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Synthesis of 1,5-Disubstituted Tetrazoles in Aqueous Micelles at Room Temperature

Mohammed Abdessalam [1,*], Madjid Ait Sidhoum [2,*], Fatima-Zohra Zradni [1,*] and Hocine Ilikti [3]

[1] Laboratory of Organic Synthesis, Physico-Chemistry, Biomolecules and Environment (LSPBE), Department of Chemical Engineering, Faculty of Chemistry, University of Sciences and Technology of Oran "Mohamed Boudiaf"—USTOMB, El Mnaouar BP 1505, Bir El Djir 31000, Oran, Algeria
[2] Laboratory of Chemistry, Department of Chemical Engineering, Faculty of Chemistry, University of Sciences and Technology of Oran "Mohamed Boudiaf"—USTOMB, El Mnaouar BP 1505, Bir El Djir 31000, Oran, Algeria
[3] Laboratory of Chemistry and Electrochemistry of Metal Complex, Department of Chemical Engineering, Faculty of Chemistry, University of Sciences and Technology of Oran "Mohamed Boudiaf"—USTOMB, El Mnaouar BP 1505, Bir El Djir 31000, Oran, Algeria; ilikti@yahoo.fr
* Correspondence: mohammed.abdessalam@univ-usto.dz (M.A.); maitsidhoum@yahoo.fr (M.A.S.); fatimazohra.zradni@univ-usto.dz (F.-Z.Z.); Tel.: +213-661-861-317 (M.A.)

Abstract: The ongoing study is a Ugi-azide four-component reaction for the synthesis of 1,5-disubstituted tetrazole(1,5-DST), which involves an aldehyde, different amines, isocyanides, and as azide's source the Trimethylsilylazide ($TMSN_3$), in water as solvent using as catalyst the tetradecyltrimethylammonium bromide (TTAB) with a load of (10% mole), which provides a hydrophobic micellar reaction site. This approach is a step toward a green chemistry reaction of 1,5 disubstituted tetrazole. A serie of 1, 5- disubstituted tetrazole was synthesized by engaging a large substrate scope, leading to yields between 43% and 56%, which are compared afterwards with those obtained with methanol as solvent. The results were confirmed by HRMS, IR, and 1D NMR experiments.

Keywords: tetrazole; Ugi-azide multicomponent reaction instead of Ugiazide reaction; Ugi-azide multicomponent reaction; micellar catalysis; green chemistry

Citation: Abdessalam, M.; Sidhoum, M.A.; Zradni, F.-Z.; Ilikti, H. Synthesis of 1,5-Disubstituted Tetrazoles in Aqueous Micelles at Room Temperature. *Molbank* **2021**, *2021*, M1194. https://doi.org/10.3390/M1194

Academic Editor: Fawaz Aldabbagh

Received: 17 January 2021
Accepted: 4 March 2021
Published: 9 March 2021

1. Introduction

Tetrazole derivatives attained remarkable attention as prime heterocycles due to a large utilization in numerous fields such as in medicine, in pharmacology, in photography, and as a potential explosives and rockets propellant components based on their high energy properties [1].

The 1,5-disubstituted tetrazole moieties (1,5-DST) has been widely and successfully used in medicinal chemistry and drug design (as shown in Figure 1), as anti-inflammatory (**I**) [2], antiviral (i.e., HIV) (**II**) [3], antibiotics (**III**) [4], antiulcer (**IV**) [5], anxiety (**V**) [6], anti-tubercular (**VI**) [7], due to their bioisosterism to carboxylic acid and amide moieties, and lipophilicity which is potentially more beneficial when cell membrane is desired [8], and also to their metabolic stability and other beneficial physicochemical properties [9].

To date, we can review in the literature several synthesis methods of 1,5-DST, but the main routes are [2+3] intermolecular cycloaddition and Ugi-azide reaction (UA) [10].

The most common used synthesis of tetrazole derivatives is the 1,3-dipolarcycloaddition reaction between nitriles and azides [11–17]. However, the requirement of the strong electron withdrawing groups in the nitrile substrate somehow limits the scope of the reaction, needing, in general, high reaction temperature and catalysts [9]. Demko and Sharpless described the synthesis of various 1,5-DSTs by a [2+3] cycloaddition of p-toluenesulfonyl cyanide (TsCN) with aromatic and aliphatic azides under solvent-free condition followed by simple isolation with good yield [18–20]. However, a high reaction temperature was required.

In 1959, Ivar Ugi introduced the Ugi-4components reaction, the most important approach to aminomethyl tetrazoles using Multicomponent reaction (MCR), since it emerged as an extremely powerful tool in combinatorial chemistry and drug discovery, offering significant advantages over conventional linear stepwise syntheses. Years later, Ugi described a Passerini MCR variation leading to α-hydroxymethyl tetrazoles [21,22]. The Ugi azide MCR differs from the classical Ugi-4CR by replacing the carboxylic acid with an azide source, which traps out the intermediate nitrilium to lead finally to the formation of 1,5-DSTs [9].

