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Research Article

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Three-Component Reaction of a 2-Aminoazine, a 2-Oxoaldehyde, and a Cyclic 1,3-Dicarbonyl Compound for the Synthesis of Imidazo[1,2-*a*]azine Derivatives

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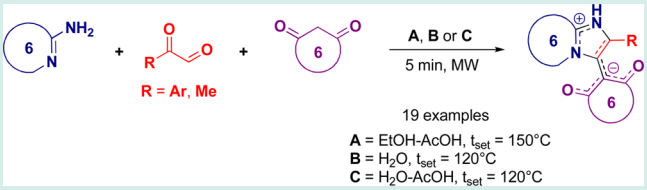
Supporting Information

ABSTRACT: A three-component reaction of a 2-aminoazine, a 2-oxoaldehyde, and a cyclic 1,3-dicarbonyl compound providing access toward a novel class of imidazo[1,2-*a*]azine derivatives was developed and studied. The scope of the process was thoroughly explored under three different reaction conditions resulting in the generation of a small library of title compounds and highlighting the possibility of case-specific approach.



KEYWORDS: *multicomponent reactions, 2-aminoazines, 2-oxoaldehydes, 1,3-dicarbonyl compounds, imidazo[1,2-a]azines*

INTRODUCTION

Among the large arsenal of methods available for the construction of heterocyclic frameworks multicomponent reactions (MCRs) are particularly advantageous, offering fast and elegant access to high levels of structural complexity and diversity.[1] The famous Biginelli reaction[2] has been successfully used for more than a century for the construction of 3,4-dihydropyrimidin-2(1*H*)-one scaffold **4**, which finds many applications in medicinal chemistry and drug discovery.[3] Typical components of the Biginelli reaction include a urea **1a** possessing two nitrogen nucleophiles, an aromatic aldehyde **2** with an electrophilic carbonyl group and a ß-ketoester **3** featuring an electrophilic keto carbonyl group and a nucleophilic activated methylene group which, upon treatment with an acid catalyst or a promoter, react to form **4** (Scheme 1a). The Biginelli reaction, like most MCRs, is known to be rather flexible to component replacements allowing the development of various modifications which, nonetheless, mostly lead to the parent 3,4-dihydropyrimidin-2(1*H*)-one or its fused derivatives.[4] Application of 2-oxoaldehydes **5** in place of common aromatic aldehydes **2** in Biginelli-type MCRs is particularly intriguing in this regard as it often leads to different reaction outcome and selectivity.[5] The additional electrophilic keto carbonyl group can act as another reactive center taking part in the condensation instead of the carbonyl group of *β*-ketoester **3**. In addition, because of its electron-withdrawing nature, the reactivity of the aldehyde carbonyl group in **5** is greater than in **2**. In 2005, Balalaie and co-workers described a $ZnCl_2$-promoted three-component reaction of *N*,*N*′-dimethylurea **1b**, phenyl glyoxal **5** and ß-ketoester **3**, yielding imidazol-2-one **7a** (Scheme 1b).[6] In 2008, Kolos and co-workers described a modification of this process using dimethyl barbituric acid **6a** instead of ß-ketoester **3**, providing access to imidazol-2-ones of type **7b** (Scheme 1c).[7] Later the Kolos group expanded this chemistry to the use of thiourea and thioacetamide as urea replacements[8] and to the use of 4-hydroxycoumarin as a 1,3-dicarbonyl compound.[9] In 2010, Quiroga, Nogueras and co-workers further contributed to this area with the three-component reaction of 6-aminopyrimidine **8**, aryl glyoxal **5**, and dimedone **6b** for the synthesis of various pyrrolo[2,3-*d*]-pyrimidines **9**.[10] In their process 6-aminopyrimidines, as exemplified by compound **8** in Scheme 1d, were used as the urea replacement with the major conceptual difference being the substitution of one N-nucleophilic reactive center with a C-nulceophile. Further, a great number of related multi-component processes have been discovered and documented.[11] In a continuation of our ongoing efforts in the development of Biginelli-type transformations[12] and methods for the assembly of fused imidazoles[13] we were interested in exploring this chemistry with 2-aminoazines **10** which, like ureas **1a** and **1b**, have two N-nucleophilic centers. Herein, we describe the resulting three-component reaction of a 2-aminoazine **10**, a 2-oxoaldehyde **5** and a cyclic 1,3-dicarbonyl compound **6** for the synthesis of imidazo[1,2-*a*]azine derivatives **11** (Scheme 1e).[14,15]

