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A SIMPLE REGIOSELECTIVE SYNTHESIS OF TRISUBSTITUTED 1,2,3-TRIAZOLES UNDER METAL-FREE CONDITIONS AND EVALUATION OF THEIR ANTIOXIDANT ACTIVITY

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ABSTRACT

1,2,3-Triazole is one of the most therapeutically privileged heterocyclic systems. In the present work, we report the regioselective synthesis of a new array of trisubstituted 1,2,3-triazoles under metal-free conditions and evaluated their antiradical activity. The title compounds were synthesized according to the well-known [3+2] cycloaddition reaction between benzyl buta-2,3-dienoate (3) and organic azides (5) giving the triazole derivatives 6(a-f). Structures of the synthesized entities corroborated spectroscopically (^{1}H NMR, ^{13}C NMR, and MASS) and screened for antiradical activity using DPPH radical scavenging assay. Among the tested compounds, the highest activity was observed with the 6b derivative.

Keywords: 1,2,3-Triazole, [3+2] Cycloaddition, Benzyl buta-2,3-dienoate, Organic Azides, Antiradical Activity.
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INTRODUCTION

It is a common notable fact that oxidants (free radicals) are responsible for oxidative stress. Oxidants are molecules, ions or atoms with their outermost electron shell with unpaired electrons. Hence oxidants are highly unstable and highly reactive. These are generated through our body's biochemical processes. Moreover, oxidative stress plays a critical role in the development of age-related, chronic diseases, and neurodegenerative and cardiovascular diseases, which transpire in a cell or in tissue when there is an imbalance of reactive oxygen species (ROS) and antioxidant potential of that cell.[1-3] To counteract ROS accumulation different cellular protection mechanisms have been developed.[4] Virtual screening through molecular docking with the antioxidant enzymes is one possible approach for the development of new antioxidant agents.[5-7] Among the classes of heterocyclic compounds that enhance SOD activity, 1,2,3-Triazoles have gained conspicuous significance.[8-9] Triazole is one of the greatest therapeutically significant heterocyclic systems and its derivatives have a vast spectrum of medicinal activities.[10-20] From the literature, we observed that many of the triazole derivatives were reported by Cu(I)–catalyzed azide-alkyne cycloaddition (CuAAC),[21] Azide –Alkyne 1,3-dipolar addition,[22-23] and Transition metal complexes of rhodium and ruthenium.[24] Hence, here we synthesized regioselective title scaffolds using benzyl buta-2,3-dienoate (Allenoate), organic azides under metal-free conditions and evaluated for their antioxidant potential.

EXPERIMENTAL

Materials and Methods

Capillary melting point apparatus was used to measure the melting points and were uncorrected. ^{1}H & ^{13}C NMR spectra were recorded at 500/126 MHz with $CDCl_3$ and TMS used as a solvent and internal

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standard respectively. Chemical shifts were reported in ppm. Mass spectra were recorded in an MS-ESI. Antioxidant properties were determined spectrophotometrically. All reagents were purchased from commercial suppliers.

General Procedures for the Synthesis of Tri Substituted 1,2,3-Triazoles 6(a-f)

Compounds 3 and 5 were prepared through literature procedures.[25-26] Organic azide (1.8 mmol, 3 equivalents) and Benzyl buta-2,3-dienoate (0.6 mmol, 1 equivalent) were added to the round bottom flask. 2 ml of dimethyl formamide solvent (DMF) was also added to the mixture and stirred at 80 ºC for 12 hrs. After completion of the reaction as evidenced by TLC, the mixture was cooled and quenched by adding 15 ml of water and extracted with ethyl acetate (3X5 ml). The combined extracts were washed with brine solution and dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography to afford the desired final derivatives 6(a-f) (Eluent: Ethylacetate/Hexane).