In the last decades, green chemistry emerged as an alternative and sustainable solution that enables to design processes and syntheses that reduce or eliminate the use or generation of hazardous substances, which sometimes give toxic residues at the end of the reaction and are difficult to remove [23]. Hence, using water as solvent instead of MeOH would be a better solution in the synthesis of 1,5-DST, since it is safe, non-toxic, inexpensive, and represents no threat to environment.

However, the use of water is rare or even unconsidered as solvent due to the limited solubility of organic compounds in it. Therefore, the incorporation of surface-active agents (surfactants) as catalyst in aqueous media has been proven to enhance the reactivity of water via the formation of micelles or vesicular cavities [24]. Micellar catalysis refers to the acceleration of the rate of a reaction by catalytic amounts of amphiphiles that self-aggregate spontaneously to form micelles in water [24].

In our report, we have tried to describe an efficient synthesis method of 1,5-DSTsin water using micellar catalyst, tetradecyltrimethylammonium bromide (TTAB).

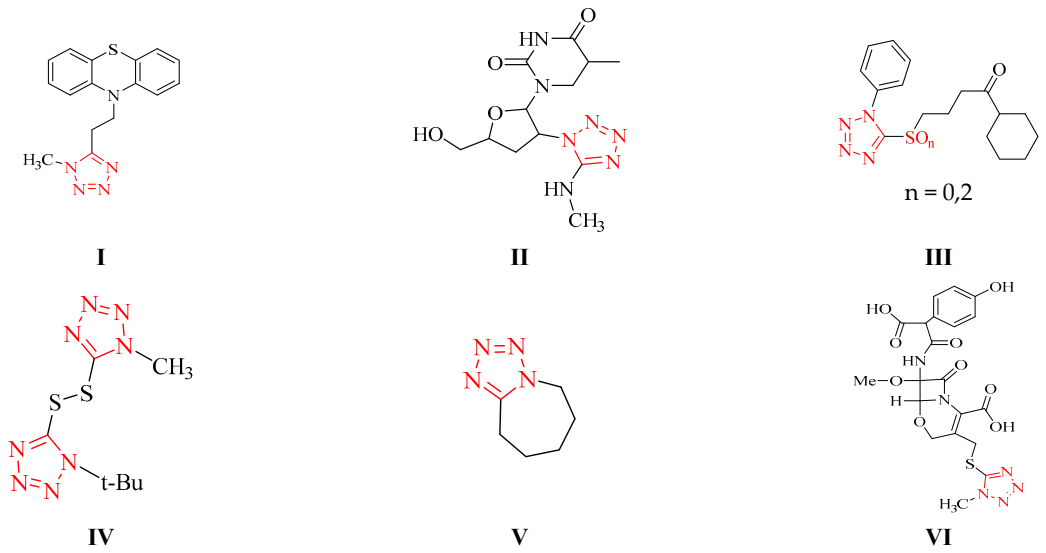


Figure 1. Examples of biologically active substances containing a 1,5-DST.

2. Results and Discussion

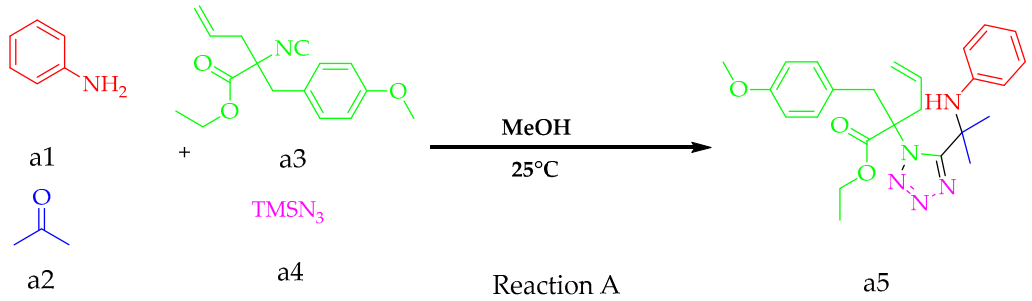
At first, the reaction was conducted with aniline (a1), propan-2-one (a2), ethyl-2-isocyano-2-(4-methoxybenzyl) pent-4-enoate (a3), and $TMSN_3$ (a4) in distilled water, without TTAB, ambient temperature (Table 1, entry1) and with heating (Table 1, entry2). No reaction occurred in both cases, which can be explained by the fact that the substrates are either less soluble or insoluble in water, something that directly affects the reaction. Afterwards, we conducted the same reaction and used TTAB as catalyst (Table 1, entry3), which enables the formation of micelles where most of organic substrates are concentrated. Those micelles are a hydrophobic reaction site, which increases in the effective concentration of organic reactants, leading to an increase of reaction rate via concentration effect. Hence, organic substrates, in micellar solution, are pushed away from water molecules towards the hydrophobic core of micelles, thus inducing efficient collision between organic substrate, which enhances the reaction rate [24], and making the reaction possible and allowing to

have a yield of 43%. The reaction was also performed under classical conditions using in MeOH (as shown in Scheme 1) at ambient temperature (Table 1, entry4), giving a yield of 55%. A variety of electronically and structurally different aldehyde, amines, and isocyanides were used to obtain 1,5-DST, in water with presence of TTAB as catalyst and also in MeOH. Thus, we obtained an acceptable yield in water which varies from 43% (Table 2, entry1) to 56% (Table 2, entry4). The yields in MeOH vary from 55% (Table 2, entry1) to 66% (Table 2, entry2). Comparing these results with those found in the literature [25–27], we can say that we obtained good yields.

