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An efficient synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines

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ABSTRACT

An efficient synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines is described via a novel multicomponent reaction between 2-aminopyridines, benzaldehydes and imidazoline-2,4,5-trione under solvent-free conditions.

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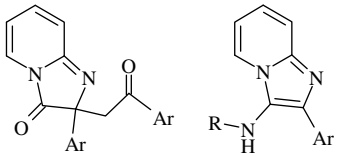
Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple, since all the organic reagents employed are consumed and are incorporated into the target compound.[1] MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules.

Imidazo[1,2-*a*]pyridines, fused bicyclic 5–6 heterocycles with one ring junction nitrogen atom and one nitrogen atom in the five-membered ring, are of interest because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds.[2] Derivatives containing the imidazo[1,2-*a*]pyridine ring system have been shown to possess a broad range of useful pharmacological activities, including antibacterial, antifungal, anthelmintic, antiviral, antiprotozoal, antiinflammatory, anticonvulsant, anxiolytic, hypnotic, gastrointestinal, antiulcer and immunomodulatory.[2–4]

So far, several synthetic methods have been reported for the preparation of 2- or 3-substituted imidazo[1,2-*a*]pyridines with the majority relying on the condensation of 2-aminopyridine with α-bromoketones to form the five-membered cyclic system.[2] Particularly interesting are those structures that contain an amino group at C-2 or C-3. There are well-established methods for the preparation of 3-aminoimidazo[1,2-*a*]pyridines; these include nitration at C-3 of the already formed heterocycle and subsequent reduction,[5] a multicomponent reaction between 2-aminopyridines, aldehydes and isonitriles[6–8] or preparation from pyridinium fluorides,[9] Strecker-type reaction between 2-aminopyridines, cyanide ions and a limited number of aldehydes,[10] or by use of benzotriazole as an auxiliary group.[11] Most of these methods involve three or more sequential synthetic steps, the use of harsh reaction conditions that give low yields, and in some cases, use of hazardous or expensive starting materials.

As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds, we recently described an efficient synthesis of 2-aryl-2-(2-oxo-2-arylethyl)imidazo[1,2-*a*]pyridin-3(2*H*)-ones **1** via a condensation reaction between 2-aminopyridines and diaroylacetylenes.[3] We have also developed an efficient synthesis of 3-alkylamino-2-arylimidazo[1,2-*a*]pyridines **2** via a catalyst-free reaction between 2-aminopyridines, aldehydes and isocyanides in water.[4]



1 **2**

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Considering the important biological properties of imidazo-[1,2-*a*]pyridines, we report herein another novel synthesis of this nucleus bearing in mind previously reported syntheses. Thus, 2-aminopyridines **3**, benzaldehydes **4** and imidazoline-2,4,5-trione **5** were found to undergo a novel one-pot multicomponent addition reaction under solvent-free conditions to produce 3-amino-2-arylimidazo[1,2-*a*]pyridines **6a–j** (Table 1).

When the reaction was performed using equivalent ratios of 2-aminopyridine (**3**, R = H), benzaldehyde (**4**, Ar = C_6H_5) and imidazoline-2,4,5-trione **5**, ^{1}H NMR analysis of the reaction mixture indicated the formation of imidazo[1,2-*a*]pyridine **6a** in nearly 45% yield. Almost half the 2-aminopyridine **3** was recovered unreacted at the end of the reaction. The best results were obtained when the reactions were carried out using the three components in a ratio of 1:2.5:1.5.[12]

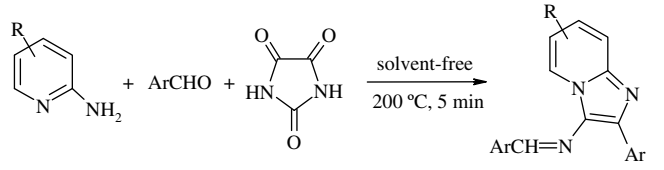
The reactions were carried out by mixing the 2-aminopyridine, the aldehyde and imidazoline-2,4,5-trione followed by heating at 200 °C and were complete within a few minutes affording 3-amino-2-arylimidazo[1,2-*a*]pyridines **6** in 92–97% yields.[12]

