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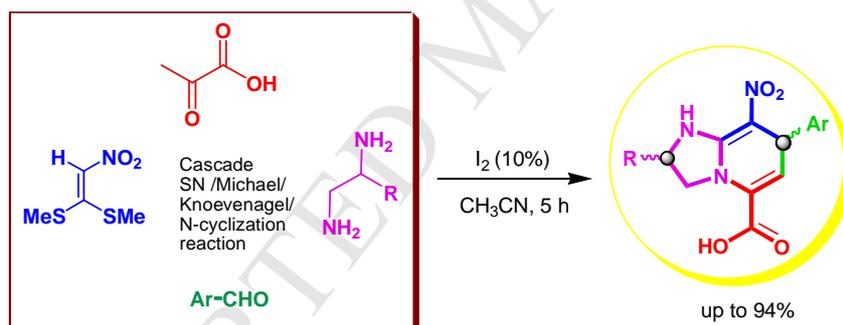
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Iodine Catalyzed Mild 4CR Protocol for Synthesis of Tetrahydroimidazo[1,2-*a*]pyridines: Cascade Construction of Multiple C–C and C–Hetero Bonds

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Abstract—A highly convergent and straightforward synthesis of N-fused heterocycles, including 1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids is successfully achieved via a one-pot four-component cascade reaction utilizing pyruvic acid, aldehydes, diamines and 1,1-bis(methylthio)-2-nitroethylene (BMTNE) in the presence of a catalytic amount of molecular iodine in acetonitrile. The new efficient domino protocol generates two rings by the concomitant formation of C–N (three) and C–C (two) multiple bonds presumably involving a sequence of *N,N*-acetal formation, Knoevenagel reaction, aza–ene reaction, imine–enamine/keto–enol tautomerization, and N-cyclization as key steps. The merit of this protocol is highlighted by its easily available and economical starting materials, operational simplicity, efficient utilization of all the reactants, clean reaction profile, simple workup procedure, and tolerance of a wide variety of functional groups.

1. Introduction

The central theme of organic synthesis is the construction and cleavage of bonds in organic molecules. Modern synthesis involves the design of efficient synthetic protocol that minimizes

Keywords: Molecular iodine, Pyruvic acid, Imidazo[1,2-*a*]pyridine-5-carboxylic acid, Four-component reaction

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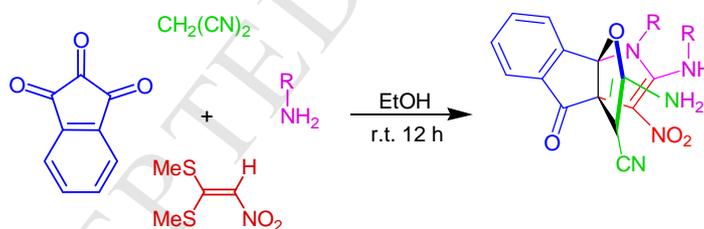
the number of synthetic steps for the rapid generation of functionalized molecules with interesting properties. One approach to achieve this goal involves the development of eco-compatible, multicomponent procedures. Multicomponent reactions (MCRs) offer a wide range of possibilities for the construction of pre-defined highly complex molecules in a single step with high atom economy, minimum time, labor, cost, and straight forward experimental procedures.¹ These benefits are highlights for multicomponent cascade reactions, which involve in situ production of an intermediate with a strategic reactive site for subsequent transformations.² In the past decade, a lot of multicomponent reactions have been reported,^{3,4} yet developing novel MCRs that meet almost all of advantages above is still in the burgeoning phase.

In recent times, the use of molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity.⁵ The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations.⁶ So the development of a reaction that uses catalytic amounts of non toxic and readily available iodine should greatly contribute to the creation of environmentally benign processes. Interestingly, to some extent, the reactions promoted by iodine usually afford unexpected results.⁷

Nitro ketene amins (NKA) and related compounds possessing the conjugated system N-C=C-EWG are important versatile synthetic intermediates in synthetic chemistry and they have received increasing attention recently.⁸ Their usage for constructing a variety of nitrogen

containing heterocycles or fused heterocyclic compounds that are hardly accessible by other synthetic methods has been extensively studied.⁹ The notable feature of NKA is the highly polarized ethylene systems with electro-donating amino group and electro-withdrawing substituent at both ends. This unique structural feature makes them serve as bis-nucleophiles reacting with various bis-electrophiles.