Table 1. Screening Conditions.

Entry	Solvent	Temp (°C)	Time (h)	Yields (%)
1	H_2O	25	24	NR
2	H_2O	80	24	NR
3	H_2O/TTAB	25	12	43
4	MeOH	25	12	55

Substrates used in equimolar are: aniline (a1), propan-2-one (a2), ethyl-2-isocyano-2-(4-methoxybenzyl) pent-4-enoate (a3), and $TMSN_3$ (a4) TTAB (10 mol %); NR: No Reaction.



Scheme 1. Ugi-azide multicomponent synthesis of 1,5-DST in MeOH.

Table 2. Synthesized 1,5 DST of reaction A and B.

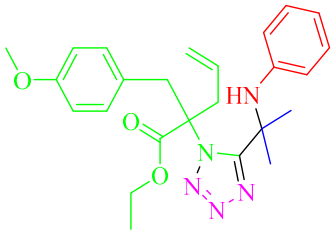
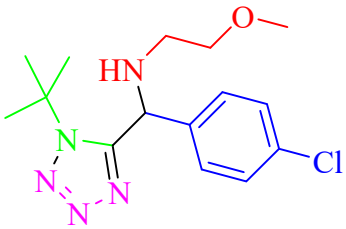
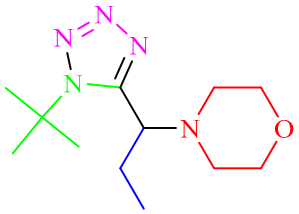
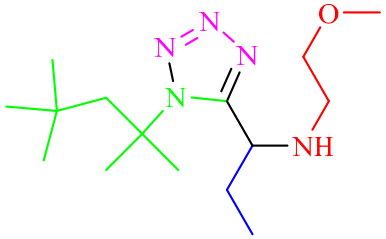
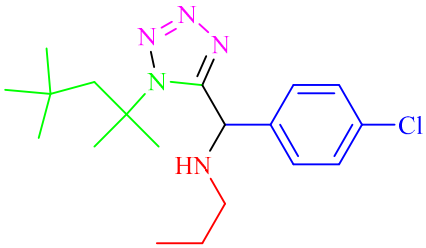
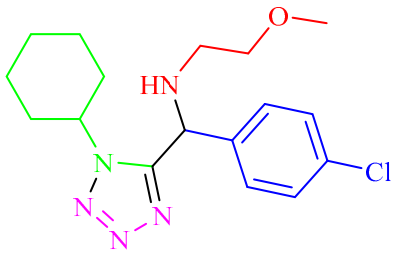
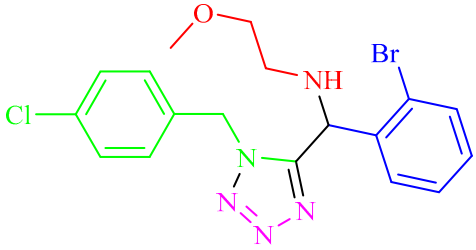
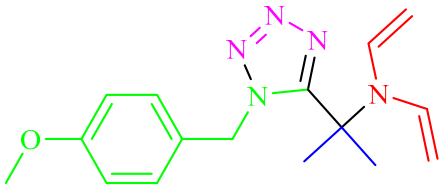
Entry	Products (a5)	Yield (%) (a)	Yield (%) (b)
1		55	43
2		66	48
3		63	51

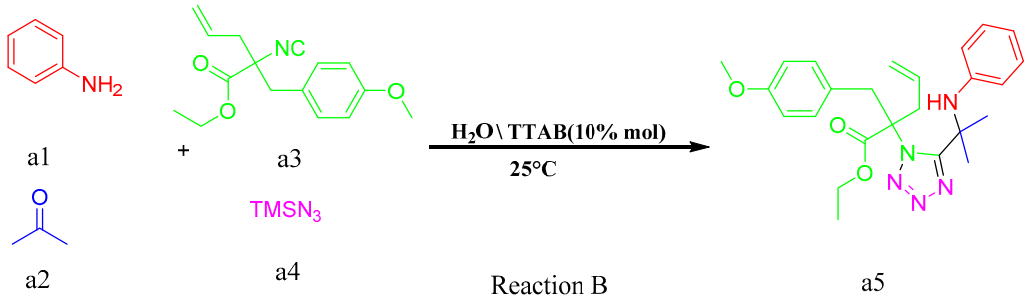
Table 2. *Cont.*

Entry	Products (a5)	Yield (%) (a)	Yield (%) (b)
4		66	56
5		62	50
6		60	47
7		58	47
8		64	56

Yield (a) corresponds to the reaction A (MeOH) at ambient temperature; yield (b) corresponds to the reaction B (water/TTAB) at ambient temperature.

