Regioselective formation of 1,2,4-triazoles by the reaction of amidrazones in the presence of diethyl azodicarboxylate and catalyzed by triethylamine

Aly, Ashraf A.

2019-02

Aly , A A , Hassan , A A , Mohamed , N K , Ramadan , M , Brown , A B , Abd El-Aal , A S , Bräse , S & Nieger , M 2019 , ' Regioselective formation of 1,2,4-triazoles by the reaction of amidrazones in the presence of diethyl azodicarboxylate and catalyzed by triethylamine ' , Molecular Diversity , vol. 23 , no. 1 , pp. 195-203 . https://doi.org/10.1007/s11030-018-9868-6

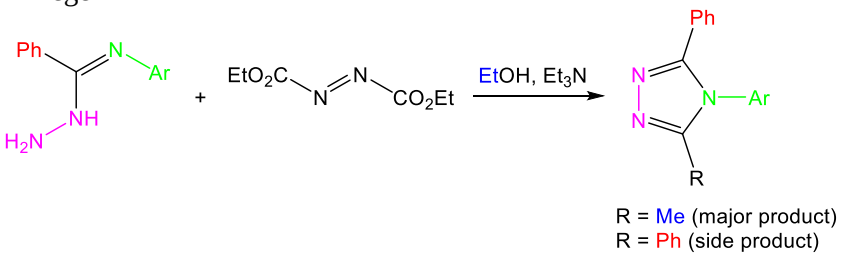
http://hdl.handle.net/10138/310814
https://doi.org/10.1007/s11030-018-9868-6

unspecified
acceptedVersion

Graphical Abstract

Regioselective formation of 1,2,4-triazoles by reaction of amidrazones in the presence of diethyl azodicarboxylate

Ashraf A. Aly, Alaa A. Hassan, Nasr K. Mohamed, Mohamed Ramadan, Alan B. Brown, Amal S. Abd El-Aal, Stefan Bräse, and Martin Nieger



Regioselective formation of 1,2,4-triazoles by reaction of amidrazones in the presence of azodicarboxylates

Ashraf A Aly,[*a] Alaa A. Hassan,[a] Nasr K. Mohamed,[a] Mohamed Ramadan,[b] Alan B. Brown,[c] Amal S. Abd El-Aal,[a] Stefan Bräse,[d] and Martin Nieger[e]

[a] *Chemistry Department, Faculty of Science, Minia University, 61519-El-Minia, Egypt*
[b] *Organic Pharmacy Department, Faculty of Pharmacy, Al-Azhar Branch of Assiut University, Egypt*
[c] *Chemistry Department, Florida Institute of Technology, Melbourne, FL 32901, USA*
[d] *Institute of Organic Chemistry, Karlsruhe Institute of Technology,76131Karlsruhe, Germany.*
[e] *Department of Chemistry, University of Helsinki, PO Box 55 (A. I. Virtasen aukio 1), 00014University of Helsinki, Finland.*

Corresponding Author: ashrafaly63@yahoo.com *and* *ashraf.shehata@mu.edu.eg*

Abstrat. A general method for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles has been developed from reaction of amidrazones with ethyl azodicarboxylate and Et_3N (Mitsunobu reagent) in EtOH. This highly regioselective one-pot process provides rapid access to highly diverse triazoles. The reaction was explained, based on Mitsunobu reagent oxidizing ethanol to acetaldehyde, which would then react with amidrazones to give the substituted 3-methyltriazoles. A [2+3] cycloaddition reaction between two oxidized forms of amidrazones produced the second type of triazoles. X-ray structure analyses proved the structure of each type of product.

Keywords: Amidrazones, Mitsunobu reagent, Regioselective, 1,2,4-Triazoles

1. Introduction

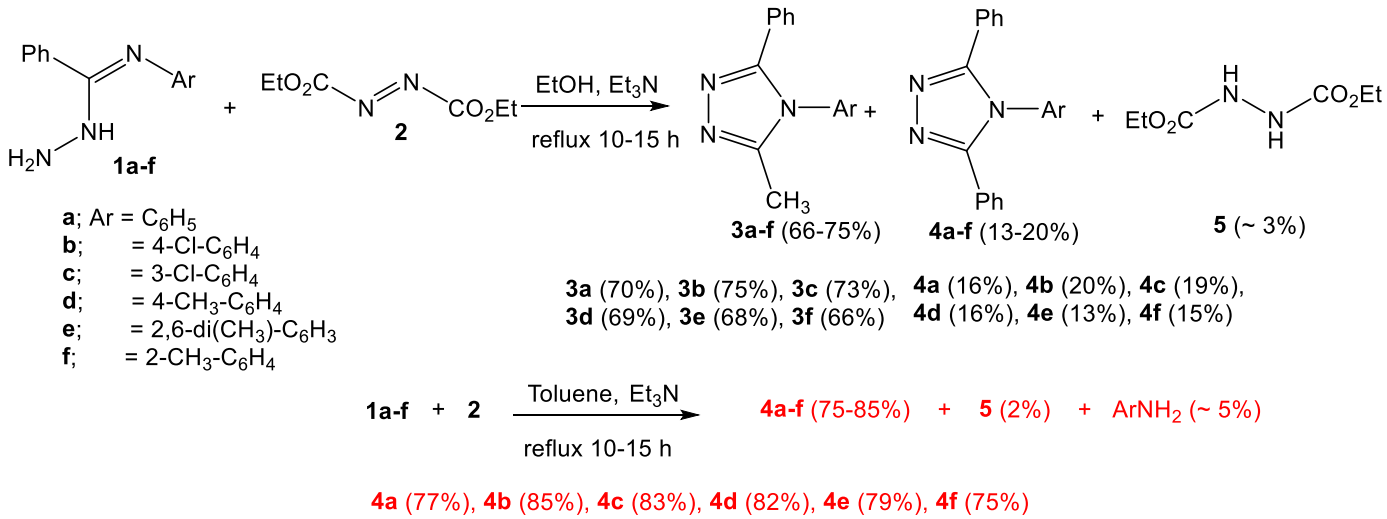
Triazoles can easily bind with a variety of enzymes and receptors in biological systems *via* diverse non-covalent interactions [1]. Therefore, triazoles display widespread biological activities. Hence, many triazole derivatives serve as medicinal drugs [2]. Triazoles also have antifungal activities [3]. More specifically, compounds having the 1,2,4-triazole moiety have shown various biological activities, such as antimicrobial [4], antitubercular [5], anticancer [6], anticonvulsant [7], hypoglycemic [8], anti-inflammatory and analgesic activities [9]. The Mitsunobu reaction is the dehydrative coupling of a primary or secondary alcohol (occasionally, tertiary alcohols have been used) to a pronucleophile (NuH), which is mediated by the reaction between a dialkyl azodicarboxylate and a trialkyl- or triarylphosphine [10,11]. Aly *et al.* reported on the syntheses of various heterocycles such as pyrazoles [12a-c], 1,2,4-triazoles [12d-f], tetrazoles [12g], 2,5,6-

triphenylpyrimidin-4(3*H*)-ones [12h], triazines [12i], indazoles and naphthotriazines [12j], naphtho[2,3-*f*]-1,2,4-triazepines [12k], and cyclopenta[*e*][1,3,4]-oxadiazepines [12l], from the reaction of amidrazones with π-deficient compounds. In this paper, we undertook to investigate the mechanism of the effect of Mitsunobu reagent on amidrazones **1a–f**, hoping to obtain heterocyclic compounds that might have biological and/or pharmaceutical applications.

