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ORIGINAL PAPER

An efficient synthesis of ferrocenyl imidazo[1,2-*a*]pyridines

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Abstract An efficient and simple synthesis of ferrocenyl 3-aminoimidazo[1,2-*a*]pyridines by the three-component reaction of ferrocenecarboxaldehyde, isocyanides, and 2-aminopyridines in the presence of a catalytic amount of $InCl_3$ in ethanol at room temperature is reported.

Keywords Ferrocenecarboxaldehyde · $InCl_3$ · Ferrocenyl imidazopyridine · Ferrocene · Isocyanide

Introduction

Ferrocene and its derivatives are paid much attention on account of their fascinating sandwich structure and unusual properties [1–4]. Moreover, they have a broad variety of potential applications in materials [5–8], medicine [9–12], organic synthesis [13–16], etc. Ferrocenes containing heterocyclic systems have attracted special attention in recent years [13, 17–20], because of their organic and inorganic properties as well as for their applications in various areas of organic materials [21–23]. They are also important because of their potential biological activity [24, 25].

Fused heteroaromatic compounds containing ring-junction nitrogen atoms are important for the preparation of biologically active molecules [26, 27]. One such class of heteroaromatic compounds, imidazo[1,2-*a*]pyridines, has received significant attention from the pharmaceutical industry owing to their interesting biological activities displayed over a broad range of therapeutic classes [28], exhibiting antibacterial [29], antifungal [30], antiviral [31], and anti-inflammatory [32] properties. Drug formulations containing imidazo[1,2-*a*]pyridines currently available on the market include alpidem (anxiolytic), zolpidem (hypnotic), and zolimidine (antiulcer) [29]. Although it was indicated that the replacement of aromatic groups by a ferrocenyl moiety had increased the antibacterial activities of penicillin and cephalosporin antibacterials [33, 34], the broad application of the ferrocenyl moiety to biologically active compounds has not gained much attention. Recent publications support that the notion that combination of pharmacologically active N-heterocycles with a ferrocene moiety can result in favorable change of biological properties, often associated with decreased toxicity [25, 35].

Although isocyanide-based multicomponent reactions have been applied to the synthesis of imidazo[1,2-*a*]pyridine derivatives [36–40], our literature survey revealed that this synthetic strategy has not been applied to the synthesis of imidazo[1,2-*a*]pyridines containing ferrocene moieties. As part of our research on the development of new synthetic methods in heterocyclic chemistry [41–47], in this paper we report for the first time an efficient synthesis of ferrocenyl imidazo[1,2-*a*]pyridines by a isocyanide-based three-component reaction.

Results and discussion

To achieve suitable conditions for the synthesis of ferrocenyl imidazo[1,2-*a*]pyridines, we tested the reaction of ferrocenecarboxaldehyde (**1**), 2,6-dimethylphenyl isocyanide (**2a**), and 2-aminopyridine (**3a**) as a simple model substrate in different solvents and in the presence of various catalysts or without any catalyst (Table 1). As can be seen from Table 1, the best result was obtained with 15 mol% of $InCl_3$ as the catalyst in ethanol (entry 4). Using

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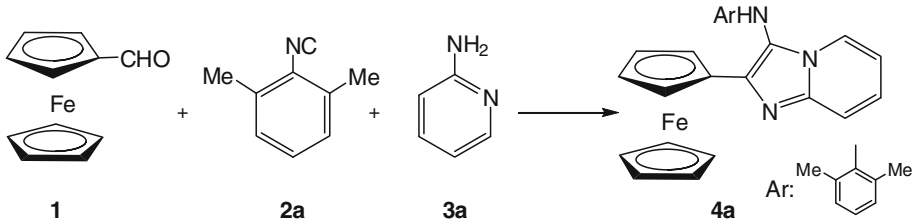
Table 1 Effect of reaction conditions



Entry	Solvent	Catalyst (mol%)	Time (h)	Yield (%)
1	EtOH	None	48	Trace
2	EtOH	$InCl_3$ (5)	24	47
3	EtOH	$InCl_3$ (10)	24	63
4	EtOH	$InCl_3$ (15)	24	78
5	EtOH	$InCl_3$ (20)	24	77
6	H_2O	$InCl_3$ (15)	24	Trace
7	CH_3CN	$InCl_3$ (15)	24	55
8	THF	$InCl_3$ (15)	24	51
9	MeOH	$InCl_3$ (15)	24	67
10	EtOH	*p*-TSA (15)	24	48
11	EtOH	$LiClO_4$ (15)	24	61
12	EtOH	$ZnCl_2$ (15)	24	<30

Ferrocenealdehyde (1 mmol), isocyanide (1 mmol), and aminopyridine (1 mmol) at room temperature

a lower amount of catalyst resulted in lower yields, while higher amounts of catalyst did not affect reaction times and yields (Table 1). When this reaction was carried out without $InCl_3$ or with other catalysts such as $ZnCl_2$, $LiClO_4$, *p*-toluenesulfonic acid (*p*-TSA), the yield of the expected product was low (Table 1). To delineate the role of solvent effect, the reaction was investigated using various solvents. Table 1 demonstrates that ethanol was the best choice of solvent and the use of $InCl_3$ in ethanol improves the rate of the reaction and also the yield of the product.

