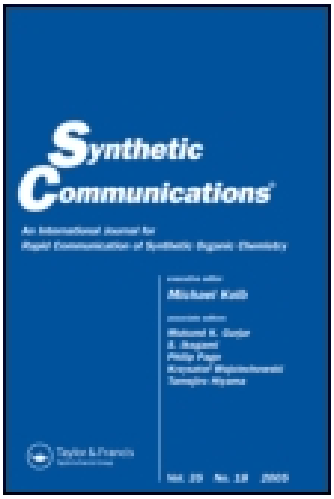


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis and Reactions of Novel 2,5-Disubstituted 1,3,4-Thiadiazoles

Mahmoud R. Mahmoud [a], Sayed A. Shiba [b], Ahmed K. El-Ziaty [a], Fatma S. M. Abu El-Azm [a] & Mahmoud F. Ismail [a]

[a] Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt

[b] Chemistry Department, Faculty of Science and Arts, Sajer, Shaqra University, Saudia Arabia

Accepted author version posted online: 08 Nov 2013.Published online: 19 Mar 2014.

To cite this article: Mahmoud R. Mahmoud, Sayed A. Shiba, Ahmed K. El-Ziaty, Fatma S. M. Abu El-Azm & Mahmoud F. Ismail (2014) Synthesis and Reactions of Novel 2,5-Disubstituted 1,3,4-Thiadiazoles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:8, 1094-1102, DOI: 10.1080/00397911.2013.846381

To link to this article: http://dx.doi.org/10.1080/00397911.2013.846381

Synthetic Communications®, 44: 1094–1102, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.846381

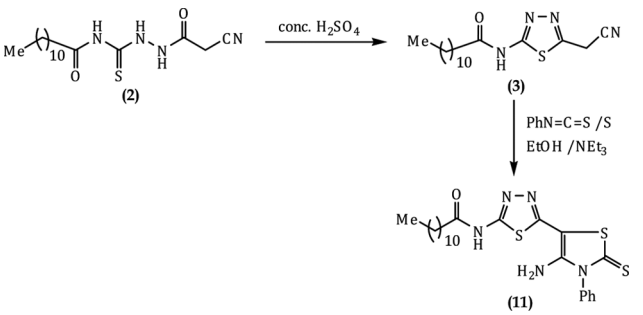
SYNTHESIS AND REACTIONS OF NOVEL 2,5-DISUBSTITUTED 1,3,4-THIADIAZOLES

Mahmoud R. Mahmoud,[1] Sayed A. Shiba,[2] Ahmed K. El-Ziaty,[1] Fatma S. M. Abu El-Azm,[1] and Mahmoud F. Ismail[1]

[1]*Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt*

[2]*Chemistry Department, Faculty of Science and Arts, Sajer, Shaqra University, Saudia Arabia*

GRAPHICAL ABSTRACT



Abstract *The desired 1,3,4-thiadiazole compounds bearing different substituents were obtained by the cyclization of the corresponding thiosemicarbazide followed by the reaction with electrophilic reagents, such as aromatic aldehydes, isatin, phenyl isothiocyanate, and carbon disulfide. The newly synthesized 2,5-disubstituted 1,3,4-thiadiazoles were obtained in good yields and their structures were elucidated by spectral data and elemental analysis.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

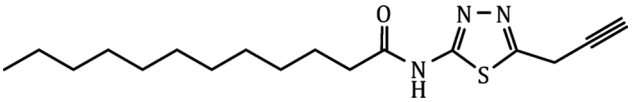
Keywords 2,5-Disubstituted 1,3,4-thiadiazoles; ring closure reaction; *S*-alkylation

INTRODUCTION

Thiadiazoles are important classes of nitrogen–sulphur-containing heterocycles. They have extensive applications as structural units of various biologically important molecules and as useful intermediates in medicinal chemistry. It is well

Received June 29, 2013.
Address correspondence to Fatma Saber Mohamed Abu El-Azm, Chemistry Department, Faculty of Science, Ain Shams University, Abbassia 11566, Cairo, Egypt. E-mail: ftmsaber@yahoo.com

