

# Cycloaddition reactions of 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione (PTAD) and 4-methyl-3H-1,2,4-triazole-3,5(4H)-dione (MTAD): A short review

Nataliya Korol <sup>\*</sup>, Mikhailo Slivka  and

Oksana Holovko-Kamoshenkova 

*Organic synthesis laboratory, Faculty of Chemistry, Uzhhorod National University, Uzhhorod 88000, Ukraine*

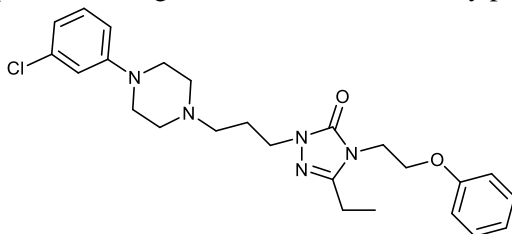
*(Received November 12, 2020; Revised December 09, 2020; Accepted December 11, 2020)*

**Abstract:** The sources, describing cycloaddition reactions with the participation of 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione (PTAD) and 4-methyl-3H-1,2,4-triazole-3,5(4H)-dione (MTAD) were reviewed from the middle 1970s and they are mentioned in chronological order. It was noted that the most investigated are Diels-Alder reactions and cycloaddition to a few cyclic mono- and dienes. Stereochemistry of obtained products are also described.

**Keywords:** Cycloaddition; PTAD; MTAD; Diels-Alder reaction. ©2020 ACG Publication. All right reserved.

## 1. Introduction

Cycloaddition reaction is one of the most effective ways for obtaining new heterocyclic compounds and their modification, which is popular for a long time from the view of both experimental and computational studies<sup>1,2</sup>. 1,2,4-Triazole system due to its chemical structure has not been used widely in cycloaddition processes. The most known representatives from the 1,2,4-triazole series, which react as aza dienophiles, are 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione (PTAD) and 4-methyl-3H-1,2,4-triazole-3,5(4H)-dione (MTAD)<sup>3,4</sup>. A derivative of 1,2,4-triazole-3,5-dione is known as an atypical antidepressant – nefazodone<sup>5</sup> (Figure 1). It is used for treating psychical and emotional illnesses – depression<sup>6</sup>, panic disorder<sup>7</sup>, and posttraumatic stress<sup>8</sup>. At the same time, fused and functionalized 1,2,4-triazole-containing substances possess antibacterial, antifungal, antitubercular, anticancer, anticonvulsant, analgesic, anti-inflammatory, antidepressant, antimalarial and antiviral activities<sup>9-12</sup>. Taking into account, the valuable properties of the above mentioned compounds, development of cycloaddition approaches using PTAD and MTAD is very perspective.

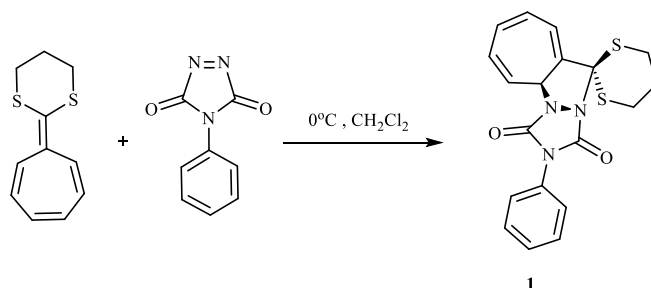


**Figure 1.** Structure of nefazodone

\* Corresponding author: E-Mail: [nataliya.korol@uzhnu.edu.ua](mailto:nataliya.korol@uzhnu.edu.ua), Phone: + 38 0957043456

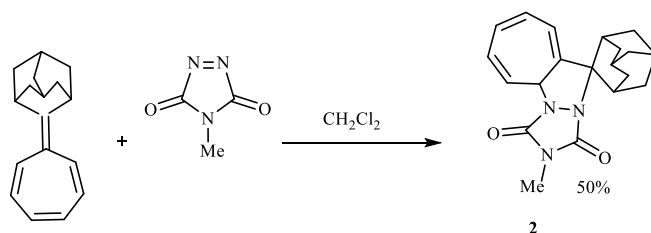
## 2. Literature Review

The earliest reviewed study describing the cycloaddition process of 1,2,4-triazole derivatives is dated back to 1976, authored by German chemists Rapp and Daub<sup>13</sup>, who investigated the reaction between 8,8-(trimethylenedithio)heptafulven and 4-phenyl-1,2,4-triazole-3,5-dione (PTAD). The reaction was performed in methylene chloride as a solvent (Scheme 1) for the formation of product **1**.



