Synthesis of 5-amino-N’-(9H-fluoren-9-ylidene)-8-nitro-7-aryl-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carbohydrazide derivatives based on heterocyclic ketene aminals†

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A new class of tetrahydroimidazo[1,2-a]pyridine derivatives has been successfully prepared via a five-component domino reaction using cyanoacetohydrazide, 9-fluorenone, aromatic aldehydes, 1,1-bis(methylthio)-2-nitroethene and ethylenediamine in ethanol at reflux. The new efficient cascade approach involves a sequence of \( N,N \)-acetal formation, Knoevenagel condensation, Michael addition, imine–enamine tautomerization and \( N \)-cyclization as key steps. The merit of this protocol is highlighted by its available and economical starting compounds, operational simplicity, clean reaction profile and tolerance of a wide diversity of functional groups.

Introduction

Imidazopyridines have shown a broad spectrum of pharmacological and biological activities. Among the various derivatives, the imidazo[1,2-a]pyridine framework is likely the most important construction due to its vital role as a key structure in drugs and biologically active compounds with properties such as anti-inflammatory, antiviral, anti-angiogenic, anti-tumor, anti-ulcer, anti-fungal, anti-cancer, anti-arthritic, etc. They are included in marketed drugs such as the clinical anti-ulcer compound zolpidem and alpidem, olpironone, zolimidine, necopidem and saripidem, soraprazan and minodronic acid (Fig. 1).

The design of reactions that minimize the number of synthetic steps for the rapid formation of functionalized molecules is one of the goals of modern synthesis. One way to achieve this purpose involves the development of multicomponent processes. Multicomponent reactions (MCRs) present a wide range of possibilities for the construction of complex molecules in a single step. The benefits of this approach include minimum time, labor and cost, high atom economy, and straight experimental procedures. These advantages are highlights for multicomponent cascade reactions, which contain in situ production of an intermediate with a reactive site for subsequent variations.

By now, various synthetic methods have been developed to prepare imidazo[1,2-a]pyridines. The common strategies were the cyclocondensations of 2-aminopyridines with \( \alpha \)-halocarbonyl compounds, 1,3-dicarboxyl compounds, nitroalkenes or alkynes.

There are still many efforts to the development of new methods for the synthesis of imidazo[1,2-a]pyridine derivatives with a variety of substituents at two rings. Some other novel synthetic approaches have been established in recent years for the synthesis of tetrahydroimidazo[1,2-a]pyridines by heterocyclic ketene aminals (HKAs). Heterocyclic ketene aminals

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Fig. 1 Drugs containing the imidazo[1,2-a]pyridine core.
(HKAs) have been proven to be efficient synths in the synthesis of heterocyclic systems. During the past few years, reactions of cyclic ketene aminals with a variety of bis-electrophilic compounds have been applied to make five- and six-membered fused heterocycles.\(^\text{10}\)

As a part of our current studies on synthesis of novel heterocyclic compounds using cyanoacetohydrazide, we describe herein an efficient one-pot five-component synthesis of novel imidazo[1,2-\(a\)]pyridine-6-carboxyhydrazides \textit{via in situ} preparation of nitroketene aminal. These structures are completely new and there is no report on their synthesis.

**Results and discussion**

We have developed an efficient synthesis of tetrahydroimidazo[1,2-\(a\)]pyridine-6-carboxyhydrazides \textit{via a one-pot five-component reaction. We used cyanoacetohydrazide 1, 9-fluoren-2-one, aromatic aldehyde 3, 1,1-bis(methylthio)-2-nitroethene 4 and ethylenediamine 5 for the synthesis of title compounds.**

**Optimization of the conditions**

Initially, to identify the optimum reaction condition, 4-fluorobenzaldehyde was used as model substrate (since 4-fluorobenzaldehyde has clear reaction with obvious TLC at appropriate \(R_t\) value). At first, ethanol was used as solvent without any catalyst at reflux conditions and it was observed the desired product was not formed (Table 1, entry 1). The use of piperidine catalyst resulted in a yield of 40% in the product (entry 2). In order to improve yield, two other types of catalysts were used. With p-TSA, the five-component product did not form, and with acetic acid in a mixture of water and ethanol the efficiency did not change significantly (entry 3 and 5). The use of water and ethanol or water or acetonitrile without any catalyst resulted in no product formation (entry 4, 7 and 8). It was found that the reaction proceeded with high yield to formation of 5-amino-\(N^1\)-(9H-fluoren-9-ylidene)-7-(4-fluorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-\(a\)]pyridine-6-carboxyhydrazide \(6a\) when ethanol was used as solvent and acetic acid was applied as catalyst at reflux conditions (entry 6).

