

Article

A Multifield Study on Dimethyl Acetylenedicarboxylate: A Reagent Able to Build a New Cycle on Diaminoimidazoles

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Abstract: A new effective method for the synthesis of imidazo[1,5-*b*]pyridazines derivatives (yields = 68–89%) by the interaction of 1,2-diamino-4-phenylimidazole with DMAD, in methanol and in the presence of a catalytic amount of acetic acid, is proposed. The course of reaction has been examined by classical organic methods, HPLC-MS analysis, and quantum-chemical calculations.

Keywords: dimethyl acetylenedicarboxylate; imidazo[1,5-*b*]pyridazines; DFT calculations



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1. Introduction

Several natural biologically active systems (from chlorophyll to hemoglobin) and many natural and synthetic drugs (from penicillin to sulfadiazine) contain in their structure heterocyclic systems (mono- or poly-cyclic) holding different hetero-atoms (from nitrogen to oxygen or sulphur).

This is likely one of the reasons that so many chemists study the syntheses, the reactivities, and the properties of several heterocyclic compounds.

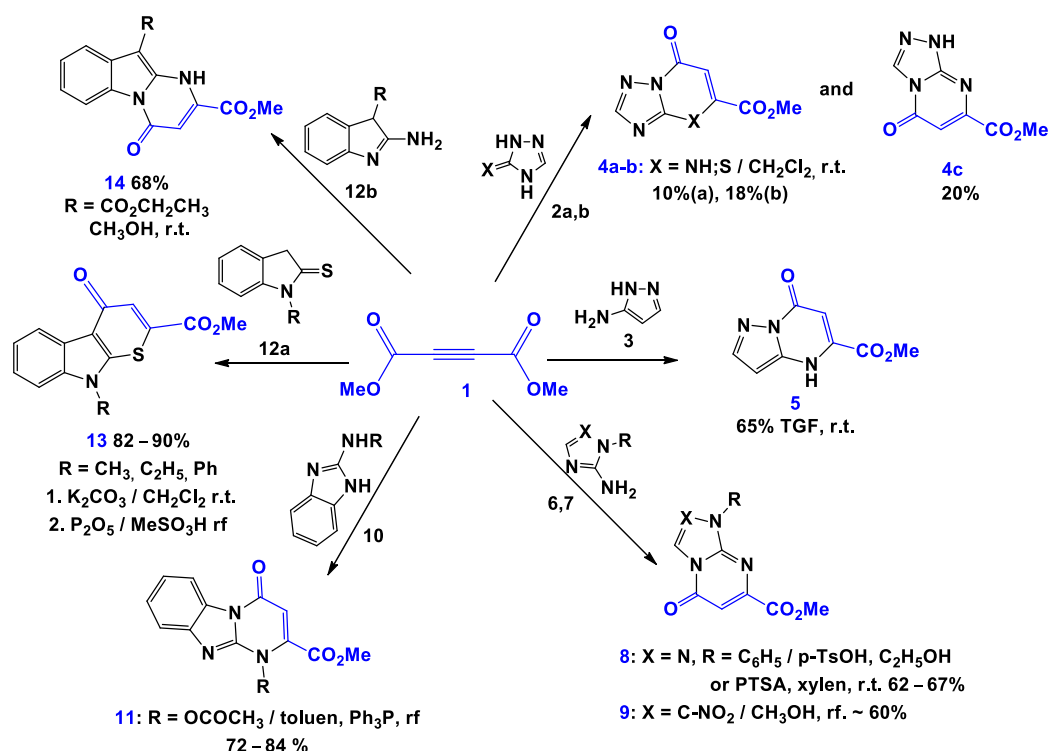
Thus, in the past few decades we have studied rearrangements [1–4], heterocyclizing-openings [5–9], and the different behaviors [10–12] of many heterocyclic compounds, also gaining useful information on their pharmacological activities (cardiovascular [13–15], antitumor [16–18], and anti-MDR1 [19,20] effects have been evaluated).

We have focused our attention on both mono- and poly-cyclic systems. Now, we are turning our interest to the study of a reaction able to "build" a new ring on an already existing one.

Among the reagents employed in this field, special attention has been devoted to the use of dimethyl acetylenedicarboxylate (1, DMAD). It represents a versatile synthetic reagent useful for the discovery of new methods in combinatorial chemistry and multi-component reactions, able to produce heterocyclic compounds. Being an electron-deficient acetylene derivative, it can act as a Michael acceptor or participate in cycloaddition reactions (Diels-Alder, 1,3-dipolar and [2 + 2] cycloaddition) depending on the chosen reagents/conditions. The ability of DMAD to form zwitterions in multicomponent processes is quite important. The interactions of DMAD with amino azoles, leading to the formation of different heterocyclic systems from structurally similar initial bi-nucleophilic substrates, depend on experimental conditions and on reagents used. In fact, the observed

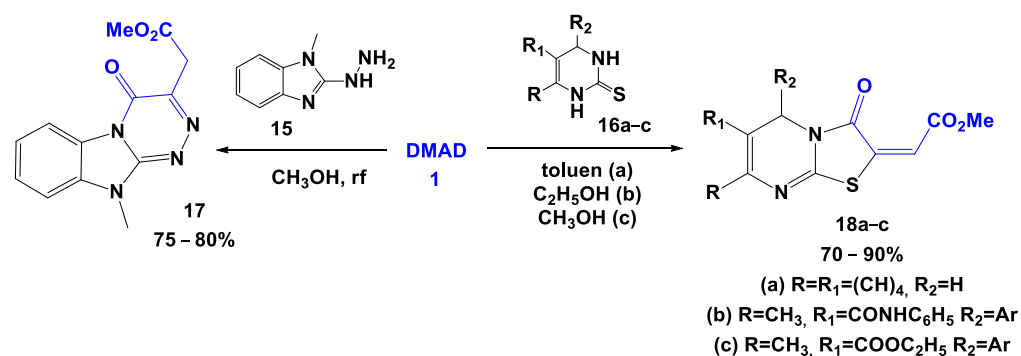
different results can depend on the used solvent, on the catalyst, and on the nature of the substituents present in the used substrates.

For example, it was found that *N,N*- and *N,S*-dinucleophiles, such as amino- and mercaptotriazoles **2a** and **2b**, respectively [21,22], by interaction with DMAD in dichloromethane, led to the formation of 4,7-dihydro-*s*-triazolo[1,5-*a*]pyrimidinones **4a**, [1,2,4]triazolo[5,1-*b*][1,3]thiazinones **4b** and dihydro[1,2,4]triazolo[4,3-*a*]pyrimidinones **4c** with high antibacterial activity [23,24] (Scheme 1). In a first step, an addition of DMAD at the multiple bond by the amino or mercapto group of the starting triazole occurs, then an intramolecular cyclization on the NH fragment due to the “far” ester group happens. A similar process, involving *N*-substituted aminotriazoles **6**, [25] aminoimidazoles **7** and **10**, [26,27] aminopyrazoles **3**, [28] 2-amino-3-carboethoxyindoles **12b** [29], and indoline-2-thiones **12a** [30] leads to the formation of [1,2,4]triazolo[4,3-*a*]pyrimidinones **8**, imidazo[1,2-*a*]pyrimidinones **9** and **11**, pyrazolo[1,5-*a*]pyrimidinones **5**, pyrimido[3,2-*a*]indolones **14**, and thiopyrano[2,3-*b*]indolones **13**.



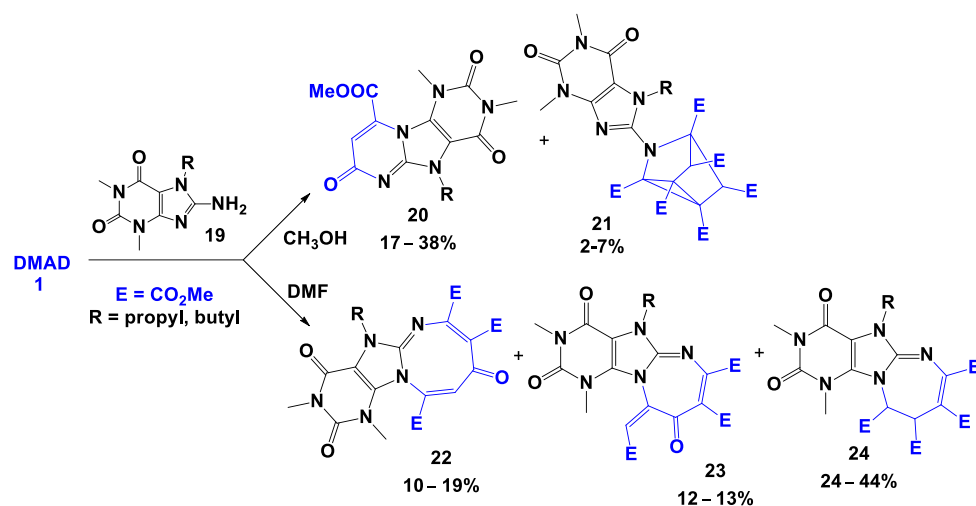
Scheme 1. Interaction of DMAD (1) with *N,N*- and *S,N*-dinucleophiles.