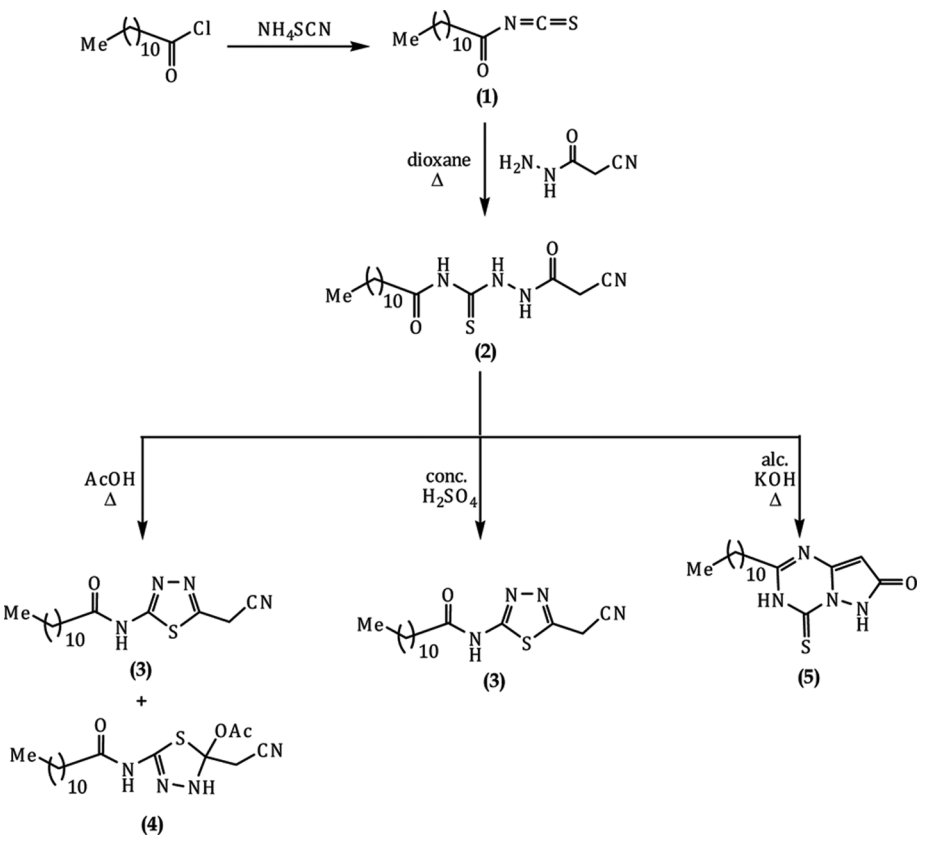
established that various 1,3,4-thiadiazole derivatives exhibit a broad spectrum of pharmacological properties such as antibacterial, antifungal,[1–3] analgesic,[4] anti-tumor,[5,6] anticonvulsant,[7] anxiolytic,[8] antidiabetic, and anti-inflammatory[9,10]. In view of the field of biologically active heterocyclic compounds and in continuation of our work,[11–15] in this article we described the synthesis of some new 2,5-disubstituted 1,3,4-thiadiazoles.



RESULTS AND DISCUSSION

Here in, treatment of lauroyl chloride with ammonium thiocyanate afforded the lauroyl isothiocyanate **1,** which in situ refluxed with cyanoethanoic acid hydrazide in dioxane to give 1-(2-cyanoacetyl)-4-dodecanoyl thiosemicarbazide **2**.

Cyclization of **2** in boiling acetic acid afforded N-[(5-cyanomethyl)-1,3,4-thiadiazol-2-yl]dodecanamide **3** together with a minor amount of the acetylated



