Research Article

Synthesis of Some New Barbituric and Thiobarbituric Acids Bearing 1,2,4-Triazine Moiety and Their Related Systems as Herbicidal Agents

Abeer N. Al-Romaizan

Department of Chemistry, Faculty of Science, King Abdul Aziz University, Jeddah 21589, Saudi Arabia

Correspondence should be addressed to Abeer N. Al-Romaizan; ar-orkied@hotmail.com

Received 5 May 2019; Revised 14 September 2019; Accepted 28 September 2019; Published 7 November 2019

Academic Editor: Manuela Curcio

Copyright © 2019 Abeer N. Al-Romaizan. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In search for highly bioactive barbituric and thiobarbituric acid derivatives, some new barbituric and thiobarbituric acids bearing 1,2,4-triazine moiety and their related systems (5–13) have been obtained from the addition of isocyanate and isothiocyanate to 3-amino-5,6-diphenyl-1,2,4-triazine (1) followed by ring closure reactions with diethyl malonate. Also, chemical reactivities of the related systems were obtained from the condensation of barbituric and thiobarbituric acid derivatives with aromatic aldehyde and/or fluoroacylation reactions. The structure of all the products was deduced from both elemental analysis and spectral data (IR, 1H NMR, 13C NMR, and MS). The herbicidal activity was also evaluated for the products.

1. Introduction

Barbituric acids play significant roles in biological activity. Also, thiobarbituric acid developed to quantitatively determine lipid peroxidation for aldehydic compounds in biological matrices also has vital roles in peroxidation of fatty acids, foods from plants and animal sources, cell membranes, and rat-liver microsomes [1–5]. Abdel-Rahman et al. [6] reported that asymmetrical 1,3-disubstituted thiobarbituric acids bearing 1,2,4-triazine moiety were used as anti-HIV and anticancer agents. Moreover, thiobarbituric acids bearing various heterocyclic moieties were used as potent anticonvulsant agents [7] in MES and PTZ models. Recently, Al-Harbi et al. [8, 9] synthesized fluorinated N1,N3-disubstituted thiobarbituric acids that can be used as anti-HIV1 agents and as inhibitors for cyclin-dependent kinase 2 (CDK2) in cell tumor division [8, 9]. Based upon these facts, the present work tends to synthesize these compounds in one system in view of their biological activities.

Therefore, the addition of cyclohexyl isocyanate, methyl isothiocyanate, and/or phenyl isothiocyanate to 3-amino-5,6-diphenyl-1,2,4-triazine (1) [10] in a polar solvent such as DMF produced the N1,N3-disubstituted thioureas 2–4 (Scheme 1).

Heterocyclization of compounds 2–4 via refluxing with diethyl malonate in dioxane afforded 1-cyclohexyl-3-(5′,6′-diphenyl-1,2,4-triazin-3-yl)barbituric acid (5), 1-methyl-3-(5′,6′-diphenyl-1,2,4-triazin-3-yl)thiobarbituric acid (6), and/or 1-phenyl-3-(5′,6′-diphenyl-1,2,4-triazin-3-yl)thiobarbituric acid (7), respectively (Scheme 1).

The polyfunctional systems of compounds 8–10 were obtained via Knoevenagel condensation by the reaction of compounds 5–7 with 4-chlorobenzaldehyde in EtOH-
piperidine to give the 5-arylidene barbituric/thiobarbituric acid derivatives 8–10 (Scheme 2).

The introduction of fluorine atoms to heterocyclic nitrogen systems, especially thiobarbituric acid derivatives, enhances their physical, chemical, and biological properties [8, 9]. Thus, fluoroacetylation of compounds 5–7 by refluxing with 2,2,2-trifluoroacetic anhydride in DMF yielded 1-(5′,6′-diphenyl-1,2,4-triazin-3′-yl)-3-cyclohexyl-5-di(trifluoroacetyl)barbituric acid (11) and/or 1-(5′,6′-diphenyl-1,2,4-triazin-3′-yl)-3-methyl/phenyl-5-di(trifluoroacetyl)thiobarbituric acids (12 and 13), respectively (Scheme 3).

Formation of compounds 11–13 is mainly due to the presence of active methylene at position 5 of barbituric and thiobarbituric acids, and it is easy to remove the acidic protons (Figure 1).

3. Results and Discussion

Recent studies reported that the barbituric and thiobarbituric acids have many tautomers, which led to a high degree of stability [8, 9]. Also, 1,2,4-triazine moiety exhibited a wide range of biological, pharmacological, and medicinal properties [10, 14]. Thus, the present work aims to combine the barbituric and thiobarbituric acids with a 1,2,4-triazine nucleus to view their enhancement for biocidal effects.