With some dinucleophiles, the intermediates initially formed by the addition on the multiple bonds of DMAD can undergo cyclization at the nearest ester group. Such reaction has been described for 2-hydrazinobenzimidazoles **15** [31] and 3,4-dihydropyrimidine-2-thiones **16a–c**, [32–34] with the formation of dihydrobenzo[4,5]imidazo[2,1-*c*][1,2,4]triazines **17** and dihydrothiazolo[3,2-*a*]pyrimidines **18**, respectively (Scheme 2).



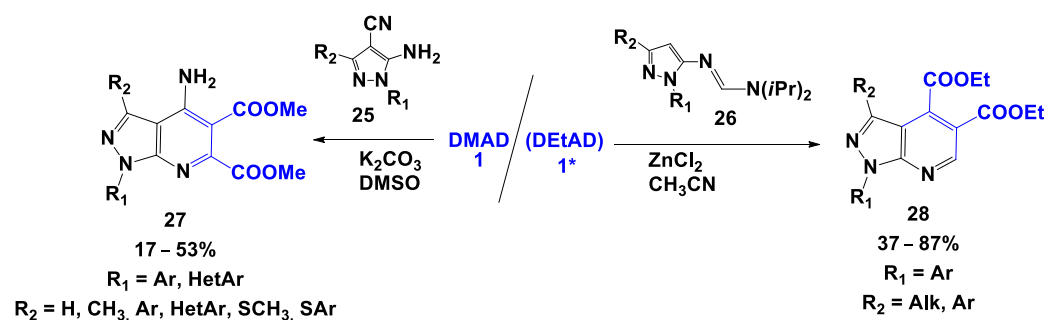
Scheme 2. Formation of cyclic products due to the “nearest” carboxyl group.

Ueda et al. [35] found that when DMAD was reacted with 7-alkyl-8-amino-1,3-dimethylxanthines amines **19** in methanol, 5-alkyl-1,3-dimethyl-9-methoxycarbonyl-1,2,3,4-tetrahydro-5*N*,7*N*-pyrimido[1,2-*e*]purine-2,4,7-triones **20** and 7-alkyl-1,3-dimethyl-1,2,3,6-tetrahydro-8-(1,2,4,5,6,7-hexamethoxycarbonyl-3-azatricyclo[2.2.1.0^{2,6}]heptyl)purine-2,6-diones **21** were formed (Scheme 3). However, the reaction, performed in dimethylformamide, led to the formation of the mixture of diazocino- and diazepinapurines **22–24**.



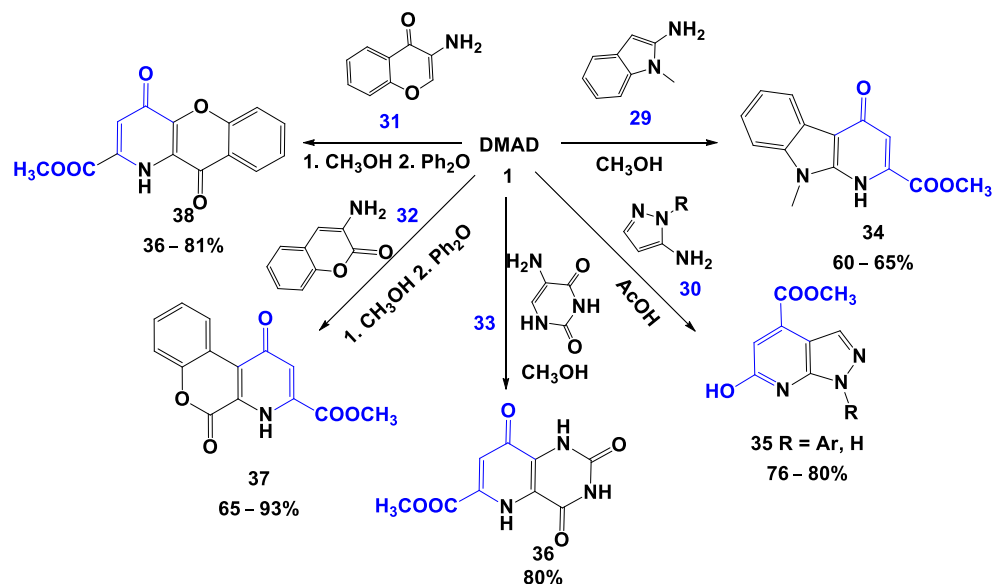
Scheme 3. Reactions of xanthines with DMAD.

It has also been observed that 1,3-substituted 5-aminopyrazole-4-carbonitriles **25** [36] (in the presence of potassium carbonate, in DMSO) and *N,N*-diisopropylamidinylpyrazolamines **26** [37] (in the presence of catalytic amounts of zinc chloride in acetonitrile) interact with DMAD (in case **26** DEtAD **1*** has been used), inducing an Aza-Diels–Alder reaction, leading to the formation of the relevant 4-aminopyrazolo[3,4-*b*]pyridine-5,6-dicarboxylates **27** and 1*H*-pyrazolo[3,4-*b*]pyridine-4,5-dicarboxylates **28** (Scheme 4), respectively.



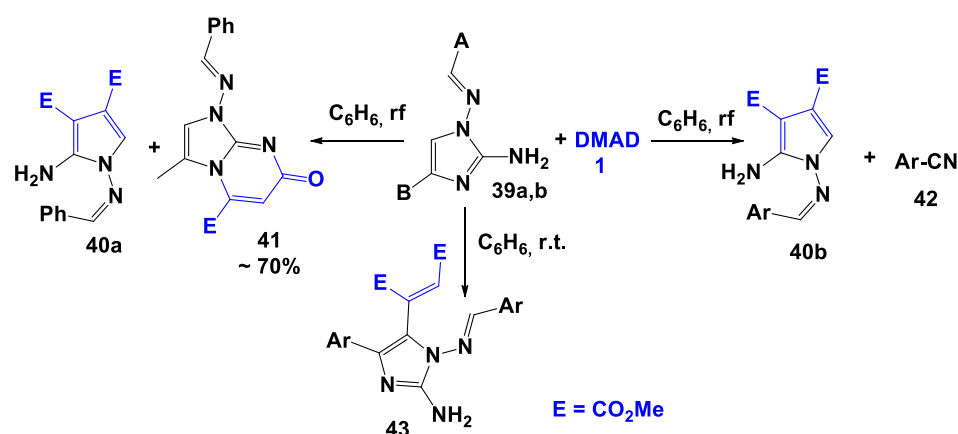
Scheme 4. Cyclization of DMAD with the involvement of C,N-dinucleophiles and systems containing nucleophilic and electrophilic groups.

It was discovered that when 1-substituted 5-aminopyrazoles 30 (prolonged boiling in acetic acid), [38] 1-methyl-2-aminoindoles 29 (prolonged boiling in methanol), [29] 3-aminocoumarin 31, 3-aminochromone 32 (in methanol and diphenyl ether) [39], and aminouracil 33 (methanol at room temperature) [40,41] were used, DMAD acts as a Michael acceptor, promoting the formation of the corresponding heterocyclic systems (Scheme 5).



Scheme 5. Cyclization of DMAD with the involvement of C,N-dinucleophiles.

Reactions with polynucleophiles are quite complex. In fact, Miyamoto [42] observed that the course of the reaction of DMAD 1 with 2-amino-4-R-1-arylideneaminoimidazoles 39 in benzene depends on the nature of the present substituents and the temperature of the reaction. For example, interaction with 2-amino-1-benzylidenamino-4-methylimidazole 39a in boiling benzene led to the formation of dimethyl-2-amino-1-benzylidenamino-1H-pyrrole-3,4-dicarboxylate 40a and methyl 1-benzylidenamino-4-methyl-5-oxo-1H-imidazole pyrimidine-7-carboxylate 41. Vice versa, in the instance of 2-amino-4-aryl-1-arylideneaminoimidazoles 39b, the previously described pyrroles 40b in a mixture with benzonitriles 42 were isolated after boiling. Moreover, performing the reaction at room temperature the formation of dimethyl-1-(2-amino-1-benzylidenamino-4-aryl-1N-imidazol-5-yl)fumarates 43 was observed (Scheme 6).



