Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Synthesis and Characterization of New Pyrazole Based Thiazoles

Abdou O. Abdelhamid & Sobhi M. Gomha

To cite this article: Abdou O. Abdelhamid & Sobhi M. Gomha (2017): Synthesis and Characterization of New Pyrazole Based Thiazoles, Synthetic Communications, DOI: 10.1080/00397911.2017.1330961

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1330961

SYNTHESIS AND CHARACTERIZATION OF NEW PYRAZOLE BASED THIAZOLES

Abdou O. Abdelhamid[1], Sobhi M. Gomha[1]

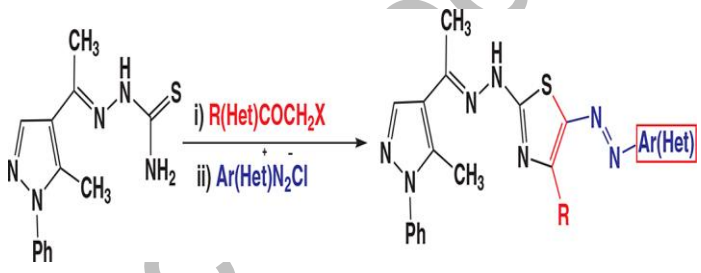
[1]Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

Correspondence: Sobhi M. Gomha. E-mail: s.m.gomha@gmail.com

Abstract

A series of new 5-(heteroaryldiazenyl)thiazole incorporating pyrazole moiety have been synthesized *via* coupling of the thiazole with the appropriate heteroaryldiazonium salts. The newly synthesized compounds were characterized by elemental analysis, spectroscopic (IR, ^{1}H NMR, and Mass) data and alternative synthesis whenever possible.

GRAPHICAL ABSTRACT



KEYWORDS: Thiazoles; pyrazoles; coupling reaction; thiosemicarbazide.

INTRODUCTION

Pyrazoles and their variously substituted derivatives are important biological agents and a significant amount of research activity has been directed towards this class. In particular,

they are used as antitumor, antibacterial and antifungal, antiviral, antiparasitic, anti-tubercular, insecticidal, anti-inflammatory, anti-diabetic, anesthetic and analgesic agents.[1–13] Also, thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as Sulfathiazol (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) with trade name Abasol cream and Bleomycine and Tiazofurin (antineoplastic drug). It has been noticed continuously over the years that interesting biological activities[14,15] were associated with thiazole derivatives. Recently, the applications of thiazoles were found in drug development for the treatment of allergies, inflammation, schizophrenia, bacterial, hypnotics and more recently for the treatment of pain, as fibrinogen receptor antagonists with antithrombotic activity and as new inhibitors of bacterial DNA gyrase B.[16-27] In continuation to our interest in the chemical and pharmacological properties of pyrazole and thiazole derivatives,[28-37] we report herein a facile synthetic strategy for preparation of some new thiazole derivatives linked to pyrazole moiety. The biological activities of the synthesized products will be reported in extended work.

RESULTS AND DISCUSSION

The required 2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethylidene)hydrazine-1-carbothioamide (**1**) was prepared following the literature method. [38] Compound **1** used as useful intermediate for synthesis of different heterocyclic compounds, thus, cyclization of **1** with various α-bromoketones in ethanol under reflux yielded the respective thiazole derivatives **3a-e** (Scheme 1). The elemental analysis together with the data derived from IR, ^{1}H NMR and mass spectra are in agreement with the proposed structure **3**. ^{1}H NMR

of compound **3b**, taken as a typical example, showed signals at δ 2.31 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.42-8.07 (m, 12H, Ar-H and thiazole H-5), 8.12 (s, 1H, pyrazole H-3), 8.42 (s, 1H, naphthalene H-1), 10.28 (s, br, 1H, NH). The mass spectrum of each of products **3** revealed the presence of a molecular ion peak (*m/z*) which is consistent with the structure of the respective compound (see experimental section). Coupling of thiazole derivatives **3a-e** with arenediazonium chlorides in ethanol containing sodium acetate at 0-5 ^{o}C, yielded 5-arylazothiazole derivatives **4a-h**. Structures **4a-h** were confirmed by elemental analysis, spectral data and alternative synthesis. Thus, reaction of thiosemicarbazone derivative **1** with (Z)-2-oxo-N,2-diphenylacetohydrazonoyl bromide (**5**)[39] in dioxane in the presence of triethylamine as a basic catalyst gave a product identical in all aspects (mp., mixed mp., and spectra) with **4a**.

