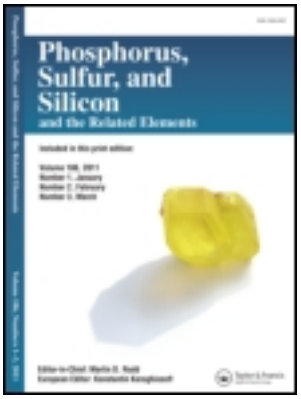

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Utility of Phthalimidoacyl Isothiocyanate in Synthesis of Quinazolines, Benzoxazoles, Benzimidazoles, 1,2,4-Triazoles, and Oxatriazepines

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UTILITY OF PHTHALIMIDOACYL ISOTHIOCYANATE IN SYNTHESIS OF QUINAZOLINES, BENZOXAZOLES, BENZIMIDAZOLES, 1,2,4-TRIAZOLES, AND OXATRIAZEPINES

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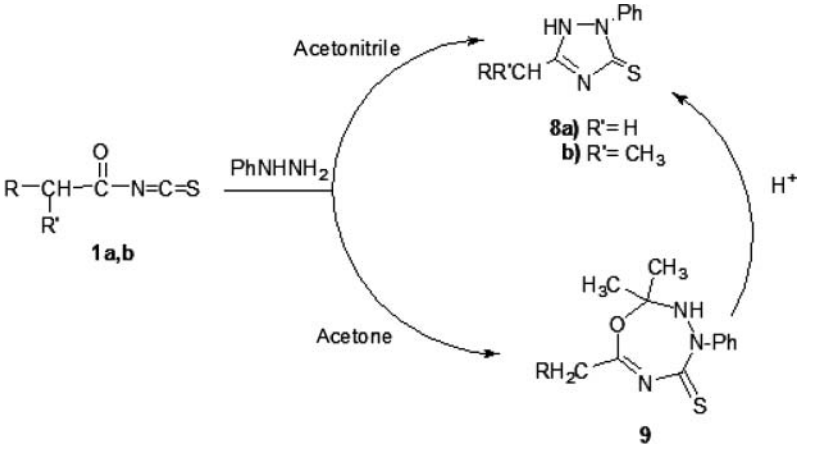
GRAPHICAL ABSTRACT



Abstract *Phthalimidoacyl isothiocyanates **Ia,b** participated in a wide range of addition–cyclization reactions. Simultaneous or subsequent cyclization of the obtained adducts gave derivatives of quinazoline, benzoxazole, benzimidazole, 1,2,4-triazole, and oxatriazepine. The structures of all the products were confirmed by microanalytical and spectroscopic data.*

Keywords Benzimidazoles; benzoxazoles; oxatriazepines; phthalimidoacyl isothiocyanate; quinazolines; 1,2,4-triazoles

INTRODUCTION

Aroyl isothiocyanates are bifunctional reagents capable of participating in a wide range of addition–cyclization reactions.[1] The strong electron-attracting power of their aroyl

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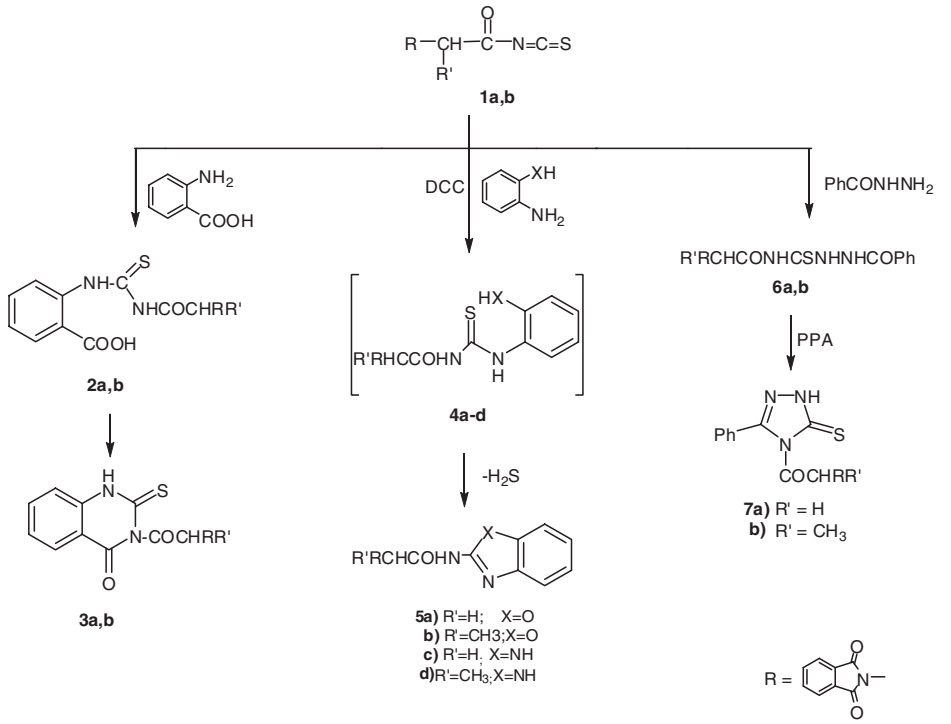
groups enhances the reactivity of the adjacent isothiocyanato function and promotes nucleophilic addition at this center.[2] Simultaneous or subsequent cyclization of the adducts gave access to a variety of heterocyclic rings of different sizes, including bicyclic condensed ring systems.[1–13] Isothiocyanates may serve as a versatile building block to prepare a wide class of nitrogen, sulfur, and oxygen heterocycles besides thiourea derivatives, which are reported to exhibit biological activities as antibacterial, antifungal, herbicides, and pesticides.[14–16]