It should be noted that initially a two-component reaction of cyanoacetohydrazide and 9-fluorenone is performed in the presence of acetic acid and then, without separating the product, aldehyde and ketene aminal are added.

With information obtained from optimization conditions table, we could synthesize target compounds \(6a-\text{k}\) using cyanoacetohydrazide 1, 9-fluorenone 2, various aromatic aldehydes \(3\text{a-\text{k}}\), 1,1-bis(methylthio)-2-nitroethene 4 and ethylenediamine 5 as starting materials (Scheme 1).

The reactions were completed after 8–12 h overall to afford corresponding heterocyclic systems \(6\text{a-\text{k}}\) in good to high yields (65–87%). The results are summarized in Table 2.

**Effect of substituents**

This reaction was performed with other derivatives of diamines (1,3-diaminopropane, 1,4-diaminobutane and 1,2-diamino cyclohexane) under the same conditions, which did not result in the desired product. Also the reaction with \textit{ortho} derivatives of benzaldehyde (2-chloro and 2-nitro) did not

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**Table 1 Optimization conditions for the formation of \(6a\) using 4-fluorobenzaldehyde**

| Entry | Solvent | Catalyst (mol%) | Time (h) | Temp. (°C) | Yield (%) |
|-------|---------|----------------|----------|------------|-----------|
| 1     | EtOH    | —              | 24       | 78         | No reaction |
| 2     | EtOH    | Piperidine     | 24       | 78         | 40        |
| 3     | EtOH    | p-TSA          | 24       | 78         | No reaction |
| 4     | H\(_2\)O/EtOH (1 : 1, v/v) | — | 24         | 78         | No reaction |
| 5     | H\(_2\)O/EtOH (1 : 1, v/v) | AcOH | 24 | 78 | 35 |
| 6     | EtOH    | AcOH           | 9        | 78         | 87        |
| 7     | H\(_2\)O | —              | 24       | 100        | No reaction |
| 8     | CH\(_3\)CN | — | 24       | 82         | No reaction |

\(^a\) Reagents and conditions: cyanoacetohydrazide (1 mmol), 9-fluorenone (1 mmol), 4-fluorobenzaldehyde (1 mmol), 1,1-bis(methylthio)-2-nitroethene (1 mmol), ethylenediamine (1 mmol), solvent (20 mL), catalyst (0.2 mmol).
### Table 2  Compounds 6a–k

| Entry | Aromatic aldehyde | Product | Time (h) | Yield (%) | Mp (°C) |
|-------|-------------------|---------|----------|-----------|---------|
| 1     | ![3a](image)      | ![6a](image) | 9        | 87        | 246–248 |
| 2     | ![3b](image)      | ![6b](image) | 10       | 80        | 240–242 |
| 3     | ![3c](image)      | ![6c](image) | 11       | 75        | 249–251 |
| 4     | ![3d](image)      | ![6d](image) | 8        | 87        | 225–228 |
| 5     | ![3e](image)      | ![6e](image) | 9        | 85        | 210–212 |
| 6     | ![3f](image)      | ![6f](image) | 10       | 78        | 209–211 |
| 7     | ![3g](image)      | ![6g](image) | 12       | 65        | 218–220 |
produce the product, probably due to steric effects. For aldehydes with an electron-withdrawing group on para position of ring (nitro and halogens), the reaction rate is the highest and with methoxy group, the rate is the lowest.

It was found that the most important side product in these reactions was a four-component structure that was previously synthesized using two equivalents of aldehyde which will be further explained in the Mechanism section.

**Structure determination**

The structures of compounds 6a–k were deduced from their IR, $^1$H NMR, $^{13}$C NMR spectroscopic and mass spectrometric data (see the ESI†).

The formation of proposed products 6a–k is clearly confirmed by the $^1$H and $^{13}$C NMR spectra of the crude products. As a representative case, the key signals of $^1$H and $^{13}$C NMR chemical shifts for 5-amino-$N^0$-(9H-fluoren-9-ylidene)-7-(4-fluorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-α]pyridine-6-carbohydrazide 6a are shown in Fig. 2.

The $^1$H NMR spectrum of 6a showed two NH groups at $\delta$ 9.43 and 10.36 ppm. The NH$_2$ group appeared at $\delta$ 8.34 ppm. The protons of three aromatic rings were seen at $\delta$ 6.99–7.84 ppm. The proton of CH at pyridine ring was observed at $\delta$ 5.76 ppm.

