A Convenient Synthesis of 3,6-Disubstituted-1,4-Dihydro-[1,2,4,5]Tetrazines and Preparation of New Acetic Acid Derivatives Containing 5-Oxo-4-Phenylamino-4,5-Dihydro-[1,2,4]Triazole

Ahmet DEMİRBAŞ
Karadeniz Technical University, Department of Chemistry, 61080 Trabzon-TURKEY
e-mail: demirbas@ktu.edu.tr

Received 08.10.2003

A series of compounds 8a-e, was synthesized by condensation of compounds 7a-e with ethyl bromoacetate. The treatment of compounds 8a-e with hydrazine hydrate afforded the corresponding hydrazide derivatives (9a-e). Subsequently, compounds 9a-e were converted to alkylidene hydrazides (10a-e). Moreover, upon heating in the presence of carboxylic acids, compounds 9a-e unexpectedly gave 1,4-dihydro-[1,2,4,5]tetrazine derivatives (11a-e).

Key Words: Conformer, geometrical isomer, ethyl bromoacetate, imine bond, 5-oxo-[1,2,4]triazole, [1,2,4,5]tetrazine.

Introduction

Compounds containing imine bond have been intensively synthesized for various reasons, one of which is their biological activities\(^1\)\(^-\)\(^4\). Some of the other reasons are the investigation of their ability to make a coordination complex with transition metal cations and the improvement of their properties for analytical applications\(^5\)\(^-\)\(^7\). In addition, there exist a number of compounds incorporating [1,2,4]triazole, 5-oxo-[1,2,4]triazole or 5-thioxo-[1,2,4]triazole rings and having diverse biological activities\(^1\)\(^-\)\(^3\),\(^8\)\(^-\)\(^25\) some of which have a group also contains an imine bond\(^1\)\(^-\)\(^3\). Among these compounds, 3-alkyl-4-alkylidene(or alkyl)amino-5-oxo-4,5-dihydro-[1,2,4]triazaoles (1,2), N, N’-bis-(3-alkyl-5-oxo-4,5-dihydro-[1,2,4]triazol-4-y1)-1,4-xylenediimines (3), 1,3-dialkyl-4-phenylamino-5-oxo-4,5-dihydro-[1,2,4]triazaoles (4), 3,5-dialkyl-4-ethoxy(t-butoxy)carbonyl-amino-4H-[1,2,4]triazaoles (5) and di-(3-alkyl-4-ethoxy(t-butoxy)carbonylamino-4H-[1,2,4]triazol-5-yl)-methanes (6) were synthesized in our laboratories (figure\(^1\)\(^8\)\(^,\)\(^9\)\(^,\)\(^12\)\(^-\)\(^14\),\(^26\),\(^27\). In addition, several [1,2,4]triazole derivatives obtained as potential biologically active compounds\(^28\),\(^29\).
Figure

The chemistry of 3-alkyl-5-oxo-4-phenylamino-4,5-dihydro-[1,2,4]-triazole compounds (7), which behave as good nucleophiles in most reactions, has been studied in detail. For example, the bromination, nitration and alkylation of these compounds have been performed in our laboratories\textsuperscript{12,13,30}.

Results and Discussion

In line with our continuing interest, we aimed to obtain possible biologically active compounds containing a 5-oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazole ring bearing a side chain incorporating an imine bond. For this purpose, compounds 8 were obtained via a nucleophilic attack of compounds 7, which were obtained from the reaction of the ester ethoxycarbonylhydrazones with phenyl hydrazine\textsuperscript{33} to the bromide-bearing carbon of ethyl bromoacetate. After that, compounds 8a-e were converted to their hydrazide derivatives (9a-e) by treating them with hydrazine hydrate. 3-Alkyl-5-oxo-4-phenylamino-4,5-dihydro [1,2,4]triazol-1-yl-acetic acid arylidenehydrazides (10a-e) were synthesized by the reaction of compounds 9a-e with various aldehydes such as salicylaldehyde, anisaldehyde, vanillin, pyridine-4-carboxaldehyde and thiophene-2-carboxaldehyde. The heating of compounds 9a-e in the presence of carboxylic acids such as acetic or benzoic acids resulted in the formation of 1,4-dihydro-[1,2,4,5]tetrazine derivatives (11a-e) (Scheme 1).

In the $^1$H NMR spectra of compounds 8a-e no signal belonging to the endocyclic-NH proton of compounds 7a-e was observed. Instead, new signals belonging to the ethyl ester group appeared between 4.77 and 4.16 ppm (-OCH$_2$CH$_3$), 4.16 and 4.19 ppm (-NCH$_2$) and 1.21 and 1.23 ppm (-OCH$_2$CH$_3$). The signals of corresponding carbons were recorded between 60.94 and 64.92 ppm (-OCH$_2$CH$_3$), 46.70 and 50.75 ppm (-NCH$_2$) and 13.92 and 17.60 ppm (-OCH$_2$CH$_3$) in the $^{13}$C NMR spectra. When compounds 8a-e were converted to their hydrazides (9a-e), these signals, except for the signal belonging to -NCH$_2$- dissappeared in the $^1$H and $^{13}$C NMR spectra. Instead, new signals belonging to the hydrazide group were observed between 8.93 and 9.24 ppm (-NH$\text{NH}_2$) and 4.30 and 4.35 ppm (-NNH$_2$) (checked by exchanging with D$_2$O).