Our research goal during the past few years has been the synthesis of a library of pharmacologically relevant fused polyheterocyclic systems employing enamines and amins.¹⁰ Recently, we have become interested in the application of nitro ketene amination intermediates resulting from the reaction of 1,1-bis(methylthio)-2-nitroethylene (BMTNE) and diamines or primary amines for the synthesis of interesting heterocycles in one-pot processes. During a previous investigation, we succeeded in developing a novel class of oxa-aza[3.3.3]propellane fused derivatives based on reaction of NKA and Knoevenagel adduct from ninhydrin and malononitrile (Scheme 1).^{10b}



Scheme 1. Synthesis of fused oxa-aza[3.3.3]propellanes via one-pot, four-component reaction

2. Results and discussion

Encouraged by this successful effort, I decided to perform the reaction of heterocyclic ketene amination (HKAs) and the Knoevenagel adduct generated in situ from pyruvic acid and benzaldehyde, to evaluate the construction of useful fused azaheterocycle molecules under mild reaction conditions. Reactions of pyruvic acid derivatives with bisnucleophiles have been applied

for the synthesis of various types of heterocycles since the beginning of the last century. On the other hand, multicomponent reactions of pyruvic acid leading to heterocycles have rarely been investigated.

During the course of our studies, molecular iodine was discovered which can be applied as a good catalyst for the activation of the carbonyl group of benzaldehyde¹¹ and the iodine catalyzed Michael reactions are well known.¹² Accordingly, at first, the reaction of pyruvic acid and 4-chlorobenzaldehyde under different conditions was evaluated that afforded the expected Knoevenagel adduct intermediate. Initially, the reaction was carried out in ethanol at room temperature. Whether the catalyst was added or not, the target compound **4a** was not obtained after 24 h (Table 1, entries 1 and 2). However, when the reaction was heated at reflux and the molecular iodine was added, I found that the reaction was complete and the desirable Knoevenagel adduct was obtained in an isolated yield of 27% within 24 h (Table 1, entry 3). Subsequently, reaction conditions was optimized by screening several solvents, and of those examined, acetonitrile was the most suitable. With molecular iodine as good promoter in hand, next I intended to optimize its loading, and it was found that the use of 10 mol% of I₂ provided the best result. Reducing the mol% of I₂ in the reaction increased the reaction time and lowered the yield, and increasing the catalyst loading did not show any improvement (Table 1, entries 6 and 7). Therefore, the best reaction conditions were achieved by employing with molecular iodine (0.1 mmol) in acetonitrile under reflux for 2 h (Table 1, entry 8).

Next, to verify the possibility to perform a “classic” one-pot four-component reaction, the reaction was carried out by sequential addition of reagents ethylenediamine, nitro ketene dithioacetal (BMTNE), pyruvic acid and 4-chlorobenzaldehyde in one flask under the same reaction conditions. This manner avoids the isolation of the intermediates and should save time

Table 1. Screening Optimum Reaction Conditions for the Formation of Intermediate Knoevenagel Condensation Product

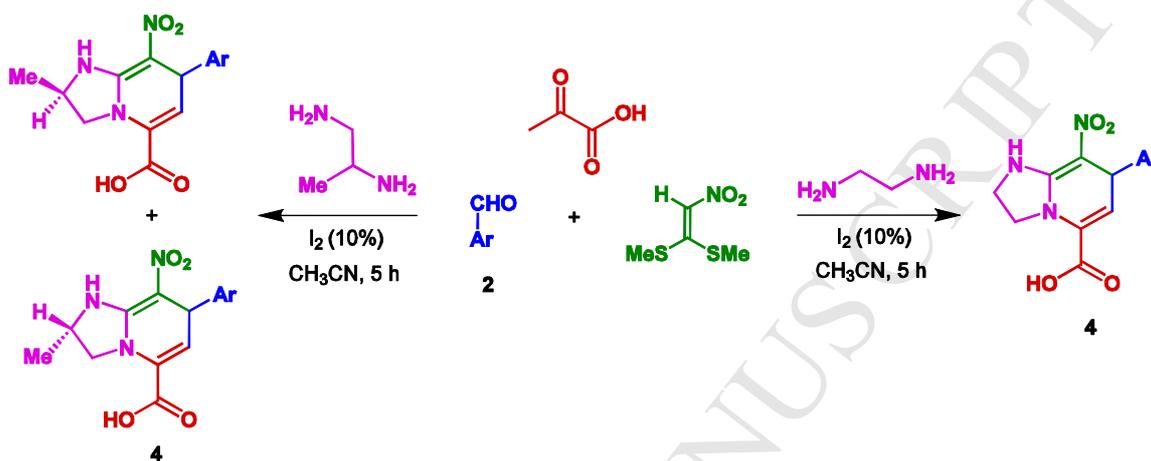
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield ^a %
1	-	EtOH	rt	24	nr ^b
2	-	EtOH	rt	24	nr
3	I ₂ (10)	EtOH	70	24	27
4	I ₂ (10)	MeOH	65	24	14
5	I ₂ (10)	THF	70	10	30
6	I ₂ (5)	MeCN	80	5	44
7	I ₂ (20)	MeCN	80	2	92
8	I ₂ (10)	MeCN	80	2	94

