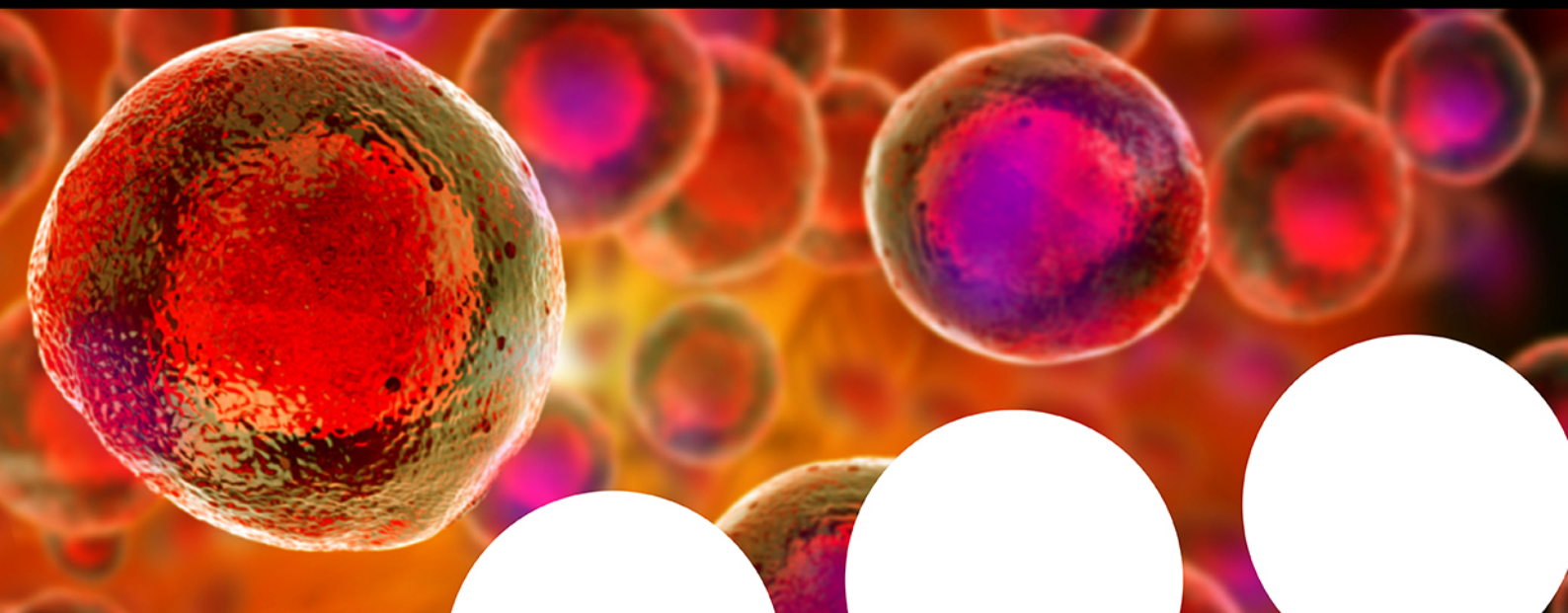


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A Three-Way Regioselective Synthesis of Amino Acid Decorated Imidazole, Purine and Pyrimidine Derivatives by Multicomponent Chemistry Starting from Prebiotic Diaminomaleonitrile

Bruno Mattia Bizzarri,^{*,[a]} Angelica Fanelli,^[a] Silvia Cesarini,^[a] and Raffaele Saladino^[a]

Amino acid decorated imidazole, pyrimidine and purine derivatives, resembling analogues of peptide nucleic acid's building blocks, have been synthesized by a three-way multicomponent chemistry of diaminomaleonitrile, one of the most studied chemical precursors in prebiotic chemistry. The regioselectivity of the multicomponent reaction between diaminomaleonitrile, trimethyl orthoacetate and a selected panel of α -amino acids, was controlled by the energy source used for triggering the condensation. Imidazole derivatives were obtained under thermal condition, while photochemical and combined photo-

thermal conditions afforded pyrimidine and purine derivatives, respectively. The three synthetic pathways were independent of each other, the type of product being controlled by the chemical intermediates prevailing in the reaction mixture. In addition to the synthetic potential of these multicomponent reactions in the preparation of a large variety of heterocycles, the control of the synthesis of peptide nucleic acid's building blocks, simply by changing the nature of the energy source, further enlarged the chemical complexity available in prebiotic conditions for the emergence of pristine pre-genetic codes.

