Reactions of amidines with some carboxylic acid hydrazides

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Ten amidrazone derivatives (seven new compounds) and twelve 1,2,4-triazole derivatives (five new compounds) are synthesized and their structures are established by elemental analysis, IR, 1H NMR and 13C NMR spectral data.

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1,2,4-Triazole derivatives are reported to show a broad spectrum of biological activities such as anti-fungal, antimicrobial, hypoglycemic, antihypertensive, analgesic, antiparasitic, hypocholesteremic, antiviral, anti-inflammatory, antitumor and anti-HIV properties1-14. These reports prompted us to synthesize some new potential biological active 1,2,4-triazole derivatives.

On the other hand, a general and convenient method is the condensation of imidic esters with acylhydrazines for the preparation of 3,5-disubstituted-1,2,4-triazoles via intermediate acylamidrazones15,16. However, another interesting route of preparing acylamidrazones followed by thermal cyclization to 3,5-disubstituted-1,2,4-triazoles have been reported17. The procedure involves the reaction of benzamidine with an acylhydrazine to give a 1,2,4-triazole as well as that of acetamidine with an acylhydrazine to afford an acylaminidrazone followed by cyclization to a 1,2,4-triazole.

In the present study, the method reported earlier17 was considerably improved and applied to dicarboxylic acid hydrazines such as oxalodihydrazide, malonodihydrazide, adipodihydrazide and terephthalodihydrazide, along with some other acylhydrazine such as cyanoacetic acid hydrazide, 4-hydroxybenzhydrazide and isonicotinic hydrazide. In contrast to the results reported17, the intermediate acylidrazones 4, 5, 8, 9 were obtained in this study from the reactions of acetamidine or benzamidine with an acylhydrazine followed by the thermal cyclization to the corresponding 1,2,4-triazoles 6, 7, 10, 11 (Scheme I).

Results and Discussion

In the present study, only compounds 6a, 7a and 10a were directly obtained without isolation of the corresponding acylamidrazones. This situation can be attributed to the rate of the ring closure step of the reaction for 10a. This rate is enhanced by the electron-withdrawing group attached to the carbonyl carbon of the expected acylamidrazone. The products of reactions were obtained in higher yields changing between 87% and 97% in the study. The improved method was applied to the aryl amide at the room temperature, and this is an important difference with the results reported earlier17.

On the other hand, amidrazones are able to exhibit tautomorphism between N2 and N3 atoms18-22. Some of acylamidrazones exist in amide hydrazone structure while some others exist exclusively in hydrazide imide form23. However, Gol’din and coworkers have shown that N3-unsubstituted acylamidrazones exist exclusively in the amide hydrazone structure24. Indeed, the spectroscopic data obtained in the present study indicate that compounds 4, 5, 8 and 9 exist exclusively in the amide hydrazone form, as shown in Scheme I.

Experimental Section

Melting points were taken on a Büchi oil-heated melting point apparatus and are uncorrected. IR spectra were registered as KBr pellets on a Perkin-Elmer 1600 FTIR spectrometer. 1H NMR and 13C NMR spectra were recorded in DMSO-d6 on a
Synthesis of bis-acylamidrazones 4 or 5. A solution of acetamidine hydrochloride (0.015 mole) or benzamidine hydrochloride (0.015 mole) in 50 mL of absolute ethanol was treated with an ethanolic sodium ethoxide solution prepared by dissolving sodium (0.015 mole) in 30 mL of absolute ethanol. The mixture was stirred at room temperature for 1 hr and then filtered. Malonodihydrazide (0.005 mole), adipodiydrazide (0.005 mole) or terephthaloihydraide (0.005 mole) was added to the ethanol filtrate and the resulting mixture was stirred at room temperature for 24 hr. After evaporating solvent at 30-35 °C under reduced pressure, the crude product was recrystallized from an appropriate solvent to give the desired compound.