2. Results and Discussion

Refluxing equimolar amounts of N^1-arylamidrazones **1a-f** with diethyl azodicarboxylate (**2**) in dry EtOH, catalyzed by a few drops of triethylamine, led to the formation of 4-aryl-5-methyl-3-phenyl-1,2,4-triazoles **3a-f** in 68-75% yields and 4-aryl-3,5-diphenyl-1,2,4-triazoles **4a-f** in 13-20% yields, together with traces of diethyl hydrazine-1,2-dicarboxylate (**5**) (Scheme 1). The products were separated by preparative TLC; compounds **4** tended to co-elute with additional **5**, which was removed by recrystallization. To confirm the structures of all the obtained products, elemental analyses, IR, NMR (^{1}H, ^{13}C, 2D NMR, ^{15}N) and mass spectra were performed; these and elemental analyses were in good agreement with the assigned structures. We chose different substituted amidrazones **1a–f** having aryl groups with electron donating and withdrawing substituents on the benzene ring, in order to examine their reactivity. Elemental analyses and mass spectra of compounds **3a-f** clearly their formulae to correspond to amidrazones **1a-f** plus one C(CH_3) group. The triazole skeleton in compounds **3a-f** showed absorption bands in the IR spectra at ν = 1640—1610 and 1540—1520 cm^{-1} from C=N and C=C groups, respectively (see the experimental section). To illustrate the NMR assignments of **3a-f** (for numbering, see Figure 1): in the ^{1}H spectra of **3c** (Table 1), the 3H singlet must be H-3a, while its attached carbon appears at δ_C 10.8. H-3a gives HMBC correlation with a carbon at δ_C 152.1, assigned as C-3, and with both visible nitrogen signals; the sp^2 nitrogen (δ_N 310.1) is assigned as N-2, and the nitrogen farther upfield (δ_N 177.5) is assigned as N-4. N-4 also gives HMBC correlation with the downfield aromatic protons. Of these, the broad singlet at δ_H 7.68 is assigned as H-2', and the "triplet" at δ_H 7.56 is assigned as H-5'; the attached carbons appear at δ_C 127.6 (C-2') and 131.4 (C-5'). The broad doublet at δ_H 7.63 is assigned as H-4', because it lacks HMBC correlation with N-1, and the signal at δ_H 7.42-7.34 gives such correlation; therefore H-6' is assigned as being in that signal. H-4' gives HSQC correlation with its attached carbon at δ_C 129.7; H-4', H-5', and H-6' give HMBC correlation with

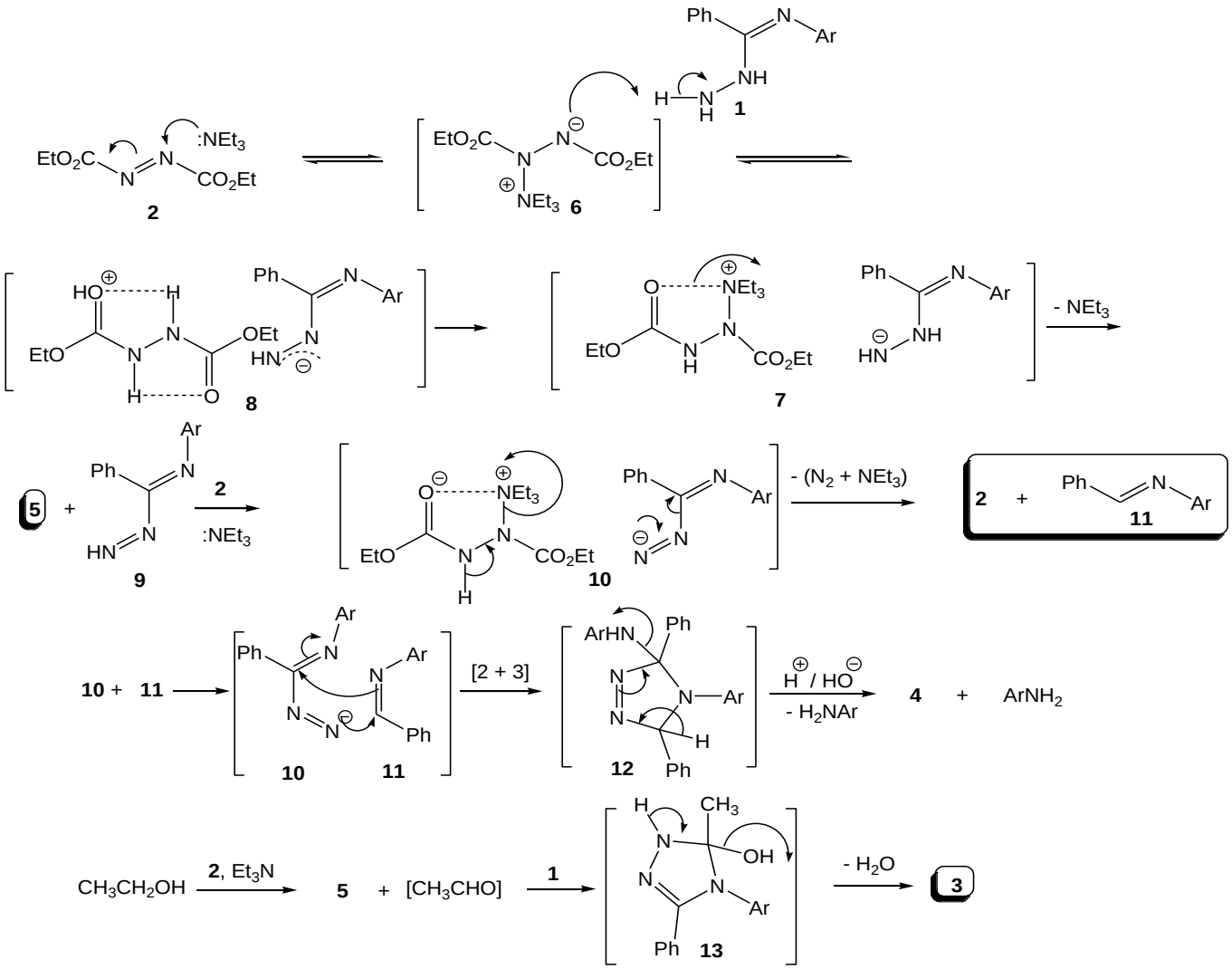
the carbons at δ_C 136.0 and 133.9, assigned on chemical-shift grounds as C-3' and C-1' in that order. The protons at δ_H 7.42-7.34 give HSQC correlation with short ^{13}C lines at δ_C 129.5 and 126.6, assigned as C-*p* and C-6', and with tall lines at δ_C 128.5 and 128.0, assigned as C-*o* and C-*m*. The remaining non-protonated carbons at δ_C 152.9 and 127.0 are assigned, on chemical-shift grounds, as C-5 and C-*i* respectively. The remaining nitrogen, N-1, is four bonds from the nearest protons and is not observed. Most indicative in **3e** was the appearance of two methyl carbon signals in the ^{13}C NMR at δ = 10.1 for CH_3-C-5 and at δ = 17.1 for the 2,6-dimethyl carbon signals. The structure of **3f** was confirmed by X-ray structure analysis (Figure 2).



