WALAILAK JOURNAL
http://wjst.wu.ac.th Health Sciences

Opinion to: Design, Synthesis, Antimicrobial, and Antioxidant Activities of Novel {4,5-(substituted diphenyl)-4*H*-1,2,4-triazol-3-ylthio}acetyl Chloride

Khamid U. KHODJANIYAZOV[1,2,*] and Kohei TORIKAI[3,*]

[1]*S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent 100170, Uzbekistan*
[2]*Faculty of Chemistry, National University of Uzbekistan named after Mirzo Ulugbek, Tashkent 100174, Uzbekistan*
[3]*Department of Chemistry, Faculty of Science, Kyushu University, Fukuoka 819-0395, Japan*

([*]Corresponding authors' e-mail: hamidkhodjaniyazov@yandex.ru; torikai@chem.kyushu-univ.jp)

Received: 28 February 2019, Revised: 30 April 2019, Accepted: 1 May 2019

Abstract

To discover novel triazole-based antimicrobial agents, design and synthesis of acid chlorides possessing a 1,2,4-triazole core was reported in this journal in 2018. However, we found that the reported spectroscopic data did not show any agreement with the proposed acid chloride structure. Herein, we described our opinion, which was supported by IR data, circumstantial evidences, and mechanistic insight, that the products obtained in the topical paper would be thioesters.

Keywords: Opinion, acid chlorides, thioesters, 1,2,4-triazole

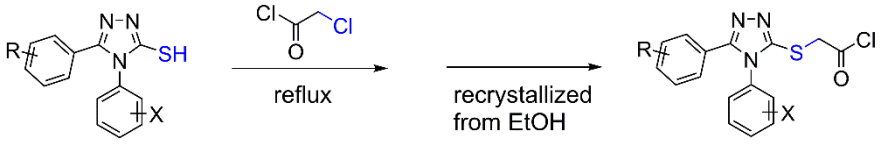
Introduction

1,2,4-Triazole derivatives are one of the most promising frameworks to obtain a wide variety of biologically active compounds, such as antibacterial, antifungal, hypoglycemic, antihypertensive and analgesic agents [1].

As one of the medicinal chemical investigations on 1,2,4-triazole derivatives, in an article published in this journal in 2018 [1], the authors reported the synthesis of acid chloride derivatives **2** by the treatment of various thiols **1** with chloroacetyl chloride, followed by the recrystallization from ethanol (**Scheme 1**). However, we started doubting these series of results after finding the inconsistent assignments of the spectral data as well as from the mechanistic insight. Herein, we propose our opinions on the characterization of the products and the usefulness of the reaction products as a lead compound of further drug development.

Results and discussion

To analyze the physical data of $\mathbf{2a_1}$ to $\mathbf{2d_7}$, the calculated (left) and reported (right) data [1], were depicted in **Table 1**. We first focused on the elemental analysis (EA). As a result, to our surprise, none of the 20 reported EA data were found to show agreement with the calculated values, taking into account that the acceptable error of EA is usually < 0.4 %. Since the reported values are far different from the calculated ones, (e.g., although EA of $\mathbf{2a_1}$ should be C 43.21 %, H 2.04 %, and N 12.63 %, the reported values were C 67.51 %, H 4.33 %, and N 10.15 %), we should wonder the authors might copy and paste incorrect data of different compounds.



1a$_1$: R = 4-NO_2, X = 2,3-Cl **1c$_1$**: R = 3,5-NO_2, X = 2,4-Me **2a$_1$ to 2d$_7$**
1a$_2$: R = 4-NO_2, X = 2,4-Me **1c$_2$**: R = 3,5-NO_2, X = 2-NO_2
1a$_3$: R = 4-NO_2, X = 4-Cl **1d$_1$**: R = 4-NH_2, X = 2,4-Me
1a$_4$: R = 4-NO_2, X = 4-OMe **1d$_2$**: R = 4-NH_2, X = 4-Cl
1a$_5$: R = 4-NO_2, X = 2-NO_2 **1d$_3$**: R = 4-NH_2, X = 2-NO_2
1a$_6$: R = 4-NO_2, X = 2,4-Cl **1d$_4$**: R = 4-NH_2, X = 2,3-Cl
1a$_7$: R = 4-NO_2, X = 4-NO_2 **1d$_5$**: R = 4-NH_2, X = 4-NO_2
1a$_8$: R = 4-NO_2, X = H **1d$_6$**: R = 4-NH_2, X = H
1b$_1$: R = 2-OH, X = 2,3-Cl **1d$_7$**: R = 4-NH_2, X = 2,4-Cl
1b$_2$: R = 2-OH, X = 2,4-Me
1b$_3$: R = 2-OH, X = 2-NO_2