Scheme 6. Interaction of DMAD with 2-amino-4-R-1-arylideneaminoimidazoles.

Looking at the complex aforementioned results, we have focused our attention on the study of the reaction of DMAD with non-symmetric polynucleophiles deriving from 1,2-diaminoimidazoles: the influence of reaction conditions on the regioselectivity will be examined using classical organic synthesis and quantum chemical calculations.

2. Results and Discussion

Considering the fact that the observed course of reaction of DMAD **1** with some nucleophiles depends on the nature of the solvent, first we have investigated and selected the optimal reaction conditions, examining the possible interactions of **1** with 1,2-diamino-4-phenylimidazole **44a**. Based on the literature data and considering the solubility of the starting diamine, we have chosen the possible solvents benzene, dioxane, chloroform, methylene chloride, methanol, and ethanol. The composition of the reaction mixture was assessed using the absolute normalization method based on HPLC-MS analysis. The signals were interpreted on the basis of preliminary calculated weights, in the form of molecular ions with $[M+H]^+$ of all the possible initial, intermediate, and expected final compounds. Samples were treated for 0, 60, and 120 min. It should also be noted that under the conditions of our HPLC-MS experiment, DMAD was not protonated or detected at a given wavelength. The results obtained are portrayed in Table 1.

Table 1. Content of 1,2-diamino-4-phenylimidazole determined by the reaction mass (%).

Solvent *	HPLC-MS Analyses of the Reactions, min		
	0	60	120
Benzene	100	80	63
1,4-Dioxane	100	50	35
CH ₂ Cl ₂	100	60	40.2
CHCl ₃	100	70	54.5
EtOH	100	37.6	0.57
MeOH	100	14.6	0
MeOH/AcOH (cat)	100	0.71	-
MeOH/AcOH (1:1)	100	42.1	32.8

* Boiling an equimolar mixture of **1** and **44a** in the appropriate solvent.

As can be observed, when solvents such as benzene, dioxane, chloroform, or methylene chloride were used, the highest conversion of the starting diamine after 2 h of boiling is about 37–65%. In this case, the mass spectra of the reactions indicate signals of the formed intermediates and products of their intramolecular cyclization.

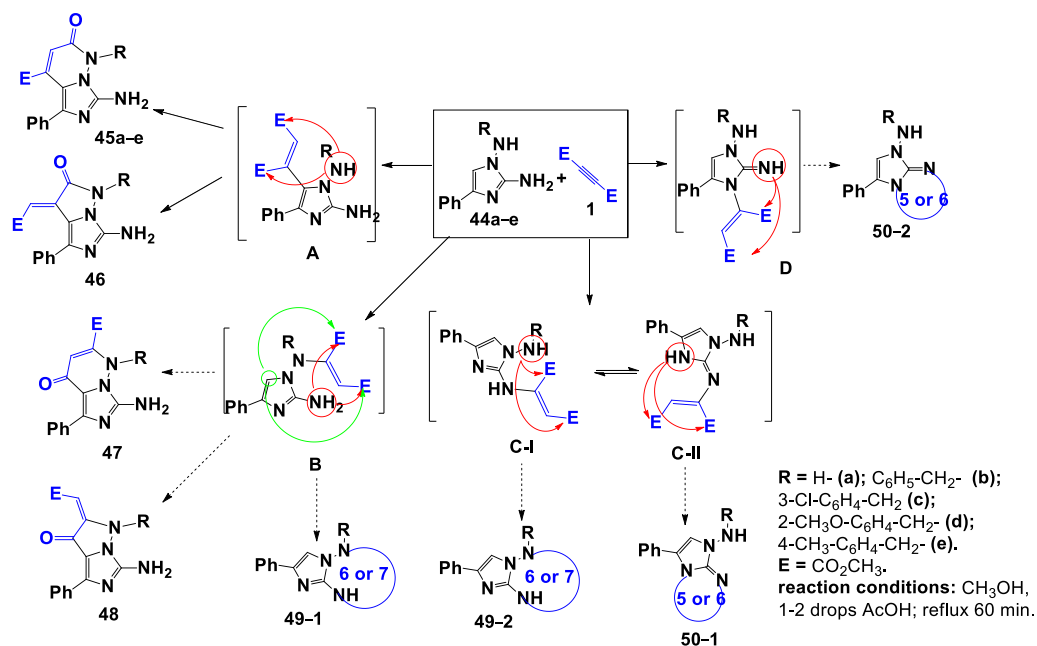
A different behavior was observed when methanol or ethanol were used as solvents: complete conversion of 1,2-diamino-4-phenylimidazole occurred in 2 h. However, using ethanol, the formation of the target reaction product was significantly low, in line with an ongoing process of transesterification of the ester group. Moreover, the formation of a

mixture of ethyl and methyl esters makes more complex the identification/analysis of the products of reaction.

We have previously observed that heterocyclization reactions involving diaminoimidazole are accelerated by acid catalysis (for example, by acetic acid) [43–45]. In this case, we have observed that the addition of acetic acid, using methanol as a solvent significantly affected the reactivity. In fact, as presented in Table 1, the addition of catalytic amounts of acetic acid allows a complete conversion of the reactant in 60 min. It should be noted that, on the contrary, conducting a reaction in a mixture of acetic acid and methanol (1:1) reduces the reactivity of the reagents and leads to the formation of several by-products.

Thus, it was discovered that the reaction between dimethylacetylenedicarboxylate **1** and 1,2-diamino-4-phenylimidazoles **44a–e** proceeds most smoothly when methanol with the addition of a catalytic amount of acetic acid was used as solvent. In this case, the complete conversion of the starting diamine and the maximum yield of the target product were achieved after an hour of boiling the reagents.

Considering the polynucleophilic nature of the starting 1,2-diaminoimidazoles **44a–e**, Scheme 7 reports the structures of all possible intermediates of their interaction with DMAD **1**. Thus, during the first step, the nucleophilic addition of **44a–e** on the triple bond of **1** due to the nucleophilic CH, NH, and NH₂ groups, in addition to the nitrogen atom of the cycle, can lead to the formation of the intermediates **A–D**. The resulting Michael adducts can undergo intramolecular cyclization, due to the “near” or “far” carboxyl group, with the formation of the corresponding products **45–50**.



Scheme 7. Possible ways of interaction of 1,2-diaminoimidazoles with DMAD.

To gain information on the real course of the reaction, we have examined the ¹H-NMR spectra of the products of reaction. We have observed that, in them, the characteristic CH signals of the imidazole ring fragment and of the amino group of the hydrazine fragment were absent; this observation allowed us to exclude the possibility that compounds **49** and **50** were formed. A further confirmation of this hypothesis was derived from the presence of the amino group signals at C-7 (6). Moreover, the spectra of the isolated compounds contained signals of the protons of the pyridazine ring at δ = 5.9–6.3 ppm, while the spectra of compound **45a**, in which R was a hydrogen atom, contained the characteristic signal of the amide proton at δ = 11.75 ppm. Thus, it was possible to also exclude the structures **46** and **48**. At this point, we can confirm that only the structures **45** and **47** are possible for the obtained products of reaction.

The key criterion for choosing between these two structures (**45** and **47**) was the presence of cross peaks in the NOESY spectrum between the protons of the methyl group of the ester fragment and the *ortho*-protons of the aromatic ring present on C-5 of the imidazole ring, as presented in Figure 1 for compound **45b**. Thus, we can conclude that the reaction of 1,2-diaminoimidazoles **44a–e** with DMAD produces the methyl esters of 7-amino-1,2-dihydro-1-R-2-oxo-5-phenylimidazo[1,5-*b*]pyridazine-4-carboxylic acids **45a–e**.