Encouraged by this success, a variety of isocyanides and aminopyridines were employed under similar conditions to evaluate the substrate scope of this reaction. The corresponding ferrocenyl imidazo[1,2-*a*]pyridine derivatives **4a**–**4k** were selectively synthesized by the one-pot, three-component condensation of ferrocenecarboxaldehyde (**1**), isocyanides **2a**–**2c**, and aminopyridines **3a**–**3e** in good yields in ethanol in the presence of $InCl_3$ (15 mol%) for 24 h. The results are summarized in Table 2.

Compound **4** apparently results from the formation of ferrocenyl imine **5** (formed in situ by reaction of amine **3** and ferrocenecarboxaldehyde). Subsequent [4 + 1] cycloaddition reaction of the imine **5** with the isocyanides **2** followed by prototropic shift afforded the corresponding products **4** (Scheme 1) [48].

The ^{1}H NMR spectra of the crude products indicated the formation of ferrocenyl imidazo[1,2-*a*]pyridines **4**. Compounds **4** are stable solids whose structures were established by IR and NMR spectroscopy and elemental analysis.

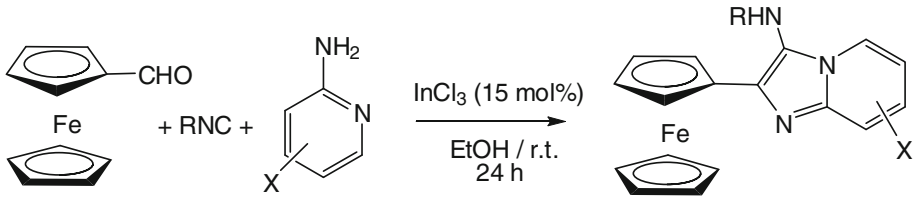
To the best of our knowledge, this new isocyanide-based three-component strategy provides the first example of an efficient synthesis of ferrocenyl imidazopyridines. This method, based on a three-component reaction in ethanol, is a simple, interesting, convenient, and acceptable one-pot method. As a result of the easy access to aminopyridines and isocyanides, this present method should be applicable to synthesis of libraries with high diversity. In addition, the work-up of these very clean reactions is simple, involves only a filtration, and simple washing step with ether.

In conclusion, we have developed an efficient straightforward procedure for the synthesis of a new class of ferrocenyl imidazopyridines of potential synthetic and biological interest by a one-pot, three-component methodology.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were recorded on a Shimadzu IR-470

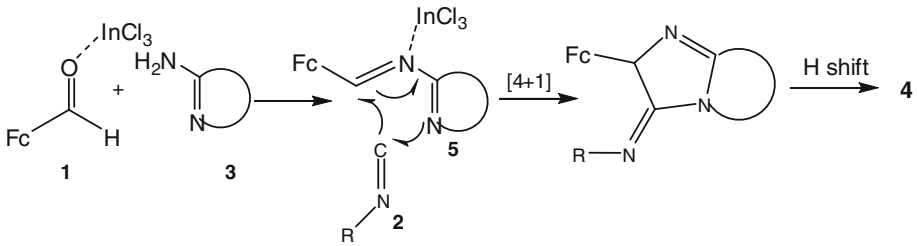
Table 2 Synthesis of ferrocenyl imidazopyridines **4**



1 **2a-2c** **3a-3e** **4a-4k**

Product **4**	R	Compound **3**	Yield (%)
a	2,6-$(Me)_2C_6H_3$	**3a** (X = H)	78
b	Cyclohexyl	**3a** (X = H)	69
c	*tert*-Butyl	**3a** (X = H)	60
d	2,6-$(Me)_2C_6H_3$	**3b** (X = 3-Me)	63
e	Cyclohexyl	**3b** (X = 3-Me)	59
f	2,6-$(Me)_2C_6H_3$	**3c** (X = 5-Me)	76
g	Cyclohexyl	**3c** X = 5-Me)	67
h	2,6-$(Me)_2C_6H_3$	**3d** (X = 6-Me)	71
i	Cyclohexyl	**3d** (X = 6-Me)	67
j	Cyclohexyl	**3e** (X = 5-Br)	74
k	*tert*-Butyl	**3e** (X = 5-Br)	61

Scheme 1



spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 MHz. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O -Rapid analyzer, and the results agreed with calculated values. Chemicals were purchased from Fluka or Merck and used as received.

