Tandem CH-Activation–Imine-Formation Reaction: A New Route to Imidazo[2,1-*a*]phthalazines

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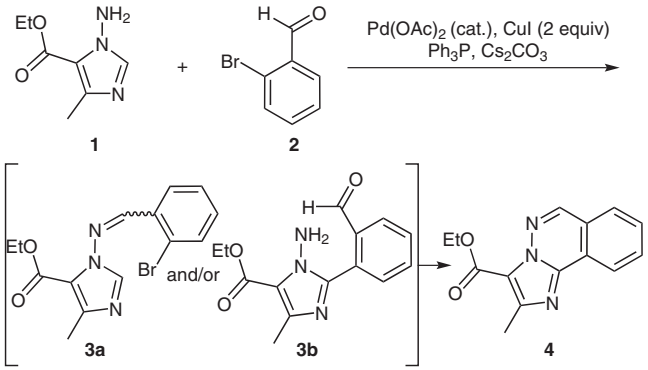
Abstract: A general and efficient synthesis of imidazo[2,1-*a*]phthalazines by palladium- and copper-mediated coupling of *N*-aminoimidazoles with 2-haloaryl aldehydes with concurrent imine formation is described. This new synthesis of the imidazo[2,1-*a*]phthalazine ring system allows for facile introduction of different substituents around the entire core.

Key words: imidazo[2,1-*a*]phthalazine, imine formation, CH activation, *N*-aminoimidazoles, 2-bromoaryl aldehydes

Imidazo[2,1-*a*]phthalazines have not been extensively explored as templates for drug discovery despite reported antihypertensive and anti-inflammatory activity.[1] One explanation could be that no efficient synthesis allowing facile SAR explorations around this heterocycle has been reported.[1,2] Most published procedures start from or require construction of the pthhalazine core and are therefore limited by the commercial availability or synthetic accessibility of suitable precursors. The most versatile synthesis, allowing for various substituents at the imidazole and pyridazine rings, involves direct cyclization of 1-aminophthalazines with α-halocarbonyl compounds.[1c] The yields for substrates having nonaromatic substituents on the imidazole moiety similar to the ones described in this paper vary from 6–33%. No substitution around the phenyl moiety is reported.

Interested in a route that would allow facile introduction of different substitutions on the imidazo as well as the phenyl portions of the imidazo[2,1-*a*]phthalazine core, we investigated a reaction sequence between *N*-aminoimidazoles and 2-haloaryl aldehydes (Scheme 1).

Unlike substituted 1-aminophthalazines, a variety of substituted 2-haloaryl aldehydes are commercially available. N-Amination of readily available substituted imidazoles furnishes *N*-aminoimidazoles such as **1**[3] which contain the nitrogen of the future pyridazine ring. Palladium-catalyzed arylation of azole CH bonds with aryl halides has developed into a powerful synthetic methodology[4] and in situ benzaldehyde imine formation under cross-coupling conditions is precedented.[5] Thus, we anticipated that a mixture of *N*-aminoimidazole **1** and 2-bromobenzaldehyde (**2**) would undergo coupling and imine formation to give the desired imidazo[2,1-*a*]phthalazine **4**.



Scheme 1 Palladium-catalyzed and copper-mediated arylation and imine formation

After reviewing several published procedures, we subjected a mixture of *N*-aminoimidazole **1** and 1.1 equivalents of 2-bromobenzaldehyde (**2**) to typical conditions for direct arylations of azoles [10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 equiv CuI, 1 equiv Cs_2CO_3, DMF, 140 °C, 12 h][4] and isolated **4** in around 30% yield. We increased the yield to 40–46% by shortening the reaction time to one hour. Regardless of the reaction time, we did not observe either of the two anticipated intermediates **3a** or **3b** by LC–MS during the course of the reaction. However, imine **3a** was formed quantitatively (LC–MS) in reactions having only one of the metals present (Table 1, entries 6 and 7).[6] We subjected imine **3a** to the standard conditions with palladium and copper(I) iodide. We observed conversion to **4** and isolated it in the same yield as in the original reaction between **1** and **2**. This demonstrated that imine **3a** is a competent substrate under these arylation conditions and may be an intermediate in the reaction of **1** and **2**. It can be hypothesized that once formed, **3a** generates a palladacycle after oxidative insertion of the palladium into the aryl bromide bond and therefore acts as its own ligand.[7] This hypothesis is supported by the fact that reducing the phosphine ligand ratio (Table 1, entry 3), changing the ligand (entry 2),[8] or removing it altogether (entry 4)[9] does not significantly influence the outcome of the reaction. However, since the yield was consistently slightly better in the presence of triphenylphosphine, it was included in the reaction conditions.