It has been reported that the compounds incorporating an arylidene (or alkylidene) hydrazide structure may exist as $Z$/$E$ geometrical isomers about a -C=N- double bond. Moreover, $Z$ and $E$ isomers may consist of their individual \textit{cis-trans} amide conformers\textsuperscript{2,4–6} (Scheme 2). According to the literature\textsuperscript{2,4}, the
Scheme 1. Synthetic pathway for the preparation of compounds 8-11.
compounds containing imine bonds are present in higher percentages in dimethyl-d₆ sulfoxide solution in the form of a geometric E isomer about a -C=N double bond. The Z isomers can be stabilized in less polar solvents by an intramolecular hydrogen bond⁶. In the present study, the stereochemical behavior of compounds 10a-e, which were obtained by using various aldehydes, was investigated in dimethyl-d₆ sulfoxide solution as E isomers and the trans/cis conformer ratios in each case were calculated by using ¹H NMR and ¹³C NMR data. In the ¹H NMR spectra of compounds 10a-e, 2 sets of signals each belonging to the individual -NCH₂, N=CH, hydrazide-NH and -OH (for 10b and 10c), of the cis and trans conformers were observed. Among these, the peaks belonging to the -NCH₂ group of 1 of 2 conformers of each compound 10 appeared at about 4.44-4.53 ppm, while the -NCH₂ peaks belonging to the other conformer appeared between 4.81 and 4.93 ppm. The -N=CH signals were observed as separate peaks for each conformer at 7.94-8.39 and 8.05-8.44 ppm. For hydrazide-NH 2 peaks were recorded at about 11.38-11.69 ppm and 11.41-11.96 ppm indicating trans and cis conformers of compounds 10a-e. In the case of compounds 10b and 10c, 2 signals belonging to the -OH group were recorded between 9.53 and 10.06 ppm and 9.59 and 10.96 ppm, respectively. In the ¹³C NMR spectra of compounds 10a-e, each signal belonging to the triazole-C-5, triazole-C-3, -N=CH and -NCH₂ groups was observed as 2 sets, indicating the formation of conformational isomers. In the present study, the trans/cis ratio changed between 71/29 and 57/43 in the mixture of the conformers. When D₂O was added to the DMSO-d₆ solution of compounds 10a-e, the trans/cis ratio changed between 58/42 and 42/58. This change is evidence of the existence of trans/cis conformers, not E/Z geometrical isomers, since E/Z isomers are rigid structures.

The formation of [1,3,4]oxadiazoles from the reaction of the compounds having a hydrazide structure with carboxylic acids was carried out³². In addition, it has been reported that the reaction of dicarboxylic acids with hydrazine hydrate resulted in the formation of a polymer containing a [1,3,4]oxadiazole ring³³. When compounds 9a-e were treated with acetic acid or benzoic acid to obtain [1,3,4]oxadiazoles, the reaction surprisingly resulted in the formation of 1,4-dihydro-[1,2,4,5]tetrazine derivatives. It could be concluded that in the first step of this reaction a dimerization took place between 2 molecules of compounds 9a-e instead of a reaction with carboxylic acid. In the second step of this reaction, although there were 2 possibilities, the
formation of either 4-amino-[1,2,4]triazole or [1,2,4,5]tetrazine derivative, we expected to obtain 4-amino-
[1,2,4]triazole derivatives due to the instability of tetrazines (Scheme 3). It has been reported that tetrazines
are generally unstable and are converted to [1,2,4]triazole derivatives or decomposed upon heating above 100
°C\textsuperscript{33,34}. Moreover, it has been reported that if there are 2 possibilities such as in the above case, 4-amino-
[1,2,4]triazoles are obtained as the main product\textsuperscript{26}. In contrast to the literature, the tetrazine derivatives
(11a-e) were obtained at a high yield in this study. In the NMR spectra of compounds 11a-e, the absence
of any signal belonging to the −CH\textsubscript{3} or −C\textsubscript{6}H\textsubscript{5} groups derived from the carboxylic acid used in the reaction
indicated that compounds 9a-e did not react with carboxylic acids. In addition, in the \textsuperscript{1}H NMR spectra of
compounds 11a-e, the additional signal belonging to tetrazine−NH protons was at 10.35 ppm (D\textsubscript{2}O exch.),
while the hydrazide-NH\textsubscript{2} observed at 4.29 ppm disappeared. \textsuperscript{13}C NMR signals of C-3 and C-6 of compounds
11a-e were recorded at 163.28-165.21 ppm. In the IR spectra of compounds 11a-e additional −NH signals
belonging to the tetrazine ring were observed at 3130-3132 cm\textsuperscript{−1} while the peak belonging to hydrazide-
NH\textsubscript{2} disappeared. Moreover, in the IR and NMR spectra of the tetrazines (11a-e), no signal representing
an −NH\textsubscript{2} group derived from the 3,5-dialkyl-4-amino-[1,2,4]triazole structure was observed. Furthermore,
elemental analysis confirmed all the structures proposed in this study.

\textbf{Scheme 3.} The formation mechanism of compounds 11a-e.
**Scheme 4.** The numbers of aromatic atoms on compounds 8-11 (Y: -OH or OCH3).

**Experimental**

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. $^1$H, $^{13}$C, APT and DEPT NMR spectra were recorded on a Varian-Mercury 200 MHz spectrometer. The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FTIR spectrophotometer. Combustion analysis was performed on a Carlo Erba 1106 elemental analyzer. All the chemicals were obtained from Fluka Chemie AG Buchs (Switzerland). The precursor compounds 7a-e were synthesized according to the published method\textsuperscript{33}. 
General method for the synthesis of compounds 8

The corresponding 3-alkyl-4-phenylamino-4,5-dihydro-1H-1,2,4-triazol-5-one (1) (0.01 mol) was refluxed with an equivalent amount of natrium in absolute ethanol for 2 h. Then, ethyl bromoacetate (0.01 mol) was added and refluxed for an additional 5 h. After evaporation at 35-40°C under reduced pressure, a solid appeared. This was recrystallized from an appropriate solvent to afford the desired compound.

