CZU: 547.793.7:547.581 https://doi.org/10.59295/mabt2026.30

1-(ALKYL/ARYL)-2-(1*H*-1,2,4-TRIAZOL-1-YL)ETHANONES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE *N*-VINYL TRIAZOLES

Marina CEABANOVA, Eugenia STÎNGACI, Natalia SUCMAN,
Serghei POGREBNOI, Lucian LUPAȘCU, Fliur MACAEV

Laboratory of Organic Synthesis, Institute of Chemistry,
Moldova State University, Chisinau, Moldova.

Abstract

This paper describes a method for the synthesis of biologically active compounds based on 1-(alkyl/aryl)-2-(1*H*-1,2,4-triazol-1-yl)ethanones with aromatic aldehydes under Knövenagel reaction conditions. The studies are based on the possibility of selectively using 1-(alkyl/aryl)-2- (1*H*-1,2,4-triazol-1-yl)ethanone derivatives, a distinctive structural feature of which is the presence of an activated methylene group; when this group reacts with aldehydes, it yields *N*-vinyl-triazoles in which the nitrogen atom is bonded to an sp²-hybridized carbon atom of a substituted olefin. In reactions with salicylic aldehyde derivatives, these compounds form hemiketals in which the carbon atom of the carbonyl group becomes asymmetric. An evaluation of the "structure-bioactivity" relationship was conducted for a series of synthesized alkyl/aryl-substituted *N*-vinyl triazoles. The resulting compounds exhibit biological activity and show promise for application in medicine and agriculture as antimicrobial agents and plant growth regulators.

Keywords: condensation, 1,2,4-triazole, 1-(alkyl/aryl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone, vinyl-triazole, aromatic aldehydes, biological activity.

Introduction

Interest in 1,2,4-triazole derivatives has grown significantly over the past decades. Triazole derivatives are widely used in medical practice: antifungal agents (fluconazole, itraconazole, terconazole, posaconazole, voriconazole), antiviral agents (ribavirin), antineoplastic agents (anastrozole, letrozole), anxiolytics and sedatives (alprazolam, triazolam, estazolam, and others), antihypertensive drugs (trapidil) [1,2], and in agriculture as fungicides [3] or growth regulators [4]. They are characterized by high activity at low concentrations and good solubility. The antifungal activity of azole compounds, including 1,2,4-triazole, is associated with the inhibition of the 14α-demethylase enzyme (CYP51), which plays a key role in the biosynthesis of sterols that ensure the proper development and functioning of the cell walls and membranes of pathogenic fungi. Disruption of biosynthesis subsequently leads to their death. The aim of this study was to synthesize 1,2,4-triazole derivatives bearing various functional groups and to investigate their activity.

Material and methods

The chemicals used were of reagent grade and used as received. Removal of all solvents was carried out under reduced pressure. ^{1}H and ^{13}C NMR spectra have been recorded for DMSO-d_6 2% solutions on a "Bruker-Avance III" (400.13 and 100.61 MHz). Chemical shifts δ are given in ppm referring to the signal center using the solvent peaks for reference: DMSO- d_6- 2.50 ppm. IR spectra were recorded on a Spectrum 100 FT-IR spectrophotometer (Perkin - Elmer) using the universal ATR sampling accessory. All products were analysed by CHN elemental analysis (Elementar Vario EL analyser). Melting points (uncorrected) were determined on a Boetius apparatus. Thin-layer chromatography was carried out on Merck aluminum TLC plates, silica gel 60 coated with fluorescent indicator F254.

2a (*Z*)-4,4-Dimethyl-1-(4-nitrophenyl)-2-(1*H*-1,2,4-triazol-1-yl)pent-1-en-3-one [5]. White crystals (ethanol). Yield 70%, mp 114-116°C. IR (ν/cm^{-1}): 3134, 2968, 2933, 2911, 1703,

1640, 1894, 1512, 1501, 1479, 1342, 1278, 1221, 1200, 1094, 1072, 1003, 942, 907, 860, 671. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29 (1H, s), 8.24 (2H, d *J* = 8.4), 8.10 (1H, s), 7.52 (2H, d, *J*= 8.4), 1.00 (9H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) 207.3, 153.0, 147.9, 141.9, 139.3, 136.2, 129.9, 124.0, 119.2, 45.7, 27.0. Anal. Calcd for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66%. $C_{15}H_{16}N_4O_3$. Found 59.83; H, 5.22; N, 18.62 %.