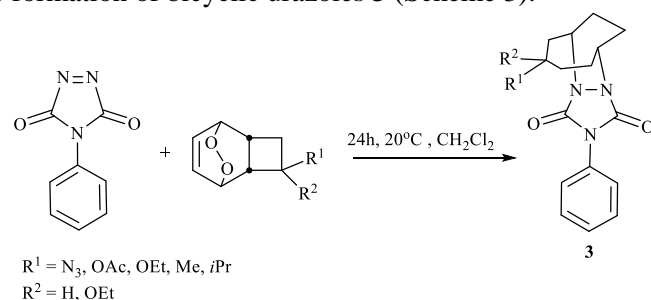
**Scheme 1.** Formation of compound **1**

Adam *et al.* were involved in the investigation of cycloaddition reactions of 4-methyl-4*H*-1,2,4-triazole-3,5-dione (MTAD) and 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (PTAD)<sup>14-16</sup>. Thus, they reported the formation of [8+2]-cycloadduct urazole **2** in 50% yield by interaction of heptafulvene with 4-methyl-4*H*-1,2,4-triazole-3,5-dione (MTAD)<sup>14</sup> (Scheme 2).



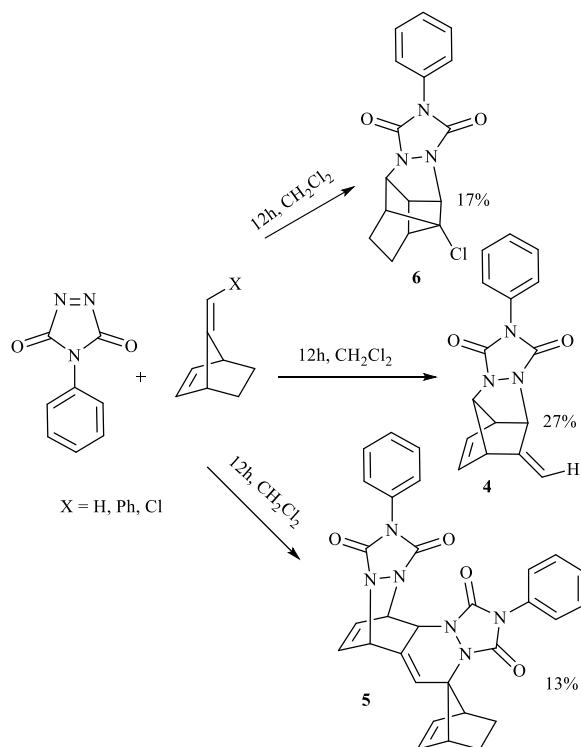
**Scheme 2.** Formation of compound **2**

A year later, the same group investigated the cycloaddition of 7-substituted 1,3,5-cyclooctatrienes with singlet oxygen and 4-phenyl-4*H*-1,2,4-triazole-3,5-dione (PTAD)<sup>16</sup>. PTAD cycloaddition led to the formation of bicyclic urazoles **3** (Scheme 3).



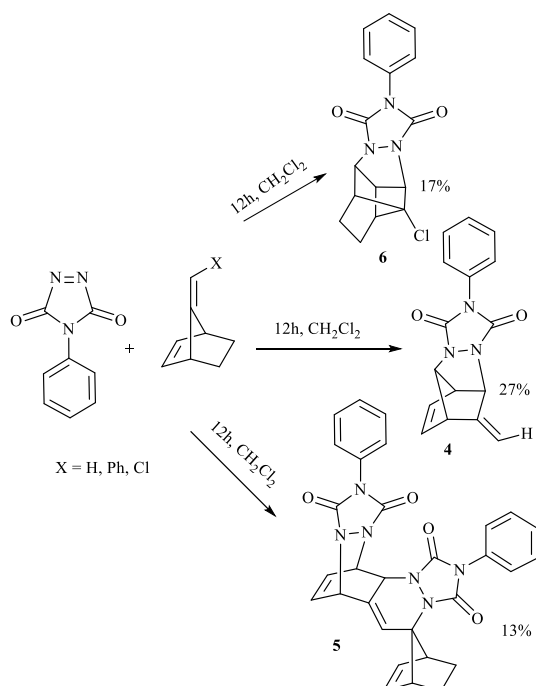
**Scheme 3.** Formation of compound **3**

Cycloaddition reaction of PTAD with 7-methylenenorbornene afforded the rearranged urazole **4**<sup>17</sup>. Moreover, while its reaction with 7-(phenylmethylene)norbornene gave the double [4+2] adduct **5**, cycloaddition of PTAD to 7-(chloromethylene)norbornene resulted in obtaining novel urazole **6** in low yields (Scheme 4).