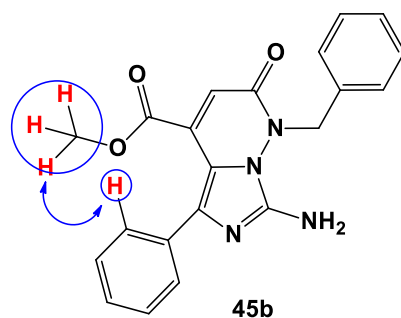
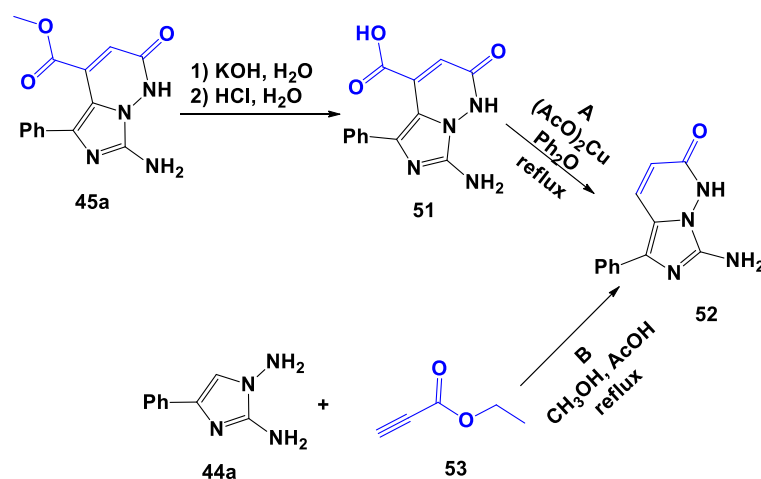


Figure 1. Key interactions for compound **45b** in the NOESY spectra.

Of course, the structures of all the obtained compounds (**45a–e**) have been confirmed by the collected spectroscopic data (^1H - and ^{13}C -NMR, in addition to HRMS data). All of the examined reactions occurred with good/excellent yields (68–89%).

To obtain an additional confirmation of the structure of the obtained imidazopyridazines **45a–e** and as a further step of our research, we have carried out the transformation of methyl 7-amino-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-*b*]pyridazine-4-carboxylate **45a** into 7-amino-5-phenylimidazo[1,5-*b*]pyridazin-2-one **52** (Scheme 8). Thus, by alkaline hydrolysis **45a** produced the relevant carboxylic acid **51**, which, in turn, by refluxing in diphenyl ether in the presence of copper acetate, furnished by decarboxylation (pathway A) the 7-amino-5-phenylimidazo[1,5-*b*]pyridazin-2-one **52**. The structure of isolated compounds **51** and **52** was proven by ^1H - and ^{13}C -NMR spectroscopy and HRMS.



Scheme 8. Alternative syntheses of 7-amino-5-phenylimidazo[1,5-*b*]pyridazin-2-one (**52**).

The structure of imidazopyridazine **52** was also confirmed by the NOESY spectrum, in which cross-interaction between the CH proton of the pyridazine ring and *ortho*-protons of the aromatic ring was observed (Figure 2). This kind of interaction is impossible for this couple of protons in all alternative structures **46–48**. Therefore, the proven structure of imidazopyridazine **52** has further confirmed that in the course of the interaction between 1,2-diaminoimidazoles **44a–e** and DMAD, methyl esters of 7-amino-1,2-dihydro-1-R-2-oxo-5-phenylimidazo[1,5-*b*]pyridazine-4-carboxylic acids **45a–e** have been obtained.

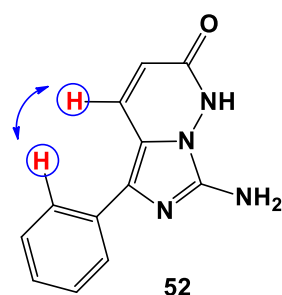


Figure 2. Key interactions concerning compound **52** in the NOESY spectra.

The structure of compound **52** was further confirmed by preparing it with an alternative synthesis, id est by treating the 1,2-diamino-4-phenylimidazole **44a** with ethyl propargylate **53** (Scheme 8, pathway B). As in the instance of the reaction with DMAD, the optimal condition was boiling for 60 min the mixture of reagents in methanol with the addition of a couple of drops of acetic acid under constant stirring.

To obtain further information on the course of the reaction between 1,2-diaminoimidazoles **44** and DMAD **1**, we have calculated the minimum energy paths (MEP) for the reaction. Quantum-chemical DFT calculations were performed using B3LYP/6-311++G(d, p) basis and considering the solvation effects by the polarizable continuum model (PCM) in methanol.

Firstly, we examined the interaction of the simplest 4-phenyl-1*H*-imidazole-1,2-diamine **44a** and DMAD **1**, leading to the formation of **45a**.

In the first step of this process, a nucleophilic attack of carbon atom C-5 of imidazole on a carbon atom of the triple bond of DMAD **1** occurred with the formation of the bipolar σ -complex **54**, which was 23.3 kcal/mol higher in energy compared to the starting reagents (Figure 3).

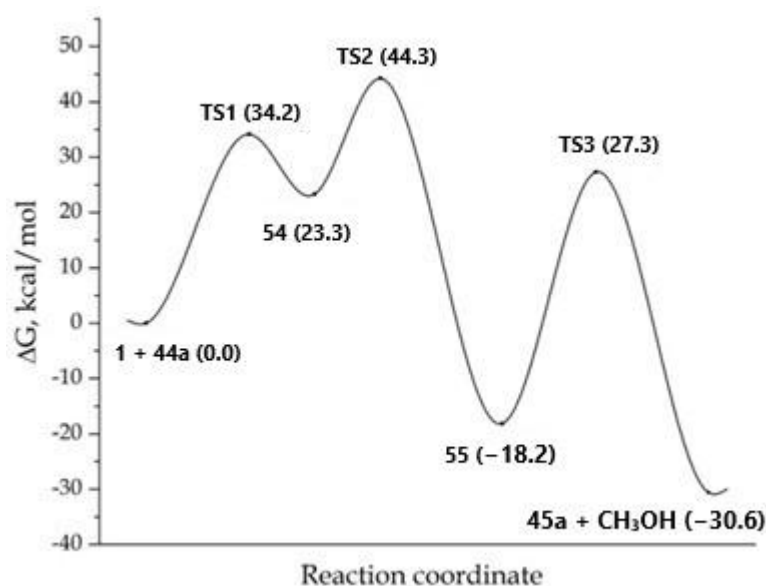
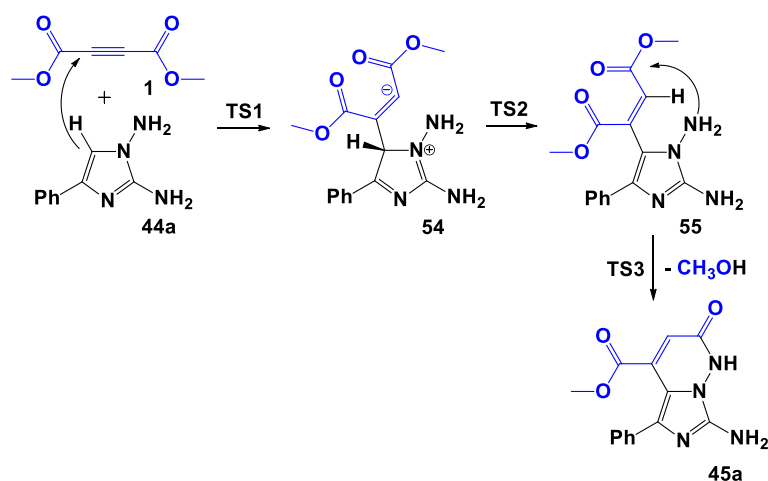


Figure 3. MEP for the reaction concerning the formation of product **45a**. The total energy of the starting reagents **1** and **44a** was taken as the reference point.

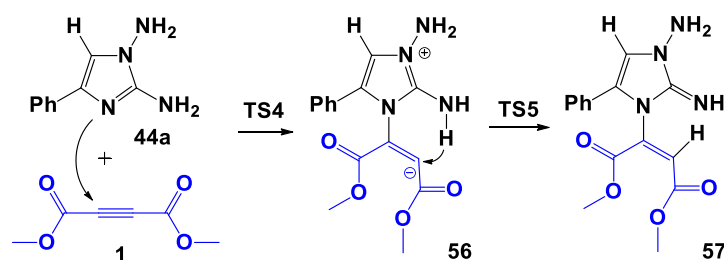
Now we will discuss the change in the relative free energy ΔG . During the second step of the process, a 1,3-hydrogen shift occurred and the covalent σ -complex **55** was formed: although the formation of this structure required an activation energy of 21.0 kcal/mol, **55** is produced, which is much more stable. In the final step, an intramolecular nucleophilic attack by the nitrogen atom of the amino group on the carbonyl carbon atom occurred, followed by the elimination of the methanol molecule and the formation of the final product

45a. The formation of **45a** was highly exothermic (a gain of 30.6 kcal/mol occurred), and it required the overcoming of a very large energy barrier (45.5 kcal/mol) in the last step (TS3) (Scheme 9).