^a Isolated yield^b No reaction

of execution and solvent amounts, and afford better yields. Thus, in a pilot reaction, ethylenediamine and BMTNE in acetonitrile, was combined. The resultant reaction mixture was stirred to complete the SN reaction as monitored by thin-layer chromatography (TLC). After the formation of HKA **5**, pyruvic acid and 4-chlorobenzaldehyde with catalytic amount of I₂ (10 mol%) were introduced and the reaction was heated at reflux in an oil bath until completion (monitored by TLC). The desired product was isolated, filtered, and washed with cold ethanol to afford the pure product **4a**. The resultant pure compound was identified on the basis of spectroscopic data. Because of the existence of two stereogenic centers in the products **4d-f**, mixture of two diastereomers was expected. For **4d** and **4f** products, two diastereomers were formed (Fig. 1). But, the ¹H and ¹³C NMR spectral data of **4e** clearly indicated that only one of the two possible diastereomers was obtained for this product.

With the optimal reaction conditions, we then investigated the use of different starting materials in order to determine the reactivity domain of the cascade reaction (Table 2). For ethylenediamines and aromatic aldehydes **2**, the substituents, whether with electron-withdrawing,

or electron-releasing groups on the aromatic ring, afforded corresponding products in excellent yields. Application of other diamines such as 1,3-propylenediamines and 1,4-butanediamine lead to a complex mixture which was difficult to purify and characterize (Table 2).



Entry	Product 4	Ar	Diamine 3	Ratio of two diastereomers	Total yield %
1	4a	4-ClC ₆ H ₄	Ethylenediamine	-	94
2	4b	4-MeC ₆ H ₄	Ethylenediamine	-	85
3	4c	4-MeOC ₆ H ₄	Ethylenediamine	-	88
4	4d	4-ClC ₆ H ₄	1,2-Propanediamine	91:9	90
5	4e	4-MeC ₆ H ₄	1,2-Propanediamine	-	84
6	4f	4-MeOC ₆ H ₄	1,2-Propanediamine	83:17	87
7	4g	4-ClC ₆ H ₄	1,3-Propylenediamine	-	-
8	4h	4-ClC ₆ H ₄	1,4-Butanediamine	-	-

Table 2. One-Pot Synthesis of Tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids **4a-f** via Domino SN/Knoevenagel condensation/Michael Addition/Cyclization Reaction

The molecular structure of products **4a-f** was elucidated from elemental analysis, IR, and ¹H NMR and ¹³C NMR spectra. The mass spectrum of **4b** displayed the molecular ion peak at *m/z* 301, which is in agreement with the proposed structure. The IR spectrum of this compound showed an absorption band due to the NH stretching frequency at 3352 cm⁻¹. Absorption bands at 1727, 1651 cm⁻¹ are due to the C=O and NC=C groups stretching frequencies. The ¹H NMR

spectrum of **4b** showed one sharp singlet for the methyl group ($\delta = 2.23$ ppm), three multiplets for two CH₂ groups, because these protons are diastereotopic ($\delta = 3.68$ - 3.74 , 4.06 - 4.16 and 4.24 - 4.32 ppm), two doublets for CH groups ($\delta = 4.80$ and 6.06 ppm, $^3J_{\text{HH}} = 5.6$ Hz), and two singlets for NH and OH groups ($\delta = 9.32$ and 13.17 ppm). Also, four aromatic hydrogens gave rise to characteristic signals in the aromatic region of the spectrum. Observation of 13 distinct signals in the ¹H-decoupled ¹³C NMR spectrum of **4b** is in agreement with the proposed structure. The most important region of the spectrum is related to resonances due to, CNO₂, CCO and CO which appear at $\delta = 119.0$, 127.0 and 163.2 ppm.