Structures of the new systems obtained were established from the correct elemental analysis and spectral data measurement.

FT-IR spectra of compounds 2–4 recorded δ at 3300, 3150, and 3090 cm⁻¹ attributed to NH, NH of urea and thiourea, and aromatic C-H, respectively; besides, δ at 1610 and 1590 cm⁻¹ is for C=N and aliphatic C-H. Also, δ at 1580 and 1180 cm⁻¹ is for CONH and C=S functional groups presented.

The products 5–7 isolated after heterocyclization with malonate showed a new additional δ stretching at 2980 cm⁻¹ with deformation at 1480 and 1440 cm⁻¹ for CH₂ and 1690 and 1660 cm⁻¹ for C=O lacking NH groups. On the contrary, FT-IR spectra of compounds 8–10 exhibited lack of active methylene, with presence of δ at 700 cm⁻¹ for C-Cl. Fluoroacetyl derivatives 11–13 recorded δ at 1720, 1710, 1690, and 1250 cm⁻¹ for the presence of new bands of CO and C-F.

1H NMR spectra of compounds 2–4 showed resonated signals at δ 5.80 and 5.61 ppm for NH, and NH protons with δ 7.90–6.99 and 2.50 ppm for aromatic and aliphatic protons which confirmed those structures.

1H NMR spectra of barbituric/thiobarbituric acids 5–7 recorded δ 4.55 ppm for active methylene protons, while those of 8–10 exhibited a new signal at δ 8.80 ppm attributed to the exo-CH=C arylidene proton. Also, compounds 11–13 showed a lack of CH₂ protons for barbituric/thiobarbituric acids with δ at 7.77 and 7.44 ppm for aromatic protons of 1,2,4-triazinones.

Moreover, 13C NMR spectra of compounds 5–7 showed mainly δ at 180, 160, and 150 ppm for C=S, and C=O with active CH₂ carbons at δ 40.11 ppm. It is interesting to note that 13C NMR spectra of compounds 8–10 recorded new exo carbons -CH=C at 119 ppm with other signals at 131-120 and 40, 32, and 19 ppm for the presence of aromatic and aliphatic carbons.

13C NMR spectra of trifluoroacetyl derivatives 11–13 showed mainly δ at 145 and 158 ppm for C-F, and a new C=O for acetyl with δ at 131-126 and 39, 30, and 19 ppm attributed to aromatic and aliphatic carbons.

19F NMR spectra of compounds 11–13 showed a characteristic at ~115 ppm for CF₃ bonds.

Mass fragmentation patterns of compound 13, for example, which give us a degree of stability, recorded a molecular ion peak at low m/z with a base peak at 178 attributes to the diphenylacetylene radical (Figure 2).

4. Materials and Methods

The melting points were recorded on a Stuart SMP30 melting point apparatus (Bibby Scientific, UK) and reported as uncorrected. A PerkinElmer (Lambda EZ-2101) double-beam spectrophotometer (190–1100 nm) was used for recording the electronic spectra. A PerkinElmer model RXI-FT-IR spectrophotometer (55,529 cm⁻¹) was used for recording the FT-IR spectra. A Bruker Advance DPX 400 MHz NMR using TMS as an internal standard was used for recording the 1H NMR, 13C NMR, and 19F NMR spectra using deuterated DMSO (δ in ppm) as a solvent. An AGC-MS-QP 1000 Ex model was used for recording the mass spectra. Elemental microanalysis was performed on a PerkinElmer CHN-2400 analyzer. 5,6-Diphenyl-1,2,4-triazin-3-amine (1) was prepared according to the reported method [10].

4.1. N1-(Cyclohexyl/methyl/phenyl)-N2-(5,6-diphenyl-1,2,4-triazin-3-yl)urea/thiourea (2–4). A mixture of compound 1 (0.01 mol) [10] and cyclohexyl isocyanate/methyl isothiocyanate/phenyl isothiocyanate (0.01 mol) in DMF (100 ml) was heated at reflux for 2 h. The mixture was cooled and then poured onto ice. The solid produced was filtered off and crystallized from dioxiane to give 2–4 as yellow crystals.