Scheme 9. Proposed bimolecular formation mechanism of **45a**.

Then we considered the reaction proceeded via the intermediate D, theoretically leading to the formation of product **50-2** (Schemes 7 and 10).



Scheme 10. Proposed bimolecular formation mechanism of **57**.

During the first step of the studied process, a nucleophilic attack by N-3 of imidazole on a carbon atom of the triple bond of DMAD **1** occurred with the formation of the bipolar σ -complex **56**. As in the previous instance, the formation of a non-classical structure is energetically unfavorable; in fact, structure **56** was 20.2 kcal/mol higher in energy than the initial reagents (Figure 4). During the second step, a 1,5-hydrogen shift occurred and the compound **57** was formed. It should be noted that **57** appears to be the final product; in fact, further cyclization into product **50-2** was not observed. In general, this path was weakly endothermic: **57** was energetically less favorable than the initial reagents, then the formation of complex **D** was unlikely.

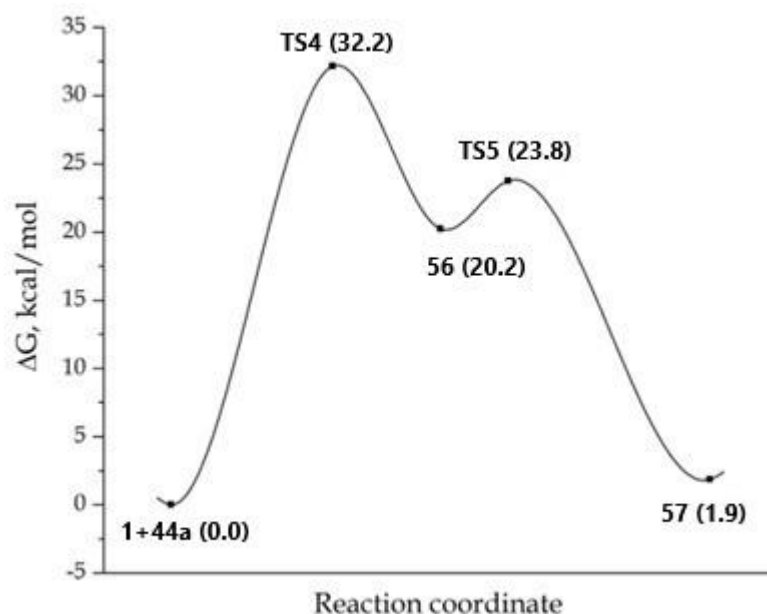
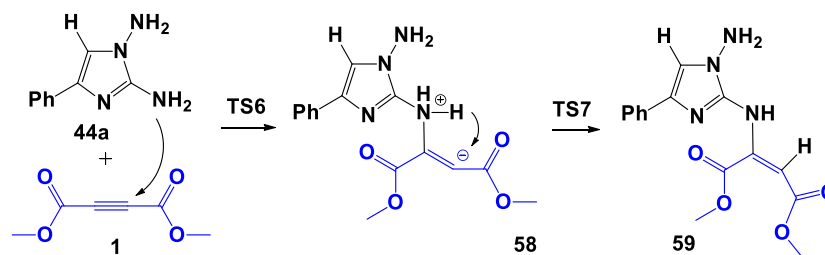


Figure 4. MEP for the reaction concerning the formation of adduct 57. The total energy of the starting reagents **1** and **44a** was taken as the reference point.

Now the formation of a complex of type C (leading to products **49-2** or **50-1**) will be examined (Schemes 7 and 11).



Scheme 11. Proposed bimolecular formation mechanism of **59**.

Now, during the first step of the reaction, anucleophilic attack of the nitrogen atom of the amino group linked at the C-2 atom of imidazole occurred on a carbon atom of the triple bond of DMAD **1** with the formation of the bipolar σ -complex **58**: it was 33.4 kcal higher in energy than the starting reagents (Figure 5). The following 1,3-hydrogen shift led to the formation of the covalent adduct **59**. However, as in the previously examined process (Scheme 10), the following cyclization into products **49-2** or **50-1** did not exist on the potential energy surface (PES).

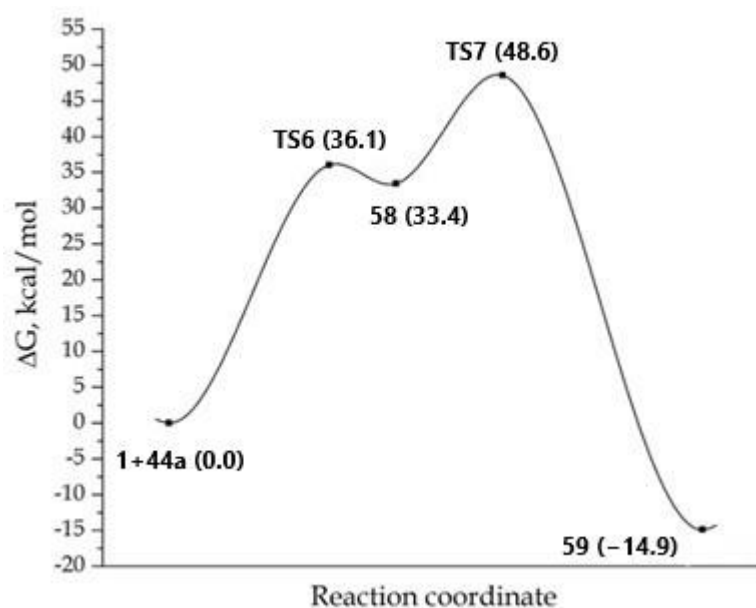
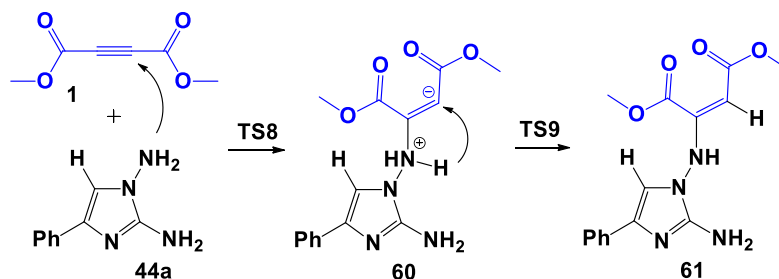


Figure 5. MEP for the reaction concerning the formation of adduct 59. The total energy of starting reagents **1** and **44a** was taken as the reference point.

The processes involving the formation of type **B** complexes proceeded through the formation of a bipolar σ -complex. Zwitterionic adduct **60** was formed by the nucleophilic attack of the *N*-amino group of imidazole **44a** on a carbon atom of the triple bond of DMAD **1** (Scheme 12), then giving the covalent adduct **61** as a result of the 1,3-hydrogen shift. The formation of adduct **61** from DMAD **1** and **44** was energetically favorable and was accompanied by an energy gain of 17.3 kcal/mol (Figure 6). The maximum barrier of the process **1** + **44** → **61** concerns the first stage (TS8) and required an activation energy of 38.2 kcal/mol. As in the two previous cases, the formation of a cyclic structure from adduct **61** was not suggested by PES.



Scheme 12. Proposed bimolecular formation mechanism of **61**.

