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An efficient access to 2,3-diarylimidazo[1,2-*a*]pyridines via imidazo[1,2-*a*]pyridin-2-yl triflate through a Suzuki cross-coupling reaction-direct arylation sequence

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ABSTRACT

An efficient method to prepare 2,3-diarylimidazo[1,2-*a*]pyridines is described. The procedure involves a Suzuki cross-coupling reaction followed by a direct arylation at position 3. Imidazo[1,2-*a*]pyridin-2-yl triflate was identified as a suitable coupling partner, permitting access to a variety of highly functionalized 2,3-diarylimidazo[1,2-*a*]pyridines.

Imidazo[1,2-*a*]pyridines are a class of nitrogen bridgehead heterocycles which have received considerable attention due to their interesting biological activities.[1] Moreover, 2,3-diarylimidazo[1,2-*a*]pyridines **1** (Fig. 1) have shown antiprotozoal,[2] antiviral,[3] and anti-apoptotic[4] activities, and have attracted attention as liver X receptor agonists[5] and kinase inhibitors.[6] The increased interest in this class of compounds led us to envisage an efficient synthetic method. To the best of our knowledge, the access to highly functionalized 2,3-diarylimidazo[1,2-*a*]pyridines has not yet been described in the literature.

Initially, 2-arylimidazo[1,2-*a*]pyridine cores must be built up. The most common route for the preparation of such compounds involves condensation between 2-aminopyridine and 2-bromoacetophenone.[7] However, such strategy is limited by the commercial availability of 2-bromoacetophenones. Thus, we envisaged that a Pd-catalysed Suzuki cross-coupling reaction could proceed at position 2 with an appropriate coupling partner.

A retrosynthetic strategy for the synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines is outlined in Scheme 1. Targeted compounds **1** could be obtained from 2-halogenoimidazo[1,2-*a*]pyridines **3**, readily available from commercially-available 2-aminopyridine followed by a two-step process including Pd-catalysed Suzuki–Miyaura and direct arylation reactions.

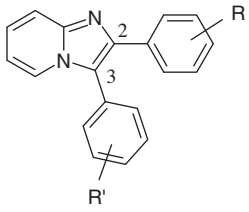
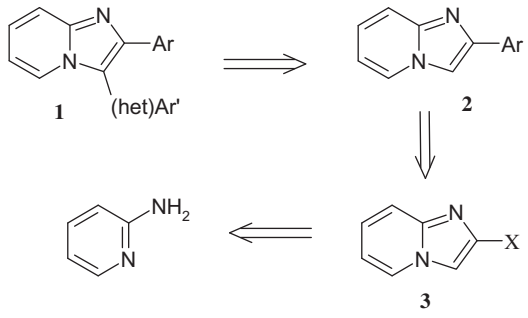


Figure 1. 2,3-Diarylimidazo[1,2-*a*]pyridines **1**.



Scheme 1. Retrosynthetic pathway of 2,3-diarylimidazo[1,2-*a*]pyridines **1**.

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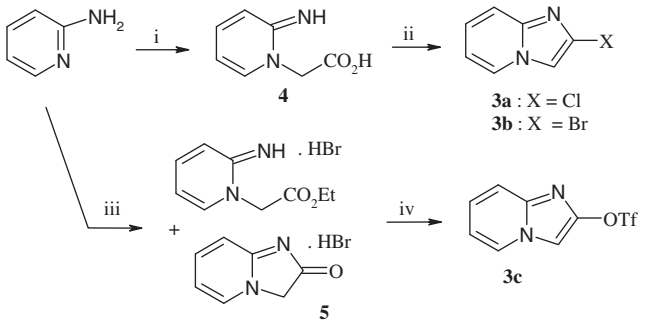
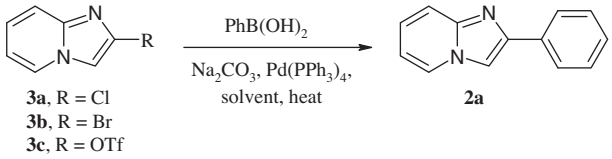