Scheme 1 Reported synthesis of acetyl chlorides **2** from thiols **1**.

Second, comparison of the mass spectrometric (MS) data gave the identical conclusion, i.e., all the reported data for **2a$_1$-2d$_7$** did not match the calculated ones. Also in this case, the differences were never in the range of acceptable error of low resolution (< 1 Da) and of high resolution MS analyses (5 ppm or 0.003 Da).

Third, important disagreement can be extracted from the reported infrared (IR) spectroscopic data. One of the most meaningful IR signals is the absorption by the stretching of carbonyls, therefore, only the carbonyl stretching (CS) signals of the 20 compounds were picked up and shown in **Table 1**. Furthermore, the average of the reported wave numbers was calculated to be 1698 cm^{-1}. Since in general, aliphatic acid chlorides are known to have CS peaks at around 1785 - 1815 cm^{-1} [2], the reported CS values seem to be too small, although only **2d$_7$** showed a reasonable one (1813 cm^{-1}) [3].

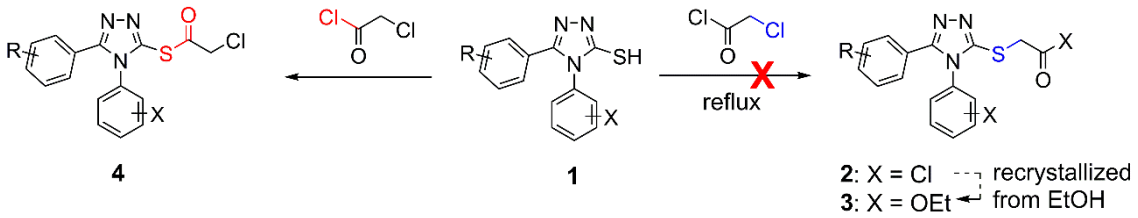
Then, if the reported IR data were all correct, what compounds would be the most suitable to rationale the reported IR data? We here suggest the formation of thioesters, whose CS signals usually appear at around 1700 cm^{-1}. Moreover, acid chlorides are usually more reactive than alkyl chlorides to nucleophiles. Hence, it is reasonable to consider thiols **1** attacked to the acid chloride moiety of chloroacetyl chloride to form thioesters **4**, faster than to the alkyl chloride part to afford thioethers **2** (**Scheme 2**).

Our hypothesis is also supported by numbers of circumstantial evidences. First evidence lies in the recrystallization that the authors conducted to purify the final products. Although it was reported in the paper that **2** were all recrystallized from ethanol, acid chlorides **2** seem to be incompatible with ethanol because they will react to form ethyl esters **3**. In contrast, this successful recrystallization makes sense if the products are thioesters **4**, which will be stable enough in ethanol, under neutral conditions. Another evidence was obtained from a literature, reported by Gineinah, Badr and co-workers (**Scheme 3**) [4]. Indeed, 4,5-diaryl-4*H*-1,2,4-triazole-3-thiols **5** and **6**, which are very similar to thiols **1**, were treated with chloroacetyl chloride in the presence of triethylamine in refluxing toluene, to afford thioesters **7** and **8**. Furthermore, the IR spectra showed that the CS signals of **7** and **8** appear at 1658 and 1662 cm^{-1}, respectively. Nonetheless, appropriate combination of spectral data, e.g., agreeable elemental analyses, (HR)MS, well-assigned ^{1}H–, ^{13}C– and some 2D–NMR (such as HMBC and HMQC), and IR, would be necessary to unambiguously determine the structure of the products.