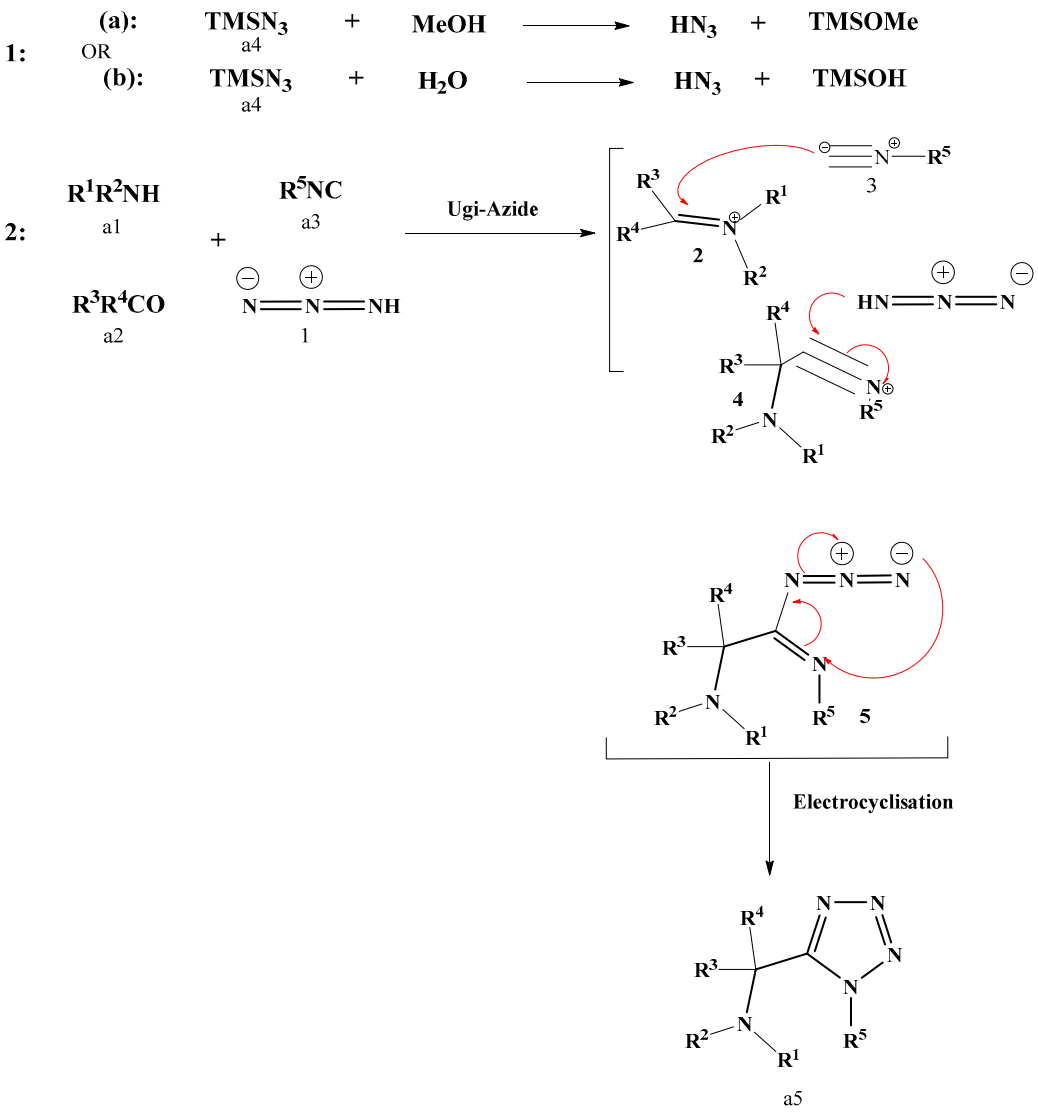
Consequently, we can notice that the yields of reaction in MeOH are higher than those in water because of what MeOH offers in term of reactivity and solubility (Table 2). However, MeOH is a harmful and toxic solvent, unlike water which stands as a safe, non-toxic, and inexpensive solvent.

A plausible Ugi Azide mechanism is proposed in Scheme 2. Firstly, aldehyde (**a2**) reacts with amine (**a1**) to give imine and water; the water coming from imine reaction reacts with $TMSN_3$ (**a4**) to generate hydrazoic acid (**1**) and trimethylsilanol. Then, hydrazoic acid protonates imine's nitrogen to give iminium ion (**2**), which reacts with isocyanide (**a3**) to form nitrilium ion (**4**), which is then attacked by azide ion, giving an intermediate (**5**), then a 1,5 electrocyclization occurs to afford the final product 1,5-DST [28].