General procedure for the preparation of ferrocenyl imidazopyridines

A mixture of ferrocenecarboxaldehyde (1 mmol), isocyanide (1 mmol), aminopyridine (1 mmol), and $InCl_3$ (15 mol%) in 5 cm^3 ethanol at room temperature was stirred for 24 h. After completion of reaction, the reaction mixture was filtered, the precipitate washed with 5 cm^3 ether and air-dried to provide the pure product **4**.

As a result of the very low solubility of the products, we cannot report the ^{13}C NMR data for **4a**–**4k**.

N-(2,6-Dimethylphenyl)-2-ferrocenylimidazo[1,2-a]-pyridin-3-amine (**4a**, $C_{25}H_{23}FeN_3$)
Brown powder (78%); m.p.: 155–157 °C; IR (KBr): $\bar{\nu}$ = 3,205, 3,043, 1,654, 1,611 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.92 (s, $2CH_3$, 6H), 3.94 (s, CH_{fer}, 5H), 4.20 (s, CH_{fer}, 2H), 4.46 (s, CH_{fer}, 2H), 6.73 (br s, NH, 1H), 6.83–8.11 (m, H–Ar, 7H) ppm; MS: *m*/*z* (%) = 421 (M^+, 23), 224 (45), 199 (52), 78 (100).

N-Cyclohexyl-2-ferrocenylimidazo[1,2-a]pyridin-3-amine (**4b**, $C_{23}H_{25}FeN_3$)
Brown powder (69%); m.p.: >280 °C; IR (KBr):$\bar{\nu}$ = 3,237, 3,117, 1,643, 1,570 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.15–1.75 (m, 5 CH_2 of cyclohexyl, 10H), 3.05 (br s, CH–N of cyclohexyl, 1H), 4.03 (s, CH_{fer}, 5H), 4.35 (s, CH_{fer}, 2H), 4.54 (br s, NH, 1H), 4.98 (s, CH_{fer}, 2H),

6.91–8.30 (br s, H–Ar, 4H) ppm; MS: *m/z* (%) = 399 (M^+, 32), 214 (35), 189 (59), 56 (100).

N-tert-Butyl-2-ferrocenylimidazo[1,2-a]pyridin-3-amine (**4c**, $C_{21}H_{23}FeN_3$)
Brown powder (60%); m.p.: 166–168 °C; IR (KBr):$\bar{\nu}$ = 3,188, 1,648, 1,608 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.01 (s, $3CH_3$, 9H), 4.02–4.20 (m, CH_{fer}, 5H), 4.28 (s, CH_{fer}, 2H), 4.34 (br s, NH, 1H), 4.97 (s, CH_{fer}, 2H), 6.80–8.30 (br s, H–Ar, 4H) ppm; MS: *m/z* (%) = 373 (M^+, 32), 188 (48), 121 (32), 57 (100).

N-(2,6-Dimethylphenyl)-2-ferrocenyl-8-methylimidazo-[1,2-a]pyridin-3-amine (**4d**, $C_{26}H_{25}FeN_3$)
Light brown powder (63%); m.p.: 124–126 °C; IR (KBr):$\bar{\nu}$ = 3,430, 2,959, 1,680, 1,643 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.92 (s, $2CH_3$, 6H), 2.52 (s, CH_3, 3H), 3.94 (s, CH_{fer}, 5H), 4.17 (s, CH_{fer}, 2H), 4.49 (s, CH_{fer}, 2H), 6.68–7.93 (m, H–Ar and NH, 7H) ppm; MS: *m/z* (%) = 435 (M^+, 20), 250 (45), 225 (30), 100 (100).

N-Cyclohexyl-2-ferrocenyl-8-methylimidazo[1,2-a]-pyridin-3-amine (**4e**, $C_{24}H_{27}FeN_3$)
Light brown powder (59%); m.p.: >280 °C; IR (KBr):$\bar{\nu}$ = 3,404, 2,918, 2,855, 1,648, 1,637 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.14–1.78 (m, 5 CH_2 of cyclohexyl, 10H), 2.46 (s, CH_3, 3H), 3.05 (br s, CH–N of cyclohexyl, 1H), 4.02 (s, CH_{fer}, 5H), 4.31 (s, CH_{fer}, 2H), 4.39 (br s, NH, 1H), 4.97 (s, CH_{fer}, 2H), 6.70–8.09 (m, H–Ar, 3H) ppm; MS: *m/z* (%) = 413 (M^+, 15), 228 (35), 56 (100).