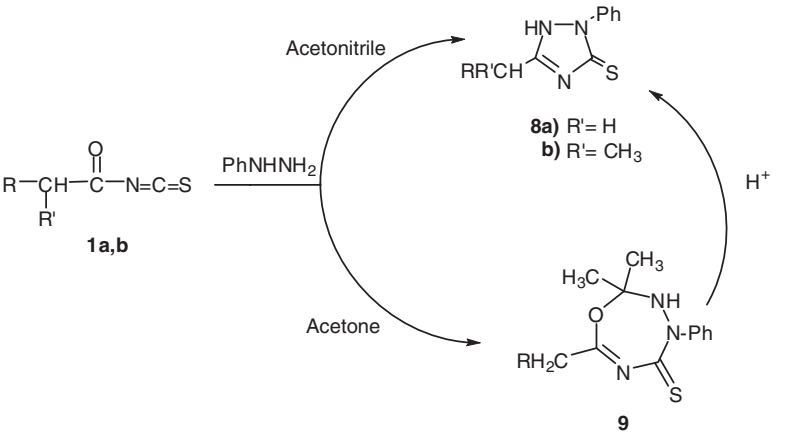
In the present investigation, phthalimidoacyl isothiocyanates underwent reactions with different nucleophilic reagents to provide a versatile synthetic route to derivatives of quinazoline, benzoxazole, benzimidazole, 1,2,4-triazole, and oxatriazepine.

RESULTS AND DISCUSSION

The new derivatives were prepared according to the reaction sequences depicted in Schemes 1 and 2. As shown in Scheme 1, the reaction of isothiocyanates **1a**,**b** with anthranilic acid produced thiourea derivatives **2a**,**b**. Heating of compounds **2a**,**b** with polyphosphoric acid gave quinazoline derivatives **3a**,**b**. The infrared (IR) spectra of compounds **2** and **3** showed absorption bands correlated with υ (NH), υ (C═O), and υ (C═S). Their ^{1}H NMR spectra displayed signals corresponding to alkyl and aromatic protons, as well as signals of NH protons. ^{13}C chemical shifts of **2a** and **3a** showed 14 types of carbon atoms in agreement with their structures. Further highlights on the assigned structures of compounds **2a**,**b** and **3a**,**b** were gained from their mass spectrum (MS) data that revealed MS peaks consistent with the assigned structures (see Experimental section).



Scheme 1



Scheme 2

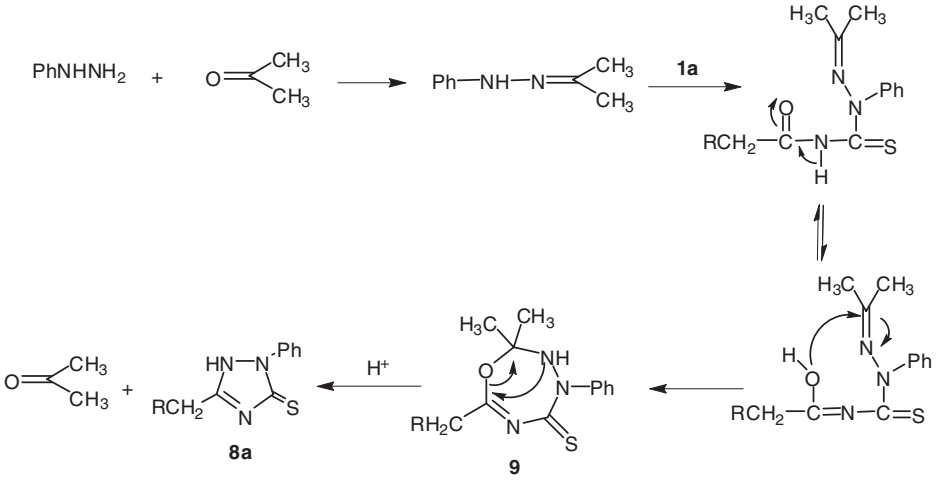
o-Aminophenol and *o*-phenylenediamine reacted with isothiocyanate **1a** in the absence of dicyclohexylcarbodiimide (DCC) to produce the thiourea derivatives **4a** and **4c**, respectively. However, the treatment of *o*-aminophenol and *o*-phenylenediamine with **1a**,**b** in the presence of an equivalent amount of DCC afforded benzoxazoles **5a**,**b** or benzimidazoles **5c**,**d**. The formation of compounds **5a–d** can be rationalized on the basis of formation of the thiourea derivatives **4** as intermediates (isolated in the absence of DCC) followed by cyclization. The structures of compounds **5a–d** were proved by their microanalytical and spectral data. Their IR spectra showed absorption bands correlated with υ (NH), υ (C=O), and υ (C=N). The ^{1}H NMR spectra of compounds **5a–d** showed signals corresponding to alkyl and aromatic protons in addition to NH protons in the downfield region. ^{13}C chemical shifts of **4a**,**c** and **5a** showed 13 types of carbon atoms, while **5c** showed only 10 signals that correspond to 10 different types of carbon atoms. The MS revealed the molecular ion peaks for compounds **5a–d** (see Experimental section). Unfortunately compounds **4a**,**c** did not show the molecular ion peaks; however, their MS peaks correspond very well to the proposed structures.