Scheme 2. Ugi-azide multicomponent synthesis of 1,5-DST in water catalyzed by TTAB.

As can be seen, the yield varies from one reaction to another, which can be explained by the steric effect, which the radicals generate (as shown in Scheme 3). Thus, the larger the molecule is, the greater is the steric effect which directly affects the reactivity of synthesis.



Scheme 3. Plausible mechanism for the synthesis of 1,5-DST.

In conclusion, we can say that we were able to explore an efficient method to synthesize 1,5 DSTs via $TMSN_3$ as an azide source, and using water as solvent that can be considered as an eco-friendly and inexpensive synthesis, with a good yield (43%–56%). In this method,

we have used TTAB (surfactant) as catalyst, which allows the reaction to occur in room temperature without any use of harmful solvent or reagent.

3. Experimental

3.1. Generalities

^{1}H and ^{13}C NMR spectra were recorded on spectrometer Brucker Avance (ENSTA, Paris, France), operating at 400 MHz and 100 MHz. The 2D NMR experiments including COSY, HSQC and HMBC spectra were carried out to determine the assignation of carbon and proton signals. NMR spectroscopic data were recorded in $CDCl_3$ using as internal standards the residual non-deuterated signal (d = 7.26 ppm) for^{1}H NMR and the deuterated solvent signal (d = 77.16 ppm) for^{13}C NMR spectroscopy. Chemical shifts (d) are given in ppm and coupling constants (J) are given in Hz. The following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, and m = multiplet. The IR spectra were recorded on Jasco FTIR 460 plus by ATR technique (ENSTA, Paris, France). High-resolution (HR) mass spectra were performed on a GC/MS system spectrometer (ENSTA, Paris, France). TLC was carried out using precoated plates of silica gel 60F254.

3.2. General Procedures

General Procedure A-Table 1 (a): To a 1 M solution of the isocyanide in methanol was successively added 1.0 equiv of amine, 1.0 equiv of aldehyde, and 1.0 equiv of trimethylsilylazide under inert atmosphere. The mixture was stirred overnight at room temperature. The solvent was then removed in vacuum to afford tetrazole after purification by flash column chromatography on silica gel.

General Procedure B-Table 1 (b): To a 1 M solution of the isocyanide in water was successively added 1.0 equiv of amine, 1.0 equiv of aldehyde, and 1.0 equiv of trimethylsilylazidewith 10% mole of TTABunder inert atmosphere. The mixture was stirred overnight at room temperature. The solvent was then removed in vacuum to afford tetrazole after purification by flash column chromatography on silica gel (Spectrum see Supplementary).

3.2.1. Compound M01

Ethyl2-(4-methoxybenzyl)-2-(5-(2-(phenylamino)propan-2-yl)-1H-tetrazol-1-yl)pent-4-enoate. This compound was synthesized according tothe general procedure **B**, using 1.0 mmolof ethyl 2-isocyano-2-(4-methoxybenzyl) pent-4-enoate.The solvent for the flash chromatography on silicagel is a 5:5 mixture of petroleum ether anddiethyloxide. An amount of 247 mg (55%) of the desired adduct was formed.

Rf: 0.4 (50:50 PE/Et_2O)

Mol. Wt: 449.54, **Nature**: Yellow oil.

NMR ^{1}H (400 MHz, $CDCl_3$)δ 7.06 (t, 2H, *J* = 7.1 Hz, H-ar), 6.81 (t, 1H, *J* = 7.1 Hz, H-ar), 6.71–6.65 (m, 4H, H-ar), 6.44 (d, 2H, *J* = 7.6 Hz, H-ar), 5.49–5.36 (m, 1H, H-10), 5.11 (d, 1H, *J* = 7.0 Hz, H-11), 5.08 (d, 1H, *J* = 15.2 Hz, H-11), 3.80 (d, 1H, *J* = 14.1 Hz, H-4), 3.70 (s, 3H, H-1), 3.69–3.62 (m, 2H, H-7), 3.50 (d, 1H, *J* = 14.1 Hz, H-4), 3.12 (s, 1H, N-H), 3.08 (d, 1H, *J* = 6.3 Hz, H-9), 2.98 (dd, 1H, *J* = 14.9, 7.1 Hz, H-9), 1.71 (s, 3H, H-14), 1.65 (s, 3H, H-14), 0.82 (t, 3H, *J* = 7.3 Hz, H-8).

NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 169.5 (C-6), 161.1 (C-12), 159.0 (C-2), 143.7 (C-15), 131.3 (C-3), 130.9 (C-10), 128.8, 128.7, 121.4 (C-ar), 120.7 (C-11), 113.9, 113.8 (C-ar), 73.5 (C-5), 61.9 (C-7), 55.3 (C-1), 55.0 (C-13), 41.5 (C-4), 39.5 (C-9), 30.2, 29.8 (C-14), 13.6 (C-8).