The structures of products **6a–j** were deduced by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The mass spectrum of **6d** displayed the molecular ion (M^+) peak at *m/z* 357, which was consistent with the adduct structure. The ^{1}H NMR spectrum of **6d** exhibited three sharp singlets, arising from the two CH_3O (δ 3.81 and 3.82 ppm) and aldimine (δ 8.67 ppm) groups along with characteristic multiplets with appropriate chemical shifts and coupling constants for the four H atoms of the electron-rich diene moiety of the six-membered ring and the eight H atoms of the two aryl substituents. The ^{1}H-decoupled ^{13}C NMR spectrum of **6d** showed 18 distinct resonances, in agreement with the suggested structure. Partial assignments of these resonances are given.[12] Single-crystal X-ray analysis of **6d** confirmed conclusively the structure of the isolated products. An ORTEP diagram of **6d** is shown in Figure 1.[13]

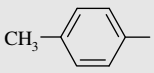
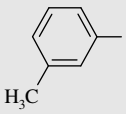
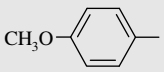
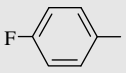
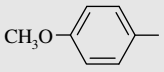
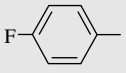
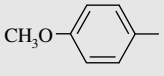
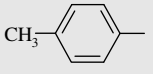
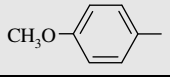
Although we have not yet established the mechanism of the reaction between 2-aminopyridines, benzaldehydes and imidazoline-2,4,5-trione in an experimental manner, a mechanistic rationalization for this reaction is provided in Scheme 1. The first step may involve condensation of the aldehyde with the 2-aminopyridine and imidazoline-2,4,5-trione with formation of aldimine **7** and imidazolium ion **8**, respectively. Then the imidazolium ion **8** is probably attacked by the pyridine-*N* atom of the aldimine **7** leading to adduct **9**. Intramolecular nucleophilic addition of alkoxide to the adjacent carbonyl group would yield epoxide intermediate **10**, which may undergo ring opening to form ylide **11**. This ylide may undergo intramolecular cyclization to dihydroimidazo[1,2-*a*]pyridine intermediate **12** from which a carbon dioxide, an isocyanic acid and an acetic acid molecule may be removed to afford the imidazo[1,2-*a*]pyridine **6**.

In conclusion, we have developed a novel, efficient, one-pot multicomponent synthesis of 3-amino-2-arylimidazo[1,2-*a*]pyridines of potential synthetic and pharmacological interest. Solvent-free conditions, excellent yields of the products and use of simple starting materials are the main advantages of this method. Further investigations on the reaction mechanism, scope and limitations are underway.

Table 1
Solvent-free synthesis of imidazo[1,2-*a*]pyridines



3 4 5 6

6	R	Ar	Mp[a] (°C)	% Yield[b]
a	H		161–163	95
b	H		154–155	92
c	H		165	92
d	H		175	94
e	H		158–160	96
f	6-CH_3		189–190	97
g	6-CH_3		154–156	97
h	7-CH_3		176	94
i	6-CH_3		139–140	92
j	8-CH_3		155–156	93

[a] Recrystallized from *n*-hexane–EtOAc (1:2).
[b] Isolated yields.

