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PII: S0040-4039(14)00553-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.03.121
Reference: TETL 44443

To appear in: *Tetrahedron Letters*

Received Date: 16 November 2013
Revised Date: 6 March 2014
Accepted Date: 27 March 2014

Please cite this article as: Marandi, G., Saghatforoush, L., Mendoza-Meroño, R., García-Granda, S., Catalyst-free synthesis of 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids via a three-component condensation, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.03.121

Catalyst-free synthesis of 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids via a three-component condensation

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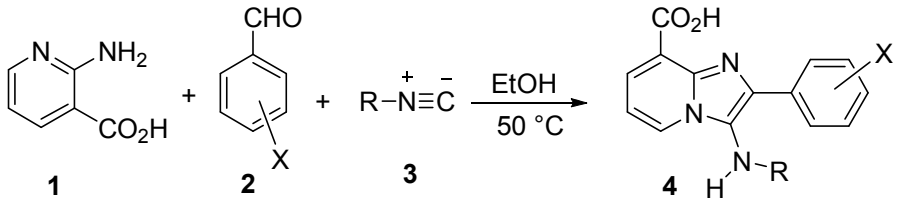
Abstract

The synthesis of a number of 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids via a facile route involving the reaction between 2-amino-3-pyridinecarboxylic acid, benzaldehyde derivatives and isonitriles is reported. The structures of the synthesized compounds are proved by X-ray crystallography.

Keywords: 2-amino-3-pyridinecarboxylic acid, isocyanides, arylcarboxaldehydes, 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids

The synthesis of new compounds of high utility by known procedures is a very important goal for organic chemists.[1] The preparation of nitrogen-containing fused heterocycles such as imidazo[1,2-*a*]pyridines is of importance to medicinal chemistry and materials science because of their interesting properties.[2-7] Zolpidem, olprinone and zolimidine are examples of such compounds which possess an imidazopyridine scaffold. Pharmaceuticals containing the imidazo[1,2-*a*]pyridine moiety have been shown to possess anticonvulsant, antipyretic, antiviral, anti-inflammatory, antiprotozoal and anti-ulcer activities.[8-14] Some of the synthetic methods for the generation of compounds with an imidazo[1,2-*a*]pyridine core have gained increased interest, among which, multicomponent reactions (MCRs) have a distinct place.[15-17] Methods for the synthesis of imidazo[1,2-*a*]pyridine derivatives have been reported using a catalyst or reflux conditions.[3,6,16-21] In continuation of our investigations on the synthesis of heterocyclic compounds using isocyanides,[22-25] we now report the catalyst-free synthesis of 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids.

We observed that the condensation reaction of 2-amino-3-pyridinecarboxylic acid (**1**) and arylcarboxaldehydes **2** in the presence of alkyl isocyanides **3** afforded 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids **4** in excellent yields (Scheme 1).



4	R	X	Yield (%)
a	cyclohexyl	4-Me	97
b	*t*-Bu	4-Me	92
c	cyclohexyl	3-NO_2	93
d	*t*-Bu	3-NO_2	98
e	cyclohexyl	3-Cl	89
f	*t*-Bu	2-NO_2	95

Scheme 1.

Compounds **4a**-**f** are stable structures, which were fully characterized on the basis of ^{1}H, ^{13}C NMR and IR spectroscopy, elemental analysis and mass spectrometry. Unambiguous structural clarification was provided by single crystal X-ray diffraction of compounds **4a** and **4d** (Figures 1 and 2).

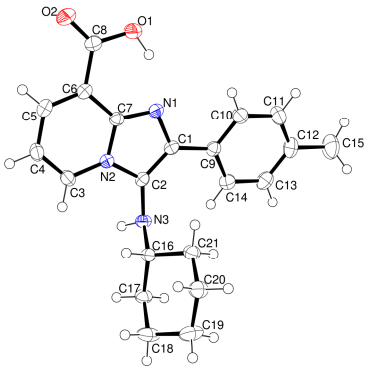


Figure 1. Molecular projection of **4a** showing the numbering scheme. Atomic displacement ellipsoids have been drawn at the 50% probability level.

