Li et al., 2006; De Aquino et al., 2008). Thus when 2,5-dihydroxyacetophenone I or 1-(1,4-dihydroxy-naphthalen-2-yl)ethanone II was heated under reflux with the selected 4-aryl thiosemicarbazide (phenyl, p-tolyl or p-chlorophenyl) in absolute ethanol containing concentrated sulfuric acid, the products obtained were not the expected 4-aryl-1-[1-(2,5-dihydroxyphenyl)ethylidene]thiosemicarbazides III nor 4-aryl-1-[1-(1,4-dihydroxy-naphthalen-2-yl)ethylidene]thiosemicarbazides IV. These products obtained from the different 4-aryl thiosemicarbazides (phenyl, p-tolyl or p-chlorophenyl) were compared by TLC, m.p., microanalytical data as well as IR and proved to be one and the same compound namely N1,N2-bis[1-(2,5-dihydroxyphenyl)ethylidene]hydrazine V or N1,N2-bis[1-(1,4-dihydroxynaphthalen-2-yl)ethylidene]hydrazine VI, respectively. This was further confirmed by preparing

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N\textsuperscript{1},N\textsuperscript{2}-bis[1-(2,5-dihydroxyphenyl)ethylidene]hydrazine \textit{V} or N\textsuperscript{1},N\textsuperscript{2}-bis[1-(4-dihydroxynaphthal-2-yl)ethylidene]hydrazine \textit{VI} from 2,5-dihydroxycetophenone \textit{I} or 1-(2,5-dihydroxy-naphthalen-2-yl)ethanone \textit{II}, respectively with 99% hydrazine hydrate in ethanol while stirring at room temperature. The products obtained by the two different routes were identical as shown by comparing their m.p., mixed m.p., IR and \textsuperscript{1}H NMR spectra in addition to their microanalytical data. The most widely applicable method for the synthesis of malonohydrazides involves the reaction of diethyl malonates with hydrazine hydrate (Metwally et al., 2010). Accordingly, 2-(2,5-dimethoxybenzyl)malonohydrazide IX was prepared via the reaction of diethyl 2-(2,5-dimethoxybenzylidene)propeniodiote VII with excess 99% hydrazine hydrate in ethanol by stirred at room temperature. Moreover, cyclocondensation of ethyl cyanoacetate derivatives with hydrazine hydrate to afford substituted 3-amino-1H-2-pyrazolin-5-one is a well established and studied synthetic procedure (Saleh et al., 2003). Accordingly, 3-amino-4-(2,5-dimethoxybenzylidene)-1H-2-pyrazolin-5-one X was prepared by stirring an ethanolic solution of ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propenoate VIII with 99% hydrazine hydrate at room temperature. However, it is to be mentioned that a totally unexpected product N\textsuperscript{1},N\textsuperscript{2}-bis(2,5-dimethoxybenzylidene)hydrazine XI was obtained when the afore-mentioned reactions involved the addition of 99% hydrazine hydrate to an equimolar amount of diethyl 2-(2,5-dimethoxybenzylidene)propeniodiote VII (Hormi et al., 1991) or ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propenoate VIII (Volmajer et al., 2003; Kon et al., 1992) in ethanol and then the reaction mixture was heated under reflux for 2 h. A thorough look into the literature revealed that diethyl malonate can be a leaving group when reacting diester compounds with hydrazine hydrate (Podesva et al., 1969). Such type of azine compound XI may be prepared by reacting aldehyde with hydrazine hydrate (Duan et al., 2005). Thus 2 mol of 2,5-dimethoxybenzaldehyde were reacted with 1 mol of 99% hydrazine hydrate to form the product. The compound was compared with the obtained compound XI by TLC, m.p., IR and microanalyses and has proved to be one and the same compound.

2. Experimental

2.1. Materials and methods

Melting points of synthesized compounds were determined in open glass capillaries using a Griffin melting point apparatus and are all uncorrected. Infrared spectra (IR) were recorded using KBr disks by a Perkin-Elmer 1430 Infrared spectrophotometer. Nuclear magnetic resonance (\textit{H} NMR, \textit{13}C NMR and DEPT) was determined using a Jeol-NMR 500 MHz spectrophotometer, in the Faculty of Science, Alexandria University and are reported as \textit{\delta} values (ppm) relative to tetramethylsilane (TMS) as an internal reference. The type of signal was indicated by one of the following letters: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet.

Mass spectra were run on a Finnigan mass spectrometer model SSQ/7000 (70 eV), in the Faculty of Science, Cairo University. Elemental microanalyses were performed at the microanalytical unit, Faculty of Science, Cairo University. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel (60 GF254, Merck) using glass plates and the spots were visualized by exposure to iodine vapor or to UV-lamp at \textit{\lambda} = 254 nm for a few seconds.