Scheme 1. Reaction of the Mitsunobu reagent **2** on amidrazones **1a-f**

The reaction presumably begins like the Mitsunobu reaction, in which the Lewis base first attacks the N=N bond of **2** to form zwitterion **6**. Abstraction of a proton from amidrazone **1** would lead to the formation of salt **7**, which would lose a molecule of Et_3N to form the stable salt **8**. We suggest that salt **8** would be stabilized due to the formation of five-member rings as shown in Scheme 2. The salt **8** would then dissociate into the isolated compound **5** and hydrazine-enamine **9** (Scheme 2). Repeating the former process in presence of a molecule of Et_3N, the reaction would form salt **10**. Elimination of triethylamine and a nitrogen molecule from **10** would give the expected imine compound **11** and reproduce the starting material **2** (Scheme 2). Since, it is well known that azomethine imines undergo 1,3-dipolar cycloaddition reactions with various alkenes [13], mechanistically, compound **4** would be formed *via* [2+3] cycloaddition reaction between **10** and **11** to give intermediate **12** (Scheme 2). Elimination of substituted anilines from **12**

would give **4** (Scheme 2). Oxidation of ethanol by **2** was previously known to give acetaldehyde [14] together with compound **5** (Scheme 2). Thus, the reaction between compound **1** and acetaldehyde would occur *in situ* to give **3** *via* intermediate **13**, accompanied by elimination of water. The mechanism is supported by isolation of **5**, indicating oxidation by **2** (Scheme 2).



Scheme 2. Mechanism describing the formation of triazoles **3a-f** and **4a-f**

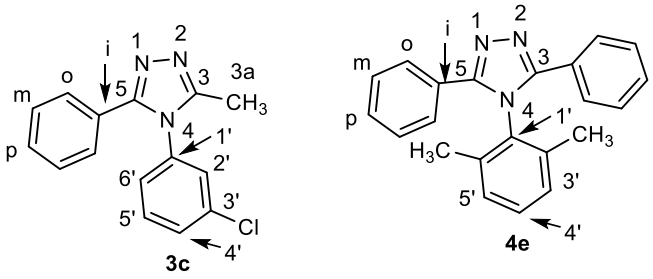


Figure 1. Structures and numbering of compounds **3c** and **4e**

The reaction was supported on the basis that Mitsunobu reaction is a versatile and widely used method for the dehydrative coupling of an alcohol with an acid/pronucleophile by using a combination of an oxidizing azo reagent, most commonly diethyl azodicarboxylate (DEAD), and a Lewis base such as

triphenylphosphine (TPP), under mild and virtually neutral reaction conditions [15]. Moreover, this reaction yielded besides the desired coupled product, a hydrazide such as diethyl hydrazinedicarboxylate (DEAD-H_2) from DEAD as by-products [15].

Table 1. NMR signals, correlations, and assignments of compound **3c.** *a:* Bold-faced chemical shifts indicate lines taller than others. *b:* Italicized correlations are weak.

^{1}H NMR:		**^{1}H-^{1}H COSY:**	**Assignment:**
7.68 (bs; 1H)		7.63, 7.56, 7.42	H-2’
7.63 (bd, *J* = 8.3;		7.68, 7.56	H-4’
7.56 (“t”, *J* = 7.9;		7.68, 7.63, 7.42	H-5’
7.42-7.34 (m; 6H		7.68, 7.56	H-6’, *o, m, p*
2.26 (s; 3H)			H-3a
^{13}C NMR:[a]	**HSC**	**HMBC:**	**Assignment:**
152.9		7.42-7.34	C-5
152.1		2.26	C-3
136.0		7.63, 7.56, 7.42	C-3’
133.9		7.63, 7.56, 7.42	C-1’
131.4	7.56		C-5’
129.7	7.63	7.68, 7.56, 7.42	C-4’
129.5	7.42	7.42-7.34	C-*p*/6’
128.5, 128.0	7.42	7.42-7.34	C-*o, m*
127.6	7.68	7.42-7.34	C-2’
127.0		7.42-7.34	C-*i*
126.6	7.42	7.42-7.34	C-6’/*p*
10.8	2.26		C-3a
^{15}N NMR:	**HSC**	**HMBC: [b]**	**Assignment:**
310.1		2.26	N-2
177.5		7.68, *7.56, 7.42*	N-4

Table 2. NMR signals, correlations, and assignments of compound **4e.** *a:* Bold-faced chemical shifts indicate lines taller than others.

^{1}H NMR:		**^{1}H-^{1}H COSY:**	**Assignment:**
7.43 (m; 3H)		7.36, 7.28	H-4’, *p*
7.36 (m; 8H)		7.43, 7.28	H-*o, m*
7.28 (d, *J* = 7.6; 2H)		7.43, 7.36, 1.85	H-3’
1.85 (s; 6H)		7.28	H-2a’
^{13}C NMR:[a]	**HSQC:**	**HMBC:**	**Assignment:**
153.1		7.36	C-3
135.2		7.43, 1.85	C-2’
133.0		7.28, 1.85	C-1’
130.3	7.43	7.36	C-*p*
130.0	7.43	7.28, 1.85	C-4’
129.3	7.28	7.28, 1.85	C-3’
128.8	7.36	7.36	C-*m*
126.9	7.36	7.43, 7.36	C-*o*
126.8		7.43, 7.36	C-*i*
17.3	1.85	7.28	C-a

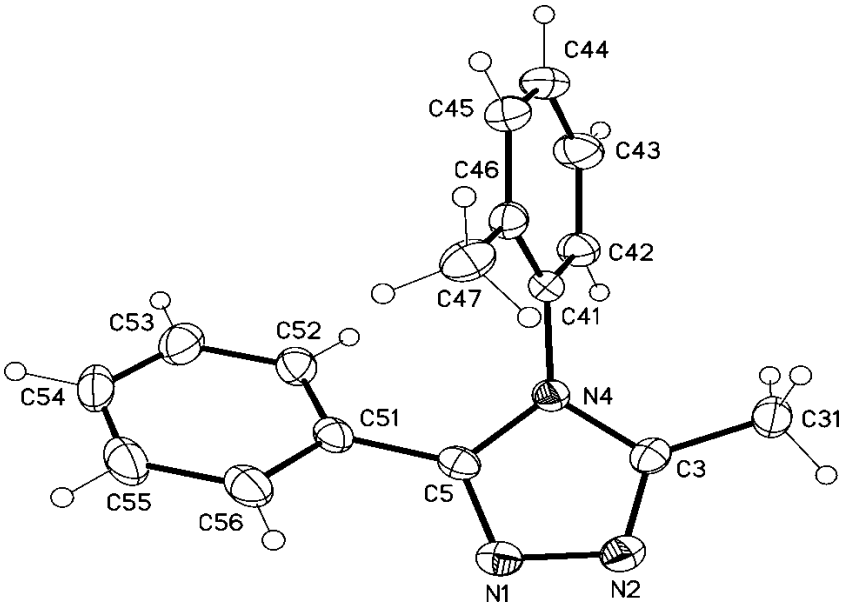


Figure 2. Molecular structure of **3f** (displacement parameters are drawn at 50 % probability level).