The overall yield of 46% seems modest, but one has to keep in mind that this is a two-step process without the use of any protecting groups. We already applied the opti-

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Table 1 Screened Conditions[a]

Entry	Pd $(OAc)_2$	CuI	Ligand	Yield of **4** (%)[b]
1	0.1	2.0	0.2 PPh_3	46
2	0.1	2.0	0.2 $MeP(t\text{-}Bu)_2 \cdot HBF_4$	35
3	0.1	2.0	0.1 PPh_3	42
4	0.1	2.0	–	35
6	–	2.0	0.2 PPh_3	0
7	0.1	–	0.2 PPh_3	0

[a] All reactions were performed with 1 equiv of Cs_2CO_3 in DMF at 140 °C for 1 h.
[b] Isolated yields.

mized conditions for azole arylations published by the experts in the field.[4] Thus, we concentrated on exploring substituents around the ring after unsatisfying results from the most commonly applied changes in screening conditions such as using $Pd_2(dba)_3$ instead of $Pd(OAc)_2$, exchanging the alternative base CsF for Cs_2CO_3, increasing or decreasing the reaction temperature and lowering the amount of copper to one equivalent. Therefore, our best conditions giving consistently moderate yields between 40–46% proved to be the original conditions with a shortened reaction time of one hour.

No significant amount of isolable by-product(s) was observed. However, decomposed starting materials, possibly deaminated aminoimidazole or debrominated benzaldehyde, would be difficult to observe by LC–MS and may be lost during the workup. Minor NMR signals characteristic of aldehyde and additional ethyl ester protons were observed in the ^1H NMR of the crude after workup.

With our optimized conditions in hand, we investigated the scope of the reaction by varying substitutions around the benzaldehyde (Table 2) and the 1-aminoimidazole precursor (Table 3).

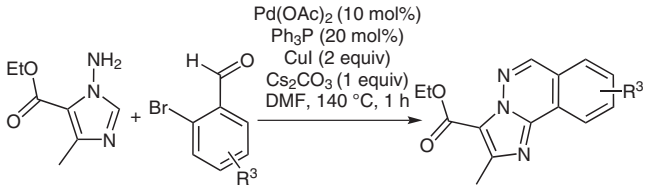
Both electron donating and electron withdrawing groups appear equally tolerated (Table 2, entries 1–7). We believe the aldehyde/imine functional groups dominate the electronics of the ring and that additional substituents have only minor effects on yield.

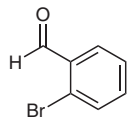
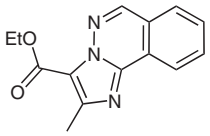
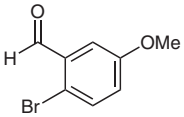
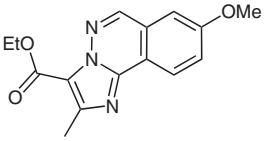
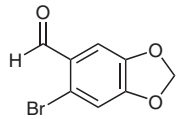
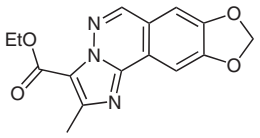
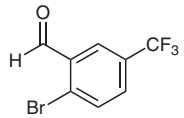
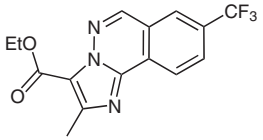
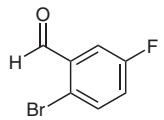
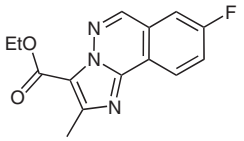
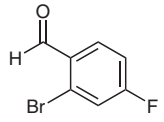
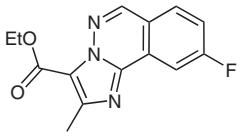
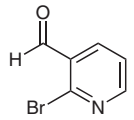
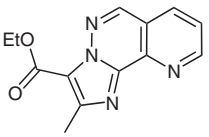
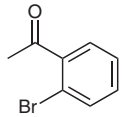
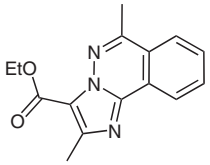
We also investigated the reaction using 2-bromoacetophenone as a model to install substituents on the pyridazine ring (Table 2, entry 8). The fact that ketones are in general less reactive than aldehydes in intermolecular imine formations may explain the very low yield.

Varying the 1-aminoimidazole precursor furnished the desired imidazo[2,1-*a*]phthalazines **12–14** (Table 3) in comparable yields to the ones obtained by using different aldehydes.