3-Methyl-5-oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid ethyl ester (8a):
Recrystallization from isobutyl acetate (yield: 82.20%), mp. 121-122°C; Analysis (Calc/Found %): for C_{13}H_{16}O_{3}N_{4} C: 56.51/56.55, H: 5.84/5.97, N: 20.28/19.78; IR (KBr) (ν, cm⁻¹), 3252 (-NH), 1715 (ester-C=O), 1704 (triazole-C=O), 1587 (-C=N), 1210 (-C-O); ¹H NMR (DMSO-d_6) δ 1.21 (t, -OCH_3, J=7.0 Hz), 2.09 (s, -CH_3), 4.19 (q, -OCH_2CH_3, J=7.0 Hz), 4.76 (s, -NCH_2), [ar H: 6.57 (d, 2H, CH-2, CH-6, J = 8.2 Hz), 6.86 (t, 1H, CH-4, J = 7.6 Hz), 7.23 (t, 2H, CH-3, CH-5, J = 7.6 Hz)], 9.03 (s, -NH); ¹³C NMR (DMSO-d_6) δ 167.82 (C=O), 152.20 (triazole C-5), 149.45 (triazole C-3), [ar C: 146.38 (C-1), 129.18 (C-3, C-5), 120.29 (C-4), 111.94 (C-2, C-6)], 63.13 (-OCH_2CH_3), 46.63 (-NCH_2), 13.92 (-OCH_2CH_3), 10.32 (-CH_3).

3-Ethyl-5-oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid ethyl ester (8b):
Recrystallization from isobutyl acetate (yield: 82.20%), mp. 125-126°C; Analysis (Calc/Found %): for C_{14}H_{18}O_{3}N_{4} C: 57.92/57.52, H: 6.25/6.67, N: 19.30/19.68; IR (KBr) (ν, cm⁻¹), 3255 (NH), 1716 (ester C=O), 1711 (triazole-C=O), 1587 (-C=N), 1210 (-C-O); ¹H NMR (DMSO-d_6) δ 1.11 (t, -CH_3, J=7.5 Hz), 1.21 (t, -OCH_2CH_3, J=7.1 Hz), 2.48 (q, -CH_2CH_3, J=7.5 Hz), 4.18 (q, -OCH_2CH_3, J=7.1 Hz), 4.76 (s, -NCH_2), [ar H: 6.59 (d, 2H, CH-2, CH-6, J = 8.2 Hz), 6.81 (t, 1H, CH-4, J = 7.4 Hz), 7.23 (t, 2H, CH-3, CH-5, J = 7.8 Hz)], 9.03 (s, -NH); ¹³C NMR (DMSO-d_6) δ 167.81 (-C=O), 152.20 (triazole C-5), 149.35 (triazole C-3), [ar C: 146.35 (C-1), 129.14 (C-3, C-5), 120.22 (C-4), 111.92 (C-2, C-6)], 63.13 (-OCH_2CH_3), 46.70 (-NCH_2), 19.71 (-CH_2CH_3), 13.92 (-OCH_2CH_3), 9.87 (-CH_2CH_3).

5-Oxo-4-phenylamino-3-n-propyl-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid ethyl ester (8c):
Recrystallization from benzene-petroleum ether (1:2) (yield: 70.43%), mp. 81-83°C; Analysis (Calc/Found %): for C_{15}H_{20}O_{3}N_{4} C: 59.20/58.51, H: 6.62/6.59, N: 18.41/19.18; IR (KBr) (ν, cm⁻¹), 3245 (NH), 1760 (ester C=O), 1708 (triazole-C=O), 1585 (-C=N), 1209 (-C-O); ¹H NMR (CDCl_3) δ 1.11 (t, -CH_2CH_3, J=7.0 Hz), 1.29 (t, -OCH_2CH_3, J=7.6 Hz), 1.68 (m, -CH_2CH_2CH_3), 2.50 (t, -CH_2CH_2CH_3, J=7.0 Hz), 4.18 (q, -OCH_2CH_3, J=7.4 Hz), 4.77 (s, -NCH_2), [ar H: 6.57 (d, 2H, CH-2, CH-6, J = 7.4 Hz), 6.92 (t, 1H, CH-4, J = 7.4 Hz), 7.23 (t, 2H, CH-3, CH-5, J = 7.8 Hz)], 7.17 (t, 2H, CH-3, CH-5, J = 7.2 Hz], 7.52 (s, -NH); ¹³C NMR (CDCl_3) δ 167.58 (-C=O), 153.50 (triazole C-5), 149.29 (triazole C-3), [ar C: 145.56 (C-1), 129.31 (C-3, C-5), 121.57 (C-4), 112.81 (C-2, C-6)], 61.80 (-OCH_2CH_3), 47.01 (-NCH_2), 26.81 (-CH_2CH_2CH_3), 19.28 (-CH_2CH_2CH_3), 14.09 (-OCH_2CH_3), 13.55 (-CH_2CH_2CH_3).