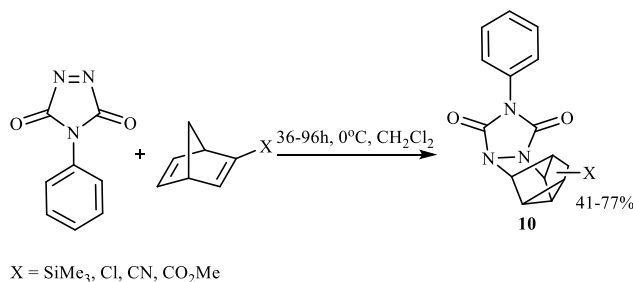
**Scheme 4.** Formation of compounds **4-6**

Johnson and Moody reported interaction of PTAD with a variety of functionalized dienes<sup>18</sup>. It was noted that, the reactions of dienes, containing conjugated electron-releasing or -withdrawing groups, with unsymmetrical azo dienophiles appear to exhibit high regioselectivity. 1-Methoxy-3-trimethylsiloxybuta-1,3-diene reacted rapidly with PTAD at room temperature to give enone **7** (Scheme 5). Cycloaddition of PTAD to bis-*exo*-methylene cyclohexanes also occurred readily at room temperature, resulting in synthesis of adducts **8** in moderate yields (Scheme 5). The reaction of PTAD with 2,3-bis-(iodomethyl)buta-1,3-diene was studied and the adduct **9** was obtained in 60% yield (Scheme 5).



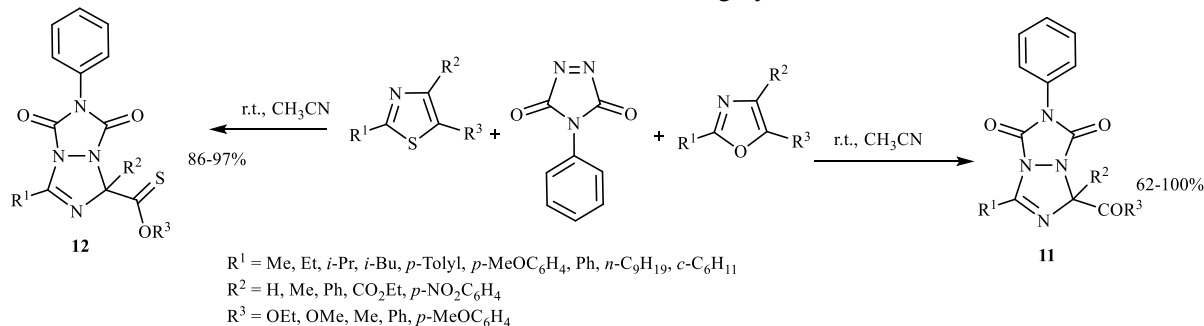
**Scheme 5.** Formation of compounds **7-9**

The reaction of PTAD with 2-trimethylsilyl-, 2-chloro-, 2-cyano-, and 2-methoxycarbonylnorbornadienes was investigated<sup>19</sup>. In all cases, homo Diels-Alder adducts **10** were obtained (Scheme 6).