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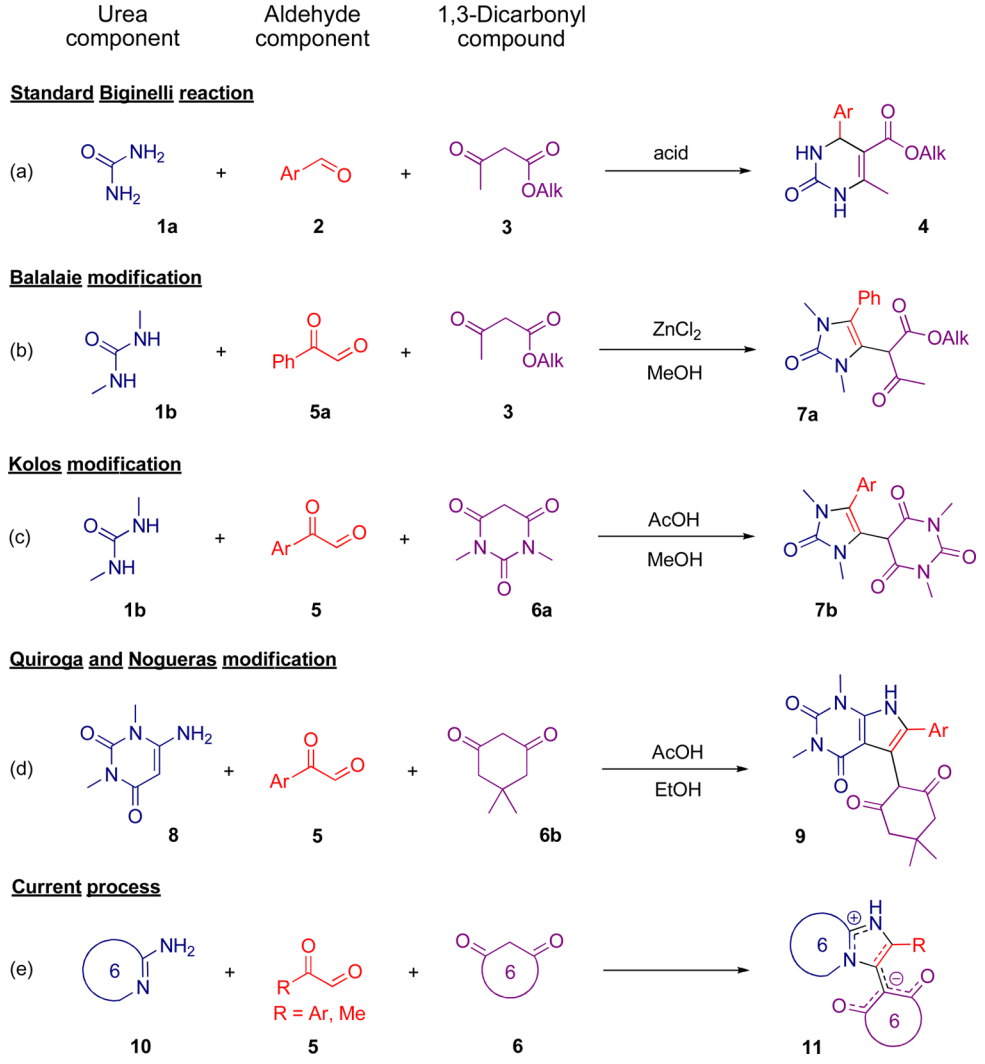
Scheme 1. Current Process in the Context of Related Biginelli-Type Transformations



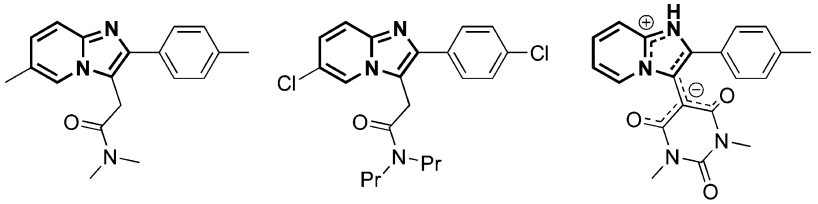


Figure 1. Comparison of zolpidem and alpidem structures with a representative compound synthesized by our methodology.