3-Benzyl-5-oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid ethyl ester (8d):
Recrystallization from benzene-petroleum ether (1:2) (yield: 58.40%), mp. 86-88°C; Analysis (Calc/Found %): for C_{19}H_{26}O_{3}N_{4} C: 64.76/65.59, H: 5.72/5.47, N: 15.90/15.93; IR (KBr) (ν, cm⁻¹), 3252 (NH), 1765 (ester-C=O), 1704 (triazole-C=O), 1640 (-C=N), 1215 (-C-O); ¹H NMR (DMSO-d_6) δ 1.21 (t, -OCH_2CH_3, J=7.6 Hz), 2.48 (s, benzy1-CH_3), 4.16 (q, -OCH_2CH_3, J=7.6 Hz), 4.61 (s, -NCH_2), [ar H: 6.64 (bs, 2H, CH-2, CH-6), 6.86 (t, 1H, CH-4, J = 7.4 Hz), 7.23 (t, 2H, CH-3, CH-5, J = 7.8 Hz), 7.30-7.45 (m, 5H), 31.7

A Convenient Synthesis of,..., A. DEMİRBAŞ
9.03 (s, -NH); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 170.05 (-C=O), 153.70 (triazole C-5), 148.70 (triazole C-3), [ar C: 147.40 (C-1), 134.10 (C-1'), 131.35 (C-3', C-5'), 129.01 (C-3, C-5), 128.20 (C-2', C-6'), 126.05 (C-4'), 124.01 (C-4), 116.45 (C-2, C-6)], 60.94 (-OCH\(_2\)CH\(_3\)), 46.20 (-NCH\(_2\)), 30.14 (benzyl-CH\(_2\)), 14.10 (-OCH\(_2\)CH\(_3\)).

5-Oxoo-3-phenyl-4-phenylamino-4,5-dihydro-[1,2,4]-triazol-5-on-1-yl-acetic acid ethyl ester (8e): Recrystallization from acetone-water (1:2) (yield: 65.18%), mp. 124-126 °C; Analysis (Calc-found %): for C\(_{18}\)H\(_{15}\)O\(_3\)N\(_4\) C: 63.89/63.75, H: 5.36/5.32, N: 16.16/16.17; IR (KBr) (\(\nu\), cm\(^{-1}\)) 3259 (NH), 1787 (ester-C=O), 1702 (triazole-C=O), 1625 (-C=N), 1217 (-C-O); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.23 (t, -OCH\(_2\)CH\(_3\), \(J = 7.2\) Hz), 4.19 (q, -OCH\(_2\)J, \(J = 7.2\) Hz), 4.76 (s, -NCH\(_2\)), [ar H: 6.64 (d, 2H, CH-2, CH-6, \(J = 7.8\) Hz), 6.85 (t, 1H, CH-4, \(J = 7.2\) Hz), 7.23 (t, 2H, CH-3, CH-5, \(J = 8.2\) Hz), 7.40-7.45 (m, 3H), 7.75-7.90 (m, 2H)], 9.33 (s, -NH); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 167.65 (C=O), 152.20 (triazole-C-5), 145.20 (triazole C-3), [ar C: 146.09 (C-1), 130.56 (C-1'), 128.74 (C-3', C-5'), 129.24 (C-3, C-5), 126.73 (C-2', C-6'), 125.70 (C-4'), 120.28 (C-4), 111.99 (C-2, C-6)], 61.25 (-OCH\(_2\)CH\(_3\)), 46.50 (-NCH\(_2\)), 13.92 (-OCH\(_2\)CH\(_3\)).

General method for the synthesis of compounds 9

A solution of the corresponding compound 8 (0.01 mol) in n-butanol was refluxed with hydrazine hydrate (0.025 mol) for 4 h. After cooling to room temperature, a white solid appeared. This was recrystallized from an appropriate solvent to afford the desired product.

3-Methyl-5-oxoo-4-phenylamino-4,5-dihydro-[1,2,4]-triazol-1-yl-acetic acid hydrazide (9a): Recrystallization from ethanol (yield: 90.20%), mp. 168-170 °C; Analysis (Calc-found %): for C\(_{11}\)H\(_{14}\)O\(_2\)N\(_6\)C: 50.38/50.12, H: 5.38/5.31, N: 32.04/31.90; IR (KBr) (\(\nu\), cm\(^{-1}\)) 3339, 3231, 2220 (NH\(_2\) + NH), 1715 (triazole-C=O), 1674 (hydrazide-C=O), 1603 (-C=N); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 2.09 (s, -CH\(_3\)), 4.36 (s, -NH\(_2\)), 4.30 (s, -NCH\(_2\)), [ar H: 6.68 (d, 2H, CH-2, CH-6, \(J = 7.8\) Hz), 6.91 (t, 1H, CH-4, \(J = 7.4\) Hz), 7.25 (t, 2H, CH-3, CH-5, \(J = 7.6\) Hz)], 8.95 (s, -NH, exch. with D\(_2\)O), 9.34 (s, -NH\(_2\)H, exch. with D\(_2\)O); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 165.93 (C=O), 152.31 (triazole C-5), 145.18 (triazole C-3), [ar C: 146.51 (C-1), 129.20 (C-3, C-5), 120.27 (C-4) 112.09 (C-2, C-6)], 38.09 (-NH\(_2\)), 10.41 (-CH\(_3\)).