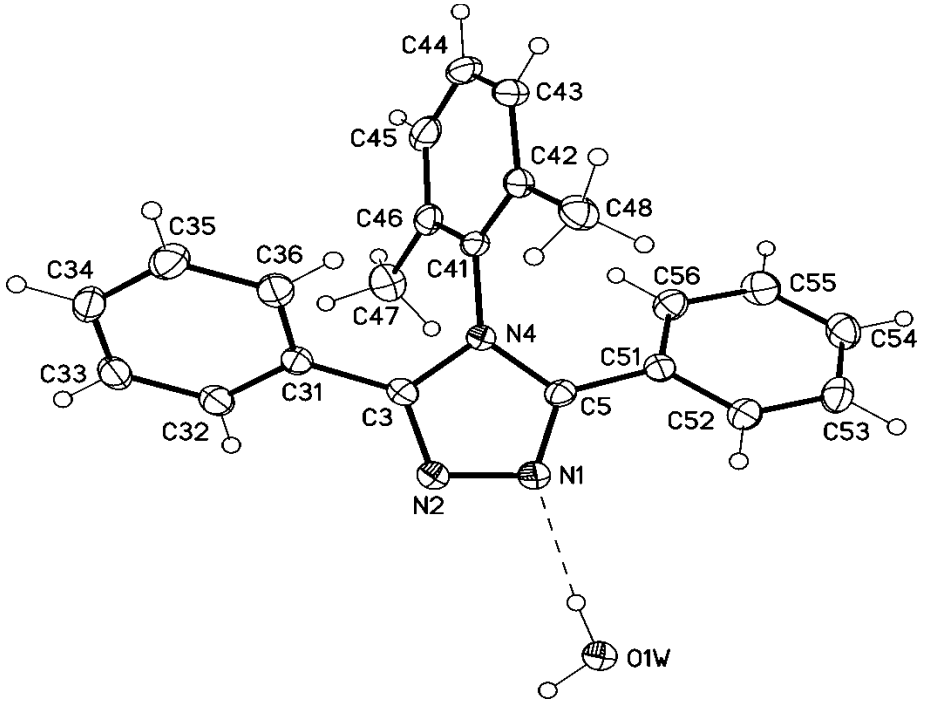


Figure 3. Molecular structure of **4e** (displacement parameters are drawn at 50 % probability level).

Dehydrogenations by diethyl azodicarboxylate have been described. To explore the course of the reaction in the absence of ethanol, we carried out reactions between **1a-f** with **2** in toluene and we successfully obtained compounds **4a-f** in 75-85% yields, together with **5** (2%) and arylamines (5%) (Scheme 1). The structures of compounds **4a-f** were established on the basis of mass, IR, ^{1}H NMR and ^{13}C NMR spectra as well as elemental analyses. Compounds **4a** – **f** show IR absorptions for the C=N and C=C groups at ν =

1632 – 1620 and 1550-1530 cm^{-1}; the NMR spectra of **4a-f** are illustrated by **4e** (Table 2). The most distinctive proton signal of **4e** is the methyl singlet at δ_H 1.85, assigned as H-2a'; its attached carbon appears at δ_C 17.3. H-2a' gives HMBC correlation with two non-protonated carbons at δ_C 135.2 and 133.0. The upfield of these also gives HMBC correlation with the 2H doublet at δ_H 7.28; since the doublet is assigned as H-3', the carbon at δ_C 133.0 is assigned as C-1'. Therefore, the carbon at δ_C 135.2 must be C-2'; it gives HMBC correlation with the 3H signal at δ_H 7.43, which thus must contain H-4'. On chemical-shift grounds, the carbon at δ_C 153.1 is assigned as C-3; it gives HMBC correlation with the 8H signal at δ_H 7.36, which thus must contain H-*o*. The two tall ^{13}C lines at δ_C 128.8 and 127.0 give HSQC correlation with the signal at δ_H 7.36 and are assigned as C-*m* and C-*o* in that order, partly on differences in correlation (which are not definitive) but partly also on chemical-shift grounds. The proton signal at δ_H 7.43 is not a clean triplet and requires two more H, so it must also contain H-*p*. The structure of **4e** (Figure 1) was ultimately confirmed by X-ray structure analysis as shown in Figure 3.

Factors affect the reactivity of Mitsunobu reaction

2.1.1. Type of alcohols

Cao and Grée reported that the combination of diethyl azodicarboxylate (DEAD) and a catalytic amount of $ZnBr_2$ is an efficient system for the dehydrogenation of 1°, 2° and 3°-alcohols to the corresponding carbonyl compounds [16].

2.1.2. Electronic effect of substitution on reaction reactivity

In our present investigation, it is interesting to mention that the presence of electron-withdrawing groups in aryl amidrazones such chlorine atom increased the yields of either products 3 or 4. Moreover *p*-substituted of aryl amidrazones relatively increased the yields of the products compared with its *m*-aryl substituents. The *o*-substituted electron donating decreased the yield percentages of the products as compared with the *p*-aryl substituents, which might be attributed due to the presence of steric effect.

2.1.3. Effect of solvents on Mitsunobu reaction

It was previously reported that Mitsunobu reaction preferred polar solvents compared to other ones [17].

2.1.4. Effect of basicity on Mitsunobu reaction

It was reported that the high efficiency of Mitsunobu reaction is increased when the pKa of the mediator like disubstituted azodicarboxylate/Lewis acids (e.g. Ph_3P or as here Et_3N) would be between 11-12 [18,19].

3. Conclusion

As previously mentioned that alcohols could be oxidized into their corresponding aldehydes and ketones by azodicarboxylate in presence of catalysts that easily abstracts hydrogen proton [15], we encourage to do more work and repeating the reaction of amidrazones with alcohols under the aforementioned condition of azodicarboxylate in presence of triethylamine, so as to obtain various new derivatives of 3-substituted 1,2,4-triazoles.

4. Acknowledgments

The authors thank DFG Collaborative Center "3MET", Karlsruhe Institute of Technology, Karlsruhe, Germany for financial support to Prof Aly enabling him to carry out analyses in the aforesaid Institute. Purchase of the NMR spectrometer at Florida Institute of Technology was assisted by the U.S. National Science Foundation (CHE 03-42251).