Benzyl-5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate (6a)

Yield 69%, Melting point 180-182 ºC, R_f = 0.56, Mol formula $C_{17}H_{15}N_3O_2$, Mol. Weight 293.3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.35 (m, 10H), 5.47 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6, 139.1, 136.6, 135.8, 135.5, 130.1, 129.7, 128.6, 128.5, 128.4, 125.4, 66.7, 10.1; Mass m/z: 294.1 (M+1).

Benzyl-1-(4-methoxyphenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6b)

Yield 71%, Melting point 149-151 ºC, R_f = 0.50, Mol formula $C_{18}H_{17}N_3O_3$, Mol Weight 323.4. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.35 (m, 5H), 7.06 (d, *J* = 7.2 Hz, 2H), 5.46 (s, 2H), 3.90 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6, 160.7, 139.2, 136.3, 135.8, 128.6, 128.5, 128.3, 128.2, 126.8, 114.8, 66.6, 55.7, 10.0; Mass m/z: 324.1 (M+1).

Benzyl-5-methyl-1-(4-nitrophenyl)-1*H*-1,2,3-triazole-4-carboxylate (6c)

Yield 68%, Melting point 165-167 ºC, R_f = 0.43, Mol formula $C_{17}H_{14}N_4O_4$, Mol Weight 338.3. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 9.1 Hz, 2H), 7.51 (d, *J* = 7.1 Hz, 2H), 7.40 – 7.37 (m, 3H), 5.47 (s, 2H), 2.69 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2, 148.3, 140.2, 139.1, 137.3, 135.5, 128.7, 128.5, 125.9, 125.2, 120.4, 66.9, 10.3; Mass m/z: 339.1 (M+1).

Benzyl-1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6d)

Yield 70%, Melting point 164-165 ºC, R_f = 0.37, Mol formula $C_{17}H_{14}FN_3O_2$, Mol Weight 311.3.^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 – 7.50 (m, 2H), 7.46 – 7.44 (m, 2H), 7.41 – 7.38 (m, 2H), 7.35 (dt, *J* = 9.8, 4.3 Hz, 1H), 7.30 – 7.26 (m, 2H), 5.46 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 164.3, 162.3, 161.5, 139.2, 136.6, 135.7, 128.6, 128.5, 128.4, 127.5, 127.4, 116.9, 116.8, 66.7, 10.0; Mass m/z: 312.5 (M+1).

Benzyl-1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6e)

Yield 73%, Melting point 152-153 ºC, R_f = 0.31, Mol formula $C_{17}H_{14}ClN_3O_2$, Mol Weight 327.8. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.36 – 7.31 (m, 5H), 7.14 (d, *J* = 6.2 Hz, 2H), 5.51 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5, 139.1, 136.7, 136.3, 135.7, 133.9, 130.0, 128.7, 128.5, 128.4, 126.6, 66.8, 10.1; Mass m/z: 328.1 (M+1).

Benzyl-1-benzyl-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (6f):

Yield 76%, Melting point 189-190 ºC, R_f = 0.25, Mol formula $C_{18}H_{17}N_3O_2$, Mol Weight 307.4. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.36– 7.31 (m, 6H), 7.14 (d, *J* = 6.2 Hz, 2H), 5.51 (s, 2H), 5.38 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5, 138.5, 136.8, 135.7, 133.9, 129.1, 128.6, 128.6, 128.5, 128.3, 127.2, 66.6, 51.9, 9.1; Mass m/z: 308.1 (M+1).

Evaluation of the Antioxidant Activity of Compounds 6(a-f)