It is worth highlighting that imidazo[1,2-*a*]azines, particularly imidazo[1,2-*a*]pyridines, demonstrate a wide range of biological activities among others acting as potent $GABA_A$ receptor agonists and that our newly generated compounds structurally resemble several drugs of this family, such as zolpidem and alpidem.[16]

RESULTS AND DISCUSSION

We started our investigation by screening reaction conditions using 2-aminopyrimidine **10a**, 4-methylphenylglyoxal **5a** (monohydrate form) and dimethyl barbituric acid **6a** as model substrates (Table 1). When the reaction was carried out in ethanol under microwave irradiation with the maximum power of 300 W and the set temperature of 120 °C the desired imidazo[1,2-*a*]pyrimidine **11a** was obtained in 44% yield (Table 1, entry 1). Increasing the set temperature to 150 °C had almost no effect on the reaction outcome (Table 1, entry 2). Next we found that the yields of **11a** seem to be slightly better when the reactions were performed in ethanol with acetic acid as an additive (Table 1, entries 3 and 4). Switching to the use of water as the solvent resulted in even more significant improvement providing **11a** in 63% yield for the reaction conducted at the set temperature of 120 °C (Table 1, entry 5). Unlike for the reactions conducted in ethanol, an increase of the set temperature to 150 °C resulted in a diminished yield of **11a** for the reaction run in water (Table 1, entry 6). At the

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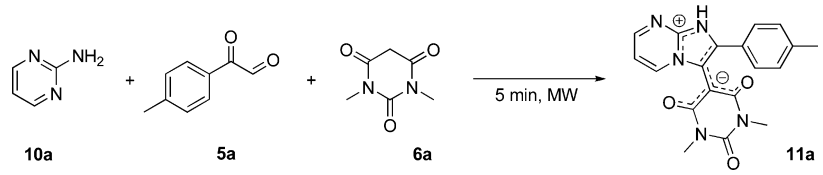
Table 1. Screening of the Reaction Parameters[a]