The treatment of **1a**,**b** with benzoyl hydrazine in acetonitrile gave thiosemicarbazide derivatives **6a**,**b** (Scheme 1). Cyclization of compounds **6a**,**b** was achieved on heating with polyphosphoric acid to give 1,2,4-triazoline derivatives **7a**,**b**. The formation of compounds **7** was explained on the basis of the removal of a molecule of water from *N*-4 and benzoyl carbonyl group. Another mode of cyclization of **6** through elimination of a molecule of water from *N*-1 and aroyl carbonyl group was excluded due to the absence of aroyl ion fragment at *m*/*z* 105 in their mass spectra.

The structures of compounds **6a**,**b** and **7a**,**b** were elucidated from their microanalytical and spectral data that revealed a pattern completely in agreement with their proposed structures. Thus, their IR spectra showed υ (NH), doublet in the region (1779–1700 cm^{-1}) for coupling carbonyl bands of cyclic imides, and υ (C=S). ^{1}H NMR of **6a** and **7a**,**b** displayed signals for CH_2, CH_3, and CH, protons at δ: 4.73–4.57, 1.59, and 5.19 ppm, integrating two, three, and one proton, respectively. Aromatic protons exhibited a multiplet in the region 7.43–8.16 ppm, integrating nine protons, as well as a broad singlet due to NH protons in the downfield region, which are exchangeable with D_2O. ^{13}C chemical shifts of **6a** and **7a** showed the different types of carbon atoms for each compound, including C=O signal in the region 162.2–167.8 ppm and C=S signal in the region 167.4–180.1 ppm.

Moreover, MS of **6b** and **7a**,**b** revealed the molecular ion peaks. The MS of compound **6a** did not show its molecular ion peak, but it showed [$M^+ - (CO_2+H_2S)$] peak in addition to some of the abundant peaks consistent with the assigned structure.

Similar treatment of phthalimidoacyl isothiocyanates **1a**,**b** with phenyl hydrazine in acetonitrile yielded 1,2,4-triazoline-3-thione derivatives **8a**,**b** in one-pot reaction (Scheme 2). The formation of compounds **8a**,**b** was visualized to proceed via condensation of phenylhydrazine with the carbonyl group of **1a**,**b** followed by cyclization with the isothiocyanato group. However, phthalimidoacetyl isothiocyanate (**1a**) was reacted with phenylhydrazine in dry acetone to afford oxatriazepine-5-thione derivative **9** in one-pot reaction. The formation of compound **9** can be explained on the basis of nucleophilic addition of isopropylidene phenylhydrazone (obtained as a side product of the reaction of phenylhydrazine with acetone) on the carbon atom of isothiocyanato group followed by cyclization (Scheme 3). Another method of preparing compound **9** was achieved by the treatment of isothiocyanate **1a** with acetone phenylhydrazone in boiling acetonitrile. Moreover, heating of an ethanolic solution of **9** with a catalytic amount of concentrated HCl yielded 1,2,4-triazoline **8a** and acetone as shown in Scheme 3. The acetone was isolated as acetone 2,4-dinitrophenylhydrazone.[17]



Scheme 3

The IR spectral data of compounds **8a**,**b** and **9** showed υ (NH), two bands corresponding to coupling carbonyl groups of cyclic imide, υ (C=N), and υ (C=S). Their ^{1}H NMR displayed a pattern completely in accord with their structures. ^{13}C chemical shifts of **8a** and **9** showed 11 and 13 peaks related to their carbon atoms, respectively. Further proof for the assigned structure of compounds **8a**,**b** was gained from their MS, which revealed their molecular ion peaks as base peaks corresponding to their molecular formulas. The MS peaks of compound **9** showed a fragment at *m*/*z* 148 as a base peak corresponding to acetone phenylhydrazone ion.

CONCLUSION

The electron-withdrawing power of the phthalimido moiety enhances the reactivity of both isothiocyanate function and carbonyl group of **1**. It is observed from all reactions

mentioned that the nucleophilic addition proceeds either at the isothiocyanate group (Scheme 1) or at the carbonyl group (Scheme 2) of the title compounds **1a**,**b**, followed by simultaneous or subsequent cyclization.