Analogously, reaction of compound **1** with chloroacetone **6** in refluxing ethanol, gave thiazole derivative **7** based on elemental analysis and spectral data. Coupling of the latter compound with arenediazonium chloride in ethanolic sodium acetate afforded thiazoles derivatives **4i-n,** respectively(Scheme 2). The structures of the latter products **4i-n** were evidenced by microanalysis and spectral (IR, ^{1}H NMR, Mass) data. For example, ^{1}H NMR displayed in each case five singlet signals near δ 2.18, 2.48, 8.73, 7.96 and 10.36 assigned for the three methyl groups, pyrazole-H3 and NH proton, in addition to the expected signals characteristic for the aryl protons (see experimental). Also, the mass spectra of products **4i-n** revealed in each case a molecular ion peak which consistent with the molecular formula of the assigned structure.

Compound **3a** was reacted with diazotized benzidine **8** in ethanolic sodium acetate afforded 4,4'-*bis* (2-(2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-4-phenylthiazol-5-yl)diazenyl)-1,1'-biphenyl (**9**) (Scheme 3). Structure **9** was elucidated by elemental analysis, spectral data. ^{1}H NMR spectra of **9** showed signals at δ 2.33 (s, 6H, CH_3), 2.64 (s, 6H, CH_3), 7.19-7.66 (m, 28H, Ar-H), 8.10 (s, 2H, pyrazole H-3), 10.38 (s, br, 2H, NH).

Finally, compound **3a** was coupled with diazotized 3-amino-4-cyanopyrazole **10** in ethanolic sodium acetate solution gave pyrazolyl-azothiazole derivative **11** (Scheme 4). Structure **11** was elucidated *via* elemental analysis and spectral data. IR (cm^{-1}) spectrum of **11** revealed peaks at 3427, 3312 (2NH), 2227 (CN) and its ^{1}H NMR showed signals at δ 2.22, 2.62 (2s, 6H, $2CH_3$), 7.13-7.65 (m, 10H, Ar-H), 7.88 (s, H, pyrazole H-3), 8.04 (s, H, pyrazole H3), 9.23 (s, br, 1H, NH), 10.33 (s, br, 1H, NH).

Analogously, the appropriate diazotized heterocyclic amines **12, 14, 16** were coupled with **3a** afforded triazolyl-azothiazole derivative **13**, benzoimidazolyl-azothiazole derivative **15** and pyrazolopyridyl-azothiazole derivative **17**, respectively (Scheme 4). The structures assigned for the products **13, 15** and **17** were confirmed based on elemental analysis and spectroscopic data (see experimental).

General Procedure For Synthesis Of Thiazoles 3a-E

To a solution of thiosemicarbazone **1** (0.273 g, 1 mmol) in ethanol (20 mL), bromoacetyl derivatives **2a-e** (l0 mmol) were added. The mixture was refluxed for 4-8 h (monitored

by TLC), then left to cool. The solid product was filtered off, washed with ethanol and recrystalized from ethanol or dioxane to afford the thiazole derivatives **3a-e,** respectively. The products **3a-e** together with their physical constants are listed below.