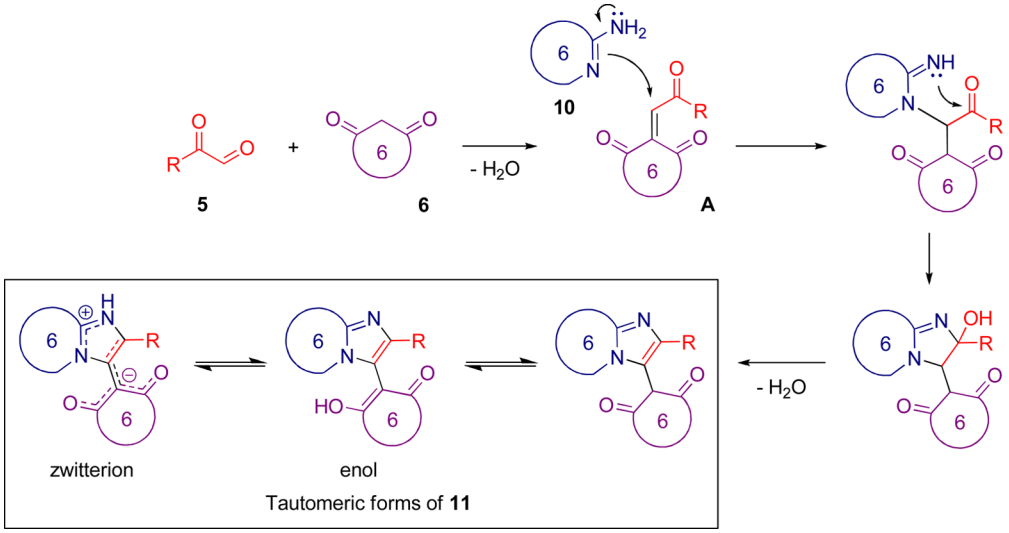


10a 5a 6a 11a

entry	solvent	additive	set temperature (°C)	yield (%)[b]
1	EtOH		120	44
2	EtOH		150[c]	45
3	EtOH	AcOH[d]	120	47
4 (condition A)	EtOH	AcOH[d]	150[c]	49
5 (condition B)	water		120	63
6	water		150	53
7 (condition C)	water	AcOH[d]	120	68
8	water	AcOH[d]	150	61
9 (conventional heating)	water	AcOH[d]	120	65

[a]The reactions were conducted on a 1 mmol scale in 2.5 mL of solvent using equimolar amounts of **10a**, **5a**, and **6a**. [b]Yields of isolated product **11a** calculated for monohydrate form are reported. [c]For these entries, the set temperature was not reached. The irradiation power was automatically adjusted to let the actual reaction temperature rising throughout the reaction time as close as possible to the set value in the way that it would not lead to the exceeding of the pressure limit of 250 psi. [d]The amount of additive is 0.1 mL.

Scheme 2. Proposed Reaction Pathway



same time, the use of acetic acid additive again proved to be advantageous delivering **11a** in 68% and 61% yield for the set temperatures of 120 and 150 °C respectively (Table 1, entries 7 and 8). A conventional oil bath heating was also found to be applicable to facilitate the reaction (Table 1, entry 9). A preference was given to a microwave heating mainly from convenience point of view.

On the basis of the results obtained from the model study, three sets of reaction parameters (Table 1, entries 4, 5, and 7), which will be herein referred to as conditions A, B, and C, were chosen to investigate the scope of our methodology. With regard to the starting materials, we selected 2-aminopyrimidines **10a,b**, 2-aminopyridines **10c−e** and 3-aminoisoquinoline **10f** as representative 2-aminoazines, various aryl glyoxales **5a−d,f** (monohydrate form) and pyruvic aldehyde **5e** (40 wt % solution in water) as 2-oxoaldehydes and finally several barbituric acids **6a,d,e** and 1,3-cyclohexanediones **6b,c** as 1,3-dicarbonyl compounds (Table 2). All reactions were tested under two or three of the selected conditions, in all cases delivering desired products in moderate to good isolated yields. Condition C utilizing water with acetic acid additive as the solvent that showed best result during model study (Table 1, entry 7) was confirmed to be the most efficient for the reactions with 2-aminopyrimidines **10a,b** (Table 2, entries 1−4, 6, and 8) with an exception of two cases (Table 2, entries 5 and 7). Condition A utilizing EtOH with acetic acid additive as the solvent was found to be the most efficient for the reactions with 2-aminopyridines **10c−e** in combination with aryl glyoxales **5a,d,f** (Table 2, entries 9, 10, 12−16). Finally, reactions with 2-aminopyridines **10c,e** and 3-aminoisoquinoline **10f** in combination with pyruvic aldehyde **5e** worked best under condition B utilizing water with no additive as the solvent (Table 2, entries 11, 17, and 18).

The proposed reaction pathway is typical for this type of processes (Scheme 2). 2-Oxoaldehyde **5** and cyclic 1,3-dicarbonyl compound **6** condense to form an adduct **A**, which is a strong Michael acceptor and would readily react with the nitrogen of

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Table 2. Scope of the Process[a]