EXPERIMENTAL

General

Melting points of the reaction products were determined in open capillary tubes on a Gallenkamp melting point apparatus and were uncorrected. The elemental analysis was performed on a Perkin-Elemer 2400 CHN elemental analyzer. The IR spectra were recorded on a Perkin-Elemer Model 297 Infrared spectrometer and Pye Unicam SP1200 spectrophotometer using the KBr wafer technique. The ^{1}H NMR and ^{13}C NMR spectra were measured on a Oxford NMR 300-Varian Gemini 2000 NMR spectrometer, JEOL JNM-EX 270 FT NMR spectrometer, Varian Gemini 200 MHz, and Brucker AC-200 MHz with chemical shift (δ) expressed in ppm downfield, with tetramethylsilane (TMS) as internal standard, in DMSO-d_6. Mass spectra were determined using a Kratos Model MS 25 mass spectrometer (Magnetic Sector) and HP Model MS-5988 at 70 eV. Thin layer chromatography (TLC) was run using TLC aluminum sheets silica gel F_{254} (Merck). It was carried out by monitoring the progress of all reactions and homogeneity of the synthesized compounds.

Synthesis of Phthalimidoacyl Isothiocyanates (1a,b)

To a solution of phthalimido acetyl chloride or 2-phthalimido propionyl chloride (3 mmol) in dry acetonitrile (30 mL) or dry acetone (30 mL), solid ammonium thiocyanate (3 mmol) was added. The reaction mixture was stirred for 30 min at room temperature.[18,19] The precipitated ammonium chloride was filtered off to give a clear solution of isothiocyanates **1a**,**b**.

Reaction of Isothiocyanate (1a,b) with Different Nucleophiles

General Procedure. To a solution of isothiocyanate **la** or **1b** (3 mmol) in dry acetonitrile or acetone (50 mL), anthranilic acid, *o*-aminophenol, *o*-phenylenediamine, benzoylhydrazine, phenylhydrazine, or acetone phenylhydrazone was added. An equivalent amount of DCC was added in the case of the reaction of **1a**,**b** with *o*-aminophenol or *o*-phenylenediamine. The mixture was refluxed for 2–3 h (TLC) and then cooled to room temperature. The precipitated solid was sucked, washed with ethanol, and crystallized from the suitable solvent to give the corresponding compounds.

*2-(3-(2-(1,3-Dioxoisoindolin-2-yl)Acetyl)Thioureido)Benzoic Acid (**2a**).* 75% yield; pale yellow crystals; mp 214 °C–217 °C (ethanol); IR (KBr) υ (cm^{-1}): 3240, 3200 (NH), 1780, 1710 (C=O), 1225 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.57 (s, 2, $\underline{CH_2}$), 7.29–8.23 (m, 8, ArH), 11.91 (br. s, 2, NH, exchangeable), 13.11 (br. s, 1, OH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.3 (CH_2), Ar—C [123.6 ($\underline{C}$—COOH), 124.4 (2CH), 126.3 (CH), 127.2 (CH), 130.5 (CH), 131.6 (2C), 132.1 (2CH), 135.0 (CH), 138.0 ($\underline{C}$—NH)], 167.3 (2CO), 167.5 (CO), 167.6 (CO), 178.9 (CS); MS (70 eV) *m/z* (%): 306 [$M^+ - (CO_2 + SH)$, 22], 262 (5), 188 (2), 160 (100), 137 (3), 105 (9); anal. calcd. for $C_{18}H_{13}N_3O_5S$ (383.40): C 56.39, H 3.42, N 10.96; found: C 56.33, H 3.20, N 10.83.

*2-(3-(2-(1,3-Dioxoisoindolin-2-yl)Propanoyl)Thioureido)Benzoic Acid (**2b**).* 70% yield; pale yellow crystals; mp 190 °C–192 °C (ethanol); IR (KBr) υ (cm^{-1}): 3288, 3032 (NH), 1780, 1694 (C=O), 1235 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.60 (d, J = 7.2 Hz, 3, $\underline{CH_3}$), 5.04 (q, J = 7.2 Hz, 1, $\underline{CH}$), 7.29–8.13 (m, 8, ArH), 11.68, 12.83 (br. s, 2, NH, exchangeable), 13.45 (br. s, 1, OH, exchangeable); MS (70 eV) *m/z* (%): 397 (M^+, 2), 205 (9), 174 (100), 146 (43), 104 (15); anal. calcd. for $C_{19}H_{15}N_3O_5S$ (397.40): C 57.42, H 3.80, N 10.57; found: C 57.13, H 3.62, N 10.43.

*N-(2-Hydroxyphenylcarbamothioyl)-2-(1,3-Dioxoisoindolin-2-yl)-Acetamide (**4a**).* 75% yield; pale yellow crystals; mp 216 °C–218 °C (ethanol); IR (KBr) υ (cm^{-1}): 3311, 3128 (NH), 1774, 1707 (C=O), 1380 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.61 (s, 2, $\underline{CH_2}$), 7.20–7.90 (m, 8, ArH), 10.18, 11.86 (br. s, 2, NH, exchangeable), 12.32 (br. s, 1, OH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.5 (CH_2), Ar—C [115.1 (CH), 118.3 (CH), 123.0 (CH), 123.4 (2CH), 125.7 (C), 126.5 (CH), 131.5 (2C), 134.8 (2CH), 148.7 ($\underline{C}$—OH)], 167.3 (C=O), 168.2 (2C=O), 176.5 (C=S); MS (70 eV) *m/z* (%): 278 [M^+ − (CO_2 + SH), 2], 188 (22), 160 (100), 146 (9), 104 (17), 76 (16); anal. calcd. for $C_{17}H_{13}N_3O_4S$ (355.4): C 57.46, H 3.69, N 11.82; found: C 57.27, H 3.54, N 11.75.