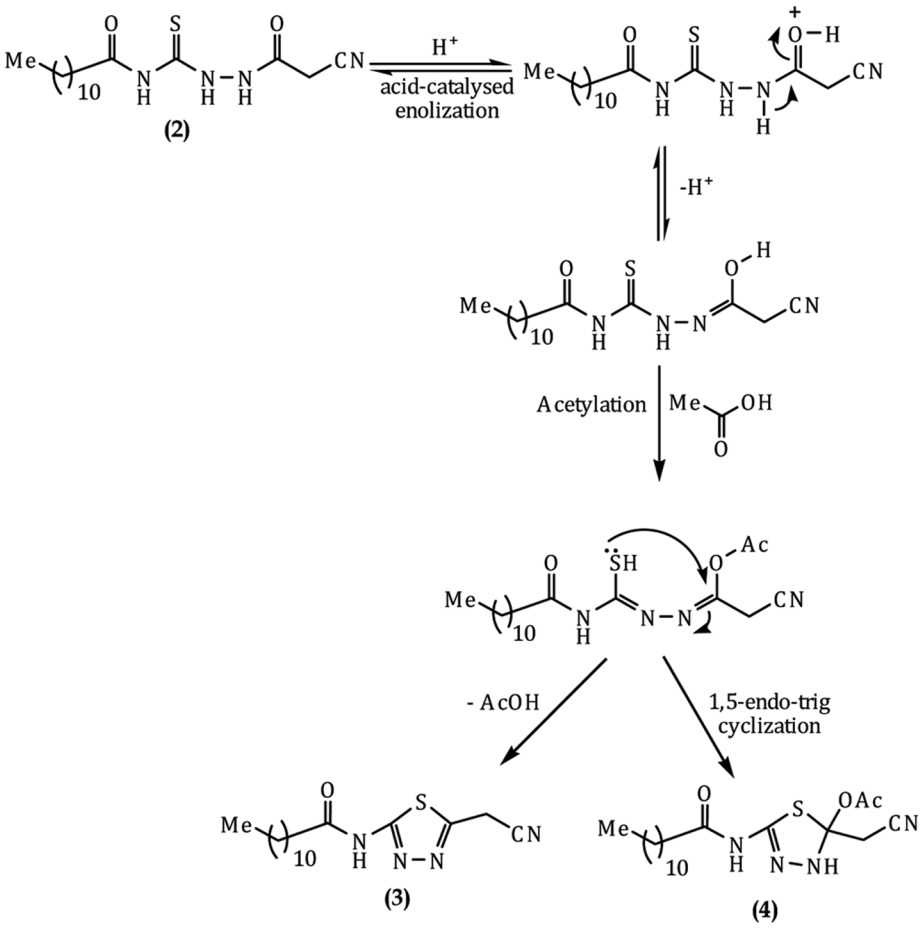
Scheme 1. Acid–base cyclization of **2**.

product **4**. Compound **3** was obtained as the sole product (66%) in pure form upon treatment of **2** with concentrated sulfuric acid at 0 °C[16,17] (Scheme 1).

Compelling evidence for the structure **3** was forthcoming from the analytical and spectroscopic data. The infrared (IR) spectrum of **3** exhibited υ_{NH} at 3199, 3124 cm^{-1}, $\upsilon_{C\text{-}H}$ (CH_2,CH_3) at 2954, 2922, 2851 cm^{-1}, $\upsilon_{C\equiv N}$ at 2264 cm^{-1} and $\upsilon_{C=O}$ at 1680 cm^{-1}. Moreover, the mass spectrum of compound **3** show the correct molecularion at $m/z = 322$ (5.3%).

Furthermore, ^{1}HNMR spectrum ($CDCl_3$) revealed the signals from low to high field at δ (ppm): 12.25 (s, 1H, NH, exchangeable with D_2O), 11.0 (s, 1H, NH, exchangeable with D_2O), 4.15 (s, 2H, CH_2CN), 2.7 (t, 2H, CH_2CO), 1.73 (m, 4H, CH_2CH_2), 1.25 (m, 14H), 0.88 (t, 3H, Me), which were completely in accord with the assigned structure.

The insoluble fraction in toluene was separated and detected as the acetylated product **4,** whose structure was investigated and confirmed using the analytical and spectroscopic data. Thus, the IR spectrum of compound **4** show the stretching



Scheme 2. Cyclization of **2** using AcOH.

absorption band for carbonyl group of ester at 1725 cm^{-1}. The electron ionization–mass spectrometry (EI-MS) spectrum of **4** displayed the radical cation peak at $m/z = 384$ (M+2, 4.9%) and the cation R-C≡O^+ at $m/z = 183$ (46.7%).

The formation of compound **3** and **4** can be visualized as shown in Scheme 2.