2-(2-(1-(5-Methyl-1-Phenyl-1H-Pyrazol-4-Yl)Ethylidene)Hydrazinyl)-4-(Naphthalen-2-Yl)Thiazole (3b)

White solid, (72% yield); mp 170-172 °C; IR (KBr) υ 3196 (NH), 1600 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.42-8.07 (m, 12H, Ar-H and thiazole H-5), 8.12 (s, 1H, pyrazole-H3), 8.42 (s, 1H, naphthalene-H1), 10.28 (s, br, 1H, NH); MS, *m/z* (%) 424 (M^++1, 34), 423 (M^+, 42), 256 (73), 167 (61), 112 (30), 77 (100), 57 (78). Anal. calcd for $C_{25}H_{21}N_5S$ (423.53): C, 70.90; H, 5.00; N, 16.54; found: C, 70.97; H, 4.92; N, 16.43%.

CONCLUSIONS

We have developed a simple and convenient method for the synthesis of 4-substituted-2-(2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-5-(heteroaryldiazenyl)thiazole and 4,4'-*bis*(2-(2-(1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethylidene)hydrazinyl)-4-phenylthiazol-5-yl)diazenyl)-1,1'-biphenyl *via* coupling of thiazole derivatives with the appropriate heteroaryldiazonium salts. Also, the structures of all the newly synthesized products were confirmed based on elemental analysis, spectral data and by alternative methods.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Taylor, E. C.; Patel, H.; Kumar, H. *Tetrahedron* **1992**, *48*, 8089.

2. Gomha, S. M.; Riyadh, S. M.; Abdalla, M. M. *Curr. Org. Synth.* **2015**, *12*, 220.

3. Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Micky, J. A.; Abdel-Megeid, F. M. E. *Bioorg. Med. Chem.* **2008**, *16*, 7102.

4. Gomha, S. M.; Shawali, A. S.; Abdelhamid, A. O. *Turk. J. Chem.* **2014**, *38*, 865.

5. Bhat, B. A.; Dhar, K. L. ; Saxena, A. K.; Shanmugavel, M. *Bioorg. Med. Chem.* **2005**, *15*, 3177.

6. Gomha, S. M.; Salah, T. A.; Abdelhamid, A. O. *Monatsh. Chem*. **2015**, *146*, 149.

7. Gomha, S. M.; Abdalla, M. A.; Abdelaziz, M.; Serag, N. *Turk. J. Chem*., **2016**, *40*, 484.

8. Michael, L. E.; David, M. S.; Prasad, S. S. *J. Med. Chem.* **1990**, *33*, 1948.

9. Kalirajan, R.; Sivakumar, S. U.; Jubie, S.; Gowramma, B.; Suresh, B. *Int. J. Chem. Tech. Res.* **2009**, *1*, 27.

10. Maggio, B.; Daidone, G.; Raffa, D.; Plescia, S.; Mantione, L.; Cutuli, V. M. C.; Mangano, N.; Caruso, G.. *Eur. J. Med. Chem.* **2001**, *36*, 737.

11. Clinton, R. O.; Manson, A. J.; Stonner, F. W.; Beyler, A. L.; Potts, G. O.; Arnold, A. *Molecules* **2012**, *17*, 4962.

12. Kalirajan, R.; Palanivelu, M.; Rajamanickam, V.; Vinothapooshan, G.; Andarajagopal, K. *Int. J. Chem. Sci.* **2007**, *5*, 73.

13. Urmila, G.; Vineeta, S.; Vineeta, K.; Sanjana, C. *Indian J. Heterocycl. Chem.* **2005**, *14*, 265.

14. Quiroga, J.; Hernandez, P.; Insuasty, B.; Abonia, R.; Cobo, J.; Sanchez, A. *J. Chem. Soc. Perkin Trans1* **2002**, *4*, 555.

15. Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2002**, *45*, 744.

16. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158.

17. Sharma, R. N.; Xavier, F. P.; Vasu, K. K.; Chaturvedi, S. C.; Pancholi, S. S. *J. Enz. Inhib. Med. Chem.* **2009**, *24*, 890.