Introduction

We recently reported the multicomponent synthesis of imidazole derivatives decorated with amino acid residues, and their successive annulation to corresponding purines, by thermal condensation of aminomalononitrile (AMN) and trimethyl orthoacetate with α -amino acids.^[1] AMN is a key intermediate in the prebiotic synthesis of purine nucleobases in the framework of prebiotic chemistry,^[2–7] while trimethyl orthoacetate is a well-recognized one-carbon donor reagent in multicomponent chemistry.^[8,9] The novel imidazole and purine derivatives resembled the basic scaffold of peptide nucleic acids (PNA),^[10] the pristine nucleic acid analogues in which the nucleobase was anchored to amino acid-like backbone instead of present-day sugar moiety.^[11] The possible role of PNA in the origin of life prior to an RNA world is reviewed, and the synthesis of PNA precursors on the primitive earth, as well as the possibility of template-directed PNA chemical replication and ligation, deeply investigated.^[12–15] In addition, the synthesis of PNA derivatives bearing heterocycle analogues and modified nucleobases have been reported in order to explore hybrid-

ization processes and emergent self-assembly and biological properties.^[16–19] Besides to AMN, diaminomaleonitrile (DAMN),^[20,21] the tetramer of HCN,^[22–24] is also a well-recognized intermediate in the prebiotic synthesis of nucleobases and of other biologically relevant heterocycles.^[5,25–28] The formation of DAMN under prebiotic conditions has been recently reviewed.^[29–32] This compound is characterized by the contemporary presence of electrophile and nucleophile reactive sites, which make it a useful reagent for the multicomponent synthesis of heterocycles. DAMN is easily photo-isomerized to diaminofumaronitrile (DAFN) which in turn can be cyclized to amino imidazole carbonitrile (AICN) under Thermal conditions. Selection of the energy sources which favor one of these transformations can furnish a tool for the control of the chemical complexity of the reaction products. The effect of different energy sources on the selectivity of prebiotic reactions was previously reported in the case of the thermal and photochemical condensation of formamide to RNA nucleobases, in which case purine derivatives (especially guanine) were selectively synthesized under photochemical conditions as a consequence of the preferential formation of AICN as a reactive intermediate.^[33] How did energy source can affect the chemo- and regioselectivity of multicomponent chemistry of DAMN to yield PNA's building-blocks? To what extent is the coexistence of different energy sources in tuning novel and unexpected reaction pathways? Here we describe the unprecedented three-way regioselective multicomponent synthesis of novel amino-acid decorated imidazole, purine and pyrimidine derivatives by condensation of DAMN with trimethyl orthoacetate and a selected panel of α -amino acids. The three synthetic pathways were independent of each other, the selectivity of the reaction being controlled by the energy source. In particular, imidazole derivatives were synthesized under thermal condi-

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tions (DAMN pathway), while pyrimidine derivatives were obtained under photoirradiation (DAFN pathway). Finally, purines were selectively isolated combining photochemical and thermal conditions (AICN pathway), further enlarging the variety of possible PNA's building blocks which can be synthesized from the same panel of starting reagents.

Results and Discussion

Synthesis of amino acid decorated imidazole derivatives–DAMN pathway

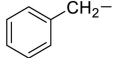
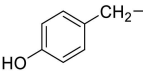
The synthesis of amino-acid decorated imidazole derivatives was performed by a slightly modification of the thermal procedure described for AMN.^[1] Under these experimental conditions the occurrence of previously reported DAMN isomerization/annulation process was not operative. DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), and glycine methyl ester **3a** (2.77 mmol, 1.2 eq.) were dissolved in three alternative reaction solvents (CH₂Cl₂, THF and MeCN) in the presence of triethylamine TEA (2.77 mmol, 1.2 eq.) and reacted under dark conditions at room temperature, or in alternative, at the reflux temperature of the selected solvents (39.6 °C, CH₂Cl₂; 66 °C, THF; and 82 °C, MeCN) for 15 h and 24 h, respectively. The best result was obtained in the presence of MeCN at 25 °C for 15 h, in which case the imidazole **4a** was isolated as the only recovered product in satisfactory yield (Table 1, entry 3). Irrespective from the experimental conditions, the reaction performed at the highest temperature was less effective, producing high conversion of DAMN and low yield of imidazole **4a** (Table 1, entry 5). The low value of the mass balance was probably due to the formation of high molecular weight oligomers of DAMN, which precipitated from the reaction solution as an insoluble dark-matter.^[34,35] In order to generalize the procedure, the reaction was repeated under the optimal experimental conditions (MeCN at 25 °C for 15 h) using the methyl esters of alanine **3b**, valine **3c**, serine **3d**, phenylalanine **3e**, and tyrosine **3f**. Amino-acid decorated imidazoles