5. Experimental

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus (Weiss-Gallenkamp, Loughborough, UK), and are uncorrected. The IR spectra were recorded from potassium bromide disks with a FT device, Minia University NMR spectra were measured on a Bruker AV-400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C, and 40.55 MHz for ^{15}N); chemical shifts are expressed in δ (ppm), versus internal tetramethylsilane (TMS) = 0 for ^1H and ^{13}C, and external liquid ammonia = 0 for ^{15}N. Coupling constants are stated in Hz. Correlations were established using ^1H-^1H COSY, and ^1H-^{13}C and ^1H-^{15}N HSQC and HMBC experiments. Mass spectra were recorded on a Finnigan Fab 70 eV, Institute of Organic Chemistry, Karlsruhe University, Karlsruhe, Germany. TLC was performed on analytical Merck 9385 silica aluminum sheets (Kieselgel 60) with Pf_{254} indicator; TLC's were viewed at λ_{max} = 254 nm. Elemental analyses were carried out at National Research Center, Al Doki, Egypt.

Starting materials

Amidrazones **1a–f** were prepared according to [20].

Reactions of amidrazones 1a-f with diethyl azodicarboxylate (2) in EtOH/Et_3N

A mixture of amidrazones **1a-f** (1 mmol) and **2** (0.348 g, 2 mmol) in 50 mL of absolute ethanol and 0.5 mL of Et_3N was refluxed for 10-15 h. The reaction was followed up by TLC analysis. The mixture was then concentrated on vacuum and the resulting solid was separated by preparative TLC using toluene: ethyl acetate (2:1). The fastest migrating zone was separated as compounds **4a-f,** which was followed by **3a-f;** the slowest migrating zone was identified as compound **5**. The formed product was then recrystallized from stated solvents.

3-Methyl-4,5-diphenyl-4*H*-1,2,4-triazole (3a). Yield 165 mg (70%), white crystals (EtOH), mp 159-161 ^oC (lit [21] mp = 158-161 ^oC). IR (KBr): ν = 3050-3010 (Ar-CH), 2980-2840 (Aliph-CH), 1630, 1610 (C=N), 1540 (C=C), 769 cm^{-1}. ^1H NMR ($CDCl_3$): 7.53–7.50 (m, 3H), 7.44–7.42 (m, 2H), 7.35–7.32 (m, 3H), 7.22-7.20 (m, 2H), 2.36 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 154.0 (N=C-Ph), 153.0 (N=C-CH_3), 134.6, 131.0 (Ar-C), 129.4, 129.2, 128.8, 128.5 (Ar-2CH), 127.2, 127.0 (Ar-CH-*p*), 11.2 (CH_3). MS (70 eV, %): *m/z* = 235 (M^+, 100), 176 (17), 154 (27), 153 (100). Anal. Calcd. For $C_{15}H_{13}N_3$ (235.29): C, 76.57; H, 5.57; N, 17.86. Found: C, 76.65; H, 5.65; N, 17.75.

4-(4'-Chlorophenyl)-3-methyl-5-phenyl-4*H*-1,2,4-triazole (3b). Yield 202 mg (75%), white crystals (EtOH), mp 234-236 ^oC. IR (KBr): ν = 3040-3008 (Ar-CH), 2970-2930 (Aliph-CH), 1625, 1610 (C=N), 1540 (C=C), 769 cm^{-1}. ^1H NMR (DMSO-d_6): 7.62 (d, *J* = 8.5, 2H; H-3'), 7.48 (d, *J* = 8.5, 2H; H-2'), 7.37 (m, 5H; H-*o,m,p*), 2.25 (s, 3H; CH_3). ^{13}C NMR (DMSO-d_6): 153.0, 152.2 (C-3,5), 134.2, 133.5 (C-1',4'), 130.0 (C-3'), 129.5 (C-2'), 128.64 (C-*p*), 128.55, 128.0 (C-*o,m*), 127.1 (C-*i*), 14.4 (CH_3). ^{15}N NMR (DMSO-d_6): 309.8 (N-2), 177.6 (N-4); N-1 not observed. MS (70 eV, %): *m/z* = 270 (M^{+1}, 32), 269 (100). Anal. Calcd. For $C_{15}H_{12}ClN_3$ (269.73): C, 66.79; H, 4.48; N, 15.58. Found: C, 76.65; H, 4.55; N, 15.60.

4-(3'-Chlorophenyl)-3-methyl-5-phenyl-4*H*-1,2,4-triazole (3c). Yield 196 mg (73%), white crystals (EtOH), mp 233-235 ^oC. IR (KBr): ν = 3060-3012 (Ar-CH), 2975-2870 (Aliph-CH), 1615 (C=N), 1520 (C=C), 780 cm^{-1}. NMR (DMSO-d_6): Table 1. MS (70 eV, %): *m/z* = 271 (M^{+1}, 34), 269 (100). Anal. Calcd. For $C_{15}H_{12}ClN_3$ (269.73): C, 66.79; H, 4.48; N, 15.58. Found: C, 76.72; H, 4.50; N, 15.62.

3-Methyl-4-(4'-methylphenyl)-5-phenyl-4*H*-1,2,4-triazole (3d). Yield 172 mg (69%), white crystals (CH_3CN), mp 161 ºC (lit. [20] mp 159-161 ºC). IR (KBr): ν = 3050-3010 (Ar-CH), 2980-2960 (Aliph-CH), 1625, 1610 (C=N), 1530 (C=C), 769 cm^{-1}. ^1H NMR ($CDCl_3$): 7.44 (dd, 2H, *J* = 1.2, 0.8 Hz), 7.36–7.28 (m, 5H), 7.10 (dd, 2H, *J* = 1.2, 0.8 Hz), 2.50 (s, 3H, CH_3), 2.35 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 154.0 (N=C-Ar), 152.4 (N=C-CH_3), 138.2, 132.5, 131.0 (Ar-C), 129.5, 128.4, 127.6, 126.8 (Ar-2CH), 127.0 (Ar-CH-*p*), 22.0 (CH_3-Ar), 10.6 (CH_3). MS (70 eV, %): *m/z* = 249 (100). Anal. Calcd. For $C_{16}H_{15}N_3$ (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 76.95; H, 5.58; N, 16.80.

4-(2',6'-Dimethylphenyl)-3-Methyl-5-phenyl-4*H*-1,2,4-triazole (3e). Yield 179 mg (68%), white crystals (CH_3CN), mp 180-182 ºC. IR (KBr): ν = 3090-3030 (Ar-CH), 2970-2840 (Aliph-CH), 1625, 1610 (C=N), 1540 (C=C), 770 cm^{-1}. ^1H NMR (DMSO-d_6): 7.43-7.36 (m, 2H; H-*p*,4'), 7.34-7.31 (m, 6H; Ar-H), 2.12 (s, 3H; H-3a), 1.89 (s, 6H; 2CH_3-Ar); ^{13}C NMR (DMSO-d_6): 151.9 (C-5), 151.6 (C-3), 135.2 (C-2'), 132.7 (C-1'), 130.0, 129.7 (C-*p*,4'), 129.1, 128.8 (Ar-2CH), 127.2 (C-*i*), 126.2 (Ar-2CH), 17.1 (2CH_3-Ar), 10.1 (CH_3-triazole). ^{15}N NMR (DMSO-d_6): 313.0 (N-2), 172.8 (N-4); N-1 not observed. MS (70 eV, %): *m/z* = 263 (100). Anal. Calcd. For $C_{17}H_{17}N_3$ (263.34): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.60; H, 6.48; N, 16.00.