3-Ethyl-5-oxoo-4-phenylamino-4,5-dihydro-[1,2,4]-triazol-1-yl-acetic acid hydrazide (9b): Recrystallization from ethanol (yield: 89.60%), mp. 221-223 °C; Analysis (Calc-found %): for C\(_{12}\)H\(_{16}\)O\(_2\)N\(_6\)C: 52.16/52.25, H: 5.84/5.91, N: 30.42/30.40; IR (KBr) (\(\nu\), cm\(^{-1}\)) 3311, 3249, 3205 (NH\(_2\) + NH), 1696 (triazole-C=O), 1680 (hydrazide-C=O), 1603 (-C=N); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 1.10 (t, -CH\(_3\)CH\(_2\)), 7.6 (C=O), 2.43 (q, -CH\(_2\)CH\(_3\), \(J = 7.6\) Hz), 4.29 (s, -NCH\(_2\)), 4.33 (s, -NH\(_2\)), [ar H: 6.65 (d, 2H, CH-2, CH-6, \(J = 7.6\) Hz), 6.84 (t, 1H, CH-4, \(J = 7.6\) Hz), 7.21 (t, 2H, CH-3, CH-5, \(J = 7.4\) Hz)], 8.93 (s, triazole-NH), 9.29 (s, -NH\(_2\)H); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) 165.84 (C=O), 152.37 (triazole C-5), 148.85 (triazole C-3), [ar C: 146.43 (C-1), 129.05 (C-3, C-5), 120.05 (C-4) 111.99 (C-2, C-6)], 46.46 (-NCH\(_2\)), 17.91 (-CH\(_2\)CH\(_3\)), 9.83 (-CH\(_3\)).

5-Oxo-4-phenylamino-3-n-propyl-4,5-dihydro-[1,2,4]-triazol-1-yl-acetic acid hydrazide (9c): Recrystallization from ethanol (yield: 85.40%), mp. 218-220 °C; Analysis (Calc-found %): for C\(_{13}\)H\(_{18}\)O\(_2\)N\(_6\) C: 53.78/53.75, H: 6.25/6.27, N: 28.95/29.28; IR (KBr) (\(\nu\), cm\(^{-1}\)) 3312, 3246, 3201 (NH\(_2\) + NH), 1697 (triazole-C=O), 1673 (hydrazide-C=O), 1604 (-C=N); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) 0.88 (s, -CH\(_3\)CH\(_2\)CH\(_3\), \(J = 7.4\) Hz), 1.56 (sex, -CH\(_3\)CH\(_2\)CH\(_3\), \(J_1 = 7.0\) Hz, \(J_2 = 7.4\) Hz), 2.42 (t, -CH\(_2\)CH\(_2\)CH\(_3\), \(J = 7.2\) Hz), 4.35 (s, -NH\(_2\)), 4.29 (s, NCH\(_2\)), [ar H: 6.65 (d, 2H, CH-2, CH-6, J = 7.6 Hz), 6.84 (t, 1H, CH-4, J = 7.4 Hz), 7.22 (t,
A Convenient Synthesis of... , A. DEMİRBAŞ

3-Benzyl-5-oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid hydrazide (9d): Recrystallization from ethanol (yield: 68.70%), mp. 208-209 °C; Analysis (Calc/found %): for C_{17}H_{18}O_{2}N_{6} C: 60.34/60.45, H: 5.36/5.37, N: 24.84/24.88; IR (KBr) (ν, cm⁻¹): 3340, 3248,3210 (NH₂+ NH), 1705 (triazole-C=O), 1669 (hydrazide-C=O), 1603 (-C=N); ¹H NMR (DMSO-d₆) δ 3.82 (s, benzyl-CH₂), 4.31 (s, -NCH₂), 4.72 (s, -NH₂), [ar H: 3.78 (d, 2H, CH-2, CH-6, J = 7.4 Hz), 6.83 (t, 1H, CH-4, J = 7.4 Hz), 7.15 (t, 2H, CH-3, CH-5, J = 7.8 Hz), 7.20-7.45 (m, 5H)], 9.29 (s, -NHNH₂), 8.97 (s, -NH); ¹³C NMR (DMSO-d₆) δ 165.77 (C=O), 152.15 (triazole C-3), [ar C: 146.31 (C-1), 134.85 (C-1'), 129.08 (C-3', C-5'), 126.25 (C-2', C-6'), 123.01 (C-3', C-5'), 126.10 (C-2', C-6'), 125.01 (C-3', C-5'), 123.01 (C-2', C-6'), 120.60 (C-1), 112.02 (C-2, C-6)].

5-Oxo-3-phenyl-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid hydrazide (9e): Recrystallization from ethanol (yield: 78.30%), mp. 215-216 °C; Analysis (Calc/found %): for C_{16}H_{14}O_{2}N_{6} C: 59.25/59.36, H: 4.97/4.90, N: 25.91/25.58; IR (KBr) (ν, cm⁻¹): 3415, 3325, 3229 (NH), 1707 (hydrazide-C=O), 1670 (triazole-C=O), 1614 (-C=N); ¹H NMR (DMSO-d₆) δ 4.47 (s, 4H, -NCH₂), [ar H: 2.42 (t, -CH₂CH₂CH₃, J = 7.2 Hz), 3.80 (s, -OCH₃), 4.88 and 4.49 (s, -NCH₂, trans/cis), [ar H: 3.78 (d, 2H, CH-2, CH-6, J = 7.4 Hz), 6.83 (t, 1H, CH-4, J = 7.4 Hz), 7.20-7.45 (m, 5H)], 9.24 (-NH₂), 9.40 (s, -NHNH₂); ¹³C NMR (DMSO-d₆) δ 165.70 (C=O), 152.50 (triazole C-5), 144.99 (triazole C-3), [ar C: 146.24 (C-1), 130.46 (C-4'), 129.22 (C-3, C-5), 128.71 (C-3', C-5'), 126.73 (C-2', C-6'), 125.67 (C-1'), 120.23 (C-4), 112.16 (C-2, C-6)].