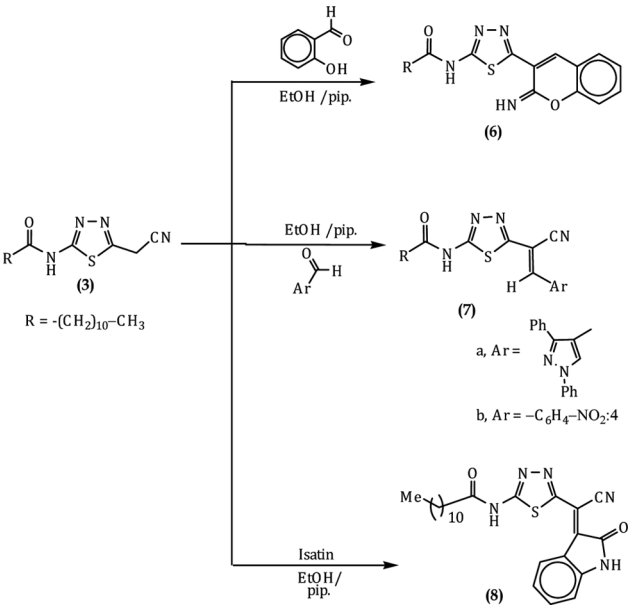
In contrast, cyclization of **2** in ethanolic KOH yielded a product with molecular formula $C_{16}H_{26}N_4OS$ (MW = 322), which lacked in the IR spectrum the stretching absorption band for the nitrile group and retained carbonyl stretching band at 1725 cm^{-1} and weak absorption band for NH at 3165 cm^{-1}. This product was identified as the pyrazolo [2,3-*a*]1,3,5-triazine derivative **5** (Scheme 1).

The proclivity of **3** toward some electrophilic reagents such as aromatic aldehydes, heterocyclic aldehydes, heterocyclic ketone, phenyl isothiocyanate, and carbon disulfide was investigated. Refluxing compound **3** with salicylaldehyde in boiling ethanol in the presence of a catalytic amount of piperidine afforded the 2-iminocoumarin derivative **6** as orange crystals[18] (Scheme 3).

The imino coumarin derivative **6** was constructed on the basis of analytical and spectroscopic data. The IR spectrum of 6 displayed υ_{NH} at 3220, 3216 cm^{-1}, $\upsilon_{C=O}$ at 1698 cm^{-1}, $\upsilon_{C=N}$ at 1669 cm^{-1} and showed the absence of a stretching absorption band for nitrile group. Furthermore, the mass spectrum of **6** showed the correct molecular ion peak characteristic for the molecular formula $C_{23}H_{30}N_4O_2S$ at $m/z = 426$ (11.7%).

The reaction of 1,3,5-thiadiazole derivative **3** with 1,3-diphenyl pyrazole-4-carboxaldehyde and/or *p*-nitrobenzaldehyde in refluxing ethanol in the presence of piperidine yielded the corresponding condensation products **7a** and **7b**, respectively.

The structure of compound **7a** was confirmed by the analytical and spectroscopic data. Thus, the IR spectrum of **7a** revealed υ_{NH} at 3144 cm^{-1}, $\upsilon_{C\equiv N}$ at 2221 cm^{-1}, and $\upsilon_{C=O}$ at 1697 cm^{-1}. The EI-MS spectrum of **7a** showed the correct molecular ion



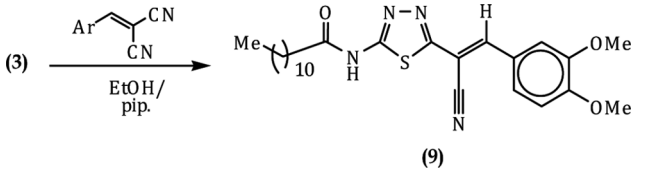
Scheme 3. Reactions of compound **3** with aromatic aldehydes and heterocyclic ketone.

peak at $m/z = 552$ (48.4%), which after lossing the acyl radical yielded the cation at $m/z = 370$ (93.5%).