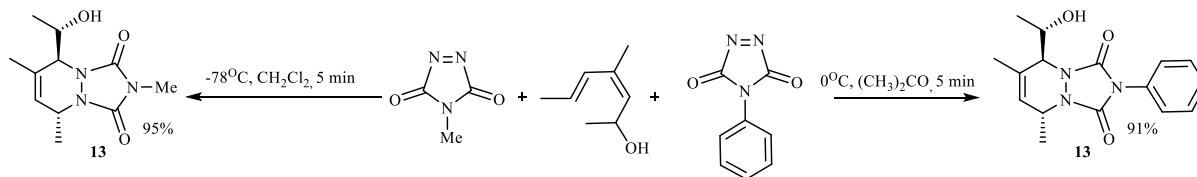
**Scheme 6.** Formation of compounds **10**

Unusual Diels-Alder reaction of PTAD with oxazoles and 5-alkoxythiazoles was described by a Japanese research group<sup>20,21</sup>. 1,2,4-Triazolines derivatives **11** were obtained through interaction of PTAD with oxazole derivatives and formal [3+2] cycloaddition, accompanying ring opening of oxazoles, took place (Scheme 7). The reaction of 5-alkoxythiazoles with equimolar amount of PTAD in an acetonitrile solution at room temperature gave *O*-alkyl-6,7-dihydro-5,7-dioxo-6-phenyl-1*H*,5*H*-[1,2,4]triazolo[1,2-*a*][1,2,4]triazole-1-carbothionates **12** in high yields.



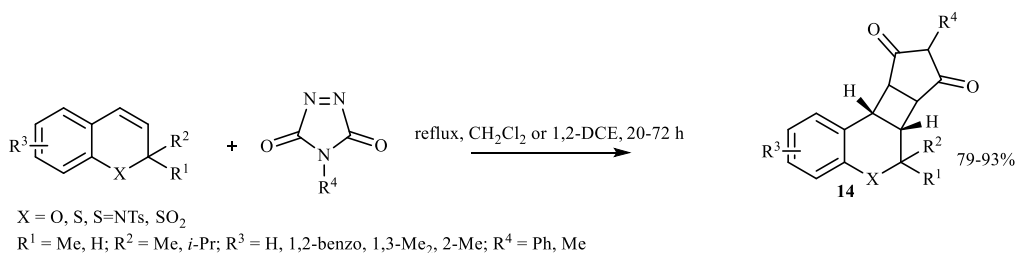
**Scheme 7.** Formation of compounds **11** and **12**

The reactions of chiral open-chain dienol, possessing 1,3-allylic strain due to the presence of a *cis* substituent, with PTAD and MTAD gave the corresponding [4+2] cycloadducts **13** in very good yields and with high *like* selectivity (Scheme 8)<sup>22</sup>.

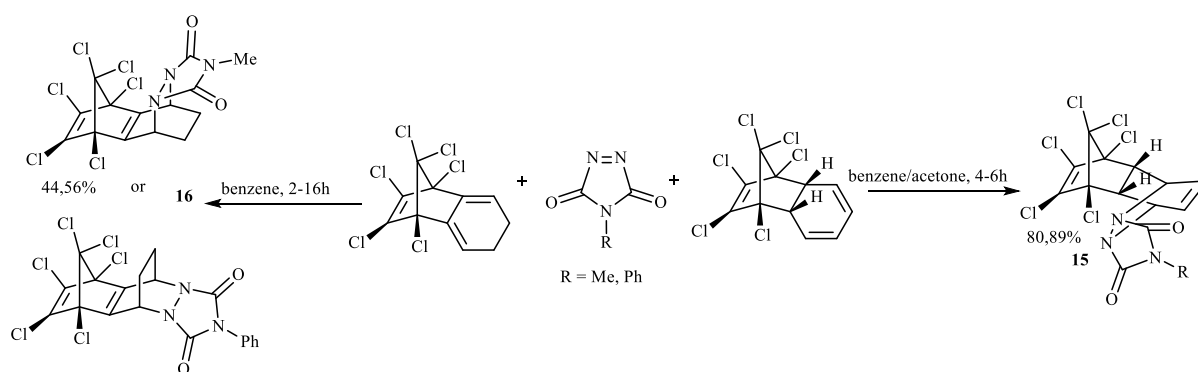


**Scheme 8.** Formation of compounds **13**

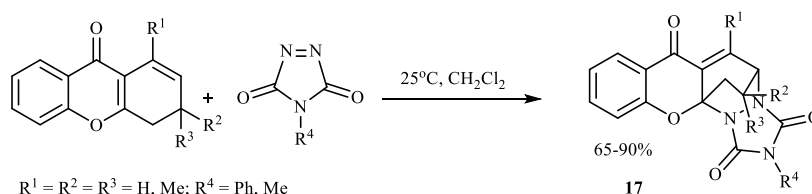
Gabbutt et al. reported that simple 2*H*-chromenes and 2*H*-thiochromenes formed the [2+2]-adducts, tetrahydro[1]benzo(tio)pyrano[3,4-*c*][1,2]diazeto[1,2-*a*][1,2,4]triazoles **14**, with triazolinediones (Scheme 9)<sup>23</sup>.