\[
\text{N}^1,\text{N}^{10b}\text{-Malonoyl-bis-acetamidrazone 4b: yield 1.93 g (90%) of colourless crystals, m.p. 154-55° (ethanol-benzene, 1:2); IR (KBr): 3415, 3310, 3160 (NH, NH), 1680 (C=O), 1620, 1595 (C=N) cm}^{-1};
\]

\[
\text{1}^\text{H NMR (DMSO-}d_6\text{): } \delta 2.30 (s, 6H, 2CH}_3\text{), 4.02 (s, 2H, CH}_2\text{), 4.50 (s, 4H, 2NH}_2\text{), 9.27 (s, 2H, 2NH)};
\]

\[
\text{13}^\text{C NMR (DMSO-}d_6\text{): } \delta 13.87 (2C), 28.13 (aliphatic carbons), 156.43, 156.60 (C=N), 158.85, 158.93 (C=O). \text{Anal. Calcd for C7H14N6O2: C, 39.24; H, 6.59; N, 39.23. Found: C, 39.53; H, 6.30; N, 39.98%}.\]

\[
\text{N}^1,\text{N}^{10b}\text{-Adipoyl-bis-acetamidrazone 4c: yield 2.40 g (94%) of colourless crystals, m.p. 177-78° (DMSO-water, 1:3); IR (KBr): 3360, 3300, 3250 (NH, NH), 1670 (C=O), 1610, 1580 (C=N) cm}^{-1};
\]

\[
\text{1}^\text{H NMR (DMSO-}d_6\text{): } \delta 1.60 (m, 4H, 2CH}_2\text{), 2.26 (s, 6H, 2CH}_3\text{), 2.53 (m, 4H, 2CH}_2\text{), 4.45 (s, 4H, 2NH}_2\text{), 9.36 (s, 2H, 2NH)};
\]

\[
\text{13}^\text{C NMR (DMSO-}d_6\text{): } \delta 14.10 (2C), 28.02 (2C), 28.86 (2C, aliphatic carbons), 157.12, 157.58 (C=N), 159.74, 160.20 (C=O). \text{Anal. Calcd for C10H20N6O2: C, 46.86; H, 7.87; N, 32.79. Found: C, 46.59; H, 7.94; N, 32.49%}.\]

\[
\text{N}^1,\text{N}^{10b}\text{-Terephthaloyl-bis-acetamidrazone 4d: it cyclized on heating (m.p. 333-34° from ethanol, lit25 m.p. 332°). \text{Anal. Calcd for C12H16N6O2: C, 52.16; H, 5.84; N, 30.42. Found: C, 51.90; H, 6.05; N, 30.22%}.\]

\[
\text{N}^1,\text{N}^{10b}\text{-Malonoyl-bis-benzamidrazone 5b: yield 3.02 g (89%) of colourless crystals, m.p. 194-95° (ethanol); IR (KBr): 3360, 3300, 3250 (NH, NH),}
\]
1670 (C=O), 1615, 1575 (C=N), 765, 685 (mono- 
substituted benzenoid ring) cm$^{-1}$; $^1$H NMR (DMSO-
$d_6$): $\delta$ 2.47 (s, 2H, CH$_2$), 4.60 (s, 4H, 2NH$_2$), 7.41-7.53 
(m, 6H, Ar-H), 7.89-8.00 (m, 4H, Ar-H), 9.30 (s, 2H, 
2NH); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 28.82 (aliphatic carbon), 127.67, 127.84, 128.05 (2C), 129.48, 129.76 
(2C), 129.94, 130.33, 130.67, 131.07, 136.54 
(aromatic carbons), 155.36 (2C=N), 157.82 (2C=O). 
Anal. Calcd for C$_{17}$H$_{18}$N$_6$: C, 60.34; H, 5.36; N, 
24.84. Found: C, 60.21; H, 5.19; N, 24.97%.

N$_1$N$_{4}$t-A dip oyl-b is-b en zamidraz one 5c: yield 
3.35 g (88%) of colourless crystals, it cyclized to 7c on heating (m.p. 265-66° from ethanol, lit m.p. 265°). 
$^1$H NMR (DMSO-$d_6$): $\delta$ 4.55 (s, 4H, 2NH$_2$), 7.70-8.50 
(m, 14H, Ar-H), 9.40 (s, 2H, 2NH); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 127.74, 127.96, 128.14 (2C), 128.54, 
129.23 (2C), 129.54, 129.96 (2C), 130.30 (2C), 
130.82, 131.14, 131.40, 132.96, 136.09, 136.60 
(aromatic carbons), 161.14 (2C=N), 169.76 (2C=O). 
Anal. Calcd for C$_{20}$H$_{24}$N$_6$O$_2$: C, 63.14; H, 6.36; 
N, 38.52. Found: C, 63.12; H, 6.24; N, 38.16%.