In summary, we have developed a general and efficient one-step synthesis for imidazo[2,1-*a*]phthalazines via palladium- and copper-mediated coupling of *N*-aminoimidazoles with 2-bromoaryl aldehydes with preceding or concurrent imine formation. This method allows the synthesis of diversely substituted derivatives on the imidazo and benzene part of the core structure. Overall, the yields

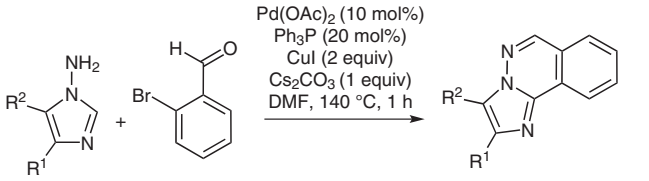
Table 2 2-Bromobenzaldehyde Variations

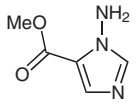
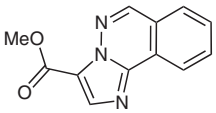
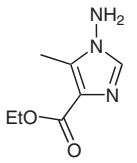
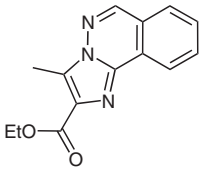
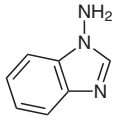
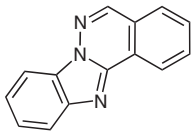


Entry	Aldehyde	Product	Yield (%)[b]
1[a]		**4** 	46
2		**5** 	39
3		**6** 	20
4		**7** 	43
5		**8** 	44
6		**9** 	28
7		**10** 	27
8		**11** 	7

[a] 2-Iodobenzaldehyde did not influence the yield.
[b] Isolated yields.

Table 3 1-Aminoimidazole Variations



Entry	Imidazole	Product	Yield (%)[a]
1		**12** 	25
2		**13** 	45
3		**14** 	31

[a] Isolated yields.

are low to moderate, but acceptable taking into account the ease of this reaction and the lack of efficient alternative one-step procedures.

All chemicals used, including anhydrous solvents, were of reagent grade and used as supplied. Chromatography was carried out on silica gel, TLC on silica plates (Merck, Art. 5554). In general, the course of reactions was followed by TLC and/or LC–MS. NMR spectra were obtained on a Bruker DPX-400 spectrometer at 400 MHz. LC–MS data was recorded utilizing the electrospray (ESI) technique. HRMS data was acquired using a Thermo LTQFT Ultra Mass Spectrometer in APCI$^+$ mode. This instrument achieved a mass resolution of greater than 100 000.

Imidazo[2,1-*a*]phthalazines; General Procedure

In a sealed tube, 1-aminoimidazole[10] (0.59 mmol), bromobenzaldehyde (0.65 mmol, 1.1 equiv), PPh_3 (31 mg, 0.12 mmol, 0.2 equiv), $Pd(OAc)_2$ (13.3 mg, 0.06 mmol, 0.1 equiv), Cs_2CO_3 (192.2 mg, 0.59 mmol, 1.0 equiv), and CuI (224.9 mg, 1.18 mmol, 2.0 equiv) were dissolved in anhyd DMF (2 mL). The tube was evacuated and flushed with argon before it was heated at 140 °C for 1 h. After cooling to r.t., EtOAc (20 mL) was added and the mixture was extracted with NH_4OH (6 M, 20 mL). The aqueous layer was re-extracted with EtOAc (20 mL) and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). After removal of the solvent, the crude residue was purified on silica gel (gradients: 0–75% EtOAc in hexane).

Ethyl 2-Methylimidazo[2,1-*a*]phthalazine-3-carboxylate (4)

Starting from ethyl 3-amino-5-methyl-3*H*-imidazole-4-carboxylate (**1**; 100 mg, 0.59 mmol) and 2-bromobenzaldehyde (**2**; 120 mg, 0.65 mmol), compound **4** was obtained as a white solid (69 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1H), 8.61 (dd, *J* = 8.0, 0.5 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.92 (m, 1 H), 7.78 (m, 1 H), 4.48 (q, *J* = 7.2 Hz, 2 H), 2.78 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C=O), 147.7, 144.8 (CH), 137.1, 132.3 (CH), 129.1 (CH), 126.5 (CH), 123.4, 122.1, 121.9 (CH), 116.3, 59.7 (CH_2), 15.4 (CH_3), 13.4 (CH_3).

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O_2$: 256.1080; found: 256.1078.