3-Methyl-4-(2'-methylphenyl)-5-phenyl-4*H*-1,2,4-triazole (3f). Yield 164 mg (66%), white crystals (EtOH), mp 130-132 ºC. IR (KBr): ν = 3090-3012 (Ar-CH), 2940-2850 (Aliph-CH), 1640, 1610 (C=N), 1535 (C=C), 770 cm^{-1}. ^1H NMR (DMSO-d_6): 7.49 ("t", *J* = 7.0; 2H), 7.44 (bs, 2H; H-3',4'5'6'), 7.34 (m, 5H; H-*o,m,p)*, 2.16 (s, 3H; H-3a), 1.83 (s, 3H; CH_3-Ar). ^{13}C NMR (DMSO-d_6): 152.6 (C-5), 152.0 (C-3), 134.9, 133.6 (C-1',2') 131.5 (C-3'), 130.2 (C-6'), 129.5 (C-*p*), 128.6 (Ar-2CH), 128.2 (C-4'), 127.7 (C-5'), 127.3 (C-i), 127.0 (Ar-2CH), 16.7 (CH_3-Ar), 10.5 (CH_3-triazole). ^{15}N NMR (DMSO-d_6): 310.7 (N-2), 176.6 (N-4). N-1 not observed. MS (70 eV, %): *m/z* = 249 (100). Anal. Calcd. For $C_{16}H_{15}N_3$ (249.32): C, 77.08; H, 6.06; N, 16.85. Found: C, 77.20; H, 6.12; N, 16.90.

3,4,5-Triphenyl-4*H*-triazole (4a). Yield: 48 mg (16%); off-white solid (EtOH); mp 287–289 °C (lit. [22] mp = 287-289 ºC). IR (KBr): ν = 3060-3045 (Ar-CH), 1632 (C=N), 1530 (C=C), 769 cm^{-1}. ^1H NMR ($CDCl_3$): 7.40–7.33 (m, 6H), 7.30–7.19 (m, 7H), 7.09–7.06 (m, 2H). ^{13}C NMR ($CDCl_3$): 154.6 (C-3, C-5),

135.1 (Ar-2C), 129.4 (N-Ph-*C*), 129.2 (Ar-2CH-*p*), 128.4, 128.6 (Ar-4CH), 128.0, 127.6 (Ar-2CH), 126.2 (Ar-CH). MS (70 eV, %): *m/z* = 297 (M^+, 98), 176 (17), 154 (27), 153 (100). Anal. Calcd. For $C_{20}H_{15}N_3$ (297.36): C, 80.78; H, 5.08; N, 14.13. Found: C, 80.60; H, 4.98; N, 14.10.

4-(4-Chlorophenyl)-3,5-diphenyl-4*H*-1,2,4-triazole (4b). Yield: 66 mg (20%); white solid (CH_3CN); mp 266–267 °C (lit. [23] mp = 266-267 °C). IR (KBr): ν = 3085-3035 (Ar-CH), 1630 (C=N), 1550 (C=C), 769 cm^{-1}. ^1H NMR ($CDCl_3$): 7.60-7.57 (dd, 2H, *J* = 1.0, 0.6 Hz), 7.45–7.38 (m, 6H), 7.25-7.20 (m, 4H), 6.98–6.96 (dd, 2H, *J* = 1.0, 0.6 Hz). ^{13}C NMR ($CDCl_3$): 155.0 (C-3, C-5), 135.0 (Ar-2*C*), 134.2 (*N*-Ph-C), 129.4 (Ar-C), 128.6, 128.4 (Ar-4CH), 128.0, 127.6 (Ar-2CH), 126.2 (Ar-2CH-*p*). MS (70 eV, %): *m/z* = 332 (M^{+1}, 34), 331 (M^+, 100), 156 (80). Anal. Calcd. For $C_{20}H_{14}ClN_3$ (331.80): C, 72.40; H, 4.25; N, 12.66. Found: C, 72.55; H, 4.30; N, 12.50.

4-(3-Chlorophenyl)-3,5-diphenyl-4*H*-1,2,4-triazole (4c). Yield: 62 mg (19%); white solid (CH_3CN); mp: 278-280 °C (lit. [22] 278-280 °C); ^1H NMR ($CDCl_3$): 7.50-7.32 (m, 12H), 7.12 (t, *J* = 4.0 Hz, 1H), 7.10-7.06 (m, 1H); ^{13}C NMR ($CDCl_3$): 154.6 (C-3, C-5), 136.3 (Ar-2C), 135.5 (Ar-N-C), 130.8 (Ar-C-Cl), 129.9, 129.0 (Ar-4CH), 128.8, 128.5, 128.0, 127.4 (Ar-CH), 126.1 (Ar-2CH-*p*); MS (70 eV, %): *m/z* = 333 ($[M+1]^+$; 34), 331 (M^+, 100). Anal. Calcd for $C_{20}H_{14}ClN_3$ (330.40) C, 72.40; H, 4.25; N, 12.66. Found: C, 72.50; H, 4.15; N, 12.64.

3,5-Diphenyl-4-*(*4'-methylphenyl)-4*H*-1,2,4-triazole (4d). Yield 50 mg (16%), white crystals (EtOH), mp 267-269 °C (lit. [24] 267-269 °C); ^1H NMR ($CDCl_3$): 7.55 (dd, 2H, *J* = 1.4, 7.0 Hz). 7.40-7.37 (m, 6H), 7.30-7.24 (m, 4H), 7.00 (dd, 2H, *J* = 1.6, 1.6 Hz), 2.15 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 154.5 (C-3, C-5), 134.1 (Ar-C-CH_3), 133.1 (Ar-2C), 129.7 (Ar-N-C), 129.2, 128.8 (Ar-4CH), 128.5, 126.5 (Ar-2CH), 123.5 (Ar-2CH-*p*), 22.5 (CH_3-Ar).

4-(2',6'-Dimethylphenyl)-3,5-diphenyl-4*H*-1,2,4-triazole (4e). Yield: 42 mg (13%); white solid (EtOH); mp 270–272 °C. IR (KBr): ν = 3400 (OH), 3230 (NH), 3090-3040 (Ar-CH), 2980-2890 (Aliph-CH), 1620 (C=N), 1550 (C=C) cm^{-1}. NMR (DMSO-d_6): Table 2. MS (70 eV, %): *m/z* = 325 (M^+, 100). Anal. Calcd. For $C_{22}H_{19}N_3$ (325.42): C, 81.20; H, 5.89; N, 12.91. Found: C, 81.30; H, 5.94; N, 13.10.

3,5-Diphenyl-4-(2'-methylphenyl)-4*H*-1,2,4-triazole (4f). Yield: 46 mg (15%); white solid (MeOH); mp 265-267°C. IR (KBr): ν = 3070-3050 (Ar-CH), 1620 (C=N), 1530 (C=C), 769 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.62-7.55 (m, 6H, Ar-H), 7.50-7.45 (m, 4H, Ar-H), 7.34-7.26 (m, 4H, Ar-H), 1.90 (s, 3H, CH_3-Ar). ^{13}C NMR ($CDCl_3$): 153.0 (N=C-Ar), 135.2 (Ar-2C), 134.5 (Ar-C-CH_3), 134.0 (N-Ar-C), 131.0, 130.0 (Ar-4CH), 128.6, 128.2, 127.8, 127.6 (Ar-CH), 126.0 (Ar-2CH-*p*), 18.9 (CH_3-Ar). MS (70 eV, %): *m/z* = 311 (M^+, 100). Anal. Calcd. For $C_{21}H_{17}N_3$ (311.39): C, 81.00; H, 5.50; N, 13.49. Found: C, 80.92; H, 5.62; N, 13.54.