**Scheme 9.** Formation of compounds **14**

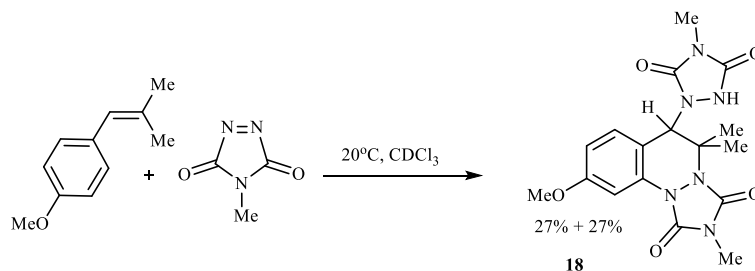
Diels-Alder reactions of hexachlorodienes with MTAD and PTAD were performed, and the structures of the resulting cycloadducts were established<sup>24</sup>. There are two methods available in the literature; Diels-Alder cycloadditions of MTAD, PTAD leading to the formation of **15** and (ii) the corresponding reactions with MTAD and PTAD to afford a mixture of two isomeric [4+2] cycloadducts **16** (Scheme 10). A theoretical study of these reactions was also performed<sup>25</sup>.

**Scheme 10.** Formation of compounds **15,16**

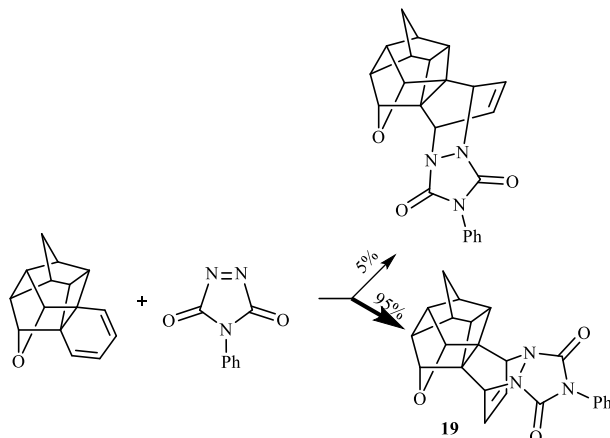
The reaction of PTAD and MTAD with dihydroxanthenes in dichloromethane at room temperature resulted in the production of adducts **17** in good yields (Scheme 11)<sup>26</sup>.

**Scheme 11.** Formation of compounds **17**

It was reported that the reaction of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) with  $\beta,\beta$ -dimethyl-*p*-methoxystyrene in chloroform afforded two stereoisomeric [4+2]/ene diadducts **18** (Scheme 12)<sup>27</sup>.

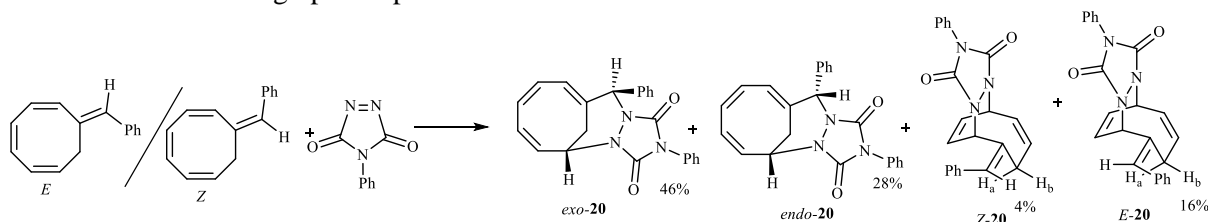
**Scheme 12.** Formation of compounds **18**

When hexacyclic ether was allowed to react with PTAD, a strong preference (95%) for addition from the face of the diene *syn* to the cyclobutane group with the formation of product **19** was observed (Scheme 13). In addition, these results were proved by calculations of the transition states to be performed at the integrated molecular - orbital molecular orbital (IMOMO) level of theory, employing a G2MS computational procedure and second-order Møller-Plesset (MP2) perturbation theory<sup>28</sup>.