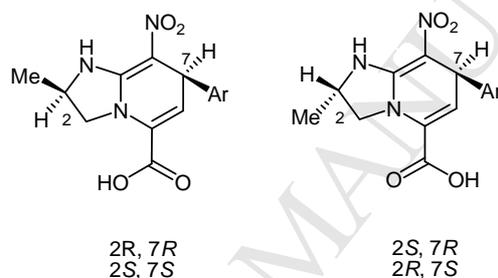
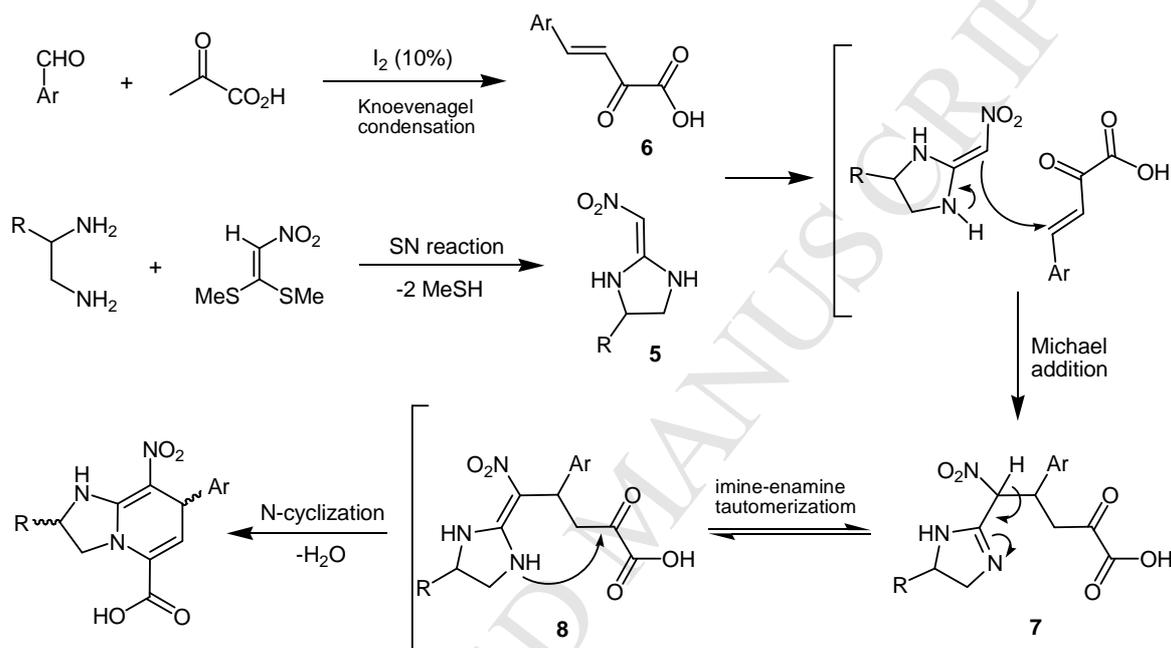


Figure 1. Expected mixture of two diastereomers of **4d-f**

Although no detailed mechanistic studies have been carried out at this point, a rational mechanism for this one-pot procedure is outlined in Scheme 2. This mechanism is proposed knowing the chemical behavior of pyruvic acid, benzaldehyde, and ketene amination intermediate HKA. Based on this mechanism, HKA **5** readily prepared in situ from the addition of ethylenediamine and BMTNE via a S_N2 reaction followed by loss of 2 equiv of MeSH. Next, the formation of second key intermediate **6** occurs through Knoevenagel condensation of benzaldehyde **2** with enol form pyruvic acid in the presence of iodine. With a strong electron-withdrawing nitro group at the α -position and electron-donating diamino groups on the diazaheterocycle of HKA, HKA **5** can serve as a nucleophilic component with the electrophilic arylidene pyruvic acid **6** in a Michael-type addition to produce an open chain azaketene type

intermediate which transformed to intermediate **8** through imine-enamine tautomerization. Subsequently, in the presence of active ketonic carbonyl in intermediate **8**, nucleophilic addition of the secondary amino group to the acidic carbonyl group followed by loss of 1 equiv of H₂O affords product **4**.