*N-(2-Aminophenylcarbamothioyl)-2-(1,3-Dioxoisoindolin-2-yl)Acetamide (**4c**).* 87% yield; pale yellow crystals; mp 220 °C–222 °C (acetic acid); IR (KBr) υ (cm^{-1}): 3360–3260 (NH_2), 3190 (NH), 1780, 1730, 1715 (C=O), 1322 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.27 (s, 2, $\underline{CH_2}$), 6.75–7.93 (m, 8, ArH), 5.3 (br. s, 2, NH_2, exchangeable), 11.33, 11.97 (br. s, 2, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.5 (CH_2), Ar—C [115.8 (CH), 116.0 (CH), 123.0 ($\underline{C}$—NH), 123.4 (2CH), 127.3 (CH), 127.8 (CH), 131.4 (2C), 134.8 (2CH), 143.3 ($\underline{C}$—NH_2)], 167.3 (C=O), 167.2 (2C=O), 179.4 (C=S); MS (70 eV) *m/z* (%): 320 (M^+ − H_2S, 12), 190 (31), 160 (100), 146 (19), 104 (27), 76 (34); anal. calcd. for $C_{17}H_{14}N_4O_3S$ (354.4): C 57.62, H 3.98, N 15.81; found: C 56.90, H 3.80, N 15.38.

*N-(Benzo[d]oxazol-2-yl)-2-(1,3-Dioxoisoindolin-2-yl)Acetamide (**5a**).* 72% yield; pale yellow crystals; mp 266 °C–268 °C (acetic acid); IR (KBr) υ (cm^{-1}): 3130 (NH), 1774, 1724, 1629 (C=O), 1578 (C=N); ^{1}H NMR (DMSO-d_6) δ: 4.71 (s, 2, CH_2), 7.11–8.00 (m, 8, ArH), 12.30 (br. s, 1, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.7 (CH_2), Ar—C [109.5 (CH), 117.9 (CH), 122.9 (CH), 123.3 (2CH), 124.2 (CH), 131.1 (2C), 134.3 (2CH), 140.1 ($\underline{C}$—N, oxazole), 147.2 ($\underline{C}$—O, oxazole)], 154.3 (C=N), 164.9 (CO), 166.9 (2CO); MS (70 eV) *m/z* (%): 321 (M^+, 5), 162 (9), 161 (93), 160 (100), 134 (23), 104 (26); anal. calcd. for $C_{17}H_{11}N_3O_4$ (321.29): C 63.55, H 3.45, N 13.08; found: C 63.51, H 3.20, N 13.00.

*N-(Benzo[d]oxazol-2-yl)-2-(1,3-Dioxoisoindolin-2-yl)Propanamide (**5b**).* 62% yield; pale yellow crystals; mp 215 °C–216 °C (toluene); IR (KBr) υ (cm^{-1}): 3236 (NH), 1778, 1719, 1635 (C=O), 1584 (C=N); ^{1}H NMR (DMSO-d_6) δ: 1.60 (d, J = 7.0 Hz, 3, $\underline{CH_3}$), 5.08 (q, J = 7.2 Hz, 1, $\underline{CH}$), 7.28–7.96 (m, 8, ArH), 11.93 (br. s, 1, NH, exchangeable); MS (70 eV) *m/z* (%): 336 (M^+ + 1, 3), 335 (M^+, 7), 202 (2), 174 (77), 161 (100), 104 (11); anal. calcd. for $C_{18}H_{13}N_3O_4$ (335.31): C 64.47, H 3.91, N 12.53; found: C 64.41, H 3.78, N 12.47.

*N-(1H-Benzo[d]imidazol-2-yl)-2-(1,3-Dioxoisoindolin-2-yl)Acetamide (**5c**).* 67% yield; pale yellow crystals; mp 282 °C–284 °C (acetic acid); IR (KBr) υ (cm^{-1}): 3350, 3264 (NH), 1776, 1717, 1638 (C=O), 1585 (C=N); ^{1}H NMR (DMSO-d_6) δ: 4.58 (s, 2, $\underline{CH_2}$), 7.11–7.98 (m, 8, ArH), 12.20 (br. s, 2, 2NH, exchangeable); ^{13}C NMR (DMSO-d_6): 41.0 (CH_2), Ar—C [113.8 (2CH), 121.4 (2CH), 123.3 (2CH), 131.7 (2C), 134.7 (2CH), 135.3 (2C)], 147.0 (imidazole-C), 167.6 (CO), 167.8 (2CO); MS (70 eV) *m/z* (%): 320

(M^+, 7), 189 (2), 162 (5), 161 (32), 160 (100), 104 (24); anal. calcd. for $C_{17}H_{12}N_4O_3$ (320.30): C 63.75, H 3.78, N 17.49; found: C 63.52, H 3.68, N 17.36.