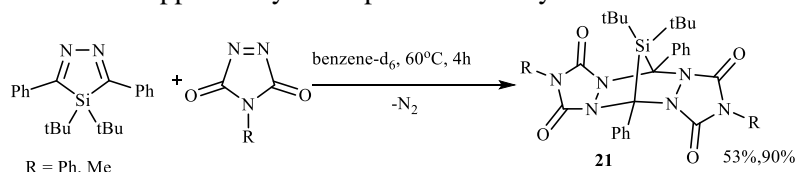
**Scheme 13.** Formation of compound **19**

It was shown that a mixture of (E)/(Z)- 7-benzylidenecycloocta-1,3,5-triene (91:9) in AcOEt reacted readily with PTAD at room temperature to give a mixture of four mono-adducts: *exo*-**20**, *endo*-**20**, (Z)-**20**, and (E)-**20** (Scheme 14). The first two and the last compounds were obtained in crystalline forms after a chromatographic separation<sup>29</sup>.



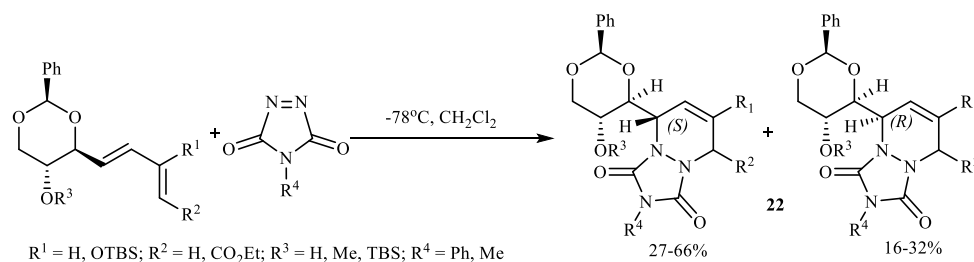
**Scheme 14.** Formation of compounds **20**

A freshly prepared diazasilole (1 equiv) was mixed with PTAD and MTAD (3 equiv) in benzene-*d*<sub>6</sub> and sealed. The polycyclic compounds **21** were isolated in 53% and 90% yields (Scheme 15)<sup>30</sup>. The reaction was also supported by a computational study.



**Scheme 15.** Formation of compounds **21**

PTAD and MTAD were reacted with the four dienes in dichloromethane at -78 °C. When the alcohol function was unprotected, the products **22** consisted of mixtures of diastereomers. In case of protected alcohol function products **22** were identified as diastereomerically pure compounds (Scheme 16)<sup>31</sup>.



**Scheme 16.** Formation of compounds **22**

### 3. Conclusion

The survey of the literature data concerning cycloaddition reaction of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD) and 4-methyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (MTAD), indicated their participation in Diels-Alder reactions, [3+2] and [4+2] cycloadditions. All the cycloaddition products possessed interesting stereoselectivity and stereocontrol.

#### ORCID

Nataliya Korol: [0000-0001-7155-1676](https://orcid.org/0000-0001-7155-1676)

Mikhailo Slivka: [0000-0003-4788-0511](https://orcid.org/0000-0003-4788-0511)

Oksana Holovko-Kamoshenkova: [0000-0002-3238-3451](https://orcid.org/0000-0002-3238-3451)