2.2. Preparation methods and physical data of synthesized compounds

2.2.1. N\textsuperscript{1},N\textsuperscript{2}-Bis[1-(2,5-dihydroxyphenyl)ethylidene]hydrazine (\textit{V})

A solution of the selected 4-aryl thiosemicarbazide (phenyl, p-tolyl, p-chlorophenyl) (5 mmol) in absolute ethanol (15 mL) was gradually added to a well stirred solution of an equimolar amount of 2,5-dihydroxycetophenone \textit{I} (5 mmol) in absolute ethanol (25 mL) followed by the addition of 5 drops of concentrated sulfuric acid. The reaction mixture was heated under reflux while stirring for 10 h and then concentrated. The formed product was filtered, washed with ethanol, air dried and crystallized from ethanol/chloroform (9:1) as orange crystals. Yields 70%, 68% and 72% (in case of phenyl, p-tolyl and p-chlorophenol, respectively); m.p. 310 °C (with decomposition). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, \textit{\delta}) ppm: 2.37 (s, 6H, 2CH\textsubscript{3}); 6.76 (d, 2H, \textit{J} = 8.4 Hz, Ar–C\textsubscript{3}–H); 6.81 (dd, 2H, \textit{J} = 8.4, 3.05 Hz, Ar–C\textsubscript{6}–H); 7.05 (d, 2H, \textit{J} = 3.05 Hz, Ar–C\textsubscript{5}–H); 9.12, 12.23 (two s, 4H, 4OH, D\textsubscript{2}O-exchangeable). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, \textit{\delta}) ppm: 13.2, 115.03, 118.28, 120.98, 124.92, 152.89 (phenyl C-6, 3, 1, 4, 5, 2 respectively); 168.15 (CH=–N). DEPT (DMSO-d\textsubscript{6}, \textit{\delta}) ppm: 15.42 (1H); 111.03, 118.28, 119.81, 120.98, 149.92, 152.89 (phenyl C-6, 3, 1, 4, 5, 2 respectively). IR (KBr, \textit{\nu} cm\textsuperscript{–1}): 3376 (OH), 1561 (C=–N), 1385 (C–N), 1151 (C–N). Anal. Calcd \textit{\%}: 301 (12) (M\textsuperscript{+}+1), 300 (58.1) (M\textsuperscript{+}), 52 (100). Anal. Calcd \textit{\%}: C\textsubscript{15}H\textsubscript{16}N\textsubscript{2}O\textsubscript{4}. Found: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.66; H, 5.45; N, 9.27.

2.2.1.1. To prove this reaction. A solution of 2,5-dihydroxyacetophenone \textit{I} (2 mmol) in ethanol (5 mL) was treated with a solution of 99% hydrazine hydrate (1 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 2 h and set aside overnight for complete precipitation. The orange precipitate formed was filtered, washed with water, air dried and crystallized from ethanol/chloroform (9:1) as orange crystals. Yields 67%. Data of the obtained product were similar to that obtained before.

2.2.2. N\textsuperscript{1},N\textsuperscript{2}-Bis[1-(4-dihydroxynaphthalen-2-yl)ethylidene]hydrazine (\textit{VI})

A solution of the selected 4-aryl thiosemicarbazide (phenyl, p-tolyl or p-chlorophenol) (5 mmol) in absolute ethanol (15 mL) was gradually added to a well stirred solution of an equimolar amount of 1-(4,5-dihydroxynaphthalen-2-yl)ethanone \textit{II} (5 mmol) in absolute ethanol (25 mL) followed by the addition of 5 drops of concentrated sulfuric acid. The reaction mixture was heated under reflux while stirring for 10 h and then concentrated. The formed product was filtered, washed with ethanol, air dried and finally recrystallized from ethanol/chloroform (9:1) as orange crystals. Yields 91%, 93% and 91% (in case of phenyl, p-tolyl and p-chlorophenol, respectively); m.p. 250 °C (with decomposition). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, \textit{\delta}) ppm: 2.61 (s, 6H, 2CH\textsubscript{3}); 7.09 (s, 2H, Ar–C\textsubscript{6}–H); 7.49–7.60 (m, 4H, Ar–C\textsubscript{3}–H); 8.06 (d, 2H, \textit{J} = 7.65 Hz, Ar–C\textsubscript{5}–H); 8.28 (d, 2H, \textit{J} = 8.4 Hz, Ar–C\textsubscript{6}–H); 9.72, 14.32 (two s, 4H, 4OH, D\textsubscript{2}O-exchangeable). \textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, \textit{\delta}) ppm: 15.67 (CH\textsubscript{3}); 105.81, 111.94, 122.51,
2.2.2.1. To prove this reaction. A solution of 1-(1,4-dihydroxynaphthalen-2-yl)ethaneone II (2 mmol) in ethanol (5 mL) was treated with a solution of 99% hydrazine hydrate (1 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 2 h and set aside overnight for complete precipitation. The orange precipitate formed was filtered, washed with water, air dried and crystallized from ethanol/chloroform (9:1) as orange crystals. Yield 55%. Data of the obtained product were similar to that obtained before.