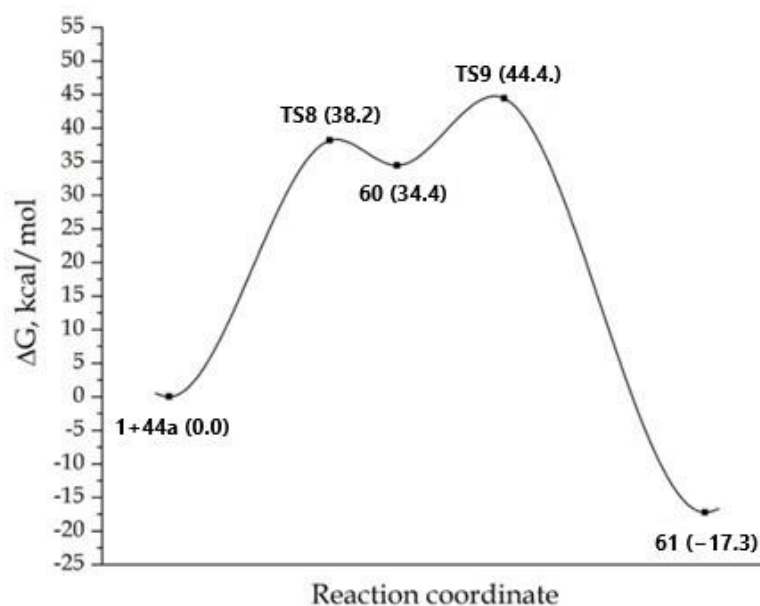
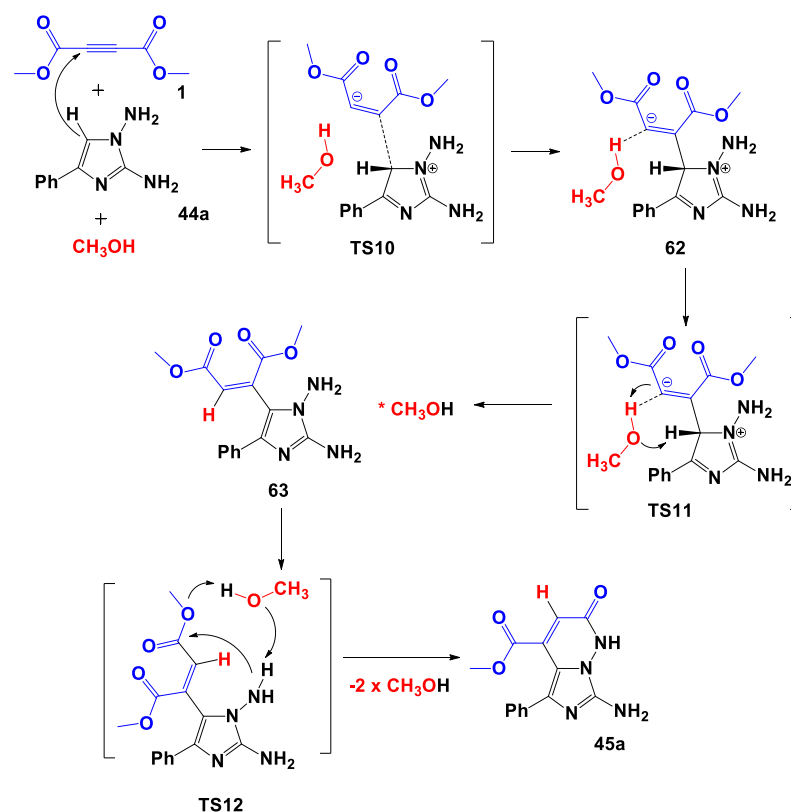


Figure 6. MEP for the reaction concerning the formation of adduct **61**. The total energy of the starting reagents **1** and **44a** was taken as the reference point.

In conclusion, calculations for the bimolecular pathways of interaction of 4-phenyl-1*H*-imidazole-1,2-diamine **44a** and DMAD **1** indicated that between the hypothetical cyclic products **45**–**50**, only the formation of a cyclic system **45a** appeared as a possible path of reaction. In addition, data of quantum-chemical calculations on the course of the bimolecular processes indicated that the open-chain covalent adducts **59** and **61** could be formed, but their formation occurred with an energy barrier in the first stage higher than in the instance of the formation of adduct **54**.

Since, according to the results of the experiments carried out using an alcohol as solvent of reaction, re-esterification products were recorded, we concluded that the interaction of 4-phenyl-1*H*-imidazole-1,2-diamine **44a** and DMAD **1** can develop not only via a bimolecular process, but also as a trimolecular process with the involvement of an alcohol molecule. For this, we performed the quantum-chemical calculation of paths involving methanol.

Firstly, we have considered the trimolecular process concerning the formation of the target product **45a** (Scheme 13, Figure 7). At the molecular level, the methanol molecule affects all steps of the process. Thus, in the first step, during the formation of the bipolar σ -complex **62**, the proton of the hydroxyl of methanol was coordinated to the carbon atom charged negatively in the multiple bond. However, no stabilization of the zwitterionic structure (compared with the process on Scheme 9) occurred; in fact, the adduct **62** was less energy-efficient by 27.1 kcal/mol compared to the starting reagents. Furthermore, the low barrier of the 1,3-hydrogen shift which led to **63** was performed through a five-center transition state (**TS11**), in which the molecule of methanol acted as a bifunctional catalyst.



Scheme 13. Proposed trimolecular formation mechanism of **45a**.

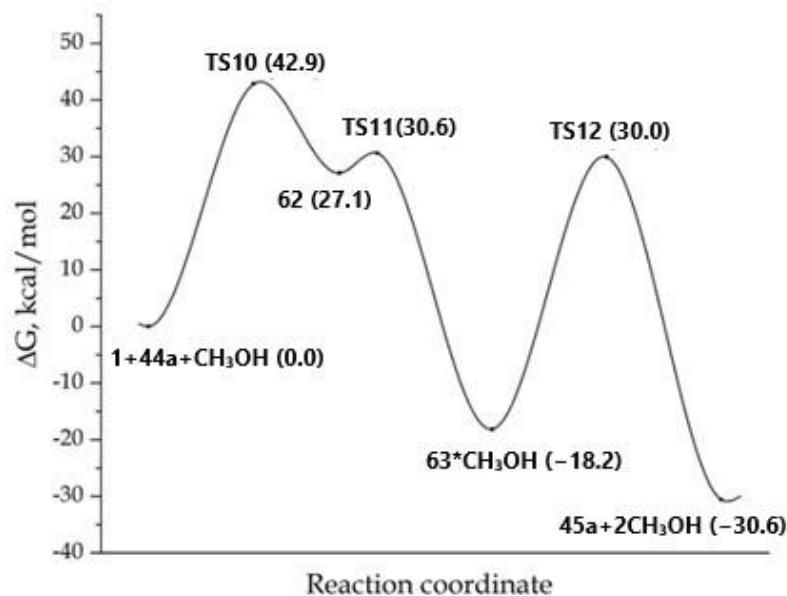
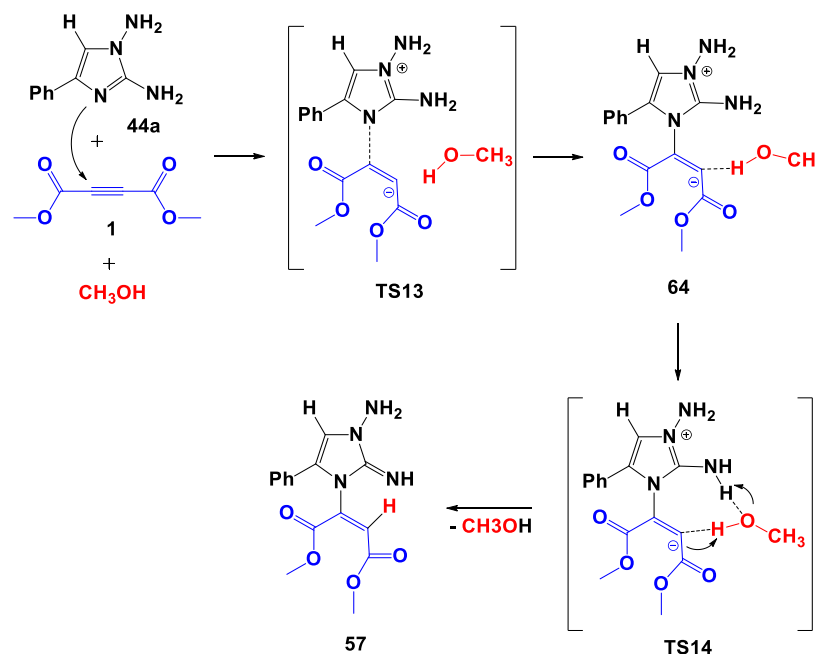


Figure 7. MEP for the trimolecular reaction concerning the formation of product **45a**. The total energy of the starting reagents **1**, **44a** and methanol was taken as the reference point.

Finally, the covalent **63** was transformed into product **45a** through the transition state **TS12**, in which the molecule of methanol again performed the function of a bifunctional catalyst and participated in the formal transfer of a proton from the *N*-amino group to the ester oxygen atom. Despite the participation of the methanol in the proton transfer, the formation of product **45a** from **63** proceeded with a barrier of 48.2 kcal/mol, which was higher than in the process portrayed in Scheme 9.

The addition of a methanol molecule in the process presented in Scheme 10 causes an effect at the molecular level (Scheme 14). Thus, when the bipolar intermediate **64** was formed from the initial reagents, the methanol coordinated the proton of the hydroxy group to the carbon atom of the double bond.



Scheme 14. Proposed trimolecular formation mechanism of **57**.