10 5 6 11

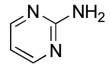
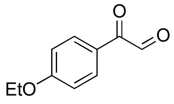
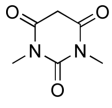
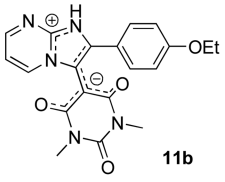
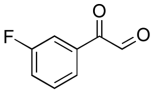
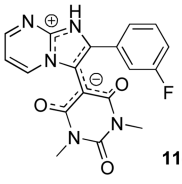
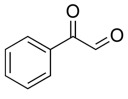
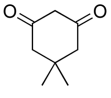
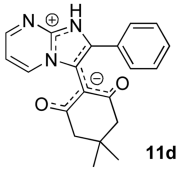
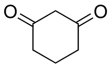
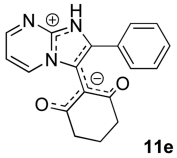
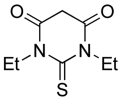
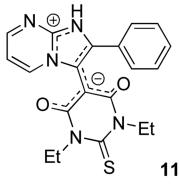
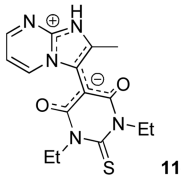
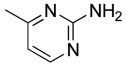
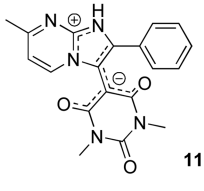
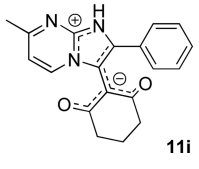
Entry	10	5	6	Product 11	Yield (%)[b] Condition A[c]	Condition B	Condition C
1	 10a	 5b	 6a	 11b	41	55	57
2	10a	 5c	6a	 11c	43	48	56
3	10a	 5d	 6b	 11d	58	60	65
4	10a	5d	 6c	 11e	61	–[d]	80
5	10a	5d	 6d	 11f	44	–[d]	42
6	10a	 5e	6d	 11g	42	44	65
7	 10b	5d	6a	 11h	49	63	45
8	10b	5d	6c	 11i	51	53	69

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Table 2. continued

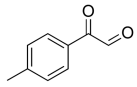
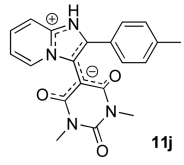
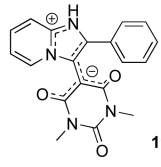
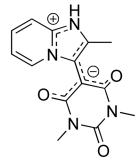
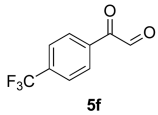
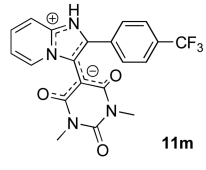
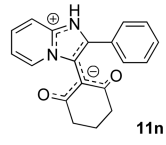
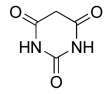
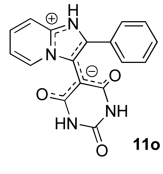
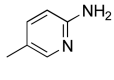
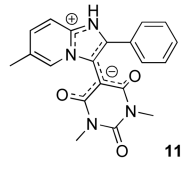
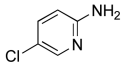
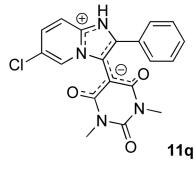
Entry	10	5	6	Product 11	Yield (%)[b] Condition A[c]	Condition B	Condition C
9	 **10c**	 **5a**	**6a**	 **11j**	72	49	52
10	**10c**	**5d**	**6a**	 **11k**	73	61	37
11	**10c**	**5e**	**6a**	 **11l**	59	72	43
12	**10c**	 **5f**	**6a**	 **11m**	70	46	–[d]
13	**10c**	**5d**	**6c**	 **11n**	71	68	–[d]
14	**10c**	**5d**	 **6e**	 **11o**	53	48	–[d]
15	 **10d**	**5d**	**6a**	 **11p**	78	–[d]	66
16	 **10e**	**5d**	**6a**	 **11q**	50	38	37

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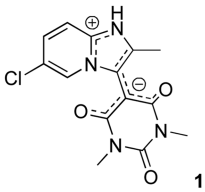
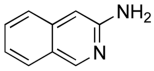
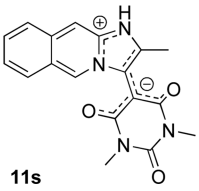
Table 2. continued

Entry	10	5	6	Product 11	Yield (%)[b] Condition A[c]	Condition B	Condition C
17	**10e**	**5e**	**6a**	 **11r**	42	56	–[d]
18	 **10f**	**5e**	**6a**	 **11s**	46	47	–[d]

[a]The reactions were conducted on a 1 mmol scale in 2.5 mL of solvent using equimolar amounts of **10**, **5**, and **6**. [b]Yields of isolated product **11** calculated for monohydrate form are reported. [c]For these entries in most of cases the set temperature was not reached. The irradiation power was automatically adjusted to let the actual reaction temperature rising throughout the reaction time as close as possible to the set value in the way that it would not lead to the exceeding of the pressure limit of 250 psi. [d]The reaction was not carried out under this conditions.