N$_1$N$_{4}$t-Terephthaloyl-b is-b en zamidraz one 5d: yield 
2.47 (s, 2H, CH$_2$), 4.60 (s, 4H, 2NH$_2$), 7.41-7.53 
(m, 6H, Ar-H), 7.89-8.00 (m, 4H, Ar-H), 9.30 (s, 2H, 
2NH); $^{13}$C NMR (DMSO-$d_6$): $\delta$ 28.82 (aliphatic 
carbon), 127.67, 127.84, 128.05 (2C), 129.48, 129.76 
(2C), 129.94, 130.33, 130.67, 131.07, 136.54 
aromatic carbons), 155.36 (2C=N), 157.82 (2C=O). 
Anal. Calcd for C$_{17}$H$_{18}$N$_6$: C, 66.65; H, 4.91; N, 
72.51. Found: C, 66.41; H, 4.25; N, 29.02%.

Synthesis of Di-(1,2,4-triazol-3-yl) methane 6b: 
Formation temperature range: 205-10°, yield 1.64 g 
(92%) of colourless crystals, m.p. 272-73° (ethanol, 
lit m.p. 274°). Anal. Calcd for C$_{6}$H$_{10}$N$_6$: C, 47.18; H, 
5.66; N, 47.17. Found: C, 47.33; H, 5.80; N, 46.94%.

1,4-Di-(5-methyl-1,2,4-triazol-3-yl)-benzene 6c: 
Formation temperature range: 165-75°, yield 2.14 g 
(97%) of colourless crystals, m.p. 190-91° (ethanol); 
IR (KBr): 3155 (NH), 1630, 1585 (C=N) cm$^{-1}$; 
$^1$H NMR (DMSO-$d_6$): $\delta$ 1.64 (m, 4H, 2CH$_2$), 2.25 (s, 
6H, 2CH$_3$), 2.60 (m, 4H, 2CH$_2$), 13.90 (s, 2H, 2NH); 
$^{13}$C NMR (DMSO-$d_6$): $\delta$ 14.24 (2C), 28.10 (2C), 
28.95 (2C) (aliphatic carbons), 157.24 (2C), 161.29 
(2C) (triazole carbons). Anal. Calcd for C$_{10}$H$_{18}$N$_6$: C, 
54.52; H, 7.32; N, 38.16. Found: C, 54.23; H, 7.27; N, 
38.16%.

1,4-Di-(5-methyl-1,2,4-triazol-3-yl) benzene 6d: 
Formation temperature range: 220-25°, yield 2.14 g 
(89%) of colourless crystals, m.p. 332°. Anal. Calcd for C$_{12}$H$_{14}$N$_6$: C, 67.53; H, 7.32; N, 38.16. Found: C, 67.76; H, 7.42; N, 
38.78%.

Di-(5-phenyl-1,2,4-triazol-3-yl) methane 7b: 
Formation temperature range: 205-10°, yield 2.81 g 
(93%) of colourless crystals, m.p. 249-50° (ethanol, 
lit m.p. 251°). Anal. Calcd for C$_{17}$H$_{14}$N$_6$: C, 69.52; H, 
5.80; N, 24.56%.

1,4-Di-(5-phenyl-1,2,4-triazol-3-yl)-benzene 7c: 
Formation temperature range: 205-10°, yield 3.07 g 
(89%) of colourless crystals, m.p. 272-73° (ethanol, 
lit m.p. 272°). Anal. Calcd for C$_{20}$H$_{20}$N$_6$: C, 69.74; H, 
5.85; N, 24.40. Found: C, 69.52; H, 5.80; N, 24.56%. 