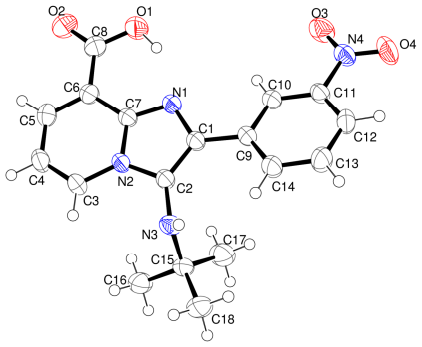


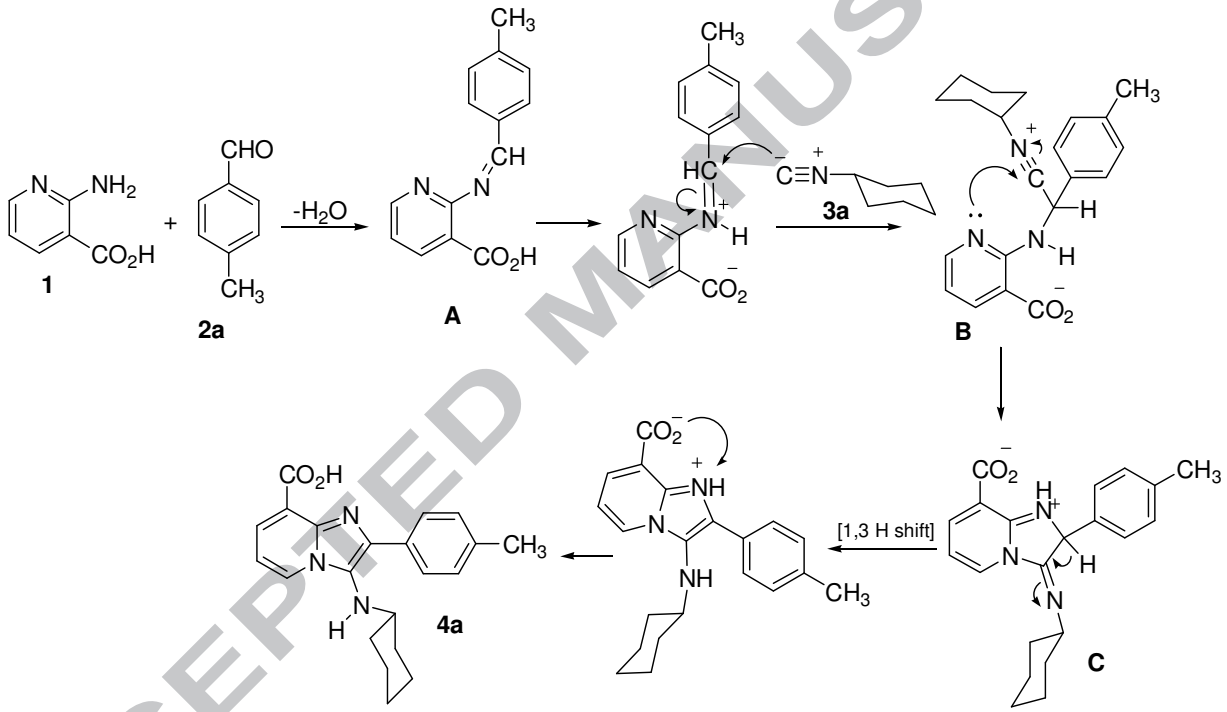
Figure 2. Molecular projection of **4d** showing the numbering scheme. Atomic displacement ellipsoids have been drawn at the 50% probability level.

The IR spectrum of compound **4a** showed distinct absorptions at 3302 cm^{-1}, attributed to the NH group at position 2 of the imidazole ring, and at 1733 cm^{-1} for the C=O of the carboxylic acid functional group. The mass spectrum of compound **4a** displayed the molecular ion peak at *m/z* = 349.

The ^{1}H NMR spectrum of compound **4a** exhibited multiplet signals arising from the cyclohexyl (5×CH_2) at 1.16–1.83 ppm and a multiplet signal due to the NC*H* of the cyclohexyl group at 3.00 ppm. A characteristic signal for the methyl group protons was observed at 2.42 ppm. In addition, the N*H* signal was recorded at 3.17 ppm, which disappeared on D_2O exchange. The resonances of all seven protons of the aromatic cores of compound **4a** were recorded between 7.00-8.31 ppm. The resonance of the carboxylic acid proton was not observed.

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed five signals readily recognized as arising from an Ar*Me* group (20.4 ppm), the five methylenes of the cyclohexyl ring (23.7, 24.6 and 33.2 ppm) and the N*C*H carbon (56.1 ppm), respectively. The carbon of the carboxylic group was recorded at 164.1 ppm, and all the other resonances were in agreement with the structure.

The proposed mechanism for the formation of products **4** is shown in Scheme 2. The first step may involve an imine condensation of 2-amino-3-pyridinecarboxylic acid (**1**) and aldehyde **2a** to generate compound **A**, which was activated by the carboxylic acid toward attack of the isocyanide **3a**, according to the Ugi reaction. This adduct undergoes intramolecular nucleophilic addition involving the lone pair of the pyridyl nitrogen resulting in cyclization to give the five-membered ring in intermediate **C**. Rearrangement and proton transfer gives the final compound **4a**.



Scheme 2. Proposed mechanism for the generation of 3-(alkylimino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids **4**

In summary, we have reported an efficient one-pot synthetic method for the preparation of 3-(alkylamino)-2-arylimidazo[1,2-*a*]pyridine-8-carboxylic acids via a three-component reaction

involving isocyanides. The products were obtained in excellent yields without addition of a catalyst.