### References

- [1] Wang, Y.; Wei, D.; Zang, W. Recent advances on computational investigations of *N*-heterocyclic carbene catalyzed cycloaddition/annulation reactions: mechanism and origin of selectivities. *ChemCatChem* 2017, DOI: 10.1002/cctc.201701119.
- [2] Remy, R.; Bochet, C.G. Arene-alkene cycloaddition. *Chem. Rev.* 2016, *116*, 9816–9849.
- [3] Korobitsyna, I.K.; Khalikova, A.V.; Rodina, L.L.; Shusherina, N.P. 4-Phenyl-1,2,4-triazoline-3,5-dione in organic synthesis (review). *Chem. Heterocycl. Compd.* **1983**, *19*, 117-136.
- [4] De Bruycker, K.; Billiet, S.; Houck, H.A.; Chattopadhyay, S.; Winne, J.M.; Du Prez, F.E. Triazolinediones as highly enabling synthetic tools. *Chem. Rev.* **2016**, *116*, 3919–3974.
- [5] Davis, R.; Whittington, R.; Bryson, H.M. Nefazodone. A review of its pharmacology and clinical efficacy in the management of major depression. *Drugs* **1997**, *53*, 608-636.
- [6] Keller, M.B.; McCullough, J.P.; Klein, D.N.; Arnow, B.; Dunner, D.L.; Gelenberg, A.J.; Markowitz, J.C.; Nemeroff, C.B.; Russell, J.M.; Thase, M.E.; Trivedi, M.H.; Blalock, J.A.; Borian, F.E.; Jody, D.N.; DeBattista, C.; Koran, L.M.; Schatzberg, A.F.; Fawcett, J.; Hirschfeld, R.M.A.; Keitner, G.; Miller, I.; Kocsis, J.H.; Kornstein, S.G.; Manber, R.; Ninan, P.T.; Rothbaum, B.; Rush, J.; Vivian, D.; Zajecka, J. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N. Engl. J. Med.* **2000**, *342*, 1462-1470.
- [7] Zulfarina, M.S.; Syarifah-Noratiqah, S.B.; Nazrun, S.A.; Sharif, R.; Naina-Mohamed, I. Pharmacological therapy in panic disorder: current guidelines and novel drugs discovery for treatment-resistant patient. *Clin. Psychopharmacol. Neurosci.* **2019**, *17*, 145-154.
- [8] Ehret, M. Treatment of posttraumatic stress disorder: Focus on pharmacotherapy. *Met.l Health Clin.* **2019**, *9*, 373–382.
- [9] Gao, F.; Wang, T.; Xiao, J.; Huang, G. Antibacterial activity study of 1,2,4-triazole derivatives. *Eur. J. Med. Chem.* **2019**, *173*, 274-281.
- [10] Malani, A.H.; Makwana, A.H.; Makwana, H. A brief review article: Various synthesis and therapeutic importance of 1, 2, 4-triazole and its derivatives. *Mor. J. Chem.* **2017**, *5*, 41-59.
- [11] Christophe, T. 1,2,4-Triazole: A privileged scaffold for the development of potent antifungal agents - a brief review. *Curr. Top. Med. Chem.* **2020**, *20*, 2235-2258.