2b (*Z*)-1-(2,4-Dichlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pent-1-en-3-one. White crystals (ethanol), yield 66%, mp 209-211°C. IR (ν/cm^{-1}): 3118, 2970, 2297, 1636, 1630, 1505, 1473, 1384, 1138, 1104, 1005, 934, 848, 834, 771, 673. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (1H, s) 7.93 (1H, s), 7.62 (1H, s), 7.45 (1H, d, *J*= 1.9), 7.04 (1H, dd, *J*= 8.4, 1.9), 6.47 (1H, d, *J*= 8.4), 1.28 (9H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) 201.90, 152.8, 144.9, 136.8, 135.7, 134.3, 130.8, 129.97, 129.87, 128.9, 127.7, 44.23, 27.6. Anal. Calcd for $C_{15}H_{15}Cl_2N_3O$: C, 55.57, H, 4.66, Cl, 21.87, N, 12.96, O, 4.93%. Found C, 55.1, H, 4.2, N, 12.5 %

2c (*Z*)-5-Methyl-1-(4-nitrophenyl)-2-(1*H*-1,2,4-triazol-1-yl)hex-1-en-3-one. Yellow crystals (ethanol), yield 54%, mp 97°C. IR (ν/cm-1): 3129, 2955, 2892, 2872, 1699, 1619, 1600, 1521, 1507, 1366, 1342, 1077, 1009, 854, 737. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.56 (1H, s), 8.24, (1H, s), 8.20(1H. s). 8.13(2H, d, *J*=8.8), 7.18 (2H, d, *J*=8.8), 2. 75(2H, d, *J*=6.8), 2.1 (1H, m), 0.92 (6H, d, *J*=6.6). ^{13}C NMR (DMSO-d_6, 100 MHz): 196.2, 152.9, 148.4, 146.5, 138.5, 137.2, 135.4, 131.3, 124.1, 46.1, 25.0, 22. Anal. Calcd for $C_{25}H_{27}Cl_2N_3O_2$, C 63.56, H 5.76%. Found C 63.64, H 5.79%.

2d (*Z*)-1-(4-Chlorophenyl)-3-(2-hydroxy-5-nitrophenyl)-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one. Yellow crystals (ethanol), yield 76%, yellowish crystals (ethanol), mp 217-218°C. IR (ν/cm^{-1}): 3631, 3058, 2536, 1659, 1583, 1509, 1440, 1402, 1339, 1270, 1213, 1129, 1091, 857, 828, 745, 667. ^{1}H NMR (DMSO- d_6, 400 MHz): 9.39(1H, br, s), 8.73(1H, s), 8.27(1H, s), 8.12(1H, dd, *J*=9, 2.8), 7.82 (2H, d, *J*=8.5), 7.74(1H, s), 7.62(2H, d, *J*=8.5), 7.26(1H, d, *J*=2.8), 7.03(1H, d, *J*=9). ^{13}C NMR (DMSO-d_6, 100 MHz): 190.0, 163.3, 153.0, 146.6, 139.7, 138.5, 135.5, 134.7, 133.4, 131.6, 129.4, 128.4, 125.7, 119.2, 117.0. C 55.15, H 3.04%, Anal. Calcd for $C_{17}H_{11}ClN_4O_4$: C 55.15, H 3.04%. Found C 55.07, H 2.99%.