4b–4f were isolated as the only recovered products from acceptable to high yield (Table 1, entries 6–10). In accordance with data previously reported for the multicomponent synthesis of imidazole derivatives bearing simple alkyl and aryl amine side-chains,^[1,36] compounds **4a–4f** were obtained by the concerted electrophile/nucleophile-oriented condensation of DAMN with **2** and **3a–3f** to yield the intermediate **1** (not isolated), followed by ring-aromatization and internal displacement of a methanol molecule (Scheme 1 DAMN pathway, Supporting Information, section 1). As a general trend, the yield of compounds **4a–4f** increased in the presence of aliphatic amino acids, imidazole **4d** being isolated in the highest yield (Table 1, entries 9–10 versus 3,6–8). This trend was in accordance with the lower pKa value and the relatively higher nucleophilicity of aromatic amino acids with respect to the aliphatic counterpart.^[37]

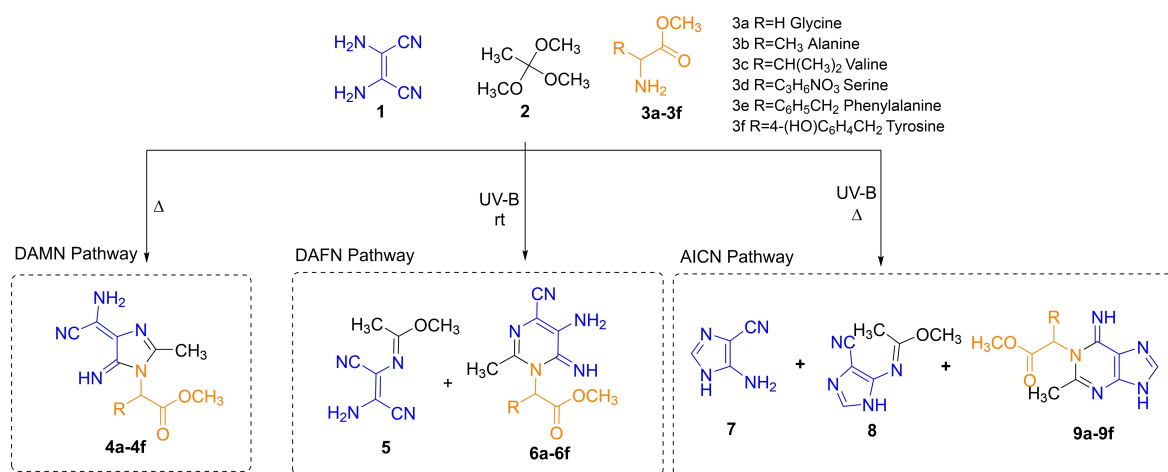
Synthesis of amino acid decorated pyrimidine derivatives–DAFN pathway

We expected that the regioselectivity of the three-components condensation between DAMN, trimethyl orthoacetate and α -amino acids should be changed under photochemical conditions, due to the fast isomerization of DAMN to DAFN. To test this possibility, DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), and glycine methyl ester **3a** (2.77 mmol, 1.2 eq.) were dissolved in MeCN (10 mL) in the presence of TEA (2.77 mmol, 1.2 eq.) and irradiated at the optimal wavelength-range reporter for the isomerization of DAMN to DAFN (280–320 nm)^[38] at 0 °C, or in alternative at 25 °C, for 15 h. Under these experimental conditions, the amino-acid decorated pyrimidine **6a** was recovered as the main reaction product from low to acceptable yield (Table 2, entries 1–3), besides low amount of the imino ether derivative **5** and traces amount of amino-imidazole carbonitrile (AICN) **7** (Scheme 1). The yield of pyrimidine **6a** at 0 °C was higher than that at 25 °C, in which case the dark insoluble residue was again observed.^[34,35] The effective formation of DAFN during the

Table 1. Synthesis of amino-acid decorated imidazole derivatives **4a–4f**.^[a]