Scheme 2. Synthesis of **3a–c**. Reagents and conditions: (i) $ClCH_2CO_2H$, Et_3N, H_2O, 90 °C, 5 h, then EtOH, 5 °C, 2 h, 71%; (ii) X = Cl, $POCl_3$, toluene, reflux, 16 h, 88%; X = Br, $POBr_3$, toluene, reflux, 16 h, 9%; (iii) $BrCH_2CO_2Et$, 0 °C→rt, 15 min, then EtOH, reflux, 18 h; (iv) $PhNTf_2$, Et_3N, toluene, reflux, 20 h, 67% (two steps).



Scheme 3. Synthesis of **2a**.

We first started with the synthesis of 2-halogenoimidazo[1,2-*a*]pyridines from 2-aminopyridine (Scheme 2). 2-Aminopyridine was reacted with chloroacetic acid to afford acetic acid derivative **4** in a good yield. Subsequent cyclization with $POCl_3$ and $POBr_3$, respectively, led to 2-chloroimidazo[1,2-*a*]pyridine **3a** and its brominated analogue **3b**.[8] These conditions proved to be successful for **3a** but afforded a very low yield of **3b** (extraction failure). We next decided to prepare imidazo[1,2-*a*]pyridin-2-yl triflate[9] **3c** which could be an efficient coupling partner in the Suzuki–Miyaura cross-coupling reaction. Thus, 2-aminopyridine reacted with ethyl bromoacetate to give **5**, as a mixture of the expected product and a non-cyclized intermediate. Subsequent treatment with *N*-phenyl-*bis*(trifluoromethanesulfonimide) led to **3c** in a satisfactory yield (67%, two steps).[10]

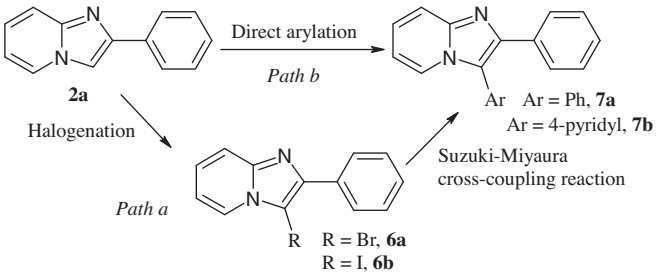
With these suitable substrates in our hand, the Suzuki–Miyaura reaction of **3a**, **3b** and **3c** with phenylboronic acid afforded 2-phenylimidazo[1,2-*a*]pyridine **2a** (Scheme 3 and Table 1).

We noticed that 2-chloroimidazo[1,2-*a*]pyridine **3a** was less reactive than the corresponding bromide **3b** (Table 1, entries 1 and 2). Interestingly, triflate **3c** proved to be effective in the coupling reaction carried out in a sealed tube with a shorter time (entry 3). No difference was observed when the reaction was performed in 1,4-dioxane (entry 4). Thus these results prompted us to employ imidazo[1,2-*a*]pyridin-2-yl triflate **3c** as a substrate for further Suzuki–Miyaura cross-coupling reaction at position 2 of the scaffold.

Table 1
Synthesis of **2a**

Entry	Substrate	Conditions	Yield of **2a**[a] (%)
1	**3a**	DME–H_2O 2:1, reflux, sealed tube, 6 h	25
2	**3b**	DME–H_2O 2:1, reflux, sealed tube, 6 h	51
3	**3c**	DME–H_2O 2:1, 100 °C, sealed tube, 4 h	46
4	**3c**	Dioxane–H_2O 2:1, 100 °C, sealed tube, 7 h	43

[a] Isolated yield.



Scheme 4. Synthesis of **7a–b** from **2a**.