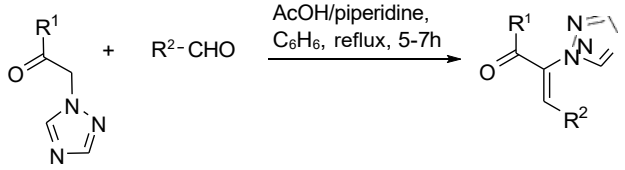
2e (*Z*)-3-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one. Yield 82%, cream colored crystals (isopropanol), mp 225°C. IR (ν/cm^{-1}): 3064, 3601, 2956, 1655, 1616, 1585, 1412, 1272, 1210, 1139, 1094, 1004, 929, 834, 784, 674. ^{1}H NMR (DMSO-d_6, 400 MHz); δ 8.6 9(1H, s), 8.29(1H, s), 7.76 (1H, d, *J*=1.7), 7.60 (1H, d, *J*=8.), 7.60 (1H, s), 7.56 (1H, d, *J*=8.3, 1.7), 6.73 (2H, s), 1.19 (18H, s). ^{13}C NMR (DMSO-d_6, 100 MHz): 190.0, 159.1, 153.1, 146.6, 146.4, 139.4, 136.3, 136.2, 131.6, 130.9, 130.1, 129.9, 129.3, 129.1, 122.5, 34.7, 30.2. Anal. Calcd for $C_{25}H_{27}Cl_2N_3O$, C 63.64, H 5.79%. Found C 63.56, H 5.76%.

2f (*Z*)-1-(2,4-dichlorophenyl)-3-(2-hydroxy-5-nitrophenyl)-2-(1*H*-1,2,4-triazol-1-yl)prop-2-en-1-one. Yellow crystals (ethanol), yield 65%, mp 127-128°C. IR (ν/cm^{-1}): 3063.8, 1678.5, 1638.4, 1584.7, 1523.1, 1506.6, 1342, 1305.1, 1268.4, 1242.3, 1134.9, 1087.7, 994.5, 835.9, 780.3, 687.8, 668.6. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.72 (1H, s), 8.27 (1H, s), 8.1 (1H, d, *J*=8.9, 1.9), 7.82 (1H, s), 7.78 (1H, td, *J*=3.9, 1.6), 7.71 (2H, d, *J*=8.3),7.59 (1H, dt, *J*=8.3, 1.9), 7.21 (2H, d, *J*=8.9). ^{13}C NMR (DMSO-d_6, 100 MHz): 189.9, 153.2, 148.7, 146.7, 141.7, 137.9, 137.0, 135.1, 135.0, 132.0, 131.7, 131.5, 130.3, 128.2, 124.2. Anal. Calcd for $C_{17}H_{10}Cl_2N_4O_3$, C 52.52, H 2.64%. Found C 52.46, H 2.59%.

Results and discussion

The starting ketones **1a-b** were obtained by the following methods [6,7] and ketone **2c-d** were purchased from Aldrich. The compounds **2a-2f** were synthesized according to the synthetic pathway shown in the Scheme. The mixture of 1-(alchil/aril)-2-(1*H*-1,2,4-triazol-1-il)etanone (**1a–1c**) and corresponding aromatic aldehyde was refluxed in benzene in the presence of

piperidine and acetic acid as catalysts The target compounds **2a–2f** were obtained in yields ranging from 54% to 82%.



1a R^1=Me_3C
1b R^1 = Me_2CHCH_2
1c R^1=2,4-Cl_2-C_6H_3
1d R^1=4-Cl-C_6H_4

2a R^1=Me_3C, R^2=4-NO_2-C_6H_4 70%
2b R^1=Me_3C, R^2=2,4-Cl_2-C_6H_3 66%
2c R^1=Me_2CHCH_2, R^2=4-NO_2-C_6H_4 54%
2d R^1=4-Cl_2-C_6H_4 R^2=2-OH,5-NO_2-C_6H_3 76%
2e R^1=2,4-Cl_2-C_6H_3, R^2=3,5-($Bu)_2$-4-OH-C_6H_2 82%
2f R^1=2,4-Cl_2-C_6H_3, R^2=2-OH,5-NO_2-C_6H_3 65%

Scheme 1. Synthesis of *N*-vinyl-1,2,4-triazoles

The structures of the synthesized compounds were confirmed by elemental analysis, IR, and NMR spectral data. The NMR spectra of the synthesized *N*-vinyl triazoles are characterized by the presence of a singlet proton of the vinyl group, indicating a specific isomer. The ketone configuration was determined based on NOESY experiments.