2.2.2.3. 2-(2,5-Dimethoxybenzyl)malonaldehydrazide (IX)

A solution of the diethyl 2-(2,5-dimethoxybenzylidene)propanedioate VII (3.6 mmol) in ethanol (2 mL) was added dropwise to a solution of 99% hydrazine hydrate (18 mmol) in ethanol (1 mL). The reaction mixture was stirred at room temperature whereupon a white precipitate was formed within 30 min. For complete precipitation the reaction mixture was allowed to set aside overnight. The white precipitate formed was filtered, washed with cold ethanol, air dried and crystallized from ethanol as white solid. Yield 66%; m.p. 178–180 °C. 1H NMR (DMSO-d6, δ ppm): 3.25 (d, 2H, J = 7.65 Hz, CH3CH); 3.27 (t, 1H, J = 7.65 Hz, CH2CH); 3.61, 3.68 (two s, each 2H, 2OCH3); 4.43 (s, 4H, 2NH2, D2O-exchangeable); 6.60 (d, 1H, J = 3.05 Hz, Ar-C5-H); 6.68 (dd, 1H, J = 8.4, 3.05 Hz, Ar-C5-H); 8.60 (d, 1H, J = 8.4 Hz, Ar-C1-H); 8.83 (s, 2H, 2NH, D2O-exchangeable). 13C NMR (DMSO-d6, δ ppm): 29.57 (CH2); 49.90 (CH); 55.78, 56.23 (2OCH3); 111.74, 111.90, 117.05, 128.42, 151.83, 153.21 (phenyl C4, 6, 3, 1, 2, 5 respectively); 168.56 (C=O). IR (KBr, μm⁻¹): 3312, 3200, 3235 (NH2, νNH), 1668 (C=O=O), 1541 (νNH), 1221, 1040 (C=O−C). EI MS, m/z (%): 328 (1.5) (M+); 77 (100). Anal. Calcd (%) for C18H17N3O4: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.62; H, 5.96; N, 8.47.

3. Results and discussion

Synthesis of the intermediates and target compounds was accomplished according to the steps illustrated in Schemes I and 2. Acetylation of hydroquinone with acetic anhydride in the presence of drops of concentrated sulfuric acid afforded hydroquinone diacetate (Pritchard, 1948). It was then subjected to Fries rearrangement using anhydrous aluminum chloride at 160–165 °C yielding 2,5-dihydroxyacetophenone I (Amin and Shah, 1948). Heating the latter with the selected 4-aryl thiosemicarbazide (phenyl, p-tolyl or p-chlorophenyl) in absolute ethanol containing concentrated sulfuric acid did not yield the expected 4-aryl-1-[1-(2,5-dihydroxyphenyl)ethylidene]thiosemicarbazides III. The product was proved to be N1,N2-bis-[1-(2,5-dihydroxyphenyl)ethylidene]hydrazine V by studying its IR, 1H NMR, 13C NMR and mass spectrum besides elemental microanalyses. To verify this reaction, the unexpected compound V was alternatively prepared by reacting 2,5-dihydroxyacetophenone I with hydrazine hydrate at room temperature (25 °C). In addition, 1-(1,4-dihydroxynaphthalen-2-yl)ethaneone II (Spruit, 1947; Green, 1982; Crum, 1949) was synthesized from 3-acyetyl-4-hydroxy-naphthalene-1-acetate which was subjected to hydrolysis using hydrochloric acid in 50% aqueous ethanol. 3-Acetyl-4-hydroxy-naphthalene-1-acetate was prepared from napthalene-1,4-diyl diacetate through the Fries rearrangement reaction. This involved heating under reflux napthalene-1,4-diylic diacetate with anhydrous zinc chloride in glacial acetic acid (Spruit, 1947). Naphthalene-1,4-diylic diacetate was prepared by reductive acetylation of 1,4-naphthoquinone by heating under reflux for 1 h using acetic anhydride, pyridine and zinc dust. When 1-(1,4-dihydroxynaphthalen-2-yl)ethaneone II was heated under reflux with the selected 4-aryl thiosemicarbazide (phenyl, p-tolyl or p-chlorophenyl) in absolute ethanol containing concentrated sulfuric acid, the products obtained were not the expected 4-aryl-1-[1-(1,4-dihydroxynaphthalen-2-yl)ethylidene]thiosemicarbazides IV as it appeared by studying the spectral and microanalytical data. The products obtained from these different 4-aryl thiosemicarbazides (phenyl, p-tolyl or p-chlorophenyl) were compared by TLC, m.p., microanalytical data as well as IR and proved to be one and the same compound namely N1,N2-bis-[1-(1,4-dihydroxynaphthalen-2-yl)ethylidene]hydrazine VI. This was further confirmed by preparing N1,N2-bis-[1-(1,4-dihydroxynaphthalen-2-yl)ethylidene]hydrazine VI from 1-(1,4-dihydroxynaphthalen-
2-y)ethanone II and 99% hydrazine hydrate in ethanol while stirring at room temperature. The two products obtained by the two different routes were identical as shown by comparing their m.p., mixed m.p., IR and $^1$H NMR spectra in addition to their microanalytical data. Proposed mechanism for this reaction is illustrated in Fig. 1. The reaction starts by the nucleophilic attack of the lone pair of electrons of the basic nitrogen of the 4-aryl thiosemicarbazides (phenyl, $p$-tolyl or $p$-chlorophenyl) to the carbonyl of 2,5-dihydroxyacetophenone I or 1-(1,4-dihydroxynaphthalen-2-yl)ethanone II followed by the elimination of a molecule of water. This is followed by the subsequent attack of lone pair of electrons of the NH in the intermediate, elimination of a molecule of water together with an aryl isothiocyanate moiety (phenyl, $p$-tolyl or $p$-chlorophenyl) to yield the unexpected $N^1,N^2$-bis[1-(2,5-dihydroxyphenyl)ethyldiene]hydrazine V or $N^1,N^2$-bis[1-(1,4-dihydroxynaphthalen-2-yl)ethyldiene]hydrazine VI, respectively. It is worth mentioning that the aryl isothiocyanates formed were monitored by TLC during the progress of the reaction.