18. Gomha, S. M.; Riyadh, S. M.; Mahmmoud, E.A.; Elaasser, M. M. *Heterocycles* **2015**, *91*, 1227.

19. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 311.

20. Gomha, S. M.; Riyadh, S. M.; Abbas, I. M.; Bauomi, M. A. *Heterocycles* **2013**, *87*, 341.

21. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601.

22. Dawood, K. M.; Gomha, S. M. *J. Heterocycl. Chem.* **2015**, *52*, 1400.

23. Ergenc, N.; Capan, G.; Gunay, N. S.; Ozkirimli, S.; Gungor, M.; Ozbey, S.; Kendi, E. *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 343.

24. Carter, J. S.; Kramer, S.; Talley, J. J.; Penning, T.; Collins, P.; Graneto, M. J.; Seibert, K.; Koboldt, C.; Masferrer, J.; Zweifel, B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1171.

25. Badorc, A.; Bordes, M. F.; Cointet, P. D.; Savi, P.; Bernat, A.; Lale, A.; Petitou , M.; Maffrand, J. P.; J. Herbert, M. *J. Med. Chem.* **1997**, *40*, 3393.

26. Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F. U. *J. Med. Chem.* **2001**, *44*, 619.

27. Abdelhamid, A.O.; Shawali, A.; Gomha, S. M.; El-Enany, W. A.M. A. *Heterocycles* **2015**, *91(11)*, 2126.

28. Abdelhamid, A. O.; El Sayed, I. E.; Hussein, M. Z.; Mangoud, M. M. *Molecules* **2016**, *21*(8), 1072.

29. Abdelhamid, A. O.; Abdelall, E. K. A.; Abdel-Riheem, N. A.; Ahmed, S. A. *Phosphorus, Sulfur, Silicon* **2010**, *185*, 709.

30. Gomha, S.M.; Zaki, Y. H.; Abdelhamid, A. O. *Molecules* **2015**, *20*, 21826.

31. Gomha, S. M.; Ahmed, S. A.; Abdelhamid, A. O. *Molecules* **2015**, *20*, 1357.

32. Abdelhamid, A. O.; Gomha, S. M. *J. Chem.* **2013**, *2013*, 1.

33. Gomha, S.M. *Monatsh. Chem.* **2009**, *140*, 213.

34. Gomha, S. M.; Eldebss, T. M. A.; Abdulla, M. M.; Mayhoub, A. S. *Eur. J. Med. Chem.* **2014**, *82*, 472-479.

35. Gomha, S. M.; Khalil, Kh. D.; El-Zanate, A. M.;. Riyadh, S. M *Heterocycles* **2013**, *87*, 1109.

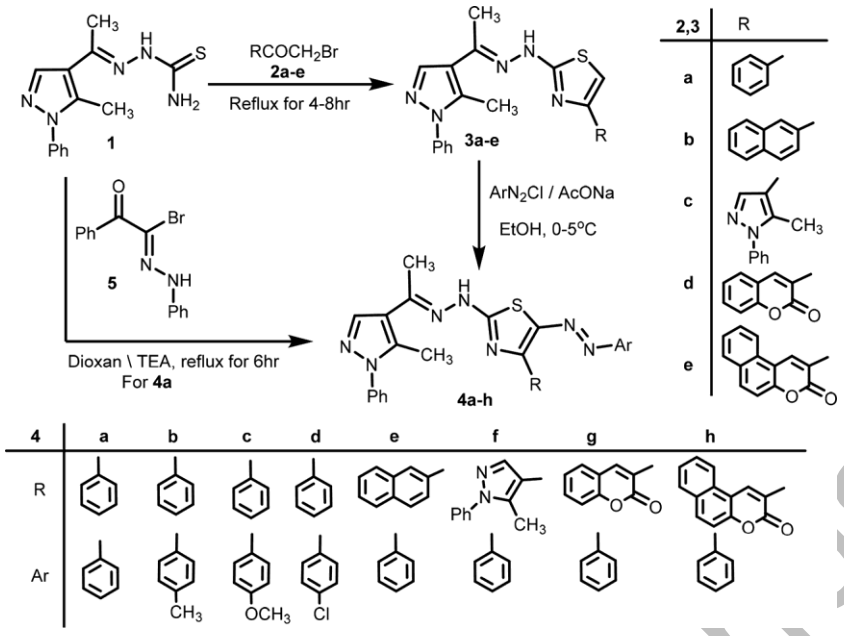
36. Gomha S. M.; Abdel-Aziz, H. A. *Bull. Korean Chem. Soc.* **2012**, *33*, 2985.