The antifungal activity was evaluated against eight different fungal species: *Aspergillus fumigatus*, *A. versicolor, A. ochramensis*, *A. niger, Trichoderma viride, Penicillium funiculosum, P. ochrochloron, P. verrucosum var. cyclopium.* Minimum inhibitory concentration (MIC) and minimum fungicidal concentration have been determined. The antifungal assay was carried out by the microdilution method [8]. All experiments were performed in duplicate and repeated three times. All of the compounds obtained exhibited fungicidal activity in vitro (Table 1) [9].

Table 1. Antifungal activity of compounds in mM

#		*Aspergillus fumigatus.*	*Aspergillus versicolor*	*Aspergillus ochraceus*	*Aspergillus niger*	*Trichoderma viride*	*Penicillium funiculosum*	*Penicillium ochrochlóron*	*Penicillium verrucosum var.cyclopium*
2a	MIC	0.25	0.25	0.13	0.25	0.09	0.18	0.13	0.25
	MFC	0.51	0.51	0.25	0.51	0.13	0.25	0.25	0.51
2b	MIC	0.14	0.14	0.07	0.14	0.07	0.19	0.14	0.14
	MFC	0.27	0.27	0.14	0.27	0.14	0.27	0.27	0.27
2c	MIC	0.02	0.04	0.02	0.02	0.03	0.04	0.03	0.04
	MFC	0.03	0.06	0.03	0.03	0.06	0.06	0.06	0.06
2d	MIC	0.20	0.10	0.10	0.15	0.10	0.15	0.10	0.20
	MFC	0.41	0.20	0.20	0.20	0.20	0.20	0.20	0.41
2e	MIC	0.08	0.08	0.08	0.08	0.03	0.12	0.08	0.16
	MFC	0.16	0.16	0.16	0.16	0.08	0.16	0.16	0.32
2f	MIC	0.56	0.16	0.16	0.16	0.27	0.37	0.16	0.37
	MFC	0.75	0.37	0.37	0.75	0.37	0.75	0.37	0.75
Ktz	MIC	0.38	0.38	0.28	0.38	1.88	0.38	1.88	0.38
	MFC	0.94	0.94	0.38	0.94	2.82	0.94	2.82	0.57
Bfz	MIC	0.48	0.32	0.48	0.48	0.48	0.64	0.64	0.32
	MFC	0.64	0.64	0.64	0.64	0.64	0.81	0.81	0.64
Ktz. – Ketoconazole, Bfz. - Bifonazole									

The minimum inhibitory concentrations (MIC) of the nitro-substituted *tert*-butyl triazole derivative **2a** against *A. fumigatus, A. versicolor, A. ochramensis*, and *A. niger* were 0.25 mM, 0.25 mM, 0.13 mM, 0.25 mM, and 0.033 mM. Replacing the *tert*-butyl group with an isobutyl group in compound **2c** resulted in a 12-fold increase in the level of inhibition against *A. fumigatus* and *A. niger*, and a 6-fold increase against *A. versicolor* and *A. ochramensis*. Replacing the nitro group with the dichlorodivergent **2b** had virtually no effect on activity against *Aspergillus* fungi, which ranged from MIC 0.07–0.14 mM at a minimum fungicidal concentration (MFC) of 0.02–0.27 mM.

Conclusions

The use of 1-(alkyl/aryl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone for the preparation of alkyl(aryl)-substituted *N*-vinyl triazoles is a convenient and accessible synthetic strategy for producing biologically active compounds with good yields. The results obtained demonstrate the potential for further research into these compounds to expand the repertoire of biologically active triazole derivatives, particularly those with antifungal activity.

Acknowledgments

This study was supported by the research project "Chemical study of secondary metabolites from local natural sources and valorization of their application potential basing on broadening molecular diversity with multiple functionality (MetNatVal)", # 010601, funded by the Ministry of Education and Research of the Republic of Moldova. The authors are grateful to Dr. Shova S. for recording and crystal X-Ray diffraction study.