Despite the coordination of the zwitterionic **56** with a molecule of methanol in complex **64**, this was 28.1 kcal/mol higher in energy than the initial reagents, which in turn means 7.9 kcal/mol higher in energy than for **56** in Scheme 10 (compare Figures 4 and 8).

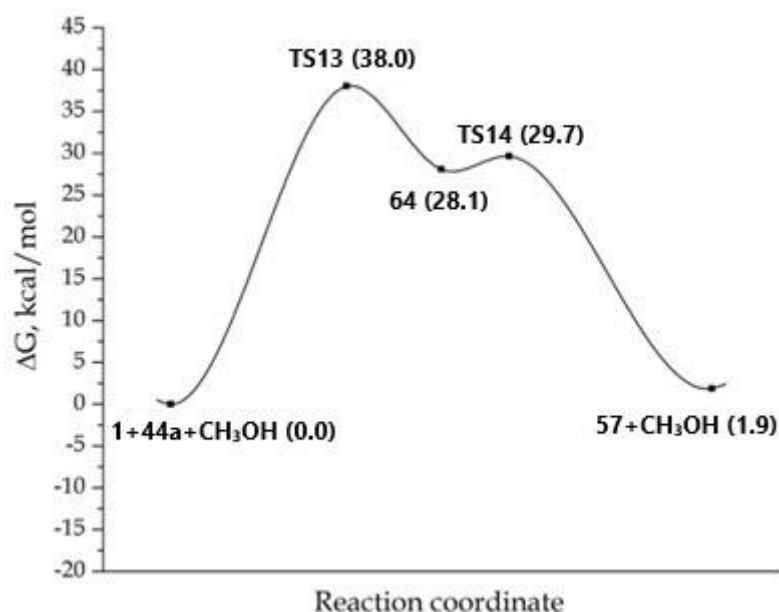


Figure 8. MEP for the trimolecular reaction concerning the formation of adduct **57**. The total energy of the starting reagents **1**, **44a** and methanol was taken as the reference point.

The methanol molecule facilitated the 1,5-proton transfer, being included in the eighth-center transition state (**TS14**), performing the function of a bifunctional catalyst. As before, the process of the formation of structure **57** was endothermic.

When the methanol molecule was involved in the processes reported in Schemes 11 and 12, we observed a similar pattern (see Supplementary Materials). It was coordinated with the zwitterion, destabilizing it. However, during the following step of the process, the methanol acted as a bifunctional catalyst facilitating the transfer of the hydrogen atom. In this case, the reactions, as in the case of the bimolecular pathway, stop at the stage of the formation of the covalent adducts.

According to the calculation data, a pattern analogous to the trimolecular processes with the involvement of methanol was observed in the case of the participation of acetic acid in the trimolecular process at the molecular level. Thus, for the process of formation of the compound **45a** from the initial compounds, the barrier of the first stage of the formation of the zwitterionic associate was 40.4 kcal/mol, and the zwitterionic associate itself was 26.3 kcal/mol higher in energy than the initial reagents. The covalent adduct into which it rearranged, as a result of electron transfer, was 9.0 kcal/mol higher in energy compared to the starting reagents. The trimolecular process with the involvement of acetic acid, as in the case of the participation of methanol, TS was higher in energy than in the corresponding bimolecular processes. Obviously, in all the cases considered, the involvement of a polar protic solvent at the molecular level can make worse the course of reactions. However, the covalent and zwitterionic intermediates in trimolecular processes were higher in energy than the intermediates infinitely separated from the solvent molecules, which means that the reaction can proceed by bimolecular pathways without switching to the trimolecular ones. Then, the experimentally observed ease of processes in polar solvents is explained exclusively by the dielectric constant (polarity of the medium). In fact, the higher the polarity of the medium, the higher the stabilization energy of zwitterionic or ionic processes [46].

When switching from the gas-phase calculations to the PCM medium accounting for the process in Scheme 9, we observed a reduction in the barrier values. Thus, the barrier of the first stage (TS1) is only 27 kcal/mol (see Supporting Materials) and the thermodynamic gain of the whole process increased to 39.3 kcal/mol.

Thus, based on quantum chemical calculations, the following conclusions can be drawn:

- the predominant cyclic product of the interaction of diaminoimidazoles **44** with DMAD **1** is imidazopyridazines **45**;
- open-chain nucleophilic addition products of diaminoimidazoles **44** to DMAD **1** at positions other than the C-2 carbon atom, which are less preferable kinetically, can participate in a further cascade of processes leading to the formation of difficultly separable mixtures not involved in further intramolecular cyclization;
- interaction of diaminoimidazoles **44** with DMAD **1** is complicated in the instance that methanol or acetic acid participate to the reaction. In fact, the participation of the molecules of the third component in the formation of the primary bipolar σ -complexes can destabilize them. Conversely, during the following steps of the process, they can facilitate the transfer of protons because of the formation of classical covalent adducts;
- the fact that all stationary points in the instance of trimolecular processes are higher in energy than the sum energies of the corresponding points and solvent molecules in case of bimolecular processes makes trimolecular processes alternative, but not real, processes.
- polar solvents can facilitate the formation processes of type **45** systems due to their polarity (ϵ value), stabilizing polar intermediates, and not due to their direct involvement in the processes.

3. Materials and Methods

3.1. General

^1H NMR, ^{13}C NMR, NOESY spectra were recorded on Bruker DRX-500 devices (500.13 and 125.75 MHz, respectively) in DMSO- d_6 and TFA- d with internal TMS standard. Melting points were taken on a Stuart SMP30 device (Cole-Parmer Ltd., St. Neots, UK). HPLC/MS spectra were recorded on an Agilent Infinity 1260 chromatograph (Agilent Technologies, Palo Alto, CA, USA) with MS interface Agilent 6230 TOF LC/MS. Conditions for the

separation: mobile phase MeCN/H₂O + 0.1% FA (formic acid), gradient elution (first CH₃CN:H₂O (60:40), then for 5 min to 90% CH₃CN), column—Poroshell 120 EC-C18 (4.6 × 50 mm, 2.7 μm), thermostat 23–28 °C, flow rate of 0.3–0.4 mL/min electrospray ionization (capillary—3.5 kV; fragmentor +191 V; OctRF +66 V—positive polarity). The course of the reaction and the purity of the obtained compounds were controlled by TLC on Merck TLC Silica gel 60 F254 plates in a 20:1 CHCl₃–MeOH system (visualization under UV light). The commercially available reagents were purchased from Acros Organics (Geel, Belgium).

Quantum chemical DFT calculations were carried out in the 6–311++G(d,p) triple-zeta basis using a B3LYP functional [47]. This basis has provided a good account of itself in reproduction of vibrational frequencies, geometry, and minimum energy reaction paths [48–50]. Full geometry optimization of molecular structures corresponding to stationary points of the potential energy surface was carried out as high as a gradient value of 10^{−7} hartree/bohr according to the Gaussian 09 software package (Wallingford, CT, USA) [51] using the Silver cluster of the Research Institute of Physical and Organic Chemistry at SFedU. The nature of stationary points was determined relying on the calculation of normal vibration frequencies (the Hessian matrix). MEPs were plotted using gradient descent from transition states in forward and reverse directions of transition vectors. In order to search for transition states, linear and quadratic synchronous transit methods were used [52,53].

3.2. General Procedure for the Synthesis of Methyl 7-Amino-1,2-dihydro-1-R-2-oxo-5-phenylimidazo[1,5-b]pyridazine-4-carboxylates (**45a–e**)

Acetylene dicarboxylic acid dimethyl ester **1** (5 mmol) was added dropwise to 5 mmol of diaminoimidazole **44a–e** dissolved in 5 mL of methanol containing catalytic amounts of acetic acid (2–3 drops). After adding **1**, the reaction mixture was refluxed for 60 min. The precipitated crystals were filtered off and recrystallized from MeOH.

3.2.1. Methyl 7-Amino-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-b]pyridazine-4-carboxylate (**45a**)

Yield (124.4 mg, 89%), orange. Mp: 239–241 °C. ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 11.75 (br.s, 1H), 7.35–7.39 (m, 2H), 7.26–7.32 (m, 3H), 6.23 (s, 1H), 5.91 (s, 2H), 3.41 (s, 3H). ¹³C{¹H} NMR (125.8 MHz, DMSO-*d*₆, δ ppm): 164.9, 158.4, 143.7, 135.4, 134.1, 129.2, 127.8, 127.6, 126.7, 111.0, 104.5, 52.2. HRMS (ESI) *m/z*: [M+H⁺] calc. for C₁₄H₁₂N₄O₃, 285.0982, found 285.0980.