*N-(1H-Benzo[d]imidazol-2-yl)-2-(1,3-Dioxoisoindolin-2-yl)Propanamide (**5d**).* 67% yield; pale yellow crystals; mp 255 °C–257 °C (ethanol); IR (KBr) υ (cm^{-1}): 3378, 3226 (NH), 1778, 1717, 1637 (C=O), 1586 (C=N); ^{1}H NMR (DMSO-d_6) δ: 1.65 (d, $J = 7.2$ Hz, 3, $\underline{CH_3}$), 5.06 (q, $J = 7.2$ Hz, 1, $\underline{CH}$), 7.09–7.95 (m, 8, ArH), 12.87 (br. s, 2, 2NH, exchangeable); MS (70 eV) *m/z* (%): 335 ($M^+ + 1$, 2), 334 (M^+, 7), 202 (1), 174 (40), 160 (100), 104 (9); anal. calcd. for $C_{18}H_{14}N_4O_3$ (334.33): C 64.66, H 4.22, N 16.76; found: C 64.18, H 3.98, N 16.65.

*N-(2-Benzoylhydrazinecarbonothioyl)-2-(1,3-Dioxoisoindolin-2-yl)Acetamide (**6a**).* 80% yield; pale yellow crystals; mp 211 °C–213 °C (ethanol); IR (KBr) υ (cm^{-1}): 3344, 3210 (NH), 1779, 1700 (C=O), 1280 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.57 (s, 2, $\underline{CH_2}$), 7.43–7.94 (m, 9, ArH) 11.05, 11.74, 12.02 (br. s, 3, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.4 (CH_2), Ar—C [123.6 (2CH), 127.8 (2CH), 128.6 (2CH), 131.6 (3C), 132.2 (CH), 135.0 (2CH)], 164.8 (C=O), 167.5 (C=O), 167.8 (2C=O), 180.1 (C=S); MS (70 eV) *m/z* (%): 304 ($M^+ - (CO_2+H_2S)$, 1 (1), 240 (9), 160 (9), 105 (100), 77 (45); anal. calcd. for $C_{18}H_{14}N_4O_4S$ (382.39): C 56.54, H 3.69, N 14.65; found: C 56.28, H 3.63, N 14.62.

*N-(2-Benzoylhydrazinecarbonothioyl)-2-(1,3-Dioxoisoindolin-2-yl)Propanamide (**6b**).* 85% yield; pale yellow crystals; mp 193 °C–195 °C (ethanol); IR (KBr) υ (cm^{-1}): 3372, 3288 (NH), 1777, 1706 (C=O), 1283 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.52 (d, $J = 7.0$ Hz, 3, $\underline{CH_3}$), 5.22 (q, $J = 7.2$ Hz, 1, $\underline{CH}$), 7.52–7.97 (m, 9, ArH) 9.8, 10.76, 12.96 (br. s, 3, NH, exchangeable); MS (70 eV) *m/z* (%): 397 ($M^+ + 1$, 0.5), 396 (M^+, 1), 174 (100), 130 (23), 105 (89), 77 (60); anal. calcd. for $C_{19}H_{16}N_4O_4S$ (396.42): C 57.57, H 4.07, N 14.13; found: C 57.28, H 3.63, N 14.32.

*2-((2-Phenyl-3-Thioxo-2,3-Dihydro-1H-1,2,4-Triazol-5-yl)Methyl)Isoindoline-1,3-Dione (**8a**).* 79% yield; pale yellow crystals; mp 228 °C–230 °C (ethanol); IR (KBr) υ (cm^{-1}): 3344 (NH), 1771, 1716 (C=O), 1599 (C=N), 1288 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.93 (s, 2, $\underline{CH_2}$), 7.40–8.18 (m, 9, ArH), 13.43 (br. s, 1, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 32.9 (CH_2), Ar—C [123.5 (2CH), 123.7 (2CH), 127.9 (CH), 128.9 (2CH), 131.9 (2C), 134.8 (2CH), 137.7 ($\underline{C}$—N)], 148.0 (C=N), 166.0 (2CO), 167.4 (CS); MS (70 eV) *m/z* (%): 338 ($M^+ + 2$, 7), 337 ($M^+ + 1$, 24), 336 (M^+, 100), 304 (20), 104 (50), 91 (72); anal. calcd. for $C_{17}H_{12}N_4O_2S$ (336.37): C 60.70, H 3.60, N 16.66; found: C 60.60, H 3.52, N 16.70.