References:

1. Rodrigues, S. C., et al. A Review on Chemistry and Methods of Synthesis of 1,2,4-Triazole Derivatives. The Chemical Record, 2025, 25(1), e202400190. DOI: 10.1002/tcr.202400190.
2. Stingaci, E., et al. New vinyl-1,2,4-triazole derivatives as antimicrobial agents: Synthesis, biological evaluation and molecular docking studies. *Bioorg. Med. Chem. Lett.*, 2020, 30(17), 127368. DOI: 10.1016/j.bmcl.2020.127368.
3. Shi, H., et al. Synthesis and biological evaluation of novel 1,2,4-Triazole Derivatives containing amino acid fragment. *Molecules*, 2025, 30(8), 1692. DOI: 10.3390/molecules30081692.
4. Guangrong, C., et al. Synthesis and Biological Evaluation of 3,3-Dimethyl-1-(1H-1,2,4-triazole-1-yl)butan-2-One Derivatives as Plant Growth Regulators. *Chem. Res. Chin. Univ.*, 2019, 35(2), 221–228. DOI: 10.1007/s40242-019-8303-6.
5. Macaev, F., Zveaghinteva, M., Stângaci, E., Pogrebnoi, S., Duca, G. Procedeu de obținere a (Z)-4,4-dimetil-1-(4-nitrofenil)-2-(1H-1,2,4-triazol-1-il)pent-1-en-3-onei. *Brevet de invenție MD 4515 C1*. Data depozit 21.12.2016, publicat 30.09.2017. In: *BOPI*, 2017, 9, 32–33.
6. Macaev, F., Stângaci, E., Pogrebnoi, S., Boldescu, V. (Z)-5-Metil-1-(4-nitrofenil)-2-(1H-1,2,4-triazol-1-il)hex-1-en-3-onă, procedeu de sinteză și utilizarea ei în calitate de remediu antifungic. *Brevet de invenție MD 4703 B1*. Data depozit 04.04.2019, publicat 31.07.2020. In: *BOPI*, 2020, 7, 43–44.
7. Macaev, F., Zveaghinteva, M., Stângaci, E., Pogrebnoi, S., Duca, G. Procedeu de sinteză a 3,3-dimetil-1-(1H-1,2,4-triazol-1-il)butan-2-onei. *Brevet de invenție MD 4505 C1*. Data depozit 21.12.2016, publicat 31.08.2017. In: *BOPI*, 2017, 8, 28.
8. Haroun, M., et al. New Benzothiazole-Based Thiazolidinones as Potent Antimicrobial Agents. Design, Synthesis and Biological Evaluation. *Curr. Top. Med. Chem.*, 2018, 18, 75–87. DOI: 10.2174/1568026618666180206101814.
9. Zveaghinteva, M. *Synthesis and study of 1-(1H-1,2,4-triazol-1-yl)ethan-2-ones* [PhD Thesis abstract]. Chișinău, 2023, p. 18. Disponibil la: https://anacec.md/files/Zveaghinteva-abstract.pdf.

Date despre autori:



Marina CEABANOVA, Institutul de Chimie, Universitatea de Stat din Moldova, Chișinău, Republica Moldova
e-mail: marina.ceabanova@sti.usm.md, mari6azv@mail.ru
ORCID: 0000-0003-1553-5246



Eugenia STÎNGACI, Institutul de Chimie, Universitatea de Stat din Moldova, Chișinău, Republica Moldova
e-mail: eugenia.stingaci@sti.usm.md
ORCID: 0000-0003-0731-3424



Natalia SUCMAN, Institutul de Chimie, Universitatea de Stat din Moldova, Chișinău, Republica Moldova
e-mail: natalia_sucman@yahoo.com
ORCID: 0000-0001-8733-3040



Serghei POGREBNOI, Institutul de Chimie, Universitatea de Stat din Moldova, Chișinău, Republica Moldova
e-mail: serghei.pogrebnoi@ichem.md
ORCID: 0000-0003-2827-505X



Lucian LUPAȘCU, doctor în științe medicale, cercetător științific coordinator, Laboratorul Sinteza Organică, Institutul de Chimie, USM, Chișinău, Republica Moldova
e-mail: Lucian.lupascu@sti.usm.md
ORCID: 0000-0001-5006-5265



Fliur MACAEV, Membru corespondent al AȘM, doctor habilitat în științe chimice, Institutul de Chimie al Universității de Stat din Moldova, profesor cercetător
e-mail: fliur.macaev@sti.usm.md
ORCID: 0000-0002-3094-1990