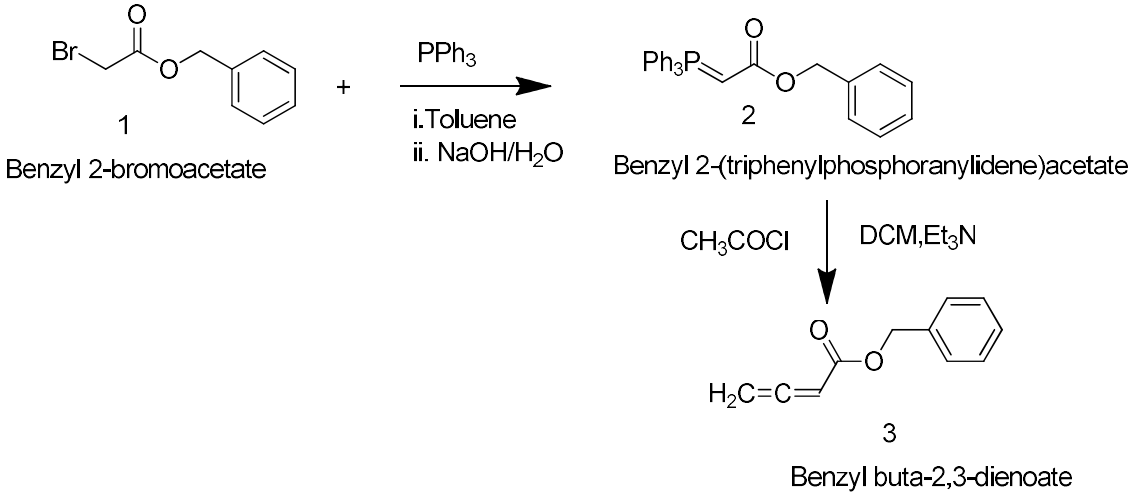
All the final products were evaluated for their free radical scavenging activity based on the capture of DPPH radical (2,2-Diphenyl-1-picrylhydrazyl) and all tests were performed in triplicate.[27] Further, Graphpad prism 8 statistical linear regression analysis program was utilized to establish the antiradical proficiency in the 95% confidence interval ($p < 0.001$).

RESULTS AND DISCUSSION

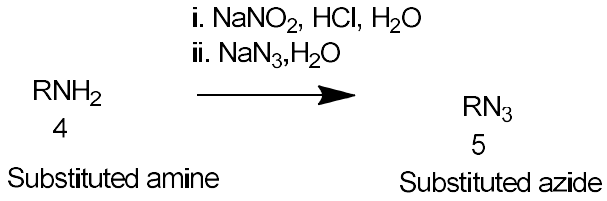
Chemistry

Benzyl buta-2,3-dienoate and phenyl azide were used as model substrates to optimize the reaction conditions. Table-1 clearly indicates that heating is essential for the formation of title products. Hence it is a thermal cycloaddition reaction. After optimizing the reaction conditions, we prepared six title compounds (6a-f) in 68-76% yields. [3+2] cycloaddition reaction is initiated by the attack of azide N atom at the β-position of allenoates to give zwitterionic intermediate. After that, it undergoes intramolecular addition and rearrangement reactions to form desired products 6(a-f).

The complete synthetic route is depicted in schemes 1, 2 and 3). All the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and Mass spectroscopy. In the ^{1}H NMR of newly synthesized compounds, methylene protons ($-CH_2-$) were found at the range of 5.46-5.51 ppm as a characteristic singlet signal. All the methyl protons ($-CH_3$) were found in the range of 2.42-2.69 ppm as a characteristic singlet signal. All the remaining aliphatic and aromatic proton peaks were observed at their expected regions. ^{13}C NMR of all the derivatives showed appropriate signals. Further, synthesized compounds were analyzed by mass spectra under ESI, molecular ions were analyzed in the form of M+1.



Scheme-1: Synthesis of Benzyl buta-2,3-dienoate



Scheme-2: Synthesis of Azides

Antiradical Activity

The pure test compounds **(**Scheme-3) were tested for *in vitro* antiradical activity using the DPPH scavenging method and the results were depicted in Table-2. Compound 6b with 4-Methoxy phenyl moiety on triazole ring exhibited significant activity with IC_{50} 36.39 µg / ml which is comparable to the standard drug. Compounds 6a, 6e, 6d, and 6f showed good antiradical activity with IC_{50} 40.02, 42.30, 45.10, and 50.28 µg / ml respectively. Compounds 6c showed moderate activity with IC_{50} 62.38 µg / ml.