*2-(1-(2-Phenyl-3-Thioxo-2,3-Dihydro-1H-1,2,4-Triazol-5-yl)Ethyl)Isoindoline-1,3-Dione (**8b**).* 72% yield; pale yellow crystals; mp 226 °C–228 °C (toluene); IR (KBr) υ (cm^{-1}): 3363 (NH), 1777, 1716 (C=O), 1592 (C=N), 1280 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.75 (d, $J = 7.0$ Hz, 3, $\underline{CH_3}$), 5.56 (q, $J = 7.0$ Hz, 1, $\underline{CH}$), 7.44–8.01 (m, 9, ArH), 13.92 (br. s, 1, NH, exchangeable); MS (70 eV) *m/z* (%): 352 ($M^+ + 2$, 6), 351 ($M^+ + 1$, 17), 350 (M^+, 100), 202 (39), 105(52), 91 (18); anal. calcd. for $C_{18}H_{14}N_4O_2S$ (350.39): C 61.70, H 4.03, N 15.99; found: C 61.67, H 4.35, N 15.78.

*2-((2,2-Dimethyl-4-Phenyl-5-Thioxo-2,3,4,5-Tetrahydro-1,3,4,6-Oxatriazepin-7-yl)Methyl)Isoindoline-1,3-Dione (**9**).* 85% yield; colorless crystals; mp 197 °C–199 °C (ethanol); IR (KBr) υ (cm^{-1}): 3218 (NH), 1768, 1714 (C=O), 1612 (C=N), 1283 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.6 (s, 6, $\underline{2CH_3}$), 5.12 (s, 2, $\underline{CH_2}$), 7.06–7.98 (m, 9, ArH), 11.70 (s, 1, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 22.7 ($2CH_3$), 43.9 (CH_2), 80.7 ($\underline{C}(CH_3)_2$), Ar—C [123.6 (2CH), 125.2 (2CH), 127.6 (CH), 128.7 (2CH), 131.7 (2C), 135.0 (2CH), 138.6 ($\underline{C}$—N)], 167.5 (oxatriazepine C=N), 168.0 (2CO), 172.8 (CS); MS (70 eV) *m/z*

(%): 188 (20), 160 (65), 148 (100), 146 (6), 104 (9), 92 (64); anal. calcd. for $C_{20}H_{18}N_4O_3S$ (394.45): C 60.90, H 4.60, N 14.20; found: C 60.91, H 4.32, N 14.01.

General Procedure. A solution of compounds **2a**,**b** or **6a,b** (0.01 mol) in glacial acetic acid (30 mL) was added to polyphosphoric acid (20 mL). The mixture was heated at 150 °C–180 °C) for 1 h and then left to cool at room temperature. The precipitated solid obtained after the addition of ice-cold water was filtered off and recrystillized from the suitable solvent to give **3a**,**b** or **7a,b**, respectively.

*2-(2-Oxo-2-(4-Oxo-2-Thioxo-1,2-Dihydroquinazolin-3(4H)-yl)Ethyl)Isoindoline-1,3-Dione (**3a**).* 69% yield; pale green crystals; mp 270 °C–272 °C (DMF); IR (KBr) υ (cm^{-1}): 3290 (NH), 1774, 1721, 1640 (C=O), 1290 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.56 (s, 2, $\underline{CH_2}$), 7.45–8.12 (m, 8, ArH), 11.68 (br. s, 1, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.5 (CH_2), Ar—C [119.4 (C), 123.5 (2CH), 124.6 (CH), 127.5 (CH), 129.2 (CH), 131.7 (2C), 135.0 (2CH), 136.6 (CH), 147.4 (C)], 152.5 (CO), 167.5 (CO), 167.7 (2CO), 184.2 (CS); MS (70 eV) *m/z* (%): 365 (M^+, 5), 306 (23), 332 (11), 178 (100), 146 (32), 104 (52); anal. calcd. for $C_{18}H_{11}N_3O_4S$ (365.40): C 59.17, H 3.03, N 11.50; found: C 58.93, H 3.22, N 11.46.

*2-(1-Oxo-1-(4-Oxo-2-Thioxo-1,2-Dihydroquinazolin-3(4H)-yl)Propan-2-yl)Isoindoline-1,3-Dione (**3b**).* 77% yield; pale green crystals; mp 260 °C–262 °C (acetic acid); IR (KBr) υ (cm^{-1}): 3212 (NH), 1778, 1716, 1637 (C=O), 1283 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.55 (d, $J = 7.2$ Hz, 3, CH_3), 5.07 (q, $J = 7.2$ Hz, 1, $\underline{CH}$), 7.49–8.05 (m, 8, ArH), 12.24 (br. s, 1, NH, exchangeable); MS (70 eV) *m/z* (%): 379 (M^+, 12), 205 (51), 174 (100), 146 (4), 104 (13); anal. calcd. for $C_{19}H_{13}N_3O_4S$ (379.40): C 60.15, H 3.45, N 11.08; found: C 60.10, H 3.22, N 10.96.