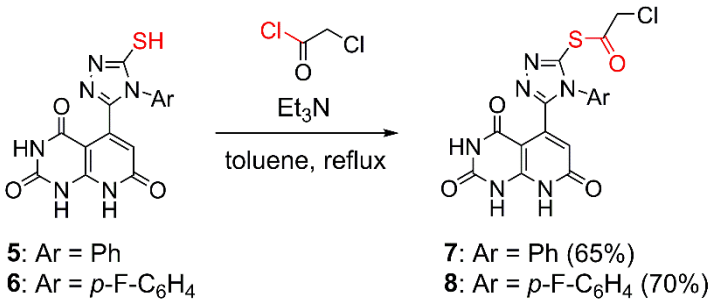
Table 1 Comparison between calculated and reported physical data.

Compounds	Calculated			Reported		
	Formula	Elem. Anal. C H N	Exact MS *m/z* $[M+H]^+$	Elem. Anal. C H N	MS *m/z* $[M+H]^+$	IR Carbonyl Stretching / cm^{-1}
2a$_1$	$C_{16}H_9Cl_3N_4O_3S$	43.21 2.04 12.63	441.95	67.51 4.33 10.15	639	1709
2a$_2$	$C_{18}H_{15}ClN_4O_3S$	53.67 3.75 13.91	402.06	49.42 3.37 7.24	439	1654
2a$_3$	$C_{16}H_{10}Cl_2N_4O_3S$	46.96 2.46 13.69	407.99	48.17 3.61 14.17	558	1614
2a$_4$	$C_{17}H_{13}ClN_4O_4S$	50.44 3.24 13.84	404.03	59.15 4.41 8.89	459	1678
2a$_5$	$C_{16}H_{10}ClN_5O_5S$	45.78 2.40 16.68	419.01	48.25 2.88 7.12	673	1686
2a$_6$	$C_{16}H_9Cl_3N_4O_3S$	43.21 2.04 12.63	441.95	45.25 3.31 12.43	509	1678
2a$_7$	$C_{16}H_{10}ClN_5O_5S$	45.78 2.40 16.68	419.01	59.39 4.07 8.41	508	1720
2a$_8$	$C_{16}H_{11}ClN_4O_3S$	51.27 2.96 14.95	374.02	43.42 2.24 7.11	659	1716
2b$_1$	$C_{16}H_{10}Cl_3N_3O_2S$	46.34 2.43 10.13	412.96	41.76 3.21 11.59	645	1728
2b$_2$	$C_{18}H_{16}ClN_3O_2S$	57.83 4.31 11.24	373.07	64.18 4.12 9.11	648	1666
2b$_3$	$C_{16}H_{11}ClN_4O_4S$	49.17 2.84 14.34	390.02	47.52 2.42 6.47	623	1624
2c$_1$	$C_{18}H_{14}ClN_5O_5S$	48.27 3.15 15.64	447.04	47.25 2.41 6.57	429	1654
2c$_2$	$C_{16}H_9ClN_6O_7S$	41.35 1.95 18.08	463.99	42.84 3.12 11.98	369	1707
2d$_1$	$C_{18}H_{17}ClN_4OS$	57.98 4.60 15.03	372.08	62.39 4.15 9.21	693	1725

Compounds	Calculated			Reported		
	Formula	Elem. Anal. C H N	Exact MS *m/z* $[M+H]^+$	Elem. Anal. C H N	MS *m/z* $[M+H]^+$	IR Carbonyl Stretching / cm^{-1}
2d$_2$	$C_{16}H_{12}Cl_2N_4OS$	50.67 3.19 14.77	378.01	41.63 2.18 6.49	483	1708
2d$_3$	$C_{16}H_{12}ClN_5O_3S$	49.30 3.10 17.97	389.03	41.92 3.11 12.69	453	1720
2d$_4$	$C_{16}H_{11}Cl_3N_4OS$	46.45 2.68 13.54	411.97	38.50 3.54 8.68	473	1717
2d$_5$	$C_{16}H_{12}ClN_5O_3S$	49.30 3.10 17.97	389.03	41.29 2.26 6.32	659	1716
2d$_6$	$C_{16}H_{13}ClN_4OS$	55.73 3.80 16.25	344.05	38.48 2.67 10.95	383	1717
2d$_7$	$C_{16}H_{11}Cl_3N_4OS$	46.45 2.68 13.54	411.97	51.40 3.22 7.30	541	1813
Average	-	-	-	-	-	1698



Scheme 2 Proposed formation of thioester **4** by the reaction of **1** with chloroacetyl chloride.