2; yield 77% and m.p. 135-136°C. FT-IR spectrum δ (cm⁻¹): 3200 and 3150 (NH and NH), 3060 (ArH), 2980 (aliphatic CH), 1620 (CONH), 1580 (C=O), 1480 and 1440 (deform. CH₂), and 880 and 820 (aromatic ring). 1H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.80-7.66 and 7.51-6.99 (each m, 2 phenyl), 5.80 (s, 1H, NHCO), 5.61 (s, 1H, NHCH), 3.65 (q, J = 7.3 Hz, HN-CH₂), 2.20 (t, 1H, CH-N), and 1.90 and 1.88 (each d, 2CH₃). 13C NMR (100 MHz, DMSO-d₆) δ (ppm): 155 (C=O), 142 (C=N), 132-128 (aromatic carbons), and 40.1, 30.7, 19.7, and 13.5 (aliphatic carbons). Calculated, C22H23N5O (M+373), %: C, 70.76; H, 6.21; and N, 18.75. Found, %: C, 70.11; H, 6.01; and N, 18.59.

3; yield 78% and m.p. 168-169°C. FT-IR spectrum δ (cm⁻¹): 3180 and 3150 (NH and NH), 3050 (ArH), 2920 and 2880 (aliphatic CH), 1580 (C=N), 1470 and 1420 (deform. CH₃), 1180 (C=S), and 880 and 820 (aromatic ring). 1H NMR (400 MHz, DMSO-d₆) δ (ppm): 7.95-7.76 and 7.55-7.35 (each m, 2 phenyl), 5.81 and 5.66 (each s, 2H, NHCS, NHMe), and 0.90 (s, 3H, J = 7.1 Hz, CH₃). 13C NMR (100 MHz, DMSO-d₆) δ (ppm): 178 (C=O), 141 (C=N), 131-122 (aromatic carbons), and 40.1 (aliphatic carbons). Calculated, C₁₇H₁₅N₅S (M+321), %: C, 63.53; H, 4.70; N, 21.79; and S, 9.69.
Scheme 1: Synthesis of compounds 2–7.

Scheme 2: Synthesis of compounds 8–10.


Figure 1: Formation of compound 13 from 7.
4.2. N\textsuperscript{1}-(Substituted)-N\textsuperscript{3}-(5,6-diphenyl-1,2,4-triazin-3-yl)barbituric and Thiobarbituric Acids (5–7). Equimolar mixtures of 2, 3, and 4 and diethyl malonate in dry dioxane (50 ml) were refluxed for 4 h and cooled. The solid produced was filtered off and crystallized from dioxane to give 5–7 as faint yellow crystals.

5: yield 55% and m.p. 180–181°C. FT-IR spectrum \(\tilde{\nu}\) (cm\(^{-1}\)): 3060 (ArH), 2970 and 2890 (aliphatic CH), 1690 and 1660 (2C=O), 1580 (C=N), 1480 and 1420 (deform. CH\(_2\)), and 820 and 790 (aromatic ring). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 7.88-7.69 and 7.55-7.11 (each \(m\), 10H ArH), 4.55 (s, 2H, CH\(_2\)), and 1.22 (s, 3Ph). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 188 (C=O), 142 (C=N), 140 (C-N), and 133-122 (aromatic carbons). Calculated, C\(_{25}\)H\(_{17}\)N\(_5\)O\(_2\)S (M\(^+\)383), \%: C, 66.51; H, 4.47; and N, 15.39. Found, \%: C, 66.41; H, 3.70; N, 15.39; and S, 7.02.

4.3. N\textsuperscript{1}-(Substituted)-N\textsuperscript{4}-(5,6-diphenyl-1,2,4-triazin-3\textsuperscript{-y1})-5-(4'-chlorobenzylidene)barbituric/thiobarbituric Acids (8–10). Equimolar mixtures of 5, 6, and 7-4-chlorobenzaldehyde in EtOH (50 ml) with a few drops of piperidine were refluxed for 6–8 h, cooled, and then poured onto ice. The solid yielded was filtered off and crystallized from EtOH to give 8–10 as yellow crystals.