*2-(2-Oxo-2-(3-Phenyl-5-Thioxo-1H-1,2,4-Triazol-4(5H)-yl)Ethyl)Isoindoline-1,3-Dione (**7a**).* 80% yield; pale yellow crystals; mp 305 °C–307 °C (acetic acid); IR (KBr) υ (cm^{-1}): 3280 (NH), 1774, 1721 (C=O), 1566 (C=N), 1270 (C=S); ^{1}H NMR (DMSO-d_6) δ: 4.73 (s, 2, $\underline{CH_2}$), 7.70–8.16 (m, 9, ArH), 12.60 (br. s, 1, NH, exchangeable); ^{13}C NMR (DMSO-d_6): 40.3 (CH_2), Ar—C [123.4 (2CH), 127.0 (2CH), 129.4 (2CH), 130.0 (C), 130.7 (CH), 131.6 (2C), 134.8 (2CH)], 158.3 (triazole C-3), 162.2 (C=O), 166.2 (2C=O), 167.4 (C=S); MS (70 eV) *m/z* (%): 364 (M^+, 5), 204 (90), 160 (100), 104 (49), 91 (37); anal. calcd. for $C_{18}H_{12}N_4O_3S$ (364.38): C 59.33, H 3.32, N 15.38; found: C 59.24, H 3.19, N 14.79.

*2-(1-Oxo-1-(3-Phenyl-5-Thioxo-1H-1,2,4-Triazol-4(5H)-yl)Propan-2-yl)Isoindoline-1,3-Dione (**7b**).* 82% yield; pale yellow crystals; mp 284 °C–286 °C (acetic acid); IR (KBr) υ (cm^{-1}): 3277 (NH), 1777, 1722 (C=O), 1558 (C=N), 1283 (C=S); ^{1}H NMR (DMSO-d_6) δ: 1.59 (d, $J = 7.2$ Hz, 3, $\underline{CH_3}$), 5.19 (q, $J = 7.2$ Hz, 1, $\underline{CH}$), 7.52–7.97 (m, 9, ArH), 12.96 (br. s, 1, NH, exchangeable); MS (70 eV) *m/z* (%): 378 (M^+, 3), 204 (100), 174 (90), 161 (90), 130 (28), 104 (12); anal. calcd. for $C_{19}H_{14}N_4O_3S$ (378.40): C 60.31, H 3.73, N 14.81; found: C 59.80, H 3.90, N 14.70.

Acid Hydrolysis of Oxatriazepine (9). A mixture of compound **9** (0.01 mol) and 2,4-dinitrophenylhydrazine (0.01 mol) in ethanol (20 mL) containing concentrated hydrochloric acid (32%; 3 mL) was boiled under reflux for 15 min. The reaction mixture was concentrated and then chromatographed over silica gel. Elution with 1:4 (v/v) ethyl acetate and petroleum ether 60 °C–80 °C gave orange crystals, mp 127 °C–128 °C, and yield 92%. It was proven to be acetone 2,4 dinitrophenylhydrazone by mp and mixed mp. However, elution with 1:1 (v/v) ethyl acetate and petroleum ether 60 °C–80 °C gave white crystals, mp 228 °C–230 °C, and 80% yield. It was proven to be a triazole derivative **8a** by mp and mixed mp.

REFERENCES

1. Esmail, R.; Kurzer, F. *Synthesis* **1975**, 301-314.
2. Ozaki, S. *Chem. Rev.* **1972**, 72, 457-496.
3. Mukerjee, A. K.; Ashar, R. *Chem. Rev.* **1991**, 91, 1-24.
4. Hemdan, M. M. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2010**, 185, 620-627.
5. M.M. Hemdan, *J. Chem. Res.* **2009**, 489-491.
6. Hemdan, M. M.; Fahmy, A. F.; El-Sayed, A. A. *J. Chem. Res.* **2010**, 219-221.
7. Hemdan, M. M.; Elshahawi, M. M. *J. Chem. Res.* **2009**, 75-77.
8. Hemdan, M. M.; Fahmy, A. F.; Ali, N. F.; Hegazi, E.; Abd-Elhaleem, A. *Chinese J. Chem.* **2007**, 25, 388-391.
9. Fahmy, A. F.; Ali, N.; Abdelhamid, H.; Shiba, S.; Hemdan, M. M. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2010**, 185, 1536-1542.
10. Benjelloun, A.; Morel, G.; Marchand, E. *Heteroatom Chem.* **2000**, 11 (1), 16-26.
11. Chowdhury, A. Z.; Shibata, Y. *Chem. Pharm. Bull.* **2001**, 49 (4), 391-395.
12. S. A. A. Youssef Hemdan, M. M. *Afindad* **2009**, LXVI, 258-263.
13. Sayed, A. F.; Aouf, A. F.; Assy, M. G. *J. Chem. Res. (M)* **1998**, 2056-2061.
14. Vamvakides, A. *Pharm. Fr.* **1990**, 48, 154-159.
15. Mullican, M. D.; Wilson, M. W.; Connor, D. T.; Kostlan, C. R.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1993**, 36, 1090-1099.
16. Demirbas, N.; Karaoglu, S. A.; Demirbas, A.; Celik, E. *Arkivoc* **2005**, i, 75-91.
17. Durant, G. J. *J. Chem. Soc. (C)* **1967**, 952-956.
18. Baeger, M.; Drabac, J.; , *Ger Offen DE*, 3504016 (1985) [*Chem. Abstr.* **1985**, 103, 215196.
19. Hull, R.; Seden, J. P. *Synth. Commun.* **1981**, 10, 489-493.