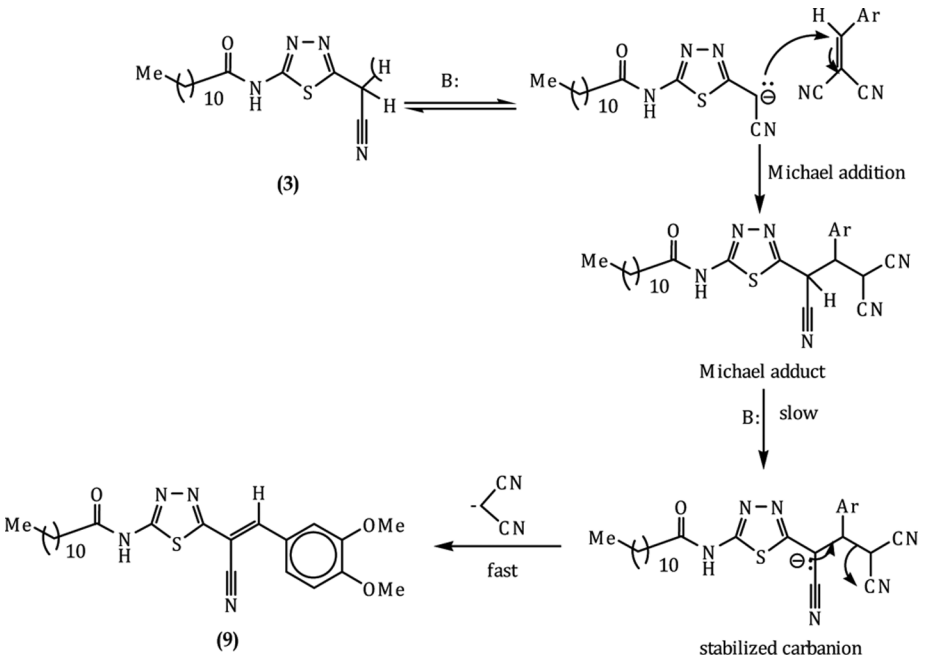
The structure of **7b** was deduced from the analytical and spectroscopic data. IR spectrum of compound **7b** exhibited υ_{NH} at 3244, 3202 cm^{-1}, $\upsilon_{C\equiv N}$ at 2228 cm^{-1} and $\upsilon_{C=O}$ at 1687 cm^{-1}. Moreover, the mass spectrum of **7b** show the correct molecular ion peak at $m/z = 455$ (5.8%) together with the peaks at $m/z = 273$ and 183 characteristic for the radical cations [M-RCO] and [RC≡O$^+$], respectively.

Similarly, isatin easily condensed with the active methylene group in compound **3** upon refluxing with ethanol in the presence of piperidine to give **8** in good yield as red crystals (Scheme 3). The structure **8** was substantiated from the microanalytical and spectroscopic data.

When compound **3** was allowed to react with α-cyano-3,4-dimethoxy cinnamonitrile in refluxing ethanol with catalytic amount of piperidine, it afforded *N*-(5-(1-cyano-2-(3,4-dimethoxyphenyl)vinyl)-1,3,4-thiadiazol-2-yl)dodecanamide **9**.



The carbanion derived from **3** was added via Michael addition to the β-carbon of the arylidene malononitrile to give the Michael adduct, which eliminates malononitrile to give **9** via E1CB mechanism (Scheme 4).

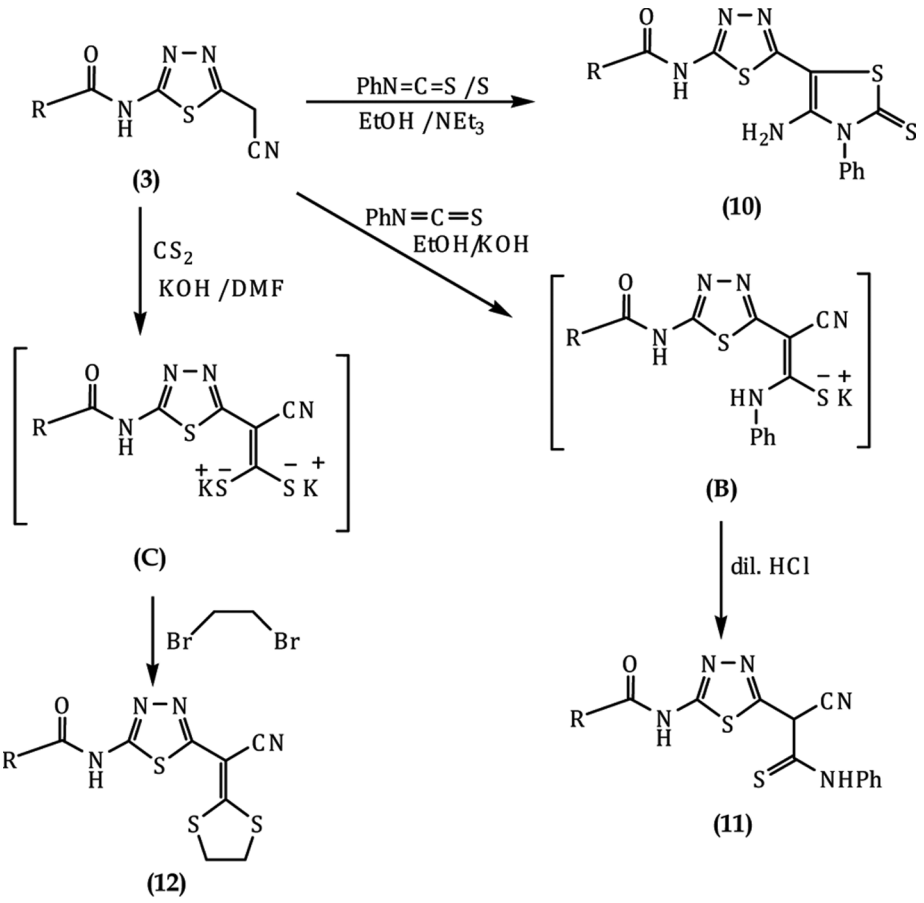


Scheme 4. A plausible mechanism for conversion of **3** to **9**.