8: yield 70% and m.p. 190–192°C. FT-IR spectrum \(\tilde{\nu}\) (cm\(^{-1}\)): 3060 (ArH), 1710 and 1699 (2C=O), 1610 (C=C), 1580 (C=N), 1480 and 1410 (deform. CH\(_2\)), and 860 and 820 (aromatic ring). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 8.81 (s, 1H, CH=Ar), 7.78-7.66 and 7.51-7.22 (each \(m\), 10H, aromatic), 7.10-7.00 and 6.98-6.88 (d, 2H, aryl), 6.60-6.45 (m, 2H, aryl), 3.51 (q, J=7.11 Hz, -CH-N), and 2.55, 2.44, 2.41, and 2.40 (each \(s\), 2H of cyclohexane). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 162, 158, and 154 (3C=O), 141 (C=N), 139 (C-N), 131-120 (aromatic carbons), and 40.1 (CH\(_2\) carbons), and 19.2 (CH\(_3\) carbons). Calculated, C\(_{25}\)H\(_{25}\)ClN\(_5\)O\(_3\) (M\(^+\)480), \%: C, 68.14; H, 4.65; Cl, 6.28; and N, 12.42. Found, \%: C, 68.02; H, 4.53; Cl, 6.49; and N, 12.37.

9: yield 72% and m.p. 180–182°C. FT-IR spectrum \(\tilde{\nu}\) (cm\(^{-1}\)): 3060 (ArH), 1710 and 1690 (C=O), 1620 (C=C), 1590 and 1560 (C=N), 1350 (NCN), 1180 (C=CS), 890 and 810 (aromatic ring), and 660 (C=Cl). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 8.99 (s, 1H, CH=Ar), 7.81-7.76 and 7.55-7.41 (each \(m\), 10H ArH), 7.22-7.20 and 7.11-7.01 (d, 2H, aryl), and 6.89-6.68 (m, 2H, aromatic). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 188 (C=O), 168 and 162.

Figure 2: Mass fragmentation pattern of compound 13.
(2C=O), 142 (C=N), 140 (C-N), 132-122 (aromatic carbons), and 20.1 (CH$_2$ carbon). Calculated, C$_2$H$_{18}$ClN$_2$O$_2$S (M$^+$512), $\%$: C, 63.34; H, 3.54; Cl, 6.92; N, 13.68; and S, 6.26. Found, $\%$: C, 63.34; H, 3.54; Cl, 6.92; N, 13.68; and S, 6.26.

**10**: yield 78% and m.p. 179-180°C. FT-IR spectrum $\tilde{u}$ (cm$^{-1}$): 3080 (ArH), 1700 and 1690 (C=O), 1610 (C=C), 1580 and 1550 (C=N), 1350 (NCSN), 1182 (C=S), and 910, 880, and 810 (aromatic ring). $^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ (ppm): 9.10 (s, 1H, CH=CH-C=Ar), 7.91-7.77, and 7.55-7.41 (each $m$, 2H, aromatic), 7.40-7.22 (m, 5H, aromatic), and 7.11-7.10 and 6.99-6.95 (each $d$, 2H, aryl). $^{13}$C NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): 189 (C=S), 162 and 155 (C-O), 142 (C=N), 140 (C-N), 132-122 (aromatic carbons), and 119 (C-C). Calculated, C$_{32}$H$_{25}$ClN$_2$O$_2$S (M$^+$574), $\%$: C, 66.95; H, 3.51; Cl, 6.18; N, 12.20; and S, 5.58. Found, $\%$: C, 66.95; H, 3.51; Cl, 6.18; N, 12.20; and S, 5.58.

**4.4. $N^1$-(Substituted)-$N^3$-(5,6-diphenyl-1,2,4-triazin-3-yl)-5,5-di(trifluoroacyl)barbituric/thiobarbituric Acids (11–13).** To compounds 5–7 (0.01 mol), trifluoroacetic anhydride (5 ml) in THF (70 ml) was added and heated under reflux for 8 h and cooled. The solids obtained were filtered off and crystallized from dioxane to give 11–13 as yellowish crystals.

**11**: yield 70% and m.p. 169-170°C. FT-IR spectrum $\tilde{u}$ (cm$^{-1}$): 3050 (ArH), 2990 and 2880 (aliphatic CH), 1750, 1710, and 1699 (2C=O), 1580 and 1560 (C=N), 1480 and 1440 (deform. CH$_2$), 1250 (C-F), and 880 and 810 (aromatic ring). $^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ (ppm): 7.88-7.75 and 7.72-7.11 (each $m$, 10H, aromatic), 3.55 ($q$, $J=7.21$ Hz, 2H, CH$_2$), 2.50 ($t$, 1H, N-CH), and 1.91 and 1.88 (each $d$, 2H, 2CH$_2$). $^{13}$C NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): 164, 152, and 152 (3C=O), 145 (C-F), 142 (C=N), 141 (C-N), 139 (O-C-O), 115-126 (aromatic carbons), and 39.01, 30.66, 19.80, and 14.01 (CH$_3$ carbons). $^{19}$F NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): -115 (CF$_3$). Calculated, C$_{29}$H$_{23}$F$_5$N$_2$O$_4$S (M$^+$633), $\%$: C, 54.98; H, 3.34; F, 17.99; and N, 11.06. Found, $\%$: C, 54.79; H, 3.21; F, 17.81; and N, 11.01.