Scheme 2. Mechanistic Rationalization for the Formation of **4**

3. Conclusion

In summary, we have successfully developed a simple and highly efficient synthesis of 1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid frameworks through four-component coupling of ketene-*N,N*-acetals, aldehydes, and pyruvic acid in the presence of 10 mol% of I₂ under metal-free conditions. This atom economic domino protocol involves SN reaction/Knoevenagel condensation/Michael addition/cyclization sequence forming three new bonds (two C–C and three C–N), and two heterocycles in a single operation with all reactants efficiently being utilized. The method involves the use of readily available commercial reagents

and operationally simple synthetic protocols and does not require advanced intermediates or anhydrous solvents. Significantly, the presence of an acidic group at the 9 position on imidazo[1,2-*a*]pyridines make these compounds excellent entrants as precursors for further synthetic renovations to meet the need for diverse useful purposes. The isolation and purification of compounds by simple filtration and ethanol washing makes the process very simple avoiding conventional chromatographic separation. I hope this clean and simple four-component coupling protocol maybe of value for both synthetic and medicinal chemists for academic research and practical applications.

4. Experimental

The diamines, 1,1-bis(methylthio)-2-nitroethene, aldehydes, and pyruvic acid were obtained from *Merck* (Germany) and *Fluka* (Switzerland) and were used without further purification. Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on a *FINNIGAN-MATT 8430* mass spectrometer operating at an ionization potential of 70 eV. ^1H NMR (300 and 400 MHz) and ^{13}C NMR (75 MHz) spectra were obtained using *Bruker DRX-300 AVANCE* and *Bruker DRX-400 AVANCE* spectrometers. IR spectra were recorded as KBr pellets on a *NICOLET FT-IR 100* spectrometer, absorbencies are reported in cm^{-1} .

4.1. Typical synthesis procedure: (for example 4a)

To a magnetically stirred 10 mL flask containing 1,1-bis(thiomethyl)-2-nitroethylene (0.16 g, 1 mmol) in acetonitrile (3 mL) was added ethylenediamine (0.06 g, 1 mmol). After 3 h, pyruvic acid (0.08 g, 1 mmol), 4-chlorobenzaldehyde (0.14 g, 1 mmol) and iodine (0.12 g, 0.1 mmol) were added to the reaction mixture, and stirring was allowed to continue at for 2 h at reflux.

After the completion of the reaction, the precipitated product was filtered and washed with cold ethanol to afford the pure product **4a**.

4.1.1. 7-(4-Chlorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid (4a). Yellow powder, mp = 178-180 °C (decomp), 0.30 g, yield: 94%. IR (KBr) (ν_{\max} , cm^{-1}): 3349 (NH), 1728 (C=O), 1652 (NC=C) cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{ClN}_3\text{O}_4$: C, 52.27; H, 3.76; N, 13.06. Found C, 52.23; H, 3.77; N, 13.09. δ_{H} (500 MHz, $\text{DMSO-}d_6$): 3.67-3.71 (m, 2 H, NCH_2), 4.09-4.11 (m, 1 H, NCH_2), 4.23-4.25 (m, 1 H, NCH_2), 4.84 (d, $^3J_{\text{HH}} = 5.5$ Hz, 1 H, CH), 6.04 (d, $^3J_{\text{HH}} = 5.5$ Hz, 1 H, CH), 7.20 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2 CH of Ar), 7.30 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2 CH of Ar), 9.31 (s, 1 H, NH), 13.17 (br, 1 H, OH). δ_{C} (100 MHz, $\text{DMSO-}d_6$): 40.9 (CH), 43.4 (CH₂N), 47.5 (CHN), 104.5 (CH), 118.3 (C-NO₂), 127.1 (CCO), 128.4 (CH of Ar), 129.2 (CH of Ar), 131.2 (*C*_{ipso}-Ar), 142.4 (*C*_{ipso}-Ar), 153.8 (NCN), 162.9 (CO);