Table 2
Synthesis of **7a–b** via halogenation-Suzuki–Miyaura coupling sequence (*path a*)

Entry	Substrate	Conditions	Product	Yield[a] (%)
1	**2a**	NBS, MeCN, rt, 2 h	**6a**	95
2	**2a**	NIS, MeCN, rt, 1 h	**6b**	73
3	**6a**	$PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, dioxane–H_2O 2:1, 110 °C, 2 h	**7a**	90
4	**6a**	(4-Pyridyl)boronic acid pinacol ester, $Pd(PPh_3)_4$, Na_2CO_3, dioxane–H_2O 2:1, 110 °C, 2 h	**7b**	93
5	**6b**	$PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, dioxane–H_2O 2:1, sealed tube, reflux, 12 h	**7a**	93
6	**6b**	(4-Pyridyl)boronic acid pinacol ester, $Pd(PPh_3)_4$, Na_2CO_3, dioxane–H_2O 2:1, sealed tube, reflux, 12 h	**7b**	95

[a] Isolated yield.

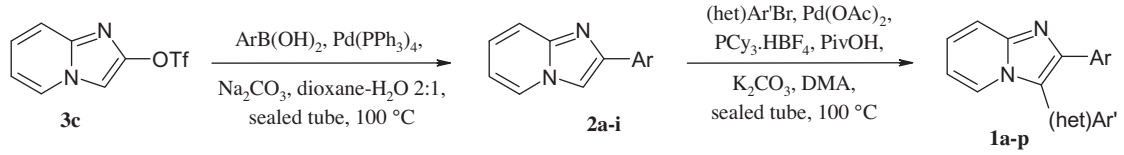
Table 3
Synthesis of **7a–b** via direct arylation (*path b*)

Entry	Substrate	Conditions	Product	Yield[a] (%)
1	**2a**	PhBr, $Pd(OAc)_2$, PPh_3, K_2CO_3, dioxane–EtOH, MW, 130 °C, 1 h	**7a**	37[b]
2	**2a**	PhBr, $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, PivOH, K_2CO_3, DMA, sealed tube, 100 °C, 16 h	**7a**	95
3	**2a**	4-Bromopyridine hydrobromide, $Pd(OAc)_2$, $PCy_3.HBF_4$, PivOH, K_2CO_3, DMA, sealed tube, 100 °C, 16 h	**7b**	85

[a] Isolated yield.
[b] Significant amount of starting material (41%, UPLC-MS) was remaining.

We next investigated the preparation of 2,3-diarylimidazo[1,2-*a*]pyridines **1** through two methods. Initially, we thought that a halogenation-Suzuki–Miyaura coupling sequence[11] could give the desired products (Scheme 4, *path a*). Halogenation with NBS or NIS in acetonitrile afforded easily the compounds **6a** and **6b**, precursors for a Suzuki–Miyaura coupling reaction (Table 2, entries 1 and 2). This reaction was carried out using phenylboronic acid and (4-pyridyl)boronic acid pinacol ester as Suzuki coupling partners in a heterogeneous mixture of 1,4-dioxane, water, sodium carbonate, in the presence of catalytic amount of tetrakis(triphenylphosphine)palladium(0). The corresponding coupling products **7a** and **7b** were both isolated in excellent yields (90–95%) (entries 3–6).

In addition, this method was compared to a palladium-catalysed direct arylation reaction starting from 2-phenylimidazo[1,2-*a*]pyridine **2a** (Scheme 4, *path b*). Following the procedure described by Guillaumet,[12] we observed that a significant amount of the starting material remained (Table 3, entry 1).



Scheme 5. Synthesis of **1a–p** from triflate **3c** through Suzuki coupling-direct arylation sequence.