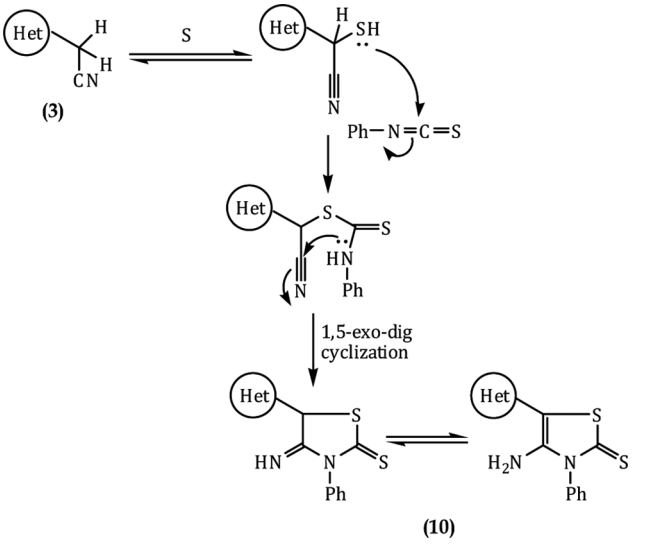
The structure **9** was confirmed by the study of IR, ^{1}HNMR, and mass spectra.

The reaction of **3** with phenyl isothiocyanate in the presence of elemental sulfur in boiling ethanol and triethyl amine gave *N*-(5-(4-amino-3-phenyl-2-thioxo-2, 3-dihydrothiazol-5-yl)-1,3,4-thiadiazol-2-yl)dodecanamide **10** (Scheme 5).

The IR spectrum of **10** displayed the coupling bands for NH_2 group at 3270, 3160 cm^{-1}, $\upsilon_{C=O}$ at 1692 cm^{-1}, and $\upsilon_{C=N}$ at 1622 cm^{-1} and lacked the stretching absorption band for the nitrile group. Moreover, ^{1}HNMR spectrum (DMSO-d_6) revealed the signals characterstic for deshielded one NH proton at δ 12.44 ppm, multiplet integrated for 3H at δ 7.67 ppm, doublet for 2H at δ 7.43–7.40 ppm corresponding to five aromatic protons, broad singlet for 2H representing the NH_2 group, and the signals upfield characteristic for the dodecanyl protons. Furthermore, the EI-MS of **10** detected the presence of a molecular ion peak at m/z=489 (79%) together with the base peak at m/z=307 (100%) characteristic for the radical cation [M-RCO·]. The formation of **10** could be visualized as shown in Scheme 6.



Scheme 5. Reaction of thiadiazole derivative **3** with CS_2 and PhNCS.



Scheme 6. The expected mechanism for the formation of compound **10**.

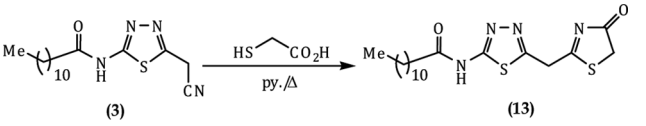
On the other hand, the reaction of **3** with phenyl isothiocyanate in ethanolic potassium hydroxide afforded after acidification the thiadiazole derivative **11** via the formation of intermediate **B** (Scheme 5). The structure **11** was confirmed by IR and mass spectra beside the correct elemental analysis. Thus, the IR spectrum displayed υ_{NH} at 3203 cm^{-1}, $\upsilon_{C\equiv N}$ at 2191 cm^{-1}, $\upsilon_{C=O}$ at 1695 cm^{-1} and $\upsilon_{C=S}$ at 1322 cm^{-1}. The EI-MS of **11** show the parent peak at $m/z=457$ (37.3%).

Treatment of **3** with carbon disulfide and potassium hydroxide in dimethyl formamide (DMF) yielded the dipotassium salt **C** which in situ undergo alkylation with 1,2-dibromoethane to give the dithiolan derivative **12** (Scheme 5).