4.1.2. 7-(4-Methylphenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid (4b). Yellow powder, mp = 172-174 °C (decomp), 0.26 g, yield: 85%. IR (KBr) (ν_{\max} , cm^{-1}): 3352 (NH), 1727 (C=O), 1651 (C=N), cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$: C, 59.80; H, 5.02; N, 13.95. Found C, 59.76; H, 5.04; N, 13.98. MS (EI, 70 eV): m/z (%) = 301 (M^+ , 2), 290 (10), 270 (10), 255 (90), 224 (21), 209 (100), 181 (42), 115 (37). δ_{H} (300 MHz, $\text{DMSO-}d_6$): 2.23 (s, 3 H, CH₃), 3.71 (m, 2 H, CH₂), 4.11 (m, 1 H, NCH_2), 4.27 (m, 1 H, NCH_2), 4.80 (d, $^3J_{\text{HH}} = 5.6$ Hz, 1 H, CH), 6.06 (d, $^3J_{\text{HH}} = 5.6$ Hz, 1 H, CH), 7.08 (br, 4 CH of Ar), 9.32 (s, 1 H, NH), 13.10 (br, 1 H, OH). δ_{C} (75 MHz, $\text{DMSO-}d_6$): 20.7 (CH₃), 41.0 (CH), 43.3 (CH₂N), 47.5 (CH₂N), 104.8 (CH), 119.0 (C-NO₂), 127.0 (CCO), 127.3 (CH of Ar), 129.0 (CH of Ar), 135.7 (*C*_{ipso}-Ar), 140.5 (*C*_{ipso}-Ar), 153.9 (NCN), 163.2 (CO).

4.1.3. 7-(4-Methoxyphenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid (4c). Yellow powder, mp = 175-177 °C (decomp), 0.28 g, yield: 88%. IR (KBr) (ν_{\max} , cm^{-1}):

3353 (NH), 1723 (C=O), 1652 (NC=C) cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_5$: C, 56.78; H, 4.76; N, 13.24. Found C, 56.84; H, 4.73; N, 13.20. δ_{H} (300 MHz, $\text{DMSO-}d_6$): 3.68 (s, 3 H, OCH_3), 3.71-3.74 (m, 2 H, NCH_2), 4.07-4.17 (m, 1 H, NCH_2), 4.23-4.32 (m, 1 H, NCH_2), 4.78 (d, $^3J_{\text{HH}} = 5.4$ Hz, 1 H, CH), 6.08 (d, $^3J_{\text{HH}} = 5.5$ Hz, 1 H, CH), 6.82 (d, $^3J_{\text{HH}} = 8.2$ Hz, 2 CH of Ar), 7.11 (d, $^3J_{\text{HH}} = 8.2$ Hz, 2 CH of Ar), 9.29 (s, 1 H, NH), 13.08 (br, 1 H, OH). δ_{C} (75 MHz, $\text{DMSO-}d_6$): 40.6 (CH), 43.3 (CH_2N), 47.6 (CH_2N), 55.1 (OCH_3), 105.1 (CH), 113.8 (CH of Ar), 119.2 (C- NO_2), 126.8 (CCO), 128.5 (CH of Ar), 135.5 ($C_{\text{ipso-Ar}}$), 153.9 (NCN), 158.2 ($C_{\text{ipso-Ar}}$), 163.2 (CO).