Reactions of amidrazones 1a-f with diethyl azodicarboxylate (2) in toluene/Et_3N

On applying the aforementioned procedure, a mixture of amidrazones **1a-f** (1 mmol) and **2** (0.348 g, 2 mmol) in 30 mL of dry toluene and 0.5 mL of Et_3N was refluxed for 10-15 h. The reaction was followed up by TLC analysis. The mixture was then concentrated on vacuum and the resulting solid was applied on plates chromatography using toluene: ethyl acetate (2:1). The fastest migrating zone was separated as compounds **4a-f,** which followed by compound **5** then followed by arylamines. The formed product was then recrystallized from stated solvents as shown before. The arylamines were identified by comparison their TLC with authentic samples.

Crystal Structure Determinations of 3f and 4e

The single-crystal X-ray diffraction studies were carried out on a Bruker D8 Venture diffractometer with Photon100 detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). dual space methods (SHELXT) [25] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F^2) [26] Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(O) free). Semi-empirical absorption corrections were applied. For **4e** an extinction correction was applied.

3f: colourless crystals, $C_{16}H_{15}N_3$, M_r = 249.31, crystal size 0.40 × 0.20 × 0.10 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 6.7135(2) Å, b = 16.7918(5) Å, c = 12.0654(4) Å, β = 101.435(1)°, V = 1333.15(7) $Å^3$, Z = 4, ρ = 1.242 Mg/m^{-3}, μ(Cu-K_α) = 0.590 mm^{-1}, F(000) = 528, $2\theta_{max}$ = 144.4°, 15794

reflections, of which 2630 were independent (R_{int} = 0.029), 174 parameters, R_1 = 0.037 (for 2443 I > 2σ(I)), wR_2 = 0.094 (all data), S = 1.03, largest diff. peak / hole = 0.177 / -0.224 e Å^{-3}.

4e: colourless crystals, $C_{22}H_{19}N_3 \cdot H_2O$, M_r = 343.42, crystal size 0.1223× 0.16 × 0.10 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 10.3387(2) Å, b = 8.8218(2) Å, c = 20.1630(4) Å, β = 99.092(1)°, V = 1815.88(7) Å^3, Z = 4, ρ = 1.256 Mg/m^{-3}, μ(Cu-K$_\alpha$) = 0.620 mm^{-1}, F(000) = 728, $2\theta_{max}$ = 144.4°, 13965 reflections, of which 3566 were independent (R_{int} = 0.029), 244 parameters, 3 restraints, R_1 = 0.036 (for 3116 I > 2σ(I)), wR_2 = 0.088 (all data), S = 1.02, largest diff. peak / hole = 0.229 / -0.204 e Å^{-3}.

CCDC 1837197 (**3f**) and 1837196 (**4e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

6. References

[1] Curtis ADM, Jennings N (2008) 1,2,4-Triazoles. Compr Heterocycl Chem. III 5:159–209. DOI: org/10.1016/B978-008044992-0.00502-2

[2] Zhou C-H, Wang Y (2012) Curr Med Chem 19:239-280. Recent researches in triazole compounds as medicinal drugs. DOI: org/10.2174/092986712803414213

[3] Shalini K, Kumar N, Drabu S, Sharma PK (2011) Advances in synthetic approach to and antifungal activity of triazoles. Beilstein J Org Chem 7:668-677. DOI: 10.3762/bjoc.7.79

[4] Turan-Zitouni G, Kaplancikli ZA, Yildiz MT, Chevallet P, Kaya D (2005) Synthesis and antimicrobial activity of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl)acetamido]thio-4H-1,2,4-triazole derivatives. Eur J Med Chem 40:607-613. DOI: org/10.1016/j.ejmech.2005.01.007

[5] Walczak K, Gondela A, Suwinski J (2004). Synthesis and anti-tuberculosis activity of N-aryl-C-nitroazoles. Eur J Med Chem 39:849-853. DOI: 10.1016/j.ejmech.2004.06.014

[6] Holla BS, Poojary KN, Rao BS, Shivananda MK (2002) New bis-aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents. Eur J Med Chem 37:511-517. DOI: org/10.1016/S0223-5234(02)01358-2

[7] Almasirad A, Tabatabai SA, Faizi M, Kebriaeezadeh A, Mehrabi N, Dalvandi A, Shafiee A (2004) Synthesis and anticonvulsant activity of new 2-substituted-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles. Bioorg Med Chem Lett 14:6057-6059. DOI: org/10.1016/j.bmcl.2004.09.072

[8] Mhasalkar MY, Shah MH, Nikam ST, Ananthanarayanan KG, Deliwala CV (1970) 4-Alkyl-5-aryl-4H-1,2,4-triazole-3-thiols as hypoglycemic agents. J Med Chem 13:672-674. DOI: 10.1021/jm00298a021

[9] Amir M, Shikha K (2004) Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino)phenyl]acetic acid derivatives. Eur J Med Chem 39:535-545. DOI: rg/10.1016/j.ejmech.2004.02.008

[10] Mitsunobu O, Yamada Y (1967) Preparation of esters of carboxylic and phosphoric acid via quaternary phosphonium salts. Bull Chem Soc Jpn 40:2380-2382. DOI: org/10.1246/bcsj.40.2380

[11] Mitsunobu O (1981) The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products. Synthesis 1-28. DOI: 10.1055/s-1981-29317

[12] a) Aly AA, Ramadan M, Abd El-Aziz M, Bräse S, Brown AB, Fathy HM, Nieger M (2017) Regioselective synthesis of 5-aminopyrazoles from reactions of amidrazones with activated nitriles: NMR investigation and X-ray structural analysis. Chem Pap 71:1409–1417. DOI: 10.1007/s11696-017-0131-x. b) Aly AA, Ramadan M, Abd El-Aziz M, Bräse S, Brown AB, Fathy HM (2017) Selectivity of amidrazones towards activated nitriles – synthesis of new pyrazoles and NMR investigation. Arkivoc (v):461-473. DOI: https://doi.org/10.24820/ark.5550190.p009.877. c) Aly AA, Hassan AA, Bräse S, Gomaa MA-M, Nemr FM (2017) Reaction of amidrazones with diaminomaleonitrile: synthesis of 4-amino-5-iminopyrazoles. J Heterocycl Chem 54:480-483. DOI: org/10.1002/jhet.2607. d) Aly AA, Hassan AA, Gomaa MA-M, Bräse S, Nemr FM (2017) Reaction of amidrazones with phthaloyl chloride—synthesis of 1,2,4-triazolium salts (part I). J Heterocycl Chem 54:775-779. DOI: org/10.1002/jhet.2643. e) Aly AA, Gomaa MA-M, NourEl-Din AM, Fahmi MS (2006) Amidrazones in the synthesis of 1*H*-1,2,4-triazoles. Z Naturforsch