3 Benzyl buta-2,3-dienoate

5 Substituted azide

6 Trisubstituted 1,2,3-Traizoles

R= -C_6H_5 (6a), 4-OCH_3-C_6H_4 (6b), 4-NO_2-C_6H_4 (6c), 4-F-C_6H_4 (6d), 4-Cl-C_6H_4 (6e), Benzyl (6f)

Scheme-3: Synthesis of Final Derivatives 6(a-f)

Table-1: Optimization of Reaction Conditions

Entry	Solvent	Tem (^{0}C)	Time (hrs)	Yield (%)
1	H_2O	80	12	17
2	Toluene	Rt	24	No reaction
3	Toluene	80	12	49
4	DMF	Rt	24	No reaction
5	DMF	80	12	69

[a]Reaction conditions- Benzyl buta-2,3-dienoate- 0.6 mmol, Phenyl azide-1.8 mmol
[b]Rt-Room temperature

Table-2: Antioxidant Activity of Compounds 6(a-f)

Sample	IC_{50} in µg/ml
6a	40.02±0.36
6b	36.39±0.58
6c	62.38±0.28
6d	45.10±1.19
6e	42.30±2.36
6f	50.28±0.23
AA	34.34±0.21

[a]IC_{50} values-Mean ± SEM, [b]AA-Ascorbic acid (standard drug)

CONCLUSION

A new series of regioselective trisubstituted 1,2,3-triazoles 6(a-f) constructed by [3+2] cycloaddition reaction allying allenoates (3) and organic azides (5) with good yields (68-76%). Final derivatives were confirmed by spectral data. Further, all the synthesized products were successfully tested for their antiradical activity by DPPH assay. Among the screened compounds, compound 6b displayed the greatest antioxidant activity.

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REFERENCES

1. H.Wiseman and B. Halliwell, *Biochemical Journal*, **313(1)**, 17(1996), https://doi.org/10.1042/bj3130017
2. E.R. Stadtman and B.S. Berlett, *Chemical Research in Toxicology,* **10(5)**, 485(1997), https://doi.org/10.1021/tx960133
3. M. Valko, M. Izakovic, M. Mazur, C.J. Rhodes and J.Telser, *Molecular and Cellular Biochemistry,* **266**, 37(2004), https://doi.org/10.1023/b:mcbi.0000049134.69131.89
4. Ozlem Gursoy-Kol1, Haydar Yuksek, Sevda Manap, S. Feyzi Tokalı, *Journal of the Turkish chemical society section A,* **3(3),** 105(2016), https://doi.org/10.18596/jotcsa.23635