**12**: yield 72% and m.p. 185-186°C. FT-IR spectrum $\tilde{u}$ (cm$^{-1}$): 3050 (ArH), 1720 and 1700 (C=O), 1580 and 1560 (C=N), 1480 and 1410 (deform. CH$_2$), 1350 (NCSN), 1240 (C-F), 1191 (C=S), and 880 and 840 (aromatic ring). $^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ (ppm): 7.88-7.79 and 7.79-7.55 (each $m$, 10HARH) and 0.90 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): 180 (C=S), 168, 162, and 156 (3C=O), 145 (C-F), 142 (C=N), 139.11 (C-N), 131-126 (aromatic carbons), 118 (O-C-O), and 40.11 (CH$_3$ carbon). $^{19}$F NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): -115 (CF$_3$). Calculated, C$_{24}$H$_{17}$F$_5$N$_2$O$_4$S (M$^+$581), $\%$: C, 49.58; H, 2.25; F, 19.60; N, 12.04; and S, 5.51. Found, $\%$: C, 49.34; H, 2.15; F, 19.46; N, 11.89; and S, 5.32.

**13**: yield 75% and m.p. 228-230°C. FT-IR spectrum $\tilde{u}$ (cm$^{-1}$): 3080 (ArH), 1720, 1700, and 1680 (C=O), 1610 and 1590 (C=N), 1330 (NCSN), 1240 (C-F), 1188 (C=S), 870 and 833 (aromatic ring), and 700 (C-F). $^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ (ppm): 7.88-7.66 and 7.64-7.55 (each $m$, 10H, aromatic) and 7.41-7.38 (m, 5H, aromatic). $^{13}$C NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): 182 (C=S), 164, 162, and 154 (C-O), 144 (C-F), 142 (C=N), 139 (C-N), 132-122 (aromatic carbons), and 116 (C-O-C). $^{19}$F NMR (100 MHz, DMSO-$_d_6$) $\delta$ (ppm): -115 (CF$_3$). M/S (int. %): (M$^+$, 643), (M+2, 1.11), 178 (100), 138 (15.11), 135 (5.31), and 69 (10). Calculated, C$_{29}$H$_{18}$F$_5$N$_2$O$_4$S (M$^+$643), $\%$: C, 54.13; H, 2.35; F, 17.71; N, 10.88; and S, 4.98. Found, $\%$: C, 54.02; H, 2.15; F, 17.54; N, 10.76; and S, 4.84.

**5. Herbicidal Activity**

All the synthesized compounds 2–13 were evaluated for herbicidal activity against eighteen individual potted plants of economically important weeds and crops, according to the standard method [15]. The minimum sample was used for these tests, 250 mg. Only the fluorinated thiobarbituric acid derivative 13 showed high herbicidal activity, while other nonfluorinated thiobarbituric acid derivatives 6, 7, 9, and 10 showed lethal activity. On the contrary, the fluorinated compounds, barbituric acid 11, and nonfluorinated barbituric acids 5 and 8 showed no activity.

The high stability of compound 13 is perhaps due to a type of electrostatic formula which causes a higher bioconjugated system (Figure 3).

**6. Conclusion**

Novel fluorinated/nonfluorinated barbituric and thiobarbituric acids bearing 1,2,4-triazin-3-yl were obtained from a simple heterocyclization $N^1,N^3$-disubstituted urea/thiourea with malonate. Also, the chemical reactivity of the barbituric and thiobarbituric acids was evaluated. Only, the fluorinated thiobarbituric acids exhibited a moderate herbicidal activity, while the nonfluorinated thiobarbituric acids showed lethal activities.

**Data Availability**

IR and $^1$H NMR spectral data of compounds 2–13 can be found in supplementary materials.

**Conflicts of Interest**

The author declares that there are no conflicts of interest.

**Acknowledgments**

Sincere thanks are due to Dr. I. Ismail, Department of Microbiology, College of Science, Ain Shams University, Egypt, for the herbicidal evaluation.
Supplementary Materials

IR and 1H NMR spectral data of compounds 2–13.

( Supplementary Materials)

References


Submit your manuscripts at
www.hindawi.com