61b:1239-1242. DOI: org/10.1515/znb-2006-1009. f) Aly AA, Brown AB, Shawky AM (2017) One-pot reaction of amidrazones, phthaloyl chloride, and triethyl amine: synthesis of (1′,2′,4′-triazole)-2-benzoic acid. J Heterocycl Chem 54:2375-2379. DOI: .org/10.1002/jhet.2829. g) Aly AA, Shaker RM (2005). 5-Benzyl-1H-tetrazoles from the reaction of 1-aryl-5-methyl-1*H*-tetrazoles with 1,2-dehydrobenzene. Tetrahedron Lett 46:2679-2682, 5095, 6777. DOI: org/10.1016/j.tetlet.2005.02.072. h) Aly AA, Ramadan, M, Abd Al-Aziz M, Fathy HM, Bräse S, Brown AB, Nieger M (2016) Reaction of amidrazones with 2,3-diphenylcyclopropenone: synthesis of 3-(aryl)-2,5,6-triphenylpyrimidin-4(3*H*)-ones. J Chem Res 40:637-639. DOI: 10.3184/174751916X14743924. i) Aly AA, Ramadan M, Morsy NM, Elkanzi NAA Inclusion of carbonyl groups of benzo[*b*]thiophene-2,5-dione into amidrazones: synthesis of 1,2,4-triazine-5,6-diones. J Heterocycl Chem 54:2067-2070. DOI: org/10.1002/jhet.2805. j) Aly AA, Gomaa MA-M, NourEl-Din AM, Fahmy MS (2007) Reactions of amidrazones with 1,4-quinones. Arkivoc (xvi):41-50. DOI:10.3998/ark.5550190.0008.g04. k) Aly AA, NourEl-Din AM, Gomaa MA-M, Fahmy MS (2008) Rapid and facile synthesis of 4-aryl-5-imino-3-phenyl-1*H*-naphtho[2,3-*f*]-1,2,4-triazepine-6,11-diones via the reaction of amidrazones with dicyanonaphthoquinone. Z Naturforsch 63B:223-228. DOI: org/10.1515/znb-2008-0217. l) Aly AA, Ishak EA, Ramadan M, Elkanzi NAA, El-Reedy AAM (2017) Amidrazones and 2-acetylcyclopentanone in the synthesis of cyclopenta[*e*][1,3,4]oxadiazepines. J Heterocycl Chem 54:1652-1655. DOI: org/10.1002/jhet.2727.

[13] Nájera C, Sansano JM, Yus M (2015) 1,3-Dipolar cycloadditions of azomethine imines. Org Biomol Chem 13:8596-8636. DOI: 10.1039/C5OB01086A

[14] Yoneda F, Suzuki K, Nitta Y (1966) A new hydrogen-abstracting reaction with diethyl azodicarboxylate. J Am Chem Soc 88:2328-2829. DOI: 10.1021/ja00962a05

[15] Hayashi M, Shibuya M, Iwabuchi Y (2011) Oxidation of alcohols to carbonyl compounds with diisopropyl azodicarboxylate catalyzed by nitroxyl radicals. J Org Chem 77:3005−3009. DOI: org/10.1021/jo300088b

[16] Cao HT, Grée R (2009). DEAD-(cat)$ZnBr_2$, an efficient system for the oxidation of alcohols to carbonyl compounds. Tetrahedron Lett 50:1493-1494. DOI: org/10.1016/j.tetlet.2009.01.080

[17] Shi M, Zhao G-L (2004). Aza-Baylis–Hillman reactions of diisopropyl azodicarboxylate or diethyl azodicarboxylate with acrylates and acrylonitrile. Tetrahedron 60:2083–2089. DOI: 10.1016/j.tet.2003.12.059

[18] a) Tsunoda T, Otsuka J, Yamamiya Y, Ito S (1994) *N*,*N*,*N*′,*N*′-Tetramethylazodicarboxamide (TMAD), a new versatile reagent for Mitsunobu reaction. Its application to synthesis of secondary amines. Chem Lett 539-542. DOI: org/10.1246/cl.1994.539; b) Tsunoda T, Kawamura Y, Uemoto K, Ito S (1998) Mitsunobu type C-N bond formation with 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD), a new cyclic azodicarboxamide. Heterocycles 47:177-179. DOI: 10.3987/COM-97-S(N)78; c) Sakamoto I, Kaku H, Tsunoda T (2003) Preparation of (cyanomethylene)trimethylphosphorane as a new Mitsunobu-type reagent. Chem Pharm Bull 51:474-476. DOI. org/10.1248/cpb.51.474; d) Hughes DL, The Mitsunobu reaction. Org React (N.Y.) 42:335-656. DOI:10.1002/0471264180.or042.02

[19] Jenkins ID, Mitsunobu O. (2001) Triphenylphosphine-diethyl azodicarboxylate. In Electronic Encyclopedia of Reagents for Organic Synthesis (Paquette LA, Ed.), John Wiley & Sons. DOI:10.1002/047084289X.rt372.

[20] Müller D, Beckert R, Görls H (2001). Bis-amidines as useful building blocks for heterofulvenes and -fulvalenes. Synthesis 601-606. DOI: 10.1055/s-2001-12366

[21] Siddaiah V, Basha GM, Srinuvasarao R, Yadav SK (2011) $HClO_4$-SiO_2: An efficient reusable catalyst for the synthesis of 3,4,5-trisubstituted 1,2,4-triazoles under solvent-free conditions. Catal Lett 141:1511-1520. DOI: org/10.1007/s10562-011-0665-4

[22] Mangarao N, Mahaboob Basha G, Ramu T, Srinuvasarao R, Prasanthi S, Siddaiah V (2014) Brønsted acid-catalyzed simple and efficient synthesis of 1,2,4-triazoles and 1,2,4-oxadiazoles using 2,2,2-trichloroethyl imidates in PEG. Tetrahedron Lett 55:177-179. DOI: org/10.1016/j.tetlet.2013.10.147

[23] Ito S, Tanaka Y, Kakehi A, Miyazawa H (1977). The reaction of *N*-(phenylsulfonyl)-benzohydrazonoyl chloride with *N*-substituted benzamidines, with benzimidates, and with 2-aminopyridines. Bull Chem Soc Jpn 50:2969-2972. DOI: org/10.1246/bcsj.50.2969

[24] Nakka M, Tadikonda R, Nakka S, Vidavalur S (2016) Synthesis of 1,2,4-triazoles, N-fused 1,2,4-triazoles and 1,2,4-oxadiazoles via molybdenum hexacarbonyl-mediated carbonylation of aryl iodides. Adv Synth Catal 358:520-525. DOI: org/10.1002/adsc.201500703

[25] Sheldrick GM (2015) *SHELXT* - Integrated space-group and crystal-structure determination. Acta Crystallogr A71:3-8. DOI: org/10.1107/S2053273314026370

[26] Sheldrick GM (2015) Crystal structure refinement with *SHELXL*. Acta Crystallogr C71:3. DOI: 10.1107/S2053229614024218