Entry	α -amino acid	Solvent	Temperature [°C]	Time [h]	Products	R	Conversion [%]	Yield [%] ^[b]
1	Glycine	CH ₂ Cl ₂	25	15	4a	H	10	5
2		THF	25	15			60	35
3		MeCN	25	15			70	62
4			25	24			72	58
5			82	15			80	21
6	Alanine	MeCN	25	15	4b	CH ₃	65	57
7	Valine				4c	CH(CH ₃) ₂	68	55
8	Serine				4d	CH ₂ OH	81	73
9	Phenylalanine				4e		58	39
10	Tyrosine				4f		65	45

[a] DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), α -amino acid derivatives **3a–3f** (2.77 mmol, 1.2 eq.) and TEA (2.77 mmol, 1.2 eq.). [b] Yield have been calculated with respect to converted DAMN **1**. The conversion of the reaction was evaluated on the basis of unreacted **1**.



Scheme 1. Regioselective synthesis of amino-acid imidazole, purine and pyrimidine derivatives.

Entry	α -amino acid	Solvent	Temperature [°C]	Time [h]	Products	R	Conversion [%]	Yield [%] ^[b]	Yield of 5 [%] ^[c]
1	Glycine	MeCN,	25	15	6a	H	80	20	5
2		MeCN ^[d]	25	15	6a	H	75	50	10
3		MeCN	0	15	6a	H	74	62	5
4	Alanine	MeCN	0	15	6b	CH ₃	65	57	7
5	Valine				6c	CH(CH ₃) ₂	71	55	10
6	Serine				6d	CH ₂ OH	80	73	8
7	Phenylalanine				6e		68	39	4
8	Tyrosine				6f		62	45	5

[a] DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), α -amino acid derivatives **3a–f** (2.77 mmol, 1.2 eq.) and TEA (2.77 mmol, 1.2 eq.) under UV-B lamp radiation (280–320 nm). [b] Yield have been calculated with respect to converted DAMN **1**. [c] Yield have been calculated with respect to converted **5**. [d] **5** (2.30 mmol, 1.0 eq.), **3a** (2.77 mmol, 1.2 eq.) and TEA (2.77 mmol, 1.2 eq.) under UV-B lamp radiation (280–320 nm).

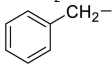
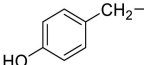
synthesis of pyrimidine **6a** was confirmed by the presence of the bathochromic effect associated to the conversion of DAMN (λ_{max} 295 nm) to DAFN (λ_{max} 304 nm) (Supporting Information, section 2, Figure S2.4–S2.5),^[39] as well as by the appearance of characteristic IR bands at 2197 and 2242 cm^{-1} (vibrations of CN), 1602 cm^{-1} (C=C stretching band), and 3434–3000 cm^{-1} (N–H stretching bands) (Supporting Information, section 3, Figure S3.2).^[40] The reaction repeated with α -amino acid derivatives **3b–3f** afforded amino-acid decorated pyrimidines **6b–6f** from good to high yield, confirming the generality of the procedure (Table 2, entries 4–8). The formation of pyrimidine **6a–6f** probably occurred by the initial reaction of DAFN with compound **2** to yield the imino ether derivative **5** (that we effectively isolated from the reaction mixture), followed by addition of amino acid derivatives **3a–3f**, and successive internal displacement of methanol molecule, to yield the six-ring closure of the pyrimidine ring (DAFN pathway, Supporting Information, section 1). The formation of the imino ether intermediate by reaction of AMN and compound **2** has been previously reported.^[1] The effective role of imino ether **5** in the annulation process was confirmed by analyzing the reaction of

isolated **5** and **3a** under reported experimental conditions, in which case pyrimidine **6a** was obtained in appreciable yield (Table 2, entry 2). Again, aliphatic amino acids **3a–3d** afforded pyrimidine derivatives in the highest yield (Table 2 entries 3–6).