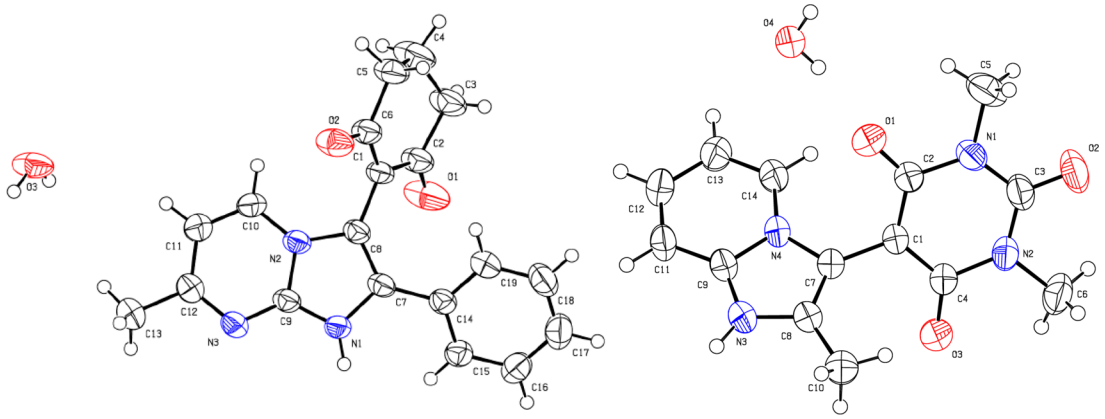


Figure 2. X-ray structures of imidazo[1,2-*a*]pyrimidine **11i** (left) and imidazo[1,2-*a*]pyridine **11l** (right).

azine ring **10**. This is followed by the attack of the second exocyclic nitrogen nucleophile on the **5**-originated keto carbonyl group and subsequent elimination of water, resulting in the formation of imidazo[1,2-*a*]azine product **11**.

All final products were characterized by ^{1}H and ^{13}C NMR and HRMS. In addition, the structures of two representative compounds (imidazo[1,2-*a*]pyrimidine **11i** and imidazo[1,2-*a*]-pyridine **11l**) were determined by X-ray crystallographic analysis (Figure 2).[17] The X-ray data suggests that the obtained imidazo[1,2-*a*]azine derivatives **11a–s** are isolated as monohydrates and in solid state exist in a zwitterion tautomeric form which, however, does not necessarily reflect the structure in solution as the recorded ^{1}H NMR spectra might also be attributed to an enol form. It should also be noted that the elemental analysis of several representative samples showed that water content might deviate from 1 equiv. Thus, the actual yields for **11a–s** may slightly differ (±2%) from the reported in Tables 1 and 2 values.

CONCLUSION

In conclusion, we have elaborated a novel Biginelli-type multicomponent process for the synthesis of imidazo[1,2-*a*]-azine derivatives, starting from readily accessible 2-aminoazines, 2-oxoaldehydes, and cyclic 1,3-dicarbonyl compounds. The method is tunable, operationally simple and utilizes environmentally benign solvents such as water and ethanol. In addition, the isolation of the desired products does not require the use of column chromatography in most cases.

EXPERIMENTAL SECTION

The reactions were carried out in 10 mL glass tubes, sealed with Teflon septum using a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz and irradiation power from 0 to 300 W. The reactions were irradiated according to the set temperature for the stipulated time and then cooled to ambient temperature with air jet cooling.