General method for the synthesis of compounds 10

A solution of the corresponding compound 9 (0.01 mol) in ethanol was refluxed with appropriate aldehyde (0.01 mol) for 3 h. After cooling to room temperature, a white solid appeared. This was recrystallized from an appropriate solvent to afford the desired product.

5-Oxo-4-phenylamino-3-n-propyl-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid p-methoxy-benzylidenehydrazide (10a): Recrystallization from ethanol (yield: 81.13%), mp. 234-237 °C; The ratio of trans/cis conformers: 71/29; Analysis (Calc/found %): for C_{24}H_{24}O_{2}N_{6} C: 61.75/60.89, H: 5.92/6.12, N: 20.58/21.05; IR (KBr) (ν, cm⁻¹): 3218 (-NH), 3118 (-NHN=), 1716 (triazole-C=O), 1607 (-C=N); ¹H NMR (DMSO-d₆) δ 0.89 (t, -CH₂CH₂CH₃, J = 7.4 Hz), 1.55 (sex, -CH₂CH₂CH₃, J₁ = 7.4 Hz, J₂ = 7.2 Hz), 2.42 (t, -CH₂CH₂CH₃, J = 7.2 Hz), 3.80 (s, -OCH₃), 4.88 and 4.49 (s, -NCH₂, trans/cis), [ar H: 3.78 (d, 2H, CH-2, CH-6, J = 7.2 Hz), 6.84 (t, 1H, CH-4, J = 7.2 Hz), 7.21 (t, 2H, CH-3, CH-5, J₁ = 7.2 Hz, J₂ = 8.2 Hz), 7.67 (d, 2H, CH-2', CH-6', J = 9.0 Hz), 6.99 (d, 2H, CH-3', CH-5', J = 9.0 Hz), 7.96 and 8.14 (s, -N=CH, trans/cis), 9.04 (s, -NH), 11.59 and 11.63 (-NHN=, trans/cis); ¹³C NMR (DMSO-d₆) δ 167.75 (C=O), 152.30 (triazole C-5), 148.10 (triazole C-3), 143.80 and 145.05 (-N=CH, trans/cis), [ar C: 160.89 (C-4'), 146.49 (C-1), 129.05 (C-3, C-5), 128.47 (C-2', C-6'), 126.39 (C-1'), 120.21 (C-4), 114.15 (C-3', C-5'), 111.95 (C-2, C-6), 55.62 (-OCH₃), 46.40 and 46.80 (-NCH₂, trans/cis), 26.13 (-CH₂CH₂CH₃), 18.74 (-CH₂CH₂CH₃), 13.30 (-CH₂CH₂CH₃).

5-Oxo-4-phenylamino-3-n-propyl-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid o-hydroxy-benzylidenehydrazide (10b): Recrystallization from ethyl acetate (yield: 78.94%), mp. 143-144 °C; The ratio...
of trans/cis conformers: 57/43; Analysis (Calc/ found %): for C_{20}H_{22}O_{3}N_{6} C: 60.90/60.14, H: 5.62/5.55, N: 21.31/21.22; IR (KBr) (μ, cm⁻¹), 3220 (-NH+OH), 3122 (-NHN=), 1716 (triazole-C=O), 1682 (hydrazide-C=O), 1605 (C=N); 1H NMR (DMSO-d₆) δ 0.89 (t, -CH₂CH₂CH₃, J= 7.4 Hz), 1.58 (sex, -CH₂CH₂CH₃, J₁ = 7.4, J₂ = 7.2 Hz), 2.42 (t, -CH₂CH₂CH₃, J = 7.2 Hz), 4.89 and 4.53 (-NCH₂, trans/cis), [ar H: 6.62 (d, 2H, CH-2, CH-6, J = 7.2 Hz), 6.80-7.00 (m, 3H, CH-4, CH-3', CH-4'), 7.20-7.40 (m, 3H, CH-3, CH-5, CH-5'), 7.76 and 7.58 (d, 1H, CH-6', J = 7.8 Hz, trans/cis), 8.33 and 8.44 (s, -N=CH, trans/cis), 9.02 (s, -NH), 10.06 and 10.96 (s, -OH, trans/cis), 11.62 and 11.96 (s, -NHN=, trans/cis); 13C NMR (DMSO-d₆) δ 167.58 (-C=O), 152.42 and 152.72 (triazole C-5, trans/cis), 147.91 and 147.65 (triazole C-3, trans/cis), 141.20 and 143.21 (N=CH, trans/cis) [ar C: 162.87 and 161.17 (C-2', trans/cis), 146.48 (C-1), 131.17 and 131.48 (C-6', trans/cis), 129.09 (C-3, C-5), 126.12 (C-5'), 120.11 (C-4), 120.04 (C-4'), 119.30 and 118.54 (C-1', trans/cis), 116.24 (C-3'), 111.97 (C-2, C-6), 46.75 and 46.95 (-NCH₂, trans/cis), 26.13 (-CH₂CH₂CH₃), 18.72 (-CH₂CH₂CH₃), 13.30 (-CH₂CH₂CH₃).