Table 4
Synthesis of **1a-p**[a]

Entry	Compd	Ar	Time	Yield[b] (%)	Compd	(het) Ar′	Time	Yield[b] (%)
1	**2a**	C_6H_5	7 h	43	**1a**	4-$(NO_2)C_6H_4$	36 h	93
2	**2b**	3-ClC_6H_4	6 h	45	**1b**	C_6H_5	21 h	83
3	**2c**	3,5-$(Cl)_2C_6H_3$	45 min	35	**1c**	C_6H_5	18 h	83
4					**1d**	3-Pyridyl	15 h	69
5	**2d**	2-FC_6H_4	1 h	97	**1e**[c]	C_6H_5	31 h	64
6					**1f**	3-Pyridyl	14 h	85
7	**2e**	4-FC_6H_4	1 h	41	**1g**	C_6H_5	15 h	60
8					**1h**	3-Pyridyl	15 h	56
9					**1i**	3-$(NO_2)C_6H_4$	16 h	92
10					**1j**[d]	3-$(MeO)C_6H_4$	72 h	44
11	**2f**	4-$(CO_2Et)C_6H_4$	45 min	9	**1k**	C_6H_5	13 h	27
12	**2g**	4-$(NO_2)C_6H_4$	4 h	26	**1l**[c]	C_6H_5	18 h	15
13	**2h**	4-$(MeO)C_6H_4$	45 min	78	**1m**	C_6H_5	10 h	81
14					**1n**	3-$(NO_2)C_6H_4$	18 h	67
15					**1o**[d]	3-$(MeO)C_6H_4$	72 h	40
16	**2i**	2-$(MeO)C_6H_4$	1 h	94	**1p**[e]	C_6H_5	21 h	84

[a] Direct arylation conditions: **2a–i** 1 equiv, (het) Ar′Br 1 equiv, $Pd(OAc)_2$ 2 mol %, $PCy_3.HBF_4$ 4 mol %, PivOH 0.3 equiv, K_2CO_3 1.5 equiv, DMA, sealed tube, 100 °C.
[b] Isolated yield.
[c] Reagents and conditions: $Pd(OAc)_2$ 4 mol %, $PCy_3.HBF_4$ 8 mol %, PivOH 0.6 equiv.
[d] Reagents and conditions: (het) Ar′Br 3.0 equiv, $Pd(OAc)_2$ 8 mol %, $PCy_3.HBF_4$ 16 mol %, PivOH 1.2 equiv, K_2CO_3 2.0 equiv.
[e] Reagents and conditions: (het) Ar′Br 1.3 equiv, $Pd(OAc)_2$ 4 mol %, $PCy_3{\cdot}HBF_4$ 8 mol %.

The reaction did not proceed to completion even after 2 h. We tried to improve the yield of this direct arylation using Fagnou's conditions.[13] The yield was significantly increased (95%) using bromobenzene in a sealed tube for 16 h (entry 2). Heteroarylation using 4-bromopyridine hydrobromide occurred in the same way (entry 3). Finally, although the two methods afforded similar results for the access to 2,3-diarylimidazo[1,2-*a*]pyridines **1**, direct arylation single-step remained preferable.

With optimal conditions in hand, we explored the scope of the Suzuki–Miyaura coupling-direct arylation sequence starting from imidazo[1,2-*a*]pyridin-2-yl triflate **3c** with a variety of aryl boronic acids and aryl bromides (Scheme 5 and Table 4).[14] The Suzuki cross-coupling is compatible with a variety of aryl groups and proceeded in various yields (9–97%) depending on the influence of the electronic properties of the coupling partner. The electron-deficient aryl boronic acids were coupled in low to moderate yields. For instance, compounds bearing halogens (**2b**, **2c**, **2e**) were obtained in moderate yields (35–45%) whereas 2-fluorophenyl boronic acid afforded unexpectedly **2d** in an excellent yield (97%, entry 5). Ester **2f** and nitro derivative **2g** proceeded in low yields (entries 11 and 12). Nevertheless, compounds **2h** and **2i** bearing a methoxy donating group were obtained in good yields (78–94%, entries 13 and 16).