3.2.2. Methyl 7-Amino-1-benzyl-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-b]pyridazine-4-carboxylate (**45b**)

Yield (127.1 mg, 68%), orange. Mp: 153–155 °C. ¹H NMR 500 MHz, DMSO-*d*₆, δ ppm): 7.30–7.38 (m, 3H), 7.23–7.29 (m, 3H), 7.20 (d, *J* = 7.2, 2H), 7.09 (d, *J* = 7.2, 2H), 6.71 (s, 2H), 5.97 (s, 1H), 5.42 (s, 2H), 3.27 (s, 3H). ¹³C{¹H} NMR (125.8 MHz, DMSO-*d*₆, δ ppm): 164.7, 164.5, 146.8, 137.4, 135.5, 135.4, 133.9, 128.6, 128.1, 128.0, 127.9, 127.7, 112.5, 108.9, 52.3, 47.8. HRMS (ESI), *m/z*: [M+H⁺] calc. for C₂₁H₁₈N₄O₃, 375.1453, found 375.1452.

3.2.3. Methyl 7-Amino-1-(3-chlorobenzyl)-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-b]pyridazine-4-carboxylate (**45c**)

Yield (145 mg, 71%), yellow. Mp: 237–239 °C. ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 7.30–7.40 (m, 5H), 7.21–7.24 (m, 2H), 7.12 (s, 1H), 7.01–7.04 (m, 1H), 6.73 (s, 2H), 5.99 (s, 1H), 5.42 (s, 2H), 3.28 (s, 3H). ¹³C{¹H} NMR (125.8 MHz, DMSO-*d*₆, δ ppm): 164.5, 164.3, 146.7, 137.7, 137.5, 135.5, 133.8, 133.0, 130.5, 128.0, 128.0, 129.9, 127.5, 126.1, 112.4, 108.8, 52.2, 47.2. HRMS (ESI), *m/z*: [M+H⁺] calc. for C₂₁H₁₇ClN₄O₃, 409.1061, found 409.1060.

3.2.4. Methyl 7-Amino-1-(2-methoxybenzyl)-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-b]pyridazine-4-carboxylate (**45d**)

Yield (175.7 mg, 87%), red. Mp: 185–187 °C. ¹H NMR (500 MHz, DMSO-*d*₆, δ ppm): 7.29–7.38 (m, 3H), 7.17–7.21 (m, 3H), 7.13 (dd, *J* = 1.65, *J* = 8.5, 1H), 6.87 (d, *J* = 7.9, 1H),

6.79 (t, $J = 7.5$, 1H), 6.64 (s, 2H), 5.89 (s, 1H), 5.30 (s, 2H), 3.64 (s, 3H), 3.29 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, DMSO- d_6 , δ ppm): 165.2, 164.7, 157.6, 147.3, 137.3, 135.1, 134.1, 130.7, 129.5, 127.9, 127.8, 127.8, 122.3, 119.7, 112.3, 110.2, 108.9, 54.9, 52.2, 46.8. HRMS (ESI), m/z : $[\text{M}+\text{H}^+]$ calc. for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_4$ 405.1558, found 405.1557.

3.2.5. Methyl 7-Amino-1-(4-methylbenzyl)-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-*b*]pyridazine-4-carboxylate (**45e**)

Yield (149.4 mg, 77%), orange. Mp: 170–172 °C. ^1H NMR (500 MHz, DMSO- d_6 , δ ppm): 7.30–7.38 (m, 4H), 7.20 (d, $J = 7.2$, 1H), 7.07 (d, $J = 7.8$, 2H), 6.98 (d, $J = 7.7$, 2H), 6.68 (s, 2H), 5.96 (s, 1H), 5.37 (s, 2H), 3.27 (s, 3H), 2.21 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, DMSO- d_6 , δ ppm): 164.5, 164.4, 146.7, 137.2, 137.2, 135.3, 133.9, 132.3, 129.1, 128.0, 127.9, 127.9, 127.6, 112.4, 108.9, 52.2, 47.3, 20.5. HRMS (ESI), m/z : $[\text{M}+\text{H}^+]$ calc. for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_3$ 389.1609, found 389.1608.

3.3. Synthesis of 7-Amino-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-*b*]pyridazine-4-carboxylic Acid (**51**)

Potassium hydroxide (5.5 mmol), dissolved in 5 mL of water, was added to 5 mmol of **45a**. The mixture was boiled for 2 h, until **45a** completely disappeared (control by TLC). After cooling, the mixture was acidified with hydrochloric acid. The formed precipitate was filtered off.

7-Amino-1,2-dihydro-2-oxo-5-phenylimidazo[1,5-*b*]pyridazine-4-carboxylic Acid (**51**)

Yield (124.2 mg, 92%), light yellow. Mp: >300 °C. ^1H NMR (500 MHz, DMSO- d_6 , δ ppm): 11.72 (br.s, 1H), 7.40–7.43 (m, 2H), 7.29–7.34 (m, 3H), 7.22 (t, $J = 7.3$, 1H), 6.17 (s, 1H), 5.94 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, DMSO- d_6 , δ ppm): 166.3, 158.8, 143.3, 137.1, 134.6, 127.8, 127.5, 126.5, 111.3, 103.9. HRMS (ESI), m/z : $[\text{M}+\text{H}^+]$ calc. for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_3$ 271.0826, found 271.0825.

3.4. Synthesis of 7-Amino-5-phenylimidazo[1,5-*b*]pyridazin-2(1H)-one (**52**)

3.4.1. Method A

Acid **51** (5 mmol) was dissolved in 5 mL of diphenyl ether under constant heating and stirring, and 15 mmol of copper (II) acetate were added. The reaction mixture was boiled for 3 h. The formed precipitate was filtered off, washed with water, and then recrystallized from a mixture of *i*-PrOH/DMF, 2:1.

3.4.2. Method B

Ethyl propionate **53** (5 mmol) was added dropwise to 5 mmol of diaminoimidazole **44a**, dissolved in 5 mL of methanol in the presence of catalytic amounts of acetic acid (2–3 drops) under constant stirring and heating at 40 °C for 60 min. The formed precipitate was filtered off and recrystallized from a mixture of *i*-PrOH/DMF, 2:1.

3.4.3. 7-Amino-5-phenylimidazo[1,5-*b*]pyridazin-2(1H)-one (**52**)

Yields (36.2 mg, 32% (method A) and 84.8 mg, 75% (method B)), yellow. Mp.: 271–273 °C. ^1H NMR (500 MHz, DMSO- d_6 , δ ppm): 11.35 (br. s, 1H), 8.08 (d, $J = 9.7$, 1H), 7.79 (d, $J = 7.5$, 2H), 7.38 (t, $J = 7.6$, 2H), 7.20 (t, $J = 7.3$, 1H), 6.08 (d, $J = 9.6$, 1H), 5.75 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (125.8 MHz, DMSO- d_6 , δ ppm): 159.0, 143.2, 134.9, 129.7, 128.6, 126.6, 125.8, 125.1, 115.7, 104.4. HRMS (ESI), m/z : $[\text{M}+\text{H}^+]$ calc. for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}$ 227.0928, found 227.0926.

4. Conclusions

A new approach for the synthesis of 7-amino-1,2-dihydro-1-*R*-2-oxo-5-phenylimidazo pyridazine-4-carboxylic acids and their esters (**45a–e**) from readily available 1,2-diamino-4-phenylimidazoles and dimethylacetylene dicarboxylate (DMAD) was suggested. DFT calculations indicated that this synthesis proceeds via the formation of low-barrier interme-

diates. The use of a protic solvent (methanol and few drops of acetic acid) accelerates the course of the processes; this fact is probably not due to their involvement as catalysts, but to a change in the dielectric constant of the medium, able to stabilize polar intermediates. DFT results confirm the experimental results, moreover, the observed course of the reaction (formation of compounds **45a–e**) is confirmed by spectroscopic results.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules27103326/s1>. Copies of ^1H , ^{13}C NMR, NOESY and HPLC/MS spectra; HPLC/MS analysis of reaction masses; methods of quantum chemical calculation; calculated transition states geometries; cartesian coordinates of all stationary point (PDF).

Author Contributions: D.Y.V. and K.S.S. supervised the experiment and provided technical guidance and wrote the original draft. D.A.M. and T.N.I. designed and synthesized all of the novel compounds. M.A.P. performed spectral and chromatographic analysis. O.N.B. and A.V.L. performed DFT calculations and described the results. A.G. and D.S. performed writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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