Synthesis of amino acid decorated purine derivatives-AICN Pathway

Finally, we combined thermal and photochemical conditions to further improve the complexity of the reaction pathway. In this latter case, the following transformations were expected the condensation process: A) photo driven isomerization of DAMN to DAFN; and B) cyclization of DAFN to AICN and successive thermal annulation of AICN to purine derivatives. The synthesis of AICN from DAFN is still matter of debate.^[41] Data are reported to confirm the occurrence of the cyclization of DAFN to AICN via unstable azetidine intermediate III.^[42] In accordance with this data, when DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), and α -amino acid derivatives **3a–3f** (2.77 mmol, 1.2 eq.) were refluxed in MeCN (10 mL) in the

Table 3. Synthesis of purine derivatives **9a–9f**^[a]

Entry	α -amino acid	Solvent	Temperature [°C]	Time [h]	Products	R	Conversion [%]	Yield [%] ^[b]	Yield of 8 [%]	Yield of AICN 7
1	Glycine	MeCN	Reflux	15	9a	H	92	64	6	3
2	Alanine				9b	CH ₃	95	65	8	4
3	Valine				9c	CH(CH ₃) ₂	98	72	9	4
4	Serine				9d	CH ₂ OH	93	70	7	3
5	Phenylalanine				9e		90	45	13	5
6	Tyrosine				9f		94	54	15	4

[a] DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), α -amino acid derivatives **3a–3f** (2.77 mmol, 1.2 eq.) and TEA (2.77 mmol, 1.2 eq.) under UV-B lamp radiation (280–320 nm) [b] Yield have been calculated with respect to converted DAMN **1**.

presence of TEA (2.77 mmol, 1.2 eq.) under photon irradiation (290–315 nm) for 15 h, the amino-acid decorated purine derivatives **9a–9f** were isolated as the main reaction products in acceptable yield (Table 3, entries 1–6), besides to 4-cyanoimidazole imino ether derivative **8** and traces amount of AICN **7** (Scheme 1, AICN pathway). The isolation of imidazole imino ether derivative **8** from the reaction mixture suggested the occurrence of the initial addition between **2** and AICN **7**, followed by annulation of **8** with α -amino acid derivatives to yield **9a–9f** (AICN pathway, Supporting Information, section 1). The efficient transformation of DAFN to compounds **7** and **8** was probably responsible for the absence of pyrimidine derivatives as possible reaction side-products, DAFN being not further available for the condensation with **2**.

Conclusion

Multicomponent chemistry is a powerful tool for the synthesis of heterocyclic compounds,^[43] especially when optimal experimental conditions are selected in order to control the regioselectivity of the condensation process. They include the use of catalysts and of assisted microwave and ultra sounds conditions.^[44] Previous works showed that the same reagents could react in a different manner under multicomponent conditions depending on the nature and intensity of the energy source.^[45,46] In the case of DAMN, the energy source can control the selectivity of the in situ isomerization and annulation of DAMN to DAFN and AICN, respectively.^[47] It is important to note that the fate of these intermediates may afford heterocycles characterized by rings of different size and chemical composition. At room temperature and in the absence of photo-irradiation, DAMN is the major condensing reagent with trimethyl orthoacetate and α -amino acid derivatives to yield five-ring closure processes and formation of amino-acid decorated imidazole derivatives. Conversely, photochemical and photothermal conditions shifted the selectivity of the reaction towards DAFN and AICN intermediates, followed by selective formation of amino-acid decorated pyrimidine and purine derivatives, respectively. Taking into account the synthetic potential of these multicomponent reactions for the prepara-

tion of bioactive heterocycles, it must not escape the attention that the energetic conditions analyzed in this study were also plausible for the primitive earth. Thus, the multicomponent chemistry of DAMN involving one-carbon atom donor and α -amino acids may be (in principle) effective for the contemporary pre-biotic formation of amino-acid decorated imidazole, purine and pyrimidine PNA's building blocks, improving chemical information in the primitive recognition code, the selectivity of the synthesis being simply controlled by the reaction temperature and the presence or absence of UV irradiation.

Experimental Section

Materials

All solvents and reagents were of analytical grade and were purchased from Aldrich Chemical Co. Silica gel 60 F254 plates and silica gel 60 were furnished from Merck. Chemical reactions were monitored using thin-layer chromatography on precoated aluminum silica gel Merck 60 F254 plates and visualization of plates was performed with standard UV lamp. Merck silica gel 60 (230–400 mesh) was used for flash-chromatography. All products were dried under high vacuum (10–3 mbar) prior of the spectroscopic characterization. NMR spectra were recorded on a Bruker Advance DRX400 (400 MHz/100 MHz) spectrometer. Chemical shifts for protons are reported in parts per million (scale) and internally referenced to DMSO-*d*₆. Coupling constants (*J*) are reported in Hz. Multiplicities are reported in the conventional form: s = singlet, d = doublet, t = triplet, dd = double doublets, m = multiplet.