We next explored direct arylation of substrates **2a–i** with various aryl bromides. Reactions proceeded in good yields with bromobenzene and 3-bromopyridine (Table 4, entries 2–6). When 2-phenylimidazo[1,2-*a*]pyridine **2a** reacted with an electron-deficient aryl bromide (i.e., 4-nitrobenzene), direct arylation was accomplished in a better yield (entry 1). Substrates **2e** and **2h** underwent direct arylation with various aryl bromides to probe the influence of an electron-deficient group on the phenyl ring or an electron-rich one. It is noteworthy that 3-bromonitrobenzene and bromobenzene were suitable coupling partners under classical conditions to provide products **1g**, **1i**, **1m** and **1n** in good yields (entries 7, 9, 13 and 14). In contrast, with both substrates, use of 3-bromoanisole gave the corresponding products in lower yields (40% and 44%) even if an excess of reagents was added (entries 10 and 15). Finally, compounds **2** bearing electron-poor substituent (i.e. ester or nitro group) were found to proceed in lower yields for direct arylation with bromobenzene (entries 11 and 12). Based on these results, C-3 direct arylation of 2-arylimidazo[1,2-*a*]pyridines **2** is influenced by electronic effects of the ring in position 2.

In summary, we have developed a straightforward method for the synthesis of 2,3-diarylimidazo[1,2-*a*]pyridines from imidazo[1,2-*a*]pyridin-2-yl triflate readily available from 2-aminopyridine. These compounds were prepared via a Suzuki–Miyaura cross-coupling reaction and a subsequent direct arylation, making the route attractive for accessing these functionalized heterocycles. Further applications to the synthesis of bioactive compounds is in progress in our laboratory.