Table 2 (Contd.)

| Entry | Aromatic aldehyde | Product | Time (h) | Yield (%) | Mp (°C) |
|-------|-------------------|---------|----------|-----------|---------|
| 8     | ![3h](image)      | ![6h](image) | 12       | 70        | 198–200 |
| 9     | ![3i](image)      | ![6i](image) | 11       | 83        | 218–220 |
| 10    | ![3j](image)      | ![6j](image) | 9        | 80        | 212–214 |
| 11    | ![3k](image)      | ![6k](image) | 9        | 75        | 226–229 |

* The reaction was performed using cyanoacetohydrazide (1 mmol), 9-fluorenone (1 mmol), aromatic aldehyde (1 mmol), 1,1-bis(methylthio)-2-nitroethene (1 mmol), ethylenediamine (1 mmol), EtOH (20 mL), AcOH (1 mL), reflux.
Two protons of two methylene groups appeared at δ 3.75–3.86 and 4.04–4.07 ppm.

The 1H-decoupled 13C NMR spectrum of 6a displayed 25 distinct signals in accordance to desired structure. The characteristic signals of three aliphatic carbons (CH and two CH2 groups) were observed at δ 36.6, 43.6 and 44.8 ppm respectively. Two signals at δ 79.9 and 108.1 ppm were related to C==C−CO and C−NO2 respectively. The carbonyl group appeared at δ 166.7 ppm (Fig. 2).

The mass spectrum of 6a displayed a molecular-ion peak at m/z 496 in agreement with the proposed product. The IR spectrum of this compound showed absorption bands at 3431, 3344, 3272 due to NH and NH3 groups, stretching vibration of aliphatic C−H bands at 2920, strong absorption of carbonyl group at 1654, stretching vibration of C==C of aromatic ring at 1445 and C−N stretching band at 1259 cm−1. Two absorption bands due to nitrile group appeared at 1363 and 1528 cm−1.

Mechanism
A typical plausible mechanism for the formation of 5-amino-N′-(9H-fluoren-9-ylidine)-7-aryl-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carboxyhydrazide 6 is depicted in Scheme 2. On the basis of well-established chemistry of 1,1-bis(methylthio)-2-nitroethene, initially, addition of ethylenediamine 5 to 1,1-bis(methylthio)-2-nitroethene 4 leads to the formation of ketene aminal 9. On the other hand condensation of cyanacetoxyhydrazide 1 with 9-fluorenone 2 leads to hydrazone 7. Further, with increasing aldehyde 3, the Knoevenagel condensation affords intermediate 8. Then, Michael addition of ketene aminal 9 to adduct 8 leads to the intermediate 10, which undergoes successive imine−enamine tautomerization followed by an intramolecular cyclization via nucleophilic addition of −NH to nitrile group. Finally, another imine−enamine tautomerization gives the corresponding products 6 (Scheme 2).

Experimental
Materials
All commercially available reagents and other solvents were purchased from Aldrich and Merck Chemical Co. and used without further purification. The NMR spectra were recorded with a Bruker DRX-300 AVANCE instrument (300 MHz for 1H and 75.4 MHz for 13C) with DMSO-d6 as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS, and coupling constant (J) are reported in Hertz (Hz). Melting points were measured with an electrothermal 9100 apparatus. Mass spectra were recorded with an Agilent 5975C VL MSD with Triple-Axis detector operating at an ionization potential of 70 eV. IR spectra were measured with Bruker Tensor 27 spectrometer. Elemental analyses for C, H and N were performed using a PerkinElmer 2004 series [II] CHN elemental analyzer.

General procedure of the synthesis of tetrahydroimidazo[1,2-a]pyridine-6-carboxyhydrazide derivatives
A mixture of ethylenediamine (66 mL, 1 mmol), 1,1-bis(methylthio)-2-nitroethylene (0.165 g, 1 mmol) and 10 mL EtOH in a 50 mL flask was refluxed for 6 hours. In another 50 mL flask the stoichiometric mixture of cyanacetoxyhydrazide (1 mmol, 0.99 g) and 9-fluorenone (1 mmol, 0.180 g) in EtOH (10 mL) and AcOH (1 mL) was stirred at reflux conditions for 5 hours. After this time, it is observed that precipitate is formed and TLC shows the consumption of the starting components. Then, aromatic aldehyde (1 mmol) and the first solution (HKA) was added to this mixture simultaneously. The progress of the reaction was monitored by TLC using ethyl acetate/n-hexane (1 : 1). After completion of the reaction, the precipitated product was collected by filtration and washed with warm ethanol to give the pure products 6a–k.