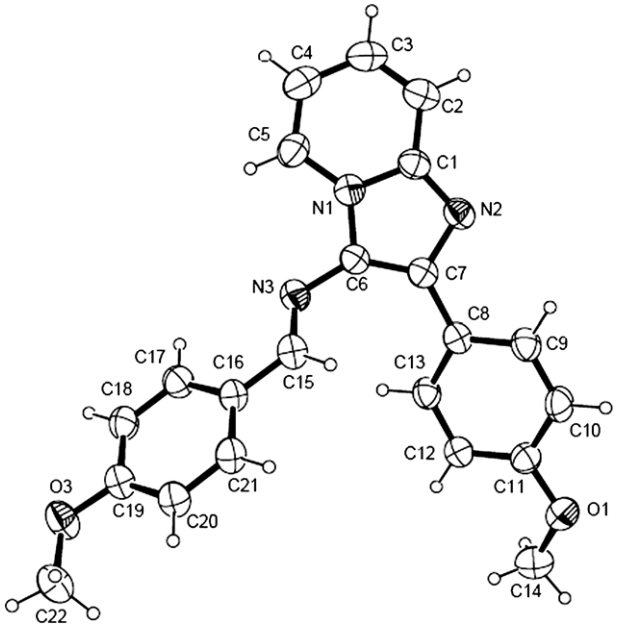
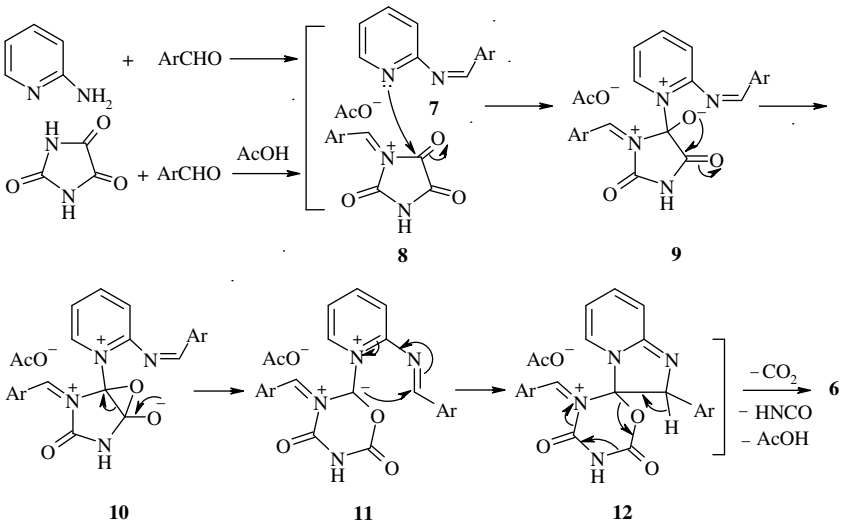


Figure 1. ORTEP diagram of the structure of **6d**.



Scheme 1.

Acknowledgement

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12. The procedure for the preparation of 2-(4-methoxyphenyl)-N^3-[(*E*)-1-(4-methoxyphenyl)methylidene]imidazo[1,2-*a*]pyridin-3-amine **6d** is described as an example: A mixture of 2-aminopyridine (0.188 g, 2 mmol), 4-methoxybenzaldehyde (0.681 g, 5 mmol) and imidazoline-2,4,5-trione (0.342 g, 3 mmol) was stirred at 200 °C for 5 min. Then the reaction mixture was cooled to room temperature and the residue was purified by column chromatography using *n*-hexane–ethyl acetate (1:3) as eluent. The solvent was removed and the product was obtained as yellow crystals, mp 175 °C, yield 0.67 g, 94% (relative to 2-aminopyridine). EI-MS, *m/z* (%): 357 (M^+, 100), 342 (8), 239 (9), 211 (88), 196 (9), 178 (5), 78 (72). Anal. Calcd for $C_{22}H_{19}N_3O_2$ (357.41): C, 73.93; H, 5.36; N, 11.76. Found: C, 73.8; H, 5.4; N, 11.6. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 3.81 and 3.82 (6H, 2s, 2 OCH_3), 6.79 (1H, dt, J = 6.8 and 1.0 Hz, CH), 6.91 (2H, d, J = 8.7 Hz, 2CH), 6.93 (2H, d, J = 8.8 Hz, 2CH), 7.14 (1H, ddd, J = 6.7, 6.6 and 1.3 Hz, CH), 7.54 (1H, d, J = 9.0 Hz, CH), 7.74 (2H, d, J = 8.7 Hz, 2CH), 7.76 (2H, d, J = 8.8 Hz, 2CH), 8.32 (1H, d, J = 6.8 Hz, CH), 8.67 (1H, s, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.24 and 55.42 (OCH_3), 112.22, 114.19, 114.20, 116.90, 123.09 and 124.83 (CH), 126.91, 128.79 and 129.28 (C), 129.48 and 130.04 (CH), 132.57 and 142.32 (C), 157.27 (CH), 159.27 and 162.31 (C).
13. *Selected X-ray crystallographic data for compound* **6d**: $C_{22}H_{19}N_3O_2$, monoclinic, space group = $P2_1/n$, a = 10.4920(16) Å, b = 8.7631(13) Å. c = 20.768(3) Å, β = 91.269(2)°, V = 1908.96(5) Å^3, T = 295(2) K, Z = 4, D_{calcd} = 1.24 g cm^{-3}, μ = 0.081 mm^{-1}, 1986 observed reflections, final R_1 = 0.054, wR_2 = 0.124 and for all data R_1 = 0.107, wR_2 = 0.124. CCDC 666888 contains the supplementary crystallographic data for the structure reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.