N-(2,6-Dimethylphenyl)-2-ferrocenyl-6-methylimidazo-[1,2-a]pyridin-3-amine (**4f**, $C_{26}H_{25}FeN_3$)
Light brown powder (76%); m.p.: 159–161 °C; IR (KBr):$\bar{\nu}$ = 3,348, 2,923, 1,653 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.92 (s, $2CH_3$, 6H), 2.29 (s, CH_3, 3H), 3.91 (s, CH_{fer}, 5H), 4.15 (s, CH_{fer}, 2H), 4.41 (s, CH_{fer}, 2H), 6.72–7.42 (m, H–Ar, 7H), 7.94 (s, NH, 1H) ppm; MS: *m/z* (%) = 435 (M^+, 28), 225 (50), 100 (100).

N-Cyclohexyl-2-ferrocenyl-6-methylimidazo[1,2-a]-pyridin-3-amine (**4g**, $C_{24}H_{27}FeN_3$)
Light brown powder (67%); m.p.: 146–149 °C; IR (KBr):$\bar{\nu}$ = 3,336, 2,964, 2,848 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.12–1.77 (m, 5 CH_2 of cyclohexyl, 10H), 2.28 (s, CH_3, 3H), 3.08 (br s, CH–N of cyclohexyl, 1H), 4.00 (s, CH_{fer}, 5H), 4.31 (s, CH_{fer}, 2H), 4.35 (br s, NH, 1H), 4.93 (s, CH_{fer}, 2H), 6.94–8.01 (m, H–Ar, 3H) ppm; MS: *m/z* (%) = 413 (M^+, 10), 228 (30), 121 (70), 56 (100).

N-(2,6-Dimethylphenyl)-2-ferrocenyl-5-methylimidazo-[1,2-a]pyridin-3-amine (**4h**, $C_{26}H_{25}FeN_3$)
Brown powder (71%); m.p.: 232–234 °C; IR (KBr):$\bar{\nu}$ = 3,341, 2,965, 1,648, 1,586 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.90 (s, $2CH_3$, 6H), 2.76 (s, CH_3, 3H), 3.99 (s, CH_{fer}, 5H), 4.24 (s, CH_{fer}, 2H), 4.50 (s, CH_{fer}, 2H), 6.63–7.45 (m, H–Ar and NH, 7H) ppm; MS: *m/z* (%) = 435 (M^+, 30), 238 (25), 213 (33), 100 (100).

N-Cyclohexyl-2-ferrocenyl-5-methylimidazo[1,2-a]-pyridin-3-amine (**4i**, $C_{24}H_{27}FeN_3$)
Light brown powder (67%); m.p.: 175–179 °C; IR (KBr):$\bar{\nu}$ = 3,190, 2,930, 2,853, 1,651, 1,605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.23–1.73 (m, 5 CH_2 of cyclohexyl, 10H), 2.99 (s, CH_3, 3H), 3.06 (br s, CH–N of cyclohexyl, 1H), 4.16 (s, CH_{fer}, 5H), 4.47 (s, CH_{fer}, 2H), 4.66 (br s, NH, 1H), 5.07 (s, CH_{fer}, 2H), 6.99–7.91 (m, H–Ar, 3H) ppm; MS: *m/z* (%) = 413 (M^+, 45), 203 (25), 121 (65), 56 (100).

6-Bromo-N-cyclohexyl-2-ferrocenylimidazo[1,2-a]-pyridin-3-amine (**4j**, $C_{23}H_{24}BrFeN_3$)
Light brown powder (74%); m.p.: 172–174 °C; IR (KBr):$\bar{\nu}$ = 3,446, 2,927, 2,854, 1,644, 1,600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.16–1.72 (m, 5 CH_2 of cyclohexyl, 10H), 2.46 (s, CH_3, 3H), 3.10 (br s, CH–N of cyclohexyl, 1H), 4.00 (s, CH_{fer}, 5H), 4.33 (s, CH_{fer}, 2H), 4.56 (br s, NH, 1H), 4.94 (s, CH_{fer}, 2H), 7.17–8.44 (m, H–Ar, 3H) ppm; MS: *m/z* (%) = 479 (M^+, 30), 477 (M^+, 30), 292 (40), 56 (100).

6-Bromo-N-tert-butyl-2-ferrocenylimidazo[1,2-a]-pyridin-3-amine (**4k**, $C_{21}H_{22}BrFeN_3$)
Light brown powder (61%); m.p.: 177–180 °C; IR (KBr):$\bar{\nu}$ = 3,316, 2,966, 1,637 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 1.00 (s, $3CH_3$, 9H), 4.01 (s, CH_{fer}, 5H), 4.29 (s, CH_{fer}, 2H), 4.42 (br s, NH, 1H), 4.97 (s, CH_{fer}, 2H), 7.21–8.43 (br s, H–Ar, 4H) ppm; MS: *m/z* (%) = 453 (M^+, 20), 451 (M^+, 20), 57 (100).

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