5-Ox0-4-phenylamino-3-n-propyl-4,5-dihydro-[1,2,4]triazol-5-on-1-yl-acetic acid 4-hydroxy-3-methoxy-benzylidenehydrazide (10c): Recrystallization from ethanol (yield: 80.53%), mp. 250-252 °C; The ratio of trans/cis conformers: 70/30; Analysis (Calc/ found %): for C_{21}H_{24}O_{4}N_{6} C: 59.42/59.99, H: 5.70/5.82, N: 19.80/20.05; IR (KBr) (μ, cm⁻¹), 3266 (-NH), 3186 (-OH), 3145 (-NHN=), 1705 (triazole-C=O), 1670 (hydrazide-C=O), 1600 (-C=N); 1H NMR (DMSO-d₆) δ 0.88 (t, -CH₂CH₂CH₃, J = 7.4), 1.57 (sex, -CH₂CH₂CH₃, J₁ = 7.4 Hz, J₂ = 7.2 Hz), 2.44 (t, -CH₂CH₂CH₃, J = 7.2 Hz), 3.81 (s, -OCH₃), 4.89 and 4.48 (-NCH₂, trans/cis), [ar H: 6.64-6.68 (m, 2H, CH-2, CH-6), 6.85-6.91 (m, 2H, CH-4, CH-5'), 7.11-7.35 (m, 3H, CH-3, CH-5, CH-6'), 7.36 and 7.27 (s, 1H, CH-2' trans/cis)], 7.89 and 8.01 (s, -N=CH, trans/cis), 9.01 (s, -NH), 9.53 and 9.59 (s, -OH, trans/cis), 11.52 and 11.54 (s, -NHN=, trans/cis); 13C NMR (DMSO-d₆) δ 167.80 (-C=O), 152.85 and 152.03 (triazole C-5, trans/cis), 149.15 and 148.91 (triazole C-3, trans/cis), 144.58 (-N=CH), [ar C: 162.81 (C-4'), 148.09 (C-3'), 146.69 (C-1), 129.27 (C-3, C-5), 125.46 (C-1'), 121.82 and 122.05 (C-2', trans/cis), 120.25 (C-4), 115.43 (C-6'), 112.16 (C-2, C-6), 109.19 (C-5'), 55.60 (-OCH₃), 47.05 and 47.22 (-NCH₂, trans/cis), 26.34 (-CH₂CH₂CH₃), 18.96 (-CH₂CH₂CH₃), 13.51 (-CH₂CH₂CH₃).

5-Ox0-4-phenylamino-3-n-propyl-4,5-dihydro-[1,2,4]triazol-1-yl-acetic acid pyridine-4-yl-methylenehydrazide (10d): Recrystallization from ethanol (yield: 83.37%), mp. 216-219 °C; The ratio of trans/cis conformers: 70/30; Analysis (% Calc/ found %) for: C_{19}H_{20}O_{4}N_{6} S C: 56.23/56.43, 320
General method for the synthesis of compounds 11

Corresponding compound 10 (0.01 mol) was heated with an equivalent amount of benzoic acid (or acetic acid) at 130-140 °C for 2 h in an oil bath. After cooling to room temperature, a solid appeared. This crude product was recrystallized from DMSO-water (1:2) to afford the desired compound.

3,6-Di(3-methyl-5-Oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl)methyl-1,4-dihydro-[1,2,4,5]tetrazine (11a): (yield: 82.45%), mp. 286 °C; Analysis (Calc/ found %): for C_{22}H_{24}O_{2}N_{12} C: 54.09/54.83, H: 4.95/4.92, N: 34.41/34.44; IR (KBr) (ν, cm⁻¹): 3289 (-NH), 3132 (-NH), 1692 (-C=O), 1644 (-C=N), 1605 (-C=N); ¹H NMR (DMSO-d₆) δ 0.87 (s, -2CH₃), 4.43 (s, -2NCH₂), [ar H: 6.88 (bs, 4H, 2CH-2, 2CH-6), 7.19 (bs, 2H, 2CH-4), 7.56 (d, 4H, 2CH-3, 2CH-5 J = 7.2 Hz), 8.97 (tetrazine-2NH), 10.35 (tetrazine-2NH); ¹³C NMR (DMSO-d₆) δ 163.57 (tetrazine 2C-3, 2C-6), 152.39 (tetrazine 2C-5), 148.09 (tetrazine 2C-3), [ar C: 146.35 (2C-1), 128.10 (2CH-3, 2CH-5), 121.01 (2CH-4), 111.78 (2CH-2, 2CH-6)], 45.97 (2NCH₂), 13.46 (2CH₃).

3,6-Di(3-ethyl-5-Oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl)methyl-1,4-dihydro-[1,2,4,5]tetrazine (11b): (yield: 83.67%), mp. 274 °C; Analysis (Calc/ found %): for C_{23}H_{26}O_{2}N_{12} C: 55.80/55.89, H: 5.46/5.90, N: 32.54/31.67; IR (KBr) (ν, cm⁻¹): 3288 (-NH), 3132 (-NH), 1697 (-C=O), 1640 (-C=N), 1607 (-C=N); ¹H NMR (DMSO-d₆) δ 1.20 (t, -CH₂CH₃, J = 7.4 Hz), 2.42 (q, 2CH₂CH₃, J = 7.4 Hz), 4.42 (s, 2NCH₂), [ar H: 6.83 (bs, 4H, 2CH-2, 2CH-6), 7.24 (bs, 2H, 2CH-4), 7.44 (bs, 4H, 2CH-3, 2CH-5), 8.97 (tetrazine-2NH), 10.34 (tetrazine-2NH); ¹³C NMR (DMSO-d₆) δ 163.28 (tetrazine 2C-3, 2C-6), 152.39 (tetrazine 2C-5), 148.08 (tetrazine 2C-3), [ar C: 146.37 (2C-1), 128.31 (2CH-3, 2CH-5), 120.92 (2CH-4), 112.03 (2CH-2, 2CH-6), 45.90 (2NCH₂), 26.07 (2CH₂CH₃), 13.44 (2CH₂CH₃).