The structure **12** was confirmed from IR and MS spectra. Thus, the IR spectrum of compound **12** revealed υ_{NH} (br) at 3153 cm^{-1}, $\upsilon_{C\equiv N}$ at 2201 cm^{-1}, and $\upsilon_{C=O}$ at 1696 cm^{-1}. The mass spectrum of **12** displayed the correct molecular ion at $m/z=424$ (14.6%) and the radical cation of $m/z=242$ (68.3%) obtained upon loss of R-C·=O radical followed by H-abstraction.

Refluxing compound **3** with thioglycollic acid in pyridine afforded the thiazolidinone derivative **13** (Scheme 7).

Compound **13** showed the disappearance of the stretching absorption band for the nitrile group and displayed a new carbonyl band at 1730 cm^{-1} for thiazolidinone beside the carbonyl group for dodecanoyl group at 1690 cm^{-1}. Furthermore, the mass spectrum of **13** showed the correct molecular ion peak at $m/z=396$ (23.4%) together with the base peak at $m/z=214$ (100%) characteristic for the radical cation [M^+-R-CO].



Scheme 7. Reaction of thiadiazole derivative **3** with thioglycollic acid.

CONCLUSION

Novel 2,5-disubstituted 1,3,4-thiadiazoles were prepared via cyclization of the corresponding thiosemicarbazide followed by the reaction with some electrophilic reagents. The synthesized compounds were obtained in good yields.

EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. Melting-points are uncorrected and were measured by an electric melting-point apparatus (G-K). The IR spectra were recorded on a Pye-Unicam SP1200 spectrophotometer using the KBr Wafer technique. The ^{1}HNMR spectra were determined on a Varian Gemini 300-MHz NMR spectrophotometer using $CDCl_3$ or dinethylsulfoxide (DMSO-d_6) as solvent with tetramethylsilane (TMS) as an internal standard. All chemical shifts are in parts per million (ppm) downfield from TMS. The elemental analyses were carried out in Faculty of Science, Ain Shams University. Mass spectra (MS) were recorded on a Shimadzu GC-MS QP1000EX instrument in the Microanalytical Laboratory, Cairo University. Monitoring of the progress of all reactions was carried out by thin-layer chromatography (TLC).

Synthesis of 1-(2-Cyanoacetyl)-4-dodecanoylthiosemicarbazide 2

Cyanoacetohydrazide (0.99 g, 0.01 mol) in boiling dioxane was added to a mixture of lauroyl chloride (2.3 mL, 0.01 mol) and ammonium thiocyanate (0.76 g, 0.01 mol) in dioxane (20 mL) and then the whole mixture was refluxed for 30 min. The colorless solid deposited while hot was collected by filtration and then recrystallized from toluene to give **2** as colorless crystals;

Selected Data

Mp: 109–110 °C, yield 67%. Anal. calcd. for $C_{16}H_{28}N_4O_2S$ (340.48): C, 56.44; H, 8.29; N, 16.46; S, 9.42. Found: C, 56.27; H, 8.51; N, 16.52; S, 9.38. IR (υ/cm^{-1}): 3265, 3208 (NH), 2955, 2922, 2885 (CH_3,CH_2), 2269 (C≡N), 1702 (C=O). MS *m/z* (%): 340 (M^+; 2.5), 257 (6.0), 183 (29.8), 157 (2.8), 99 (39.0), 57 (100). ^{1}HNMR (DMSO-d_6) δ (ppm): 12.88 (s, 1H, NH, exchangeable with D_2O), 9.55 (s, 1H, NH, exchangeable with D_2O), 8.614 (s, 1H, NH, exchangeable with D_2O), 3.56 (s, 2H, CH_2CN), 2.38 (t, 2H, CH_2CO), 1.645 (m, 4H, CH_2CH_2-), 1.26 (m, 14H, $(CH_2)_7$), 0.88 (t, 3H, Me).

SUPPORTING INFORMATION

Full experimental details and spectroscopic data for compounds **3–13** can be found via the Supplementary Content section of this article's Web page.