4.1.4. 7-(4-Chlorophenyl)-2-methyl-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid (4d). Yellow powder, mp = 179-181 °C (decomp), 0.30 g, yield: 90%. IR (KBr) (ν_{max} , cm^{-1}): 3347 (NH), 1729 (C=O), 1650 (NC=C) cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{ClN}_3\text{O}_4$: C, 53.66; H, 4.20; N, 12.52. Found C, 53.62; H, 4.21; N, 12.56. Major isomer **4d**: δ_{H} (300 MHz, $\text{DMSO-}d_6$): 1.31 (d, $^3J_{\text{HH}} = 5.6$ Hz, 3 H, CH_3), 3.83-3.88 (m, 1 H, NCH_2), 4.10-4.18 (m, 1 H, NCH_2), 4.25-4.32 (m, 1 H, NCH), 4.87 (d, $^3J_{\text{HH}} = 5.4$ Hz, 1 H, CH), 6.05 (d, $^3J_{\text{HH}} = 5.1$ Hz, 1 H, CH), 7.25 (d, $^3J_{\text{HH}} = 8.3$ Hz, 2 CH of Ar), 7.32 (d, $^3J_{\text{HH}} = 8.3$ Hz, 2 CH of Ar), 9.47 (s, 1 H, NH), 13.17 (br, 1 H, OH). δ_{C} (75 MHz, $\text{DMSO-}d_6$): 20.5 (CH_3), 40.8 (CH), 51.1 (CH_2N), 54.0 (CHN), 104.0 (CH), 118.0 (C- NO_2), 127.1 (CCO), 128.3 (CH of Ar), 129.1 (CH of Ar), 131.1 ($C_{\text{ipso-Ar}}$), 142.4 ($C_{\text{ipso-Ar}}$), 152.9 (NCN), 162.9 (CO). Minor isomer **4d**: δ_{H} (300 MHz, $\text{DMSO-}d_6$): 1.19 (d, $^3J_{\text{HH}} = 6.1$ Hz, 3 H, CH_3), 3.39-3.46 (m, 1 H, NCH_2), 3.68-3.74 (m, 1 H, NCH_2), 4.37-4.33 (m, 1 H, NCH), 4.91 (d, $^3J_{\text{HH}} = 5.2$ Hz, 1 H, CH), 6.12 (d, $^3J_{\text{HH}} = 5.1$ Hz, 1 H, CH), 7.25 (d, $^3J_{\text{HH}} = 8.4$ Hz, 2 CH of Ar), 7.32 (d, $^3J_{\text{HH}} = 8.3$ Hz, 2 CH of Ar), 9.42 (s, 1 H, NH), 13.09 (br, 1 H, OH). δ_{C} (75 MHz, $\text{DMSO-}d_6$): 20.1 (CH_3), 40.3 (CH), 51.3 (CH_2N), 54.2 (CHN), 104.1 (CH), 118.2 (C-

NO₂), 127.2 (CCO), 128.3 (CH of Ar), 129.1 (CH of Ar), 131.1 (*C*_{ipso}-Ar), 142.4 (*C*_{ipso}-Ar), 153.1 (NCN), 162.9 (CO).

4.1.5. 2-Methyl-7-(4-methylphenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid (4e). Yellow powder, mp = 174-176 °C (decomp), 0.26 g, yield: 84%. IR (KBr) (ν_{\max} , cm⁻¹): 3349 (NH), 1778 (C=O), 1658 (NC=C) cm⁻¹. Anal. Calcd for C₁₆H₁₇N₃O₄: C, 60.95; H, 5.43; N, 13.33. Found C, 60.91; H, 5.46; N, 13.36. δ_{H} (300 MHz, DMSO-*d*₆): 1.30 (d, ³*J*_{HH} = 5.6 Hz, 3 H, CH₃), 2.23 (s, 3 H, CH₃), 3.66-3.72 (m, 1 H, NCH₂), 4.13-4.15 (m, 1 H, NCH₂), 4.37-4.43 (m, 1 H, NCH), 4.80 (d, ³*J*_{HH} = 5.3 Hz, 1 H, CH), 6.07 (d, ³*J*_{HH} = 5.4 Hz, 1 H, CH), 7.07 (br, 4 CH of Ar), 9.41 (s, 1 H, NH), 13.12 (br, 1 H, OH). δ_{C} (75 MHz, DMSO-*d*₆): 20.2 (CH₃), 20.7 (CH₃), 41.0 (CH), 51.3 (CH₂N), 54.3 (CHN), 104.5 (CH), 119.2 (C-NO₂), 126.8 (CCO), 127.3 (CH of Ar), 129.0 (CH of Ar), 135.8 (*C*_{ipso}-Ar), 140.5 (*C*_{ipso}-Ar), 153.3 (NCN), 163.1 (CO).