I.R. (cm^{-1}, thin film):3501υ_{N-H}, 2956υ_{CH3}, 1739$\upsilon_{C=O}$, 1558$\upsilon_{C=N}$, 1504$\upsilon_{C=C}$, 1485δ_{N-H}, 1457$\upsilon_{N=N}$, 1350υ_{C-N}, 1264υ_{C-O}, 1088υ_{N-N}, 1029υ_{C-N}

HRMS Calculated for $C_{25}H_{31}N_5O_3$: 449.2427, found: 449.2435

3.2.2. Compound M02

N-((1-tert-butyl-1H-tetrazol-5-yl)(4-chlorophenyl)methyl)-2-methoxyethanamine. This compound was synthesized according to the general procedure **B**, using 1.0 mmol of 2-isocyano-2-

methylpropane. The solvent for the flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 214 mg (66%) of the desired adduct was formed.
Rf: 0.5 (50:50 PE/Et_2O)
Mol. Wt: 323.82, **Nature**: Colorless oil.
NMR ^{1}H (400 MHz, $CDCl_3$)δ 7.36 (d, 2H, *J* = 8.8 H_Z, H-ar), 7.32 (d, 2H, *J* = 8.8 H_Z, H-ar), 5.46 (s, 1H, H-4), 3.54 (t, 2H, *J* = 5.3 H_Z, H-6), 3.36 (s, 3H, H-7), 2.81–2.69 (m, 2H, H-5), 2.60 (s, 1H, N-H), 1.69 (s, 9H, H-1).
NMR ^{13}C (100.6 MHz, $CDCl_3$) δ 155.5 (C-3), 137.3 (C-8), 134.3 (C-11), 129.6 (C-9), 129.2 (C-10), 72.7 (C-6), 61.5 (C-2), 58.9 (C-7), 58.3 (C-4), 47.0 (C-5), 30.1 (C-1).
I.R. (cm^{-1}, thin film): 3490υ_{N-H}, 2959υ_{CH3}, 1558$\upsilon_{C=N}$, 1506$\upsilon_{C=C}$, 1485δ_{N-H}, 1458$\upsilon_{N=N}$, 1271υ_{C-C}, 1091υ_{N-N}, 1035υ_{C-N}
HRMS Calculated for $C_{15}H_{22}ClN_5O$: 323.1513, found: 323.1505

3.2.3. Compound M03

4-(1-(1-tert-butyl-1H-tetrazol-5-yl)propyl)morpholine. This compound was synthesized according to the general procedure B, using 1.0 mmol of 2-isocyano-2-methylpropane. The solvent for the flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 160 mg (63%) of the desired adduct was formed.
Rf: 0.6 (50:50 PE/Et_2O)
Mol. Wt: 253.34, **Nature**: Brown oil.
NMR 1H (400 MHz, $CDCl_3$)δ 4.05–3.99 (m, 1H, H-4), 3.66–3.53 (m, 4H, H-8), 2.76–2.67 (m, 2H, H-7), 2.61–2.53 (m, 2H, H-7), 2.30–2.20 (m, 1H, H-5), 2.03–1.91 (m, 1H, H-5), 1.77 (s, 9H, H-1), 0.84 (t, 3H, J = 7.3 Hz, H-6).
NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 153.5 (C-3), 67.2 (C-8), 61.7 (C-2, C-4), 48.8 (C-7), 30.0 (C-1), 18.6 (C-5), 11.4 (C-6).
I.R. (cm^{-1}, thin film): 2959 υ_{CH3}, 1555 $\upsilon_{C=N}$, 1505δ_{CH2}, 1486$\delta_{CH3,as}$, 1448 $\upsilon_{N=N}$, 1359$\delta_{CH3,s}$, 1272 υ_{C-C}, 1097 υ_{N-N}, 1048 υ_{C-N}
HRMS Calculated for $C_{12}H_{23}N_5O$: 253.1903, found: 253.1895

3.2.4. Compound M04

N-(2-methoxyethyl)-2-methyl-1-(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)propan-1-amine. This compound was synthesized according to the general procedure B, using 1.0 mmol of 2-isocyano-2,4,4-trimethylpentane. The solvent for the flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 205 mg (66%) of the desired adduct was formed.
Rf: 0.6 (50:50 PE/Et_2O)
Mol. Wt: 311.47, **Nature**: Brown oil.
NMR ^{1}H (400 MHz, $CDCl_3$) δ 4.10 (t, 1H, *J* = 6.3 Hz, H-7), 3.47–3.40 (m, 2H, H-11), 3.30 (s, 3H, H-12), 2.80–2.72 (m, 1H, H-10), 2.59–2.51 (m, 1H, H-10), 2.33–2.22 (m, 1H, H-8), 2.13–2.06 (m, 2H, H-3, N-H), 2.03–1.95 (m, 1H, H-3), 1.87 (s, 3H, H-5), 1.80 (s, 3H, H-5), 1.05 (d, 3H, *J* = 6.6 Hz, H-9), 0.98 (d, 3H, *J* = 6.6 Hz, H-9).
NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 156.4 (C-6), 72.6 (C-11), 65.2 (C-4), 59.4 (C-12), 58.7 (C-7), 53.8 (C-3), 45.1 (C-10), 31.7 (C-2), 31.5 (C-8), 30.7 (C-1), 30.6, 30.3 (C-5), 20.5, 17.3 (C-9).
I.R. (cm^{-1}, thin film): 3499 υ_{N-H}, 2959 υ_{CH3}, 1558 $\upsilon_{C=N}$, 1501δ_{CH2}, 1489δ_{N-H}, 1455 $\upsilon_{N=N}$, 1358$\delta_{CH3,s}$, 1275 υ_{C-C}, 1064 υ_{N-N}
HRMS Calculated for $C_{16}H_{33}N_5O$: 311.2685, found: 311.2698