5. P. Gurunanjappa, M.B. Ningappa and A.K. Kariyappa, *Chemical Data Collections*, **5(6)**, 1(2016), https://doi.org/10.1016/j.cdc.2016.09.002
6. B. Hatai and S.K. Banerjee, *Journal of Pharmacognosy and Phytochemistry*, **8(2)**, 1700(2019)
7. A.D. Kumar, S. Naveen, H.K. Vivek, M. Prabhuswamy, N.K. Lokanath and K.A. Kumar, *Chemical Data Collections*, **5(6)**, 36(2016), https://doi.org/10.1590/0001-3765202120201672
8. P. Satapute, R.D. Psanakal, S.I. Mulla and B. Kaliwal, *Environmental Sustainability*, **2**, 429(2019), https://doi.org/10.1007/s42398-019-00083-z
9. G. Biagi, O. Livi, G.L. Ramacciotti, V. Scartoni, I. Bazzichi, M.R. Mazzoni and A. Lucacchini, *Farmaco*, **45(1)**, 49(1990), https://doi.org/10.1002/chin.199037191
10. O.A. Phillips, E.E. Udo, M.E. Abdel-Hamid and R.Varghese, *European Journal of Medicinal Chemistry,* **44(8)**, 3217(2009), https://doi.org/10.1016/j.ejmech.2009.03.024
11. A. Rajasekaran, S. Murugesan and K. Ananda Rajagopal, *Archives of Pharmacal Research*, **29(7)**, 535(2006), https://doi.org/10.1007/bf02969261
12. M.J. Giffin, H. Heaslet, A. Brik, Y.C. Lin, G. Cauvi, C.H. Wong, D.E. McRee, J.H. Elder, C.D. Stout and B.E. Torbett, *Journal of Medicinal Chemistry*, **51(20)**, 6263(2008), https://doi.org/10.1021/jm800149
13. J.L. Yu, Q.P. Wu, Q.S. Zhang, Y.H. Liu, Y.Z. Li and Z.M, *Bioorganic & Medicinal Chemistry Letters*, **20(1)**, 240(2010), https://doi.org/10.1016/j.bmcl.2009.10.127
14. Tae Wookim, Yeojoong Yong, Soon YoungShin, Hyeryoung Jung, Kwan Hapark, Young HanLee, YoonghoLim, Kang Yeounjung, *Bioorganic Chemistry*, **59**, 1(2015), https://doi.org/10.1016/j.bioorg.2015.01.003
15. S.B. Ferreira, M.S. Costa, N. Boechat, R.J.S. Bezerra, M.S. Genestra, M.M. Canto- Cavalheiro, W.B. Kovera and V.F. Ferreira, *European Journal of Medicinal Chemistry*, **42(11)**, 1388(2007), https://doi.org/10.1016/j.ejmech.2007.02.020
16. H. Gallardo, G. Conte, F. Bryk, M.C.S. Lourenço, M.S. Costa and V.F. Ferreira, *Journal of the Brazilian Chemical Society*, **18(6)**, 1285(2007), https://doi.org/10.1590/s0103-50532007000600027
17. I.K. Boddy, G.G. Briggs, R.P. Harrison, T.H. Jones, M. J. O'Mahony, I.D. Marlow, B.G. Roberts, R. J. Willis, R. Bardsley and J. Reid, *Pesticide Science*, **48(2)**, 189(1996), https://doi.org/10.1002/(sici)1096-9063(199610)48:23
18. Ram Janam Singh, *Rasayan journal of chemistry*, **2(3)**, 706(2009)
19. P.S. Desai and D.V. Paresh, *Rasayan Journal of Chemistry*, **14(2)**, 959(2021), http://dx.doi.org/10.31788/RJC.2021.1426274
20. V. Pavani and Jagadeesh Kumar Ega, *Rasayan Journal of Chemistry*, **15(2)**, 757(2022), http://dx.doi.org/10.31788/RJC.2022.1526855
21. Yukino Furukawa, Ryuhei, Suzuki, Tsubasa Nakashima, Rafael Gramage Doria, Kohuske, Ohmatsu and Takashi Ooi, *Bulletin of the Chemical Society of Japan*, **91(8)**, 1252(2018), https://doi.org/10.1246/bcsj.20180098
22. R. Huisgen, *Proceedings of the Chemical Society*, 357(1961), https://doi.org/10.1039/PS9610000357
23. R. Huisgen, *Journal of the German Chemical Society*, **2(10)**, 565(1963), http://dx.doi.org/10.1002/anie.196305651
24. W. Song, N. Zheng, M. Li, K. Dong, J. Li, K. Ullah and Y. Zheng, *Organic Letters*, **20(21),** 6705(2018), https://doi.org/10.1021/acs.orglett.8b02794
25. Ridong Li, Penglin Leng, Bin Liu, Xin Wang, Zemel Ge and Runtao Li, *Tetrahedron*, **72(37),** 5707(2016), https://doi.org/10.1016/j.tet.2016.07.075
26. M.I. Mangione, R.A. Spanevello and M.B. Anzardi, RSC Advances, **7(75)**, 47681(2017), https://doi.org/10.1039/C7RA09558A
27. A. Danne, M.V. Deshpande, J.N. Sangshetti, V.M. Khedkar and B.B. Shihgate, *American Chemical Society Omega*, **6**, 24879(2021), https://doi.org/10.1021/acsomega.c03734

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