In Scheme 2, diethyl 2-(2,5-dimethoxybenzylidene)propanedioate VII (Hormi et al., 1991) and ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propenoate VIII (Kon et al., 1992; Volmajer et al., 2003) were prepared by the Knoevenagel reaction through the gradual addition of an ethanolic solution of 2,5-dimethoxybenzaldehyde to a well stirred ethanolic solution of diethyl malonate or ethyl cyanoacetate, respectively containing drops of piperidine as a catalyst. Reacting diethyl 2-(2,5-dimethoxybenzylidene)propanedioate VII with excess 99% hydrazine hydrate in ethanol by stirring at room temperature yielded 2-(2,5-dimethoxybenzyl)malonohydrazide IX.
Whereas, reacting ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propenoate VIII with excess 99% hydrazine hydrate in ethanol by stirring at room temperature afforded 3-amino-4-(2,5-dimethoxybenzylidene)-1H-2-pyrazolin-5-one X. However, a totally unexpected product N1,N2-bis(2,5-dimethoxybenzylidene)hydrazine XI was obtained when the afore-mentioned reaction was carried out by the addition of 99% hydrazine hydrate to an equimolar amount of diethyl 2-(2,5-dimethoxybenzylidene)propanedioate VII or ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propenoate VIII in ethanol and then heating the reaction mixture under reflux for 2 h. To prove the identity of this unexpected product, 2 mol of 2,5-dimethoxybenzaldehyde were allowed to react with 1 mol of 99% hydrazine hydrate in ethanol at room temperature. The product formed was compared with the obtained compound XI by TLC, m.p., IR and microanalyses and has proved to be one and

Figure 1  Suggested mechanism for the unexpected reaction of I or II with 4-aryl thiosemicarbazides.

Figure 2  Suggested mechanism for the unexpected reaction of VII or VIII with hydrazine hydrate.
the same compound. A thorough look into the literature revealed that diethyl malonate can be a leaving group when reacting diester compounds with hydrazine hydrate (Podesva et al., 1969). Accordingly, the formation of compound XI can be through the mechanism illustrated in Fig. 2. The reaction involves the attack of lone pair of electrons of the hydrazine to the \(\alpha,\beta\)-unsaturated ester compounds diethyl 2-(2,5-dimethoxy-benzylidene)propanedioate VII or ethyl 2-cyano-3-(2,5-dimethoxyphenyl)propenoate VIII followed by the elimination of a moiety of diethyl malonate or ethyl cyanoacetate, respectively. The lone pair of electrons of the amino group of the formed intermediate attacks another molecule of the starting \(\alpha,\beta\)-unsaturated ester compound VII or VIII, followed by the elimination of another moiety of diethyl malonate or ethyl cyanoacetate, respectively to yield the final product \(N^1, N^2\)-bis(2,5-dimethoxybenzylidene)hydrazine XI.

References