3.2.5. Compound M05

N-((4-chlorophenyl)(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl)methyl)propan-1-amine. This compound was synthesized according to the general procedure B, using 1.0 mmol of 2-isocyano-2,4,4-trimethylpentane. The solvent for the flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 226 mg (62%) of the desired adduct was formed.

Rf: 0.6 (50:50 PE/Et_2O)
Mol. Wt: 363.93, **Nature**: Yellow oil.
NMR ^{1}H (400 MHz, $CDCl_3$)δ 7.41–7.34 (m, 4H, H-ar), 5.30 (s, 1H, H-7), 2.54–2.45 (m, 2H, H-8), 2.24 (s, 1H, N-H), 1.93 (s, 2H, H-3), 1.84 (s, 3H, H-5), 1.76 (s, 3H, H-5), 1.61–1.49 (m, 2H, H-9), 0.93 (t, 3H, *J* = 7.3 Hz, H-10), 0.71 (s, 9H, H-1).
NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 155.7 (C-6), 137.3 (C-11), 134.3 (C-12), 129.7, 129.2 (C-ar), 65.1 (C-4), 58.8 (C-7), 53.6 (C-3), 50.1 (C-8), 31.6 (C-2), 30.6 (C-1), 30.5, 30.2 (C-5), 23.2 (C-9), 11.7 (C-10).
I.R. (cm^{-1}, thin film): 3511 υ_{N-H}, 2959 υ_{CH3}, 1558 $\upsilon_{C=N}$, 1505 $\upsilon_{C=C}$, 1485δ_{N-H}, 1454 $\upsilon_{N=N}$, 1360$\delta_{CH3,s}$, 1274 υ_{C-C}, 1091 υ_{N-N}, 1042 υ_{C-N}
HRMS Calculated for $C_{19}H_{30}ClN_5$: 363.2190, found: 363.2180

3.2.6. Compound M06

N-((4-chlorophenyl)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)-2-methoxyethanamine. This compound was synthesized according to the general procedure B, using 1.0 mmol of isocyanocyclohexane. The solvent for the flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 210 mg (60%) of the desired adduct was formed.
Rf: 0.6 (50:50 PE/Et_2O)
Mol. Wt: 349.86, **Nature**: Yellow oil.
NMR ^{1}H (400 MHz, $CDCl_3$)δ 7.40–7.34 (m, 4H, H-ar), 5.36 (s, 1H, H-3), 4.41–4.31 (m, 1H, H-cy), 3.59–3.54 (m, 2H, H-5), 3.38 (s, 3H, H-6), 2.86–2.78 (m, 1H, H-4), 2.77–2.69 (m, 1H, H-4), 2.61–2.42 (m, 1H, N-H), 1.97–1.84 (m, 4H, H-cy), 1.77–1.60 (m, 3H, H-cy), 1.36–1.24 (m, 1H, H-cy).
NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 154.3 (C-7), 136.7 (C-2), 134.4 (C-1), 129.2, 128.6 (C-ar), 71.9 (C-5), 58.9 (C-6), 58.1 (C-3), 56.9 (C-cy), 47.2 (C-4), 32.7, 32.6, 25.4, 24.8 (C-cy).
I.R. (cm^{-1}, thin film): 3515 υ_{N-H}, 2959 υ_{CH3}, 1561$\upsilon_{C=N}$, 1502$\upsilon_{C=C}$, 1483δ_{N-H}, 1359$\delta_{CH3,s}$, 1263 υ_{C-C}, 1091 υ_{N-N}, 1041 υ_{C-N}
HRMS Calculated for $C_{17}H_{24}ClN_5O$: 349.1669, found: 349.1660