The analysis of the photo-isomerization processes were performed by Varian Cary 50 UV scan (Crawley, U.K.) in the range from 190 nm to 450 nm at 25 °C under gentle stirring, and data were elaborated by standard UV-scan software. ATR-IR analyses were performed at room temperature by Agilent Cary 630 ATR-FTIR analyzer. Selected compounds were directly placed on the diamond attenuated total reflectance (ATR) crystal of the apparatus. The analyses were recorded in less than 30 seconds (64 scans at 4 cm^{−1} resolution).

General procedure for the synthesis of amino acid decorated imidazole derivatives **4a–4f** DAMN pathway

DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), and α -amino acid derivatives **3a–3f** (2.77 mmol, 1.2 eq.)

were dissolved in the appropriate solvent (10 mL) in the presence of TEA (2.77 mmol, 1.2 eq.) and the reaction was gently stirred at 25 °C for 15 hours. At the end, the solvent was removed under reduced pressure and the crude was purified by flash-chromatography by eluting with ethyl acetate (AcOEt):petroleum ether (PET) (1:1) to afford compounds **4a–4f**. Spectroscopic data are in Supporting Information, section 4.

General procedure for the synthesis of amino acid decorated pyrimidine derivatives **6a–6f** DAFN pathway

DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), and α -amino acid derivatives **3a–3f** (2.77 mmol, 1.2 eq.) were dissolved in MeCN (10 mL) in the presence of TEA (2.77 mmol, 1.2 eq.) and irradiated in the range between 290 nm and 315 nm (UV-B photons) by 3 × 100 W UV-B Philips Broadband TL at 0 °C, or in alternative at 25 °C, for 15 hours. At the end, the solvent was removed under reduced pressure and the crude was purified by flash-chromatography by eluting with CH₂Cl₂:MeOH (10:0.5 v/v) to afford compounds **6a–6f** as the main reaction products, besides imino ether intermediate **5**. Spectroscopic data are in Supporting Information, section 4.

General procedure for the synthesis of amino-acid decorated purine derivatives **9a–9f** AICN pathway

DAMN **1** (2.30 mmol, 1.0 eq.), trimethyl orthoacetate **2** (3.25 mmol, 1.4 eq.), and α -amino acid derivatives **3a–3f** (2.77 mmol) were refluxed in MeCN (10 mL) in the presence of TEA (2.77 mmol, 1.2 eq.) under photon irradiation for 15 h using wavelength λ value in the range from 280 nm to 320 nm by 3 × 100 W UV-B Philips Broadband TL. At the end, the solvent was removed under reduced pressure and the crude was purified by flash-chromatography by eluting with CH₂Cl₂:MeOH (5:0.5 v/v) to afford compounds **9a–9f** as the main reaction products, besides to imidazole intermediate **8** and traces amount of compound **7**. Spectroscopic data are in Supporting Information, section 4.

UV-visible analyses of compound **1**, **5**, **6a**, **7**, **8** and **9a**

Accurately weighed 10 mg of the powdered compounds **1**, **5**, **6a**, **7**, **8** and **9a** were taken in a 10 mL volumetric flask and 10 mL of MeCN were added to reach the concentration of 1 mg/mL. 1 mL of each stock solution was pipetted into quartz cuvette and diluted with 2 mL of MeCN and the absorbance measured in the range from 190 nm to 450 nm. Original UV-visible spectra are reporter in Supporting Information, section 2.1.

UV-visible analyses of reaction affording compounds **6a** and **9a**

50 μ L of the reaction mixtures affording compounds **6a** and **9a** were sampled at 0, 15 and 30 min into a quartz cuvette filled with 2950 μ L of MeCN and immediately analyzed in the range from 190 nm to 450 nm. Original UV-visible spectra are reporter in Supporting Information, section 2.

ATR FT-IR Analysis of compounds **1**, **7** and of the reaction mixture affording compound **6a**

3 mg of compounds **1** and **7** were placed on the diamond attenuated total reflectance (ATR) crystal of the apparatus. The analyses were recorded in less than 30 seconds (64 scans at 4 cm⁻¹ resolution). For reaction mixture, the crude analyzed in a similar

way at 15 min from the beginning of the irradiation and after the complete evaporation of the solvent. Original ATR FT-IR spectra are reporter in Supporting Information, section 3.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Diaminomaleonitrile • Multicomponent chemistry • Photothermal activation • Prebiotic chemistry • Regioselective synthesis

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