5-Amino-N′-(9H-fluoren-9-ylidine)-7-(4-fluorophenyl)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carboxyhydrazide (6a), Orange solid; yield: 0.431 g (87%); mp: 246–248 °C; IR (KBr) (max/cm−1): 3431, 3344, 3272, 2920, 1654, 1528, 1445, 1363, 1259, 1160; 1H NMR (300 MHz, DMSO): δ 3.73–3.86 (2H, m, CH2), 4.04–4.07 (2H, m, CH2), 5.76 (1H, s, CH), 6.99–7.45 (9H, m, ArH), 7.68 (1H, d, J = 7.2 Hz, ArH), 7.78 (1H, d, J = 7.5 Hz, ArH), 7.83 (1H, d, J = 7.5 Hz, ArH), 8.34 (2H, brs, NH2), 9.43 (1H, s, NH), 10.36 (1H, s, NH); 13C (100 MHz, DMSO): δ 108.1 (C==C−CO), 110.5, 120.6, 120.9, 121.8, 126.9, 128.0, 128.5, 130.0, 130.1, 130.3, 131.1, 137.4, 139.5, 141.2, 141.8, 160.0 (Ar), 150.7 (C==C−NH), 151.7 (C==N), 152.1 (C==C−NH2), 166.7 (C==O); MS (EI, 70 eV); m/z (%) = 496 (0.07) [M]+, 453 (0.17), 407 (0.10), 356 (100), 327 (35), 276 (42), 254 (4), 230 (4), 194 (3), 178 (12), 164 (15), 150 (2), 133 (1), 97 (1), 69 (1);
anal. calecd for C_{27}H_{26}ClN_{6}O_{5}: C, 64.6; H, 4.87; N, 15.60. Found: C, 64.3; H, 4.6; N, 15.7.

5-Amino-N-(9H-fluoren-9-ylidene)-7-(4-nitrophenyl)-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid (6d). Yellow solid; yield: 0.455 g (87%); mp: 225–228 °C. 1H NMR (300 MHz, DMSO-d6): δ 3.78–3.88 (2H, CHs), 4.06–4.09 (2H, CHs), 5.87 (1H, s, CH), 7.02–7.82 (12H, ArH), 8.33 (2H, brs, NHs), 9.49 (1H, s, CH), 10.5 (1H, s, NH); 13C{1H} NMR (75.4 MHz, DMSO-d6): δ 37.6 (CH), 43.7 (CH2-NH), 44.8 (CH2-N), 79.4 (C=C=O), 107.0 (C=NO2), 120.6, 120.9, 121.8, 127.0, 128.6, 129.6, 130.2, 131.1, 131.7, 134.6, 141.3, 146.5 (Ar), 151.7 (C=N–NH), 151.8 (C=N), 152.1 (C=N–NH2), 153.4 (C=O–NO2), 166.8 (C=O); anal. calecd for C_{27}H_{24}N_{6}O_{3}: C, 61.95; H, 4.04; N, 18.53. Found: C, 61.6; H, 4.3; N, 18.5.

5-Amino-N-(4-chlorophenyl)-N-(9H-fluoren-9-ylidene)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid (6e). Light red solid; yield: 0.435 g (85%); mp: 210–212 °C. 1H NMR (300 MHz, DMSO-d6): δ 3.75–3.83 (2H, CHs), 4.04–4.10 (2H, CHs), 5.70 (1H, s, CH), 7.10–7.50 (9H, ArH), 7.68 (1H, d, J = 7.2 Hz, ArH), 7.78 (1H, d, J = 7.2 Hz, ArH), 7.83 (1H, d, J = 7.5 Hz, ArH), 8.30 (2H, brs, NHs), 9.41 (1H, s, NH), 10.32 (1H, s, NH); 13C{1H} NMR (75.4 MHz, DMSO-d6): δ 36.8 (CH), 43.6 (CH2-NH), 44.8 (CH2-N), 79.8 (C=C=O), 107.7 (C=NO2), 120.6, 120.9, 121.8, 126.9, 127.9, 128.4, 128.5, 129.2, 130.1, 130.3, 131.1, 131.5, 137.4, 139.5, 141.2, 144.6 (Ar), 150.9 (C=C–NH), 151.7 (C=N), 152.1 (C=C=NH2), 166.7 (C=O–OMe), 166.7 (C=O); MS (EI, 70 eV): m/z (%) = 508 (0.06) [M]+, 435 (0.1), 356 (4), 327 (1), 295 (2), 275 (4), 220 (7), 194 (6), 163 (100), 134 (55), 105 (14), 85 (7), 57 (12); anal. calecd for C_{24}H_{30}N_{6}O_{3}: C, 66.13; H, 4.76; N, 16.53. Found: C, 66.3; H, 4.5; N, 16.3.

5-Amino-N-(9H-fluoren-9-ylidene)-8-nitro-1,2,3,7-tetrahydroimidazo[1,2-a]pyridine-6-carboxylic acid (6f). Light brown solid; yield: 0.408 g (83%); mp: 218–220 °C. 1H NMR (300 MHz, DMSO-d6): δ 2.20 (3H, s, CH3), 3.74–3.86
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Conflicts of interest

The authors declare no competing financial interest.
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