3.2.7. Compound M07

N-((1-(4-chlorobenzyl)-1H-tetrazol-5-yl)(2-bromophenyl)methyl)-2-methoxyethanamine. This compound was synthesized according to the general procedure B, using 1.0 mmol of 1-chloro-4-(isocyanomethyl) benzene. The solvent for the flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 253 mg (58%) of the desired adduct was formed.
Rf: 0.5 (50:50 PE/Et_2O)
Mol. Wt: 436.73, **Nature**: Yellow oil.
NMR ^{1}H (400 MHz, $CDCl_3$)δ 7.52 (d, 1H, *J* = 7.8 Hz, H-ar), 7.27–7.20 (m, 4H, H-ar), 7.18–7.13 (m, 1H, H-ar), 7.04 (d, 2H, *J* = 8.3 Hz, H-ar), 5.60 (s, 1H, H-5), 5.53 (s, 2H, H-3), 3.51 (m, 2H, H-9), 3.29 (s, 3H, H-10), 2.74 (t, 2H, *J* = 5.1 Hz, H-8), 2.44 (s, 1H, N-H).
NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 155.4 (C-4), 136.6 (C-6), 134.7 (C-2), 133.3 (C-ar), 131.6 (C-1), 130.2, 129.2, 129.1, 129.0, 128.4 (C-ar), 124.1 (C-7), 72.0 (C-9), 58.8 (C-10), 56.0 (C-5), 50.3 (C-3), 46.9 (C-8).
I.R. (cm^{-1}, thin film): 3510 υ_{N-H}, 2951 υ_{CH3}, 1649, 1551 $\upsilon_{C=N}$, 1500 $\upsilon_{C=C}$, 1482δ_{N-H}, 1359$\delta_{CH3,s}$, 1268 υ_{C-C}, 1079 υ_{N-N}, 1033 υ_{C-N}
HRMS Calculated for $C_{18}H_{19}BrClN_5O$: 435.0462, found: 435.0453.

3.2.8. Compound M08

2-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-N,N-divinylpropan-2-amine. This compound was synthesized according to the general procedure B, using 1.0 mmol of 1-(isocyanomethyl)-4-methoxybenzene. The solvent forthe flash chromatography on silica gel is a 5:5 mixture of petroleum ether and diethyl oxide. An amount of 191.6 mg (64%) of the desired adduct was formed.
Rf: 0.5 (50:50PE/Et_2O)

Mol. Wt: 299.37, **Nature**: Yellow oil.
NMR ^{1}H (400 MHz, $CDCl_3$)δ 7.22 (d, 2H, *J* = 8.1 Hz, H-ar), 6.92 (d, 2H, *J* = 8.1 Hz, H-ar), 5.97 (s, 2H, H-4), 5.91–5.78 (m, 2H, H-8), 5.15 (d, 2H, *J* = 5.1 Hz, H-9), 5.13 (d, 2H, *J* = 13.4 Hz, H-9), 3.85 (s, 3H, H-1), 1.54 (s, 6H, H-7).
NMR ^{13}C (100.6 MHz, $CDCl_3$)δ 159.8 (C-2), 159.5 (C-5), 136.4 (C-8), 128.9 (C-ar), 126.7 (C-3), 117.2 (C-9), 114.3 (C-ar), 58.7 (C-1), 55.4 (C-6), 52.2 (C-4), 24.0 (C-7).
I.R. (cm^{-1}, thin film): 2959 υ_{CH3}, 1650, 1558 $\upsilon_{C=N}$, 1537, 1503 $\upsilon_{C=C}$, 1485$\delta_{CH3,as}$, 1454 $\upsilon_{N=N}$, 1359$\delta_{CH3,s}$, 1268 υ_{C-C}, 1092 υ_{N-N}, 1043 υ_{C-N}
HRMS Calculated for $C_{16}H_{21}N_5O$: 299.1746, found: 299.1735

Supplementary Materials: The following data are available online, Figure S1: ^{1}H-NMR Spectrum of compound M01, Figure S2: ^{13}C-NMR Spectrum of compound M01, Figure S3: ^{1}H-NMR Spectrum of compound M02, Figure S4: ^{13}C-NMR Spectrum of compound M02, Figure S5: ^{1}H-NMR Spectrum of compound M03, Figure S6: ^{13}C-NMR Spectrum of compound M03, Figure S7: ^{1}H-NMR Spectrum of compound M04, Figure S8: ^{13}C-NMR Spectrum of compound M04, Figure S9: ^{1}H-NMR Spectrum of compound M05, Figure S10: ^{13}C-NMR Spectrum of compound M05, Figure S11: ^{1}H-NMR Spectrum of compound M06, Figure S12: ^{13}C-NMR Spectrum of compound M06, Figure S13: ^{1}H-NMR Spectrum of compound M07, Figure S14: ^{13}C-NMR Spectrum of compound M07, Figure S15: ^{1}H-NMR Spectrum of compound M08, Figure S16: ^{13}C-NMR Spectrum of compound M08.

Author Contributions: M.A. designed the experiments; M.A.S. performed the experiments; H.I. analyzed NMR spectral data; M.A., M.A.S., F.-Z.Z. analyzed the IR, MS and NMR spectral data and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: Authors thank University of Sciences and Technology of Oran "Mohamed Boudiaf"—USTOMB (Algeria) and ENSTA PARIS (France).

Conflicts of Interest: The authors declare no conflict of interest.

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