REFERENCES

1. Georgeta, S.; Tunde, H. 5-Arylamino-1,3,4-thiadiazol-2-yl-acetamide: Synthesis and spectral studies. *Clujul Medical* **2011**, *84*(4), 547–549.
2. Foroumadi, A.; Emani, S.; Hassanzadeh, A. Synthesis and antibacterial activity of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and *N*-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl) piperazinyl quinolone derivatives. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4488–4492.
3. Mamolo, M. G.; Vio, L.; Banfi, E. Synthesis and antimicrobial activity of some 2,5-disubstituted 1,3,4,-thiadiazole derivatives. *Farmaco* **1996**, *51*, 71–74.
4. Schenone, S.; Brullo, C.; Bruno, O.; Bondavalli, F.; Ranise, A.; Filippelli, W.; Rinaldi, B.; Capuano, A.; Falcone, G. New 1,3,4-thiadiazole derivatives endowed with analgesic and anti-inflammatory activities. *Bioorg. Med. Chem*. **2006**, *14*(6), 1698–1705.
5. Hirpara, S. B.; Parikh, K. A.; Merja, B. C. 2-Methoxy-5-methylphenylthiosemicarbazide: A versatile molecule for the synthesis of thiadiazoles and imidazolinones possessing multiple biological activities. *Indian J. Chem.* **2003**, *42B*, 1172.
6. Matysiak, J.; Nasulewicz, A.; Pelczynska, M. Synthesis and antiproliferative activity of some 5-substituted 2-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles. *Eur. J. Med. Chem*. **2006**, *41*, 475–482.
7. Chapleo, C. B.; Myers, P. L.; Smith, A. C.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S. Substituted 1,3,4-thiadiazoles with anticonvulsant activity, 4: Amidines. *J. Med. Chem*. **1988**, *31*, 7–11.
8. Clerici, F.; Pocar, D.; Guido, M.; Loche, A.; Perlini, V.; Brufani, M. Synthesis of 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives and evaluation of their antidepressant and anxiolytic activity. *J. Med. Chem*. **2001**, *44*, 931–936.
9. Arum, K. P.; Nag, V. L.; Panda, C. S. Studies on the synthesis and bioactivity of some thiadiazole derivatives. *Indian J. Chem*. **1999**, *38B*, 998.
10. Pattan, S. R.; Desai, N. S.; Rabara, P. A. Synthesis and antimicrobial evaluation of some 1,3,4-thiadiazole derivatives. *Indian J. Pharm. Edu. Res*. **2008**, *42*(4), 314–318.
11. Mahmoud, M. R.; Abu El-Magd, W. S. I.; Abd El-Wahab, S. S.; Soliman, S. A. Synthesis and spectral characterisation of novel 2,3-disubstituted quinazolin-4(3*H*)-one derivatives. *J. Chem. Res*. **2012**, 66–71.
12. Mahmoud, M. R.; Abu El-Magd, W. S. I.; Derbala, H. A.; Hekal, M. H. Synthesis and spectral characterisation of some phthalazinone derivatives. *J. Chem. Res*. **2012**, 75–82.
13. Mahmoud, M. R.; Abu El-Magd, W. S. I.; Abd El-Wahab, S. S.; Soliman, S. A. Spectral characterization of novel 3-phenyl-2-substituted quinazoline and fused quinazoline derivatives. *Synth. Commun.* **2013**, *43*, 1484–1490.
14. Mahmoud, M. R.; Abu El-Azm, F. S. M. Synthesis and spectral studies of novel heterocycles from 2-cyano-N'-(9H-fluoren-9-ylidene) acetohydrazide. *Eur. Chem. Bull.* **2013**, *2*(6), 335–340.
15. Mahmoud, M. R.; El-Ziaty, A. K.; Abu El-Azm, F. S. M.; Ismail, M. F.; Shiba, S. A. Utility of cyano-*N*-(2-oxo-1,2-dihydroindol-3-ylidene)acetohydrazide in the synthesis of novel heterocycles. *J. Chem. Res.* **2013**, 80–85.
16. Harish, K.; Sadique, A. J.; Suroor, A. K.; Mohammad, A. 1,3,4-Oxadiazole/thiadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid: Synthesis and preliminary evaluation of biological properties. *Eur. J. Med. Chem.* **2008**, *43*, 2688–2698.
17. Anelia, T. M.; Diana, W.; Yordan, A. T.; Pavletta, D. Synthesis, cytotoxicity, and effects of some 1,2,4-triazole and 1,3,4-thiadiazole derivatives on immunocompetent cells. *Eur. J. Med. Chem*. **2009**, *44*, 63–69.
18. Volmajer, J.; Toplak, R.; Leban, I.; Le Marechal, A. M. Synthesis of new iminocoumarins and their transformations into *N*-chloro and hydrazono compounds. *Tetrahedron* **2005**, *61*, 7012–7021.