4.1.6. 7-(4-Methoxyphenyl)-2-methyl-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acid (4f). Yellow powder, mp = 176-178 °C (decomp), 0.29 g, yield: 87%. IR (KBr) (ν_{\max} , cm⁻¹): 3345 (NH), 1733 (C=O), 1666 (NC=C) cm⁻¹. Anal. Calcd for C₁₆H₁₇N₃O₅: C, 58.0; H, 5.17; N, 12.68. Found C, 58.04; H, 5.15; N, 12.65. Major isomer **4f**: δ_{H} (300 MHz, DMSO-*d*₆): 1.30 (d, *J* = 5.6 Hz, 3 H, CH₃), 3.69 (s, 3 H, OCH₃), 3.85-3.86 (m, 1 H, NCH₂), 4.13-4.15 (m, 1 H, NCH₂), 4.24-4.30 (m, 1 H, NCH₂), 4.79 (d, ³*J*_{HH} = 4.7 Hz, 1 H, CH), 6.09 (d, ³*J*_{HH} = 6.3 Hz, 1 H, CH), 6.83 (d, ³*J*_{HH} = 6.3 Hz, 2 CH of Ar), 7.11 (d, ³*J*_{HH} = 7.3 Hz, 2 CH of Ar), 9.39 (s, 1 H, NH), 13.16 (br, 1 H, OH). δ_{C} (75 MHz, DMSO-*d*₆): 20.2 (CH₃), 40.3 (CH), 51.1 (CH₂N), 54.1 (CHN), 55.1 (OCH₃), 104.7 (CH), 113.9 (CH of Ar), 119.3 (C-NO₂), 126.5 (CCO), 128.4 (CH of Ar), 135.4 (*C*_{ipso}-Ar), 153.0 (NCN), 158.1 (*C*_{ipso}-Ar), 163.1 (CO). Minor isomer **4f**: δ_{H} (300 MHz, DMSO-*d*₆): 1.29 (d, ³*J*_{HH} = 6.1 Hz, 3 H, CH₃), 3.73 (s, 3 H, OCH₃), 3.88-3.92 (m,

1 H, NCH₂), 4.13-4.15 (m, 1 H, NCH₂), 4.24-4.27 (m, 1 H, NCH), 4.81 (d, ³J_{HH} = 4.7 Hz, 1 H, CH), 6.15 (d, ³J_{HH} = 6.04 Hz, 1 H, CH), 6.82-7.12 (m, 4 CH of Ar), 9.44 (s, 1 H, NH), 13.16 (br, 1 H, OH). δ_C (75 MHz, DMSO-*d*₆): 20.7 (CH₃), 40.5 (CH), 51.3 (CH₂N), 54.3 (CHN), 55.1 (OCH₃), 104.8 (CH), 113.9 (CH of Ar), 119.5 (C-NO₂), 126.6 (CCO), 128.5 (CH of Ar), 135.5 (C_{ipso}-Ar), 153.2 (NCN), 158.1 (C_{ipso}-Ar), 163.1 (CO).

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Table 1. Screening Optimum Reaction Conditions for the Formation of Intermediate Knoevenagel Condensation Product

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield ^a %
1	-	EtOH	rt	24	nr ^b
2	-	EtOH	rt	24	nr
3	I ₂ (10)	EtOH	70	24	27
4	I ₂ (10)	MeOH	65	24	14
5	I ₂ (10)	THF	70	10	30
6	I ₂ (5)	MeCN	80	5	44
7	I ₂ (20)	MeCN	80	2	92
8	I ₂ (10)	MeCN	80	2	94

^a Isolated yield^b No reaction

Entry	Product 4	Ar	Diamine 3	Ratio of two diastereomers	Total yield %
1	4a	4-ClC ₆ H ₄	Ethylenediamine	-	94
2	4b	4-MeC ₆ H ₄	Ethylenediamine	-	85
3	4c	4-MeOC ₆ H ₄	Ethylenediamine	-	88
4	4d	4-ClC ₆ H ₄	1,2-Propanediamine	91:9	90
5	4e	4-MeC ₆ H ₄	1,2-Propanediamine	-	84
6	4f	4-MeOC ₆ H ₄	1,2-Propanediamine	83:17	87
7	4g	4-ClC ₆ H ₄	1,3-Propylenediamine	-	-
8	4h	4-ClC ₆ H ₄	1,4-Butanediamine	-	-

Table 2. One-Pot Synthesis of Tetrahydroimidazo[1,2-*a*]pyridine-5-carboxylic acids **4a-f** via Domino SN/Knoevenagel condensation/Michael Addition/Cyclization Reaction