1,4-Di-(5-phenyl-1,2,4-triazol-3-yl) benzene 7d: 
Formation temperature range: 225-30°, yield 3.20 g 
(88%) of colourless crystals, m.p. 267-68° (DMSO-
water, 1:3) (lit m.p. 267°). Anal. Calcd for C$_{22}$H$_{20}$N$_6$: C, 
67.53; H, 4.67; N, 27.80. Found: C, 67.76; H, 4.62; N, 
27.65%.

Synthesis of 1,2,4-triazole derivatives 6a or 7a: 
The general procedure established for the synthesis of bis-
acylamidrazones 4, 5 was applied using oxalodi-
hydrazide (0.005 mole) as described above. This 
method led to the formation of 6a or 7a without 
iso lation of the corresponding intermediate 
bis-acylamidrazone of type 4 or 5.

Di-(5-methyl-1,2,4-triazol-3-yl)- methane 6a: yield 1.50 g 
(95%) of colourless crystals, m.p. 325-26° (water, 
lit m.p. 325°). Anal. Calcd for C$_{6}$H$_{8}$N$_6$: C, 43.89; H, 
4.91; N, 51.20. Found: C, 43.67; H, 5.07; N, 50.98%.

Di-(5-phenyl-1,2,4-triazol-3-yl)- methane 7a: yield 2.43 g 
(84%) of colourless crystals, m.p. 361-62° (ethanol, 
lit m.p. 363°). Anal. Calcd for C$_{6}$H$_{12}$N$_6$: C, 66.65; 
H, 4.19; N, 29.15. Found: C, 66.41; H, 4.25; N, 
29.02%.

Synthesis of 1,2,4-triazole derivatives 6b-d or 
7b-d: The corresponding bis-acylamidrazone (4b-d or 
5b-d) (0.01 mole) was heated at a temperature range 
changing between 165 and 230° for 1 hr. The crystals 
formed on cooling were recrystallized from an 
appropriate solvent to afford the desired compound.
benzhydrazide (0.01 mole) or isonicotinic hydrazide (0.01 mole) to give the corresponding acylamidrazone 8b, 8c or 9c.

N1-(4-Hydroxybenzoyl)-acetamidrazone 8b: yield 1.88 g (90%) of colourless crystals, m.p. 170-71° (ethanol-butyl acetate, 1:2); IR (KBr): 3390, 3310, 3230, 3060 (NH, NH2, NH), 1645 (C=O), 1595 (C=N), 840 (1,4-disubstituted benzenoid ring) cm⁻¹; ¹H NMR (DMSO-d⁶): δ 2.28 (s, 3H, CH₃), 7.89 (d, 2H, Ar-H, J=8.2 Hz), 7.80 (d, 2H, Ar-H, J=8.1 Hz), 9.51 (s, 1H, NH); ¹³C NMR (DMSO-d⁶): δ 14.62 (aliphatic carbon), 116.26, 116.76, 116.93, 124.93, 131.20, 162.40 (aromatic carbons), 167.06 (C=N=O) (C=O). Anal. Caled for C₁₃H₁₀N₄O: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.65; H, 5.52; N, 21.65%.

N1-Isonicotinoylacetamidrazone 8c: yield 1.68 g (94%) of colourless crystals, m.p. 163-64° (ethanol); IR (KBr): 3380, 3300, 3120 (NH, NH), 1665 (C=O), 1585 (C=N) cm⁻¹; ¹H NMR (DMSO-d⁶): δ 2.46 (s, 3H, CH₃), 4.50 (s, 2H, NH₂), 7.97 (d, 2H, Ar-H, J=5.9 Hz), 8.65 (d, 2H, Ar-H, J=5.2 Hz), 7.91 (s, 1H, NH); ¹³C NMR (DMSO-d⁶): δ 14.68 (aliphatic carbon), 121.64, 139.97, 151.88, 152.20, 156.58 (aromatic carbons), 159.84 (C=N=O) (C=O). Anal. Caled for C₁₃H₁₀N₄O: C, 53.92; H, 5.66; N, 31.45. Found: C, 54.20; H, 5.54; N, 31.21%.