General procedure for synthesis of compounds 4 (exemplified by 4a)

To a magnetically stirred solution of 2-amino-3-pyridinecarboxylic acid (**1**) (1 mmol) and 4-methylbenzaldehyde (**2a**) (1 mmol) in EtOH (10 mL) was added, dropwise, a mixture of cyclohexyl isocyanide (1 mmol) in EtOH (5 mL) over 5 min at room temperature. The mixture was heated at 50 °C for 3 h to complete the reaction (monitored by TLC). The solvent was removed by slow evaporation. The residue was washed with cold Et_2O (2 × 3 mL), and the desired product was then collected by filtration and recrystallized from EtOH (3 mL).

3-(cyclohexylamino)-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-8-carboxylic acid (**4a**)

Light yellow crystals, (0.34 g), yield 97%; mp 198–201 °C, IR (solid) (ν_{max}, cm^{-1}): 3302 (NH), 1733 (C=O). MS, *m/z* (%) = 350 (M^+ + 1, 22), 349 (M^+, 72), 305 (32), 266 (83), 239 (100), 223 (20), 147 (27), 119 (41), 94 (15), 55 (29). Anal. Calcd for $C_{21}H_{23}N_3O_2$ (349.43): C, 72.18; H, 6.63; N, 12.03%. Found: C, 72.13; H, 6.57; N, 12.11%. ^{1}H NMR (400.1 MHz, $CDCl_3$): 1.16–1.83 (10H, m, 5×CH_2 of cyclohexyl), 2.42 (3H, s, ArCH_3), 3.00 (1H, m, NC*H* of cyclohexyl), 3.17 (1H, br s, N*H*), 7.00 (1H, t, *J* = 6.9 Hz, CH_{pyr}), 7.30 (2H, d, *J* = 7.9 Hz, 2×CH_{aryl}), 7.90 (2H, d, *J* = 7.9 Hz, 2×CH_{aryl}), 8.09 (1H, d, *J* = 6.7 Hz, CH_{pyr}), 8.31 (1H, d, *J* = 6.7 Hz, CH_{pyr}). ^{13}C NMR (100.6 MHz, $CDCl_3$): 20.4 (s, Ar*C*H_3), 23.7, 24.6 and 33.2 (3s, 5×*C*H_2 of cyclohexyl), 56.1 (s, N*C*H of cyclohexyl), 111.2 (s, C_{pyr} and CH_{pyr}), 116.2 (s, N*C*$NH_{imidazo}$), 124.3 (s, C_{aryl}), 125.4 (s, CH_{pyr}), 126.0 (s, 2×CH_{aryl}), 128.1 (s, CH_{pyr}), 128.5 (s, 2×CH_{aryl}), 135.1 (s, $C_{imidazo}$), 137.3 (s, C_{aryl}), 139.3 (s, C_{fused}), 164.1 (s, *C*O_2H).

Single Crystal X-ray structure determination

The diffraction data from selected single crystals of compounds **4a** and **4d** were collected at room temperature and 150 K with MoKα radiation (λ=0.7107 Å). The data were processed with CrysAlis software, and empirical absorption correction using spherical harmonics were implemented using the SCALE3 ABSPACK scaling algorithm.[26] The crystallographic data and the refinement parameters for these crystals are summarized in Table 1 in the Supporting Information.

Crystal structures were solved by direct methods using Sir 2008[27] and refined by full-matrix least-squares calculations against F2 using SHELXL.[28] All non-hydrogen atoms were refined with anisotropic displacement parameters. For both structures, aromatic *C-H*, *-CH_3* methyl and *-CH_2* cyclohexane hydrogen atoms were included in calculated positions and treated as riding atoms: C—H = 0.93 Å for aromatic CH [U iso(H) = 1.2 × Ueq(C)], C—H = 0.96 Å for methyl group [U iso(H) = 1.5 × Ueq(C)] and C—H = 0.97 Å for -CH_2 [U iso(H) = 1.2 × Ueq(C)]. The Figures were produced using ORTEP-3.[29] Deposition numbers CCDC 965018 for **4a**, and CCDC 965019 for **4d** contain the supplementary crystallographic data for 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.

Acknowledgments

Financial support was provided by the Research Council of Urmia University, Payame Noor University, the Ministerio de Economía Competitividad de España (MAT2010-15094, Factoría de Cristalización–Consolider Ingenio 2010) and ERDF.

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Graphical abstract

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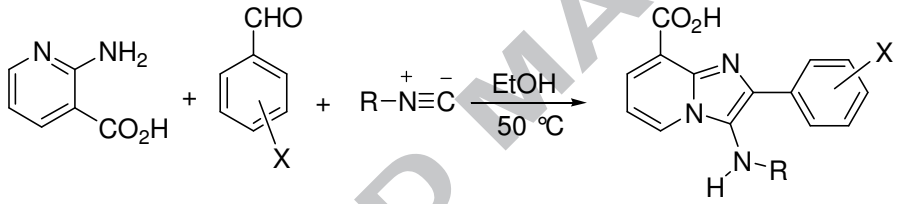

R: cyclohexyl, *t*-butyl

X: 4-methyl, 2-nitro, 3-nitro, 3-chloro