- [12] Slivka, M.V.; Korol, N.I.; Fizer, M.M. Fused bicyclic 1,2,4-triazoles with one extra sulfur atom: Synthesis, properties, and biological activity. *J. Heterocycl. Chem.* **2020**, *57*, 3236-3254.
- [13] Rapp, K.M.; Daub, J. Elektronenpeiche heptafulvene: trimethylen-8.8-dithiaheptafulven. *Tetrahedron Lett.* **1976**, *24*, 2011-2014.
- [14] Adam, W.; Peters, E.M.; Peters, K.; Rebollo, H.; Rosenthal, R.J.; Schnering, H.G.D. Cycloaddition of singlet oxygen and 4-methyl-4h-1,2,4-triazole-3,5-dione to 7-adarnantylidene-1,3,5-cycloheptatriene and derivatives. *Chem. Ber.* **1984**, *117*, 2393-2408.
- [15] Adam, W.; Carballeira, N. On the mechanism of the cycloaddition of 1,2,4-triazoline-3,5-diones with bicycloalkenes leading to rearranged urazoles. *J. Am. Chem. Soc.* **1984**, *106*, 2874-2882.
- [16] Adam, W.; Gretzke, N.; Hasemann, L.; Klug, G.; Peters, E.M.; Peters, K.; Rebollo, H.; Schnering, H.G.D.; Will, B. Cycloaddition of singlet oxygen and 4-phenyl-4H-1,2,4-triazole-3,5-dione to 7-substituted 1,3,5-cyclooctatrienes. *Chem. Ber.* **1985**, *118*, 3357-3379.
- [17] Adam, W.; Lucchini, V.; Pasquato, L.; Peters, E.M.; Peters, K.; Schnering, H.G.D.; Seguchi, K. Unusual rearrangement products in the cycloaddition of 4-phenyl-4H-1,2,4-triazole-3,5-dione (PTAD) to substituted 7-methylenenorbornenes. *Chem. Ber.* **1986**, *119*, 2932-2941.
- [18] Johnson, M.P.; Moody, C.J.; Azo dienophiles. Diels-Alder reactions of 4-phenyl-1,2,4-triazole-3,5-dione and 5-phenylpyrazol-3-one with functionalised dienes. *J. Chem. Soc. Perkin Trans.* **1985**, *1*, 71-74.
- [19] Adam, W.; Lucchi, O.; Pasquato, L.; Will, B. Cycloaddition behavior of 2-substituted norbornadienes towards 4-phenyl-4H-1,2,4-triazole-3,5-dione (PTAD): homo Diels-Alder reactivity versus insertion, rearrangement, and [2 + 2] cycloaddition. *Chem. Ber.* **1987**, *120*, 531-535.
- [20] Iyata, T.; Suga, H.; Isogami, Y.; Tamura, H.; Shi, X. Abnormal Diels-Alder reaction of oxazoles with 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione and diethyl azodicarboxylate, and X-ray crystal structure of an adduct. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2998-3007.
- [21] Shi, X.; Iyata, T.; Suga, H.; Matsumoto, K. Abnormal Diels-Alder reaction of 5-alkoxythiazoles with highly reactive dienophiles; 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione, diethyl azodicarboxylate, and diethyl oxomalonate. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3315-3321.
- [22] Adam, W.; Glaser, J.; Peters, K.; Prein, M. Highly like-selective [4+2] cycloadditions of chiral dienols: the importance of 1,3-allylic strain in the hydroxy-directed stereocontrol. *J. Am. Chem. Soc.* **1995**, *117*, 9190-9193.
- [23] Gabbutt, C.D.; Hepworth, J.D.; Heron, B.M. Reactions of some 2H-chromenes and 2H-thiochromenes with triazolinediones. *Tetrahedron* **1995**, *51*, 13277-13290.
- [24] Marchand, A.P.; Dong, E.Z.; Shukla, R.; Prasad, A.D.; Bott, S.G. Stereoselectivities of Diels-Alder cycloadditions of tricyclic dienes to MTAD, PTAD, and N-methylmaleimide. *Tetrahedron* **1997**, *53*, 14895-14902.
- [25] Marchand, A.P.; Ganguly, B.; Shukla, R. Stereoselectivities of Diels-Alder cycloadditions of  $\pi$ -facially nonequivalent dienes to MTAD, PTAD, and N-methylmaleimide: A theoretical study. *Tetrahedron* **1998**, *54*, 4477-4484.
- [26] Gabbutt, C.D.; Hepworth, J.D.; Urquhart, M.W.J.; Miguel, L.M.V. Acid catalysed rearrangements of 1-hydroxy-2,3,4,4a-tetrahydro-9H-xanthen-9-ones: synthesis and cycloaddition reactions of 3,4-dihydro-9H-xanthen-9-ones. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 1547-1553.
- [27] Stratakis, M.; Hatzimarinaki, M.; Froudakis, G.E. Orfanopoulos, M. Stereochemistry in the reaction of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) with  $\beta,\beta$ -dimethyl-*p*-methoxystyrene. Are open biradicals the reaction intermediates? *J. Org. Chem.* **2001**, *66*, 3682-3687.
- [28] Marchand, A.P.; Coxon, J.M. On the origins of diastereofacial selectivity of [4+2] cycloadditions in cageannulated and polycarbocyclic diene/dienophile systems. *Acc. Chem. Res.* **2002**, *35*, 271-277.
- [29] Clements, P.; Gream, G.E.; Kirkbride, P.K.; Pyke, S.M. Cycloaddition reactions of 7-benzylidenecycloocta-1,3,5-triene with ethenetetracarbonitrile and 4-phenyl-3h-1,2,4-triazole-3,5(4h)-dione. *Helv. Chim. Acta* **2005**, *88*, 2003-2021.



- [30] Nakamura, T.; Takegami, A.; Abe, M. Generation and intermolecular trapping of 1,2-diaza-4-silacyclopentane-3,5-diyls in the denitrogenation of 2,3,5,6-tetraaza-7-silabicyclo[2.2.1]hept-2-ene: An experimental and computational study. *J. Org. Chem.* **2010**, *75*, 1956–1960.
- [31] Alves, M.J.; Duarte, V.C.M.; Faustino, H.; Fortes, A.G. Diastereo-controlled Diels–Alder cycloadditions of erythrose benzylidene-acetal 1,3-butadienes by 4-substituted-1,2,4-triazoline-3,5-dione: Evidence for the stereoelectronic effects on the dienes. *Tetrahedron: Asymm.* **2010**, *21*, 1817–1820.

**A C G**  
**publications**

© 2020 ACG Publications