^{1}H and ^{13}C NMR spectra were recorded with 300 and 75 MHz respectively using Bruker Avance instrument unless otherwise specified. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. For the spectra recorded in DMSO-d_6 heating was required in most cases to dissolve the analyzed compound during sample preparation. High-resolution EI mass spectra were recorded on a Kratos MS50TC system with a resolution of 10000. The ion source temperature was 150–250 °C, as required. High-resolution ESI mass spectra were acquired on a quadrupole

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orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL/min and spectra were obtained in positive ionization mode with a resolution of 15000 (fwhm) using leucine enkephalin as lock mass. Elemental analysis (carbon, hydrogen, nitrogen) was performed on a CE Instruments EA-1110 element analyzer. Melting points were recorded on a Reichert Thermovar apparatus and are uncorrected.

General Procedures for the Three-Component Reaction of 2-Aminoazine, 2-Oxoaldehyde, and Cyclic 1,3-Dicarbonyl Compound for the Synthesis of Imidazo[1,2-*a*]azine Derivatives. *Condition A:* Ethanol (2.5 mL) was added to a mixture of 2-aminoazine (1 mmol), 2-oxoaldehyde (1 mmol), and cyclic 1,3-dicarbonyl compound (1 mmol) followed by acetic acid (0.1 mL). The resulting mixture was heated with a stirring under microwave irradiation for 5 min applying the set temperature of 150 °C and the maximum power of 300 W. The desired product was isolated as described below or in Supporting Information.

Condition B: Distilled water (2.5 mL) was added to a mixture of 2-aminoazine (1 mmol), 2-oxoaldehyde (1 mmol), and cyclic 1,3-dicarbonyl compound (1 mmol). The resulting mixture was heated with a stirring under microwave irradiation for 5 min applying the set temperature of 120 °C and the maximum power of 300 W. The desired product was isolated as described below or in Supporting Information.

Condition C: Distilled water (2.5 mL) was added to a mixture of 2-aminoazine (1 mmol), 2-oxoaldehyde (1 mmol), and cyclic 1,3-dicarbonyl compound (1 mmol) followed by acetic acid (0.1 mL). The resulting mixture was heated with a stirring under microwave irradiation for 5 min applying the set temperature of 120 °C and the maximum power of 300 W. The desired product was isolated as described below or in Supporting Information.

1,3-Dimethyl-2,4,6-trioxo-5-(2-*p*-tolylimidazo[1,2-*a*]-pyrimidin-1-ium-3-yl)hexahydropyrimidin-5-ide (11a). Isolation: Table 1, entries 1−3 and 4 (condition A). The desired product was filtered from the reaction mixture and washed with EtOH (1 mL) and EtOAc (2 + 1 mL). Table 1, entries 5 (condition B), 6, 7 (condition C), 8 and 9. The desired product was filtered from the reaction mixture and washed with water (2 mL), EtOH (2 mL) and EtOAc (2 mL). Yield: 187 mg, 49% (condition A); 240 mg, 63% (condition B); 259 mg, 68% (condition C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99 (dd, J = 1.6, 4.4 Hz, 1H), 8.72 (dd, J = 1.6, 6.8 Hz, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.58 (dd, J = 4.4, 6.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 3.13 (s, 6H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.5, 155.8, 152.9, 142.3, 139.1, 136.5, 132.2, 129.2, 127.3, 125.1, 119.7, 112.9, 72.5, 27.1, 20.8. HRMS (EI, $[M]^+$) for $C_{19}H_{17}N_5O_3$ calcd. 363.1331, found 363.1349. Elemental analysis: calcd. for $C_{19}H_{17}N_5O_3 \cdot H_2O$ C, 59.84; H, 5.02; N, 18.36; found (condition A):\ C, 59.02; H, 4.86; N, 17.81; found (condition B) C, 59.16; H, 5.09; N, 17.76. The results of elemental analysis might be attributed to higher than 1 equiv water content.

■ ASSOCIATED CONTENT

Supporting Information

Crystallographic data in CIF format, further details on the experimental and isolation procedures, spectral data, and copies of ^{1}H and ^{13}C NMR spectra for all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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