37. Gomha, S. M.; Kheder, N. A.; Abdelhamid, A. O.; Mabkhot, Y. N. *Molecules* **2016**, *21*, 1532.

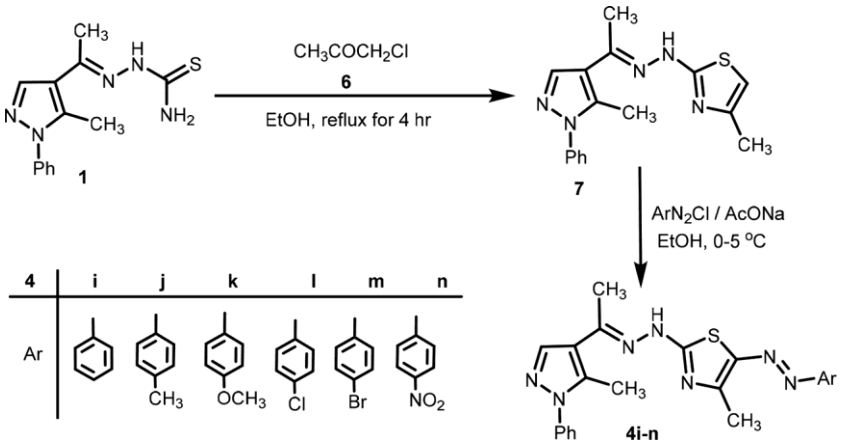
38. Salem, M. E.; Darweesh, A. F.; Mekky, A.E. M.; Farag, A. M.; Elwahy, A. H. M. *J. Heterocycl. Chem.* 2016, DOI 10.1002/jhet.2571.

39. Shawali, A. S.; Abdelhamid, A. O. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 321.

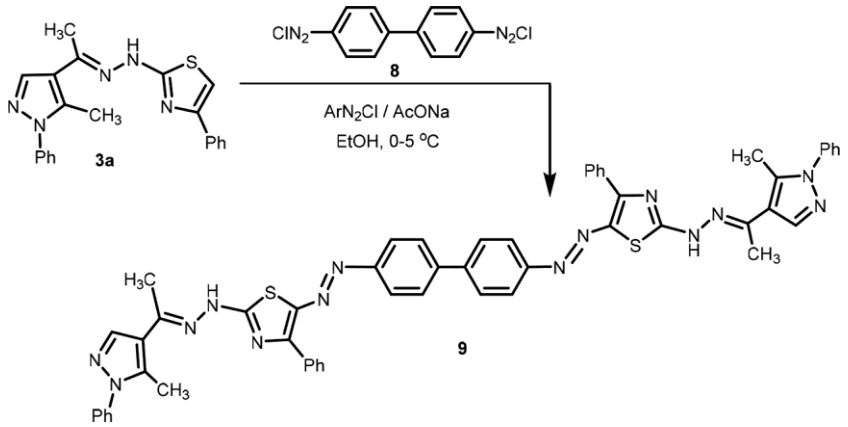
Scheme 1. Synthesis of thiazoles **3a-e** and its azo derivatives **4a-h**



Scheme 2. Synthesis of thiazole **7** and its azo derivatives **4i-n**



Scheme 3. Synthesis of *bis*-thiazole **9**



Scheme 4. Synthesis of thiazoles **11**, **13**, **15** and **17**