Scheme 3 Thioester formation via the reactions between aromatic thiols and chloroacetyl chloride, reported by Gineinah, Badr and co-workers.

Finally, we should also recommend the reconsideration of the authors' design. This is because, in the modern medicinal chemistry, it is considered that both α-halo-substituted carbonyl and thioester functionalities should be excluded from the drug candidate [5], due to their high electrophilicity, which tends to accept S_N2 and acyl nucleophilic substitution reactions, respectively. That is, these moieties will easily react with endogenous nucleophiles (e.g. cysteine residues of peptides and proteins [6], or amines) to form undesired conjugates that may trigger unfavorable events in physiological conditions.

Conclusions

Herein, we discussed the possibility of misassignment of the products, synthesized from 4,5-(substituted diphenyl)-4*H*-1,2,4-triazol-3-thiols and chloroacetyl chloride, which had been reported in a paper published in this journal. Our interpretation of the reported IR spectra, search of literatures, and the mechanistic insight suggested the formation of α-chloro-substituted thioesters, which may still have a concern to show unfavorable properties as a drug from the viewpoint of modern medicinal chemistry.

Acknowledgments

We are grateful to Professors Shamansur Sagdullaev (the director of S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan) and Tohru Oishi (Kyushu University, Japan), for their kind support of our collaboration.

References

[1] M Kumar, N Malik, P Dhiman, PK Verma and A Khatahar. Design, synthesis, antimicrobial, and antioxidant activities of novel {4,5-(substituted diphenyl)-4*H*-1,2,4-triazol-3-ylthio}acetyl chloride. *Walailak J. Sci. & Tech.* 2018; **15**, 157-67.

[2] RM Silverstein, FX Webster and DJ Kiemle. *Spectrometric Identification of Organic Compounds*. 7th ed. John Wiley & Sons, 2005.

[3] Other than these, there are some minor points: The reported ^{1}H–NMR data do not show any multiplicities and *J* values, to hamper the detailed structure confirmation of the readers. Nomenclatures are occasionally incorrect (e.g. compound **2a$_1$** is named as 2-(4-(2,6-dichlorophenyl)-5-(4-nitrophenyl)-4H-1,2,4-triazol-3-ylthio)acetyl chloride, but it should be 2-(4-(2,3-dichlorophenyl)-5-(4-nitrophenyl)-4H-1,2,4-triazol-3-ylthio)acetyl chloride).

[4] MM Gineinah, MNA Nasr, SMI Badr and WM El-Husseiny. Synthesis and antitumor activity of new pyrido[2,3-*d*]pyrimidine derivatives. *Med. Chem. Res*. 2013; **83**, 155-66.

[5] (a) AF Stepan, DP Walker, J Bauman, DA Price, TA Baillie, AS Kalgutkar and MD Aleo. Structural alert/reactive metabolite concept as applied in medicinal chemistry to mitigate the risk of idiosyncratic drug toxicity: A perspective based on the critical examination of trends in the top 200 drugs marketed in the United States. *Chem. Res. Toxicol*. 2011; **24**, 1345-410.
(b) TW Schultz, KE Ralston, DW Roberts, GD Veith and AO Aptula. Structure-activity relationships for abiotic thiol reactivity and aquatic toxicity of halosubstituted carbonyl compounds. *SAR QSAR Environ. Res*. 2007; **18**, 21-9.

[6] T Wieland, E Bokelmann, L Bauer, HU Lang and H Lau. Über peptidsynthesen. 8. Mitteilung bildung von S-haltigen peptiden durch intramolekulare wanderung von aminoacylresten. *Liebigs Ann. Chem*. 1953; **583**, 129-49.