3,6-Di(5-Oxo-3-n-propyl-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl)methyl-1,4-dihydro-[1,2,4,5]tetrazine (11c): (yield: 80.98%), mp. 267 °C; Analysis (Calc/ found %): for C_{26}H_{32}O_{2}N_{12} C: 57.34/57.89, H: 5.92/5.90, N: 30.86/30.67; IR (KBr) (ν, cm⁻¹): 3288 (-NH), 3130 (-NH), 1698 (-C=O), 1643 (-C=N), 1604 (-C=N); ¹H NMR (DMSO-d₆) δ 0.84 (t, 2CH₂CH₂CH₃, J = 7.4 Hz), 1.53 (m, 2CH₂CH₂CH₃), 2.39 (t, 2CH₂CH₂CH₃, J = 7.4 Hz), 4.42 (s, 2NCH₂), [ar H: 6.83 (d, 4H, 2CH-2, 2CH-6, J = 7.6 Hz), 7.21 (t, 2H, 2CH-4, J = 7.4 Hz), 7.59 (t, 4H, 2CH-3, 2CH-5, J = 7.6 Hz), 8.97 (tetrazine-2NH), 10.35 (tetrazine-2NH); ¹³C NMR (DMSO-d₆) δ 165.12 (tetrazine -2C-3, 2C-6), 152.37 (tetrazine 2C-5), 147.85 (tetrazine 2C-3), [ar C: 146.38 (2C-1), 129.03 (2CH-3, 2CH-5), 120.03 (2CH-4), 111.92 (2CH-2, 2CH-6)], 46.17 (2NCH₂), 13.29 (-CH₂CH₂CH₃).
26.07 (2CH₂CH₂), 18.63 (2CH₂CH₂CH₃), 13.29 (2CH₂CH₃).

3,6-Di(3-benzyl-5-Oxo-4-phenylamino-4,5-dihydro-[1,2,4]triazol-1-yl)methyl-1,4-dihydro-
[1,2,4,5]tetrazine (11d): (yield: 82.28%), mp. 252°C; Analysis (Calc/found %): for C₃₄H₃₂O₂N₁₂ C:
63.74/63.59, H: 5.03/5.07, N: 26.23/26.45; IR (KBr) (ν, cm⁻¹), 3288 (-2NH), 3136 (-2NH), 1699
(-C=O), 1643 (-C=N), 1604 (-C=N); ¹H NMR (DMSO-d₆) 3.80 (s, 2CH₂), 4.32 (s, 2NCH₂), [ar
H: 6.58 (d, 4H, 2CH-2, 2CH-6 J = 7.4 Hz), 6.83 (t, 2H, 2CH-4, J = 7.4 Hz), 7.13 (t, 4H,CH-3, CH-5, J = 7.8 Hz), 7.25-7.42 (m, 10H, benzyl-CH)], 8.95 (triazole-2NH), 10.33 (tetrazine-2NH); ¹³C NMR (DMSO-d₆) 165.21
(tetrazine 2C-3, 2C-6), 152.87 (triazole 2C-5), 147.01 (triazole 2C-3), [ar C: 146.30 (2C-1), 134.12 (2C-1’), 131.39 (2C-3’, 2C-5’), 129.22 (2C-2’, 2C-6’), 126.61 (2C-4’, 2C-5’), 119.27 (2C-4’), 112.15 (2CH-2, 2CH-6)], 46.47 (2NCH₂), 30.20 (2CH₂).

3,6-Di(5-Oxo-3-phenyl-4-phenylamino-4,5-dihydro-[1,2,4]triazol-5-on-1-yl)methyl-1,4-
dihydro-[1,2,4,5]tetrazine (11e): (yield: 85.25%), mp. 292°C; Analysis (Calc/found %): for C₃₂H₂₈O₂N₁₂ C:
62.74/63.19, H: 4.61/4.67, N: 27.43/27.15; IR (KBr) (ν, cm⁻¹), 3288 (-NH), 3135 (-NH), 1694
(-C=O), 1640 (-C=N), 1602 (-C=N); ¹H NMR (DMSO-d₆) 4.45 (s, 2NCH₂), [ar H: 6.71 (d, 4H, 2CH-2, 2CH-6, J = 7.2), 6.91 (t, 2H, 2CH-4, J = 7.4 Hz), 7.30 (t, 4H, 2CH-3, 2CH-5, J = 7.2 Hz), 7.43-7.72 (m, 6H), 7.80-8.03 (m, 4H)], 9.25 (triazole-2NH), 10.35 (tetrazine-2NH); ¹³C NMR (DMSO-d₆) δ 164.92 (tetrazine-2C-3, 2C-6), 152.50 (triazole-2C-5), 147.92 (triazole 2C-3), [ar C: 146.93 (2C-1), 135.91 (2C-4’), 132.46 (2C-3, 2C-5), 130.45 (2C-3’, 2C-5’), 127.31 (2C-2’, 2C-6’), 125.56 (2C-1’), 119.34 (2C-4), 114.85 (2CH-2, 2CH-6)], 46.87 (2NCH₂).

References

A Convenient Synthesis of..., A. DEMİRBAŞ