Acknowledgment

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10. *Imidazo[1,2-a]pyridin-2-yl triflate* (**3c**). At 0 °C, 2-aminopyridine (8.37 g, 89 mmol) was added portionwise to ethyl bromoacetate (34.5 mL, 311 mmol). The reaction mixture was stirred for 30 min at room temperature. The precipitate was collected and washed with diisopropylic ether. Then, a solution of the crude product in absolute ethanol (200 mL) was refluxed for 18 h. The reaction mixture was cooled to room temperature for 2 h and to 0 °C for 1 h. The precipitate was collected and washed with diisopropylic ether to give 18.24 g of the crude product **5**. This material was used in the next reaction without further purification.
    To a solution of compound **5** (5.0 g, 21 mmol) in toluene (300 mL) was added *N*-phenyl-bis(trifluoromethanesulfonimide) (13.0 g, 37 mmol) and triethylamine (5 mL). The reaction was refluxed. Triethylamine (2 × 12.5 mL) was then added after 2 and 4 h respectively. The reaction mixture was refluxed for 12 h, cooled to room temperature and poured into water. The aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluent: petroleum ether/EtOAc 9:1) to give **3c** as a white powder (3.91 g, 67% yield, two steps). Mp 62–63 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 6.8 Hz, 1 H), 8.25 (s, 1 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.48 (ddd, J = 8.4 Hz, J = 7.0 Hz, J = 1.2 Hz, 1 H), 7.14 (ddd, J = 7.0 Hz, J = 6.8 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.76, 140.15, 127.69, 126.92, 118.17 (q, J = 319 Hz), 116.78, 113.92, 101.48; IR (KBr) δ 3158, 3053, 1508, 1429, 1361, 1219, 1137, 995, 882, 799 cm^{-1}; MS (ESI) m/z (%): 267.0 (83) [M+H]$^+$, 133.8 (100).
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14. *Representative Suzuki coupling-direct halogenation sequence procedure*: 2-(3,5-dichlorophenyl)-3-(3-pyridyl)imidazo[1,2-*a*]pyridine (**1d**). To a 10 mL vial with a magnetic stir bar was added triflate **5** (400 mg, 1.5 mmol), 3,5-dichlorophenylboronic acid (344 mg, 1.8 mmol), Na_2CO_3 (382 mg, 3.6 mmol) and $Pd(PPh_3)_4$ (5% mol, 87 mg) in a mixture 1,4-dioxane–water (4 mL, 2:1). The vial was sealed and purged with argon through the septum inlet for 5 min. The suspension was then heated at 100 °C for 45 min. After cooling, the resulting mixture was diluted with EtOAc, filtered through Celite and washed with EtOAc. Water was added and the organic layer was extracted twice with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography using petroleum ether/EtOAc (9:1) as eluent. Trituration with diisopropylic ether afforded 2-(3,5-dichlorophenyl)imidazo[1,2-*a*]pyridine **2c** as a white powder (138 mg, 35% yield). Mp 142–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1 H), 8.57 (d, J = 6.8 Hz, 1 H), 8.04 (d, J = 2.0 Hz, 2 H), 7.63 (d, J = 8.6 Hz, 1 H), 7.58 (t, J = 2.0 Hz, 1 H), 7.33 (ddd, J = 8.6 Hz, J = 7.2 Hz, J = 1.2 Hz, 1 H), 6.97 (ddd, J = 7.2 Hz, J = 6.8 Hz, J = 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6)δ 144.88, 141.38, 137.51, 134.54, 127.13, 126.79, 125.68, 123.88, 116.83, 112.78, 110.81; IR (KBr) δ 3483, 3375, 2924, 1723, 1600, 1370, 1282, 1252, 1126, 1098, 800, 754 cm^{-1}; MS (ESI) m/z (%): 263.0 (100) [M+H]$^+$, 265.0 (88) [M+H+2]$^+$, 267.0 (16) [M+H+4]$^+$; Anal. Calcd for $C_{13}H_8Cl_2N_2$: C 59.34; H 3.06; N 10.65. Found: C 58.96; H 3.12; N 10.25.
    To a 10 mL vial with a magnetic stir bar was added **2c** (280 mg, 1.1 mmol), 3-bromopyridine (168 mg, 1.1 mmol), $Pd(OAc)_2$ (2% mol, 5 mg), $PCy_3.HBF_4$ (4% mol, 16 mg), PivOH (33 mg, 0.3 mmol) and K_2CO_3 (221 mg, 1.6 mmol) in DMA (4 mL). The vial was sealed and purged with argon through the septum inlet for 10 min. The suspension was then heated at 100 °C for 15 h. After cooling, the resulting mixture was diluted with EtOAc and water and the organic layer was extracted twice with EtOAc. The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography using petroleum ether/EtOAc (4:1) as eluent. Trituration with diisopropylic ether afforded 2-(3,5-dichlorophenyl)-3-(3-pyridyl)imidazo[1,2-*a*]pyridine **1d** as a beige powder (250 mg, 69% yield). Mp 155–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (dd, J = 5.0 Hz, J = 1.6 Hz, 1 H), 8.76 (d, J = 1.6 Hz, 1 H), 8.15 (d, J = 7.4 Hz, 1 H), 8.10 (ddd, J = 8.0 Hz, J = 1.6 Hz, J = 1.6 Hz, 1 H), 7.76 (d, J = 8.2 Hz, 1 H), 7.71 (ddd, J = 8.0 Hz, J = 5.0 Hz, J = 0.8 Hz, 1 H), 7.58 (t, J = 2.0 Hz, 1 H), 7.51 (d, J = 2.0 Hz, 2 H), 7.44 (ddd, J = 8.2 Hz, J = 6.6 Hz, J = 0.8 Hz, 1 H), 7.00 (ddd, J = 7.4 Hz, J = 6.6 Hz, J = 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.14, 150.39, 144.52, 139.17, 138.63, 137.40, 134.16, 126.93, 126.38, 125.61, 124.86, 124.52, 124.26, 118.75, 117.09, 113.44; IR (KBr) δ 3422, 2925, 2364, 2345, 1589, 1561, 1371, 1345, 1256, 1112, 860, 800, 739 cm^{-1}; MS (ESI) m/z (%): 340.0 (100) [M+H]$^+$, 342.0 (70) [M+H+2]$^+$, 343.0 (12) [M+H+3]$^+$, 344.0 (12) [M+H+4]$^+$; Anal. Calcd for $C_{18}H_{11}Cl_2N_3$: C 63.55; H 3.26; N 12.35. Found: C 63.89; H 3.59; N 12.54.