N1-Isonicotinoylbenzamidrazone 9c: yield 2.10 g (88%) of colourless crystals, m.p. 184-85° (ethanol); IR (KBr): 3320, 3130, 3030 (NH, NH), 1660 (C=O), 1585 (C=NH), 775, 680 (monosubstituted benzenoid ring) cm⁻¹; ¹H NMR (DMSO-d⁶): δ 4.50 (s, 2H, NH₂), 7.35-8.12 (m, 7H, Ar-H), 8.61 (d, 2H, Ar-H, J=5.5 Hz), 9.25 (s, 1H, NH); ¹³C NMR (DMSO-d⁶): δ 121.55, 127.48, 129.57, 129.82, 130.32, 130.72, 133.73, 141.64, 151.59, 151.73, 160.57 (aromatic carbons), 162.11 (C=N=O) (C=O). Anal. Caled for C₁₃H₁₀N₅O: C, 74.68; H, 5.03; N, 31.21. Found: C, 74.65; H, 4.99; N, 31.21%.

Synthesis of 3,5-dialkyl-1,2,4-triazoles 10b, 10c or 11c. The corresponding acylamidrazones (8b, 8c or 9c) (0.01 mole) was heated at a temperature range changing between 170 and 210° for 1 hr. The crude product formed on cooling was recrystallized from an appropriate solvent to give the desired compound.

3-Methyl-5-(4-hydroxyphenyl)-1,2,4-triazole 10b: Formation temperature range: 205-10°, yield 1.82 g (93%) of colourless crystals, m.p. 249-50° (water); IR (KBr): 3200, 3080 (OH, NH), 1610, 1595 (C=N), 840 (1,4-disubstituted benzenoid ring) cm⁻¹; ¹H NMR (DMSO-d⁶): δ 2.34 (s, 3H, CH₃), 6.85 (d, 2H, Ar-H, J=8.6 Hz), 7.75 (d, 2H, Ar-H, J=8.7 Hz), 9.69 (s, 1H, OH), 13.48 (s, 1H, NH); ¹³C NMR (DMSO-d⁶): δ 14.50 (aliphatic carbon), 117.07, 117.23 (2C), 129.10 (2C), 160.06 (aromatic carbons), 160.12, 160.16 (triazole carbons). Anal. Caled for C₁₃H₁₀N₅O: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.94; H, 5.18; N, 24.13%.

3-Methyl-5-(4-pyridyl)-1,2,4-triazole 10c: Formation temperature range: 170-75°, yield 1.52 g (95%) of colourless crystals, m.p. 184-85° (ethanol); IR (KBr): 3175 (NH), 1610, 1585 (C=N) cm⁻¹; ¹H NMR (DMSO-d⁶): δ 2.46 (s, 3H, CH₃), 7.88 (d, 2H, Ar-H, J=6.1 Hz), 8.63 (d, 2H, Ar-H, J=5.2 Hz), 14.05 (s, 1H, NH); ¹³C NMR (DMSO-d⁶): δ 13.55 (aliphatic carbon), 121.71, 139.97, 152.00 (2C), 156.52 (aromatic carbons), 156.58, 167.66 (triazole carbons). Anal. Caled for C₁₃H₁₀N₅O: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.69; H, 4.96; N, 34.69%.

3-Phenyl-5-(4-pyridyl)-1,2,4-triazole 11c: Formation temperature range: 200-05°, yield 2.00 g (90%) of colourless crystals, m.p. 135-36° (acetone) (lit 28 m.p. 135.5°). Anal. Caled for C₁₃H₁₀N₅O: C, 74.68; H, 5.03; N, 24.97. Found: C, 74.50; H, 4.99; N, 24.97%.

Synthesis of 3-methyl-5-cyanomethyl-1,2,4-triazole 10a. The general procedure described for the synthesis of acylamidrazones 8b, 8c or 9c was applied using acetylamine hydrochloride (0.015 mole) and cyanoacetic acid hydrazide (0.01 mole). This reaction resulted in the formation of 10a without isolation of the corresponding intermediate acylamidrazones of type 8; yield 1.18 g (97%) of colourless crystals, m.p. 135-36° (acetone) (lit 28 m.p. 135.5°). Anal. Caled for C₁₃H₁₀N₅O: C, 49.17; H, 4.95; N, 45.88. Found: C, 49.28; H, 4.93; N, 45.65%.

References