Ethyl 8-Methoxy-2-methylimidazo[2,1-*a*]phthalazine-3-carboxylate (5)

Starting from **1** (100 mg, 0.59 mmol) and 2-bromo-5-methoxybenzaldehyde (140 mg, 0.65 mmol), compound **5** was obtained as a white solid (66 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 8.49 (d, *J* = 8.9 Hz, 1 H), 7.24 (d, *J* = 2.3 Hz, 1 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 3.96 (s, 3 H), 2.74 (s, 3 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 160.2 (C=O), 149.2, 145.0 (CH), 138.7, 124.9, 124.7 (CH), 123.6 (CH), 118.8, 116.7, 107.5 (CH), 60.5 (CH_2), 55.8 (CH_3), 16.6 (CH_3), 14.5 (CH_3).

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N_3O_3$: 286.1186; found: 286.1184.

Ethyl 2-Methyl-7,9-dioxa-1,3a,4-triazadicyclopenta[*a*,*g*]naphthalene-3-carboxylate (6)

Starting from **1** (100 mg, 0.59 mmol) and 6-bromobenzo[1,3]dioxole-5-carbaldehyde (149 mg, 0.65 mmol), compound **6** was obtained as a white solid (36 mg, 20%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.91 (s, 1 H), 7.78 (s, 1 H), 7.62 (s, 1 H), 6.31 (s, 2 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 2.62 (s, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (C=O), 152.4, 149.9, 148.4, 144.5 (CH), 137.9, 121.1, 119.6, 115.9, 105.2 (CH), 102.9 (CH), 99.8 (CH_2), 59.9 (CH_2), 16.1 (CH_3), 14.3 (CH_3).

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_4$: 300.0978; found: 300.0977.

Ethyl 2-Methyl-8-trifluoromethylimidazo[2,1-*a*]phthalazine-3-carboxylate (7)

Starting from **1** (100 mg, 0.59 mmol) and 2-bromo-5-trifluoromethylbenzaldehyde (165 mg, 0.65 mmol), compound **7** was obtained as a white solid (83 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (s, 1 H), 8.73 (d, *J* = 8.4 Hz, 1 H), 8.24 (s, 1 H), 8.11 (dd, *J* = 8.4, 1.5 Hz, 1 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 2.79 (s, 3 H), 1.47 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8 (C=O), 149.6, 145.1 (CH), 136.9, 131.7 (q, *J* = 33.3 Hz, *C*CF_3), 129.2 (d, *J* = 3.0 Hz, CH), 126.7, 124.9 (d, *J* = 4.0 Hz, CH), 124.1 (CH), 123.4 (d, *J* = 273.0 Hz, CF_3), 122.4, 118.0, 60.9 (CH_2), 16.6 (CH_3), 14.4 (CH_3).

HRMS (APCI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}F_3N_3O_2$: 324.0954; found: 324.0951.

Ethyl 8-Fluoro-2-methylimidazo[2,1-*a*]phthalazine-3-carboxylate (8)

Starting from **1** (100 mg, 0.59 mmol) and 2-bromo-5-fluorobenzaldehyde (132 mg, 0.65 mmol), compound **8** was obtained as a white solid (65 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 1 H), 8.62 (dd, *J* = 9.0, 5.1 Hz, 1 H), 7.64 (m, 1 H), 7.58 (dd, *J* = 8.2, 2.4 Hz, 1 H), 4.48 (q, *J* = 7.2 Hz, 2 H), 2.76 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (d, *J* = 253 Hz, CF), 159.9 (C=O), 149.3, 144.5 (d, *J* = 3.4 Hz, CH), 137.8, 125.9 (d, *J* = 8.6 Hz, CH), 124.5 (d, *J* = 8.6 Hz, C), 122.4 (d, *J* = 24 Hz, CH), 121.4, 117.3, 112.3 (d, *J* = 22 Hz, CH), 60.1 (CH_2), 16.5 (CH_3), 14.5 (CH_3).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}FN_3O_2$: 274.0986; found: 274.0984.

Ethyl 9-Fluoro-2-methylimidazo[2,1-*a*]phthalazine-3-carboxylate (9)

Starting from **1** (100 mg, 0.59 mmol) and 2-bromo-4-fluorobenzaldehyde (132 mg, 0.65 mmol), compound **9** was obtained as a white solid (47 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 8.22 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.96 (dd, *J* = 8.8, 5.1 Hz, 1 H), 7.48 (m, 1 H), 4.48 (q, *J* = 7.2 Hz, 2 H), 2.76 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (d, *J* = 256 Hz, CF), 159.9 (C=O), 149.2, 144.7 (CH), 137.5 (d, *J* = 3.9 Hz, C), 130.6 (d, *J* = 9.5 Hz, CH), 126.8 (d, *J* = 11.0 Hz, C), 119.9, 119.2 (d, *J* = 24.0 Hz, CH), 117.6, 108.4 (d, *J* = 24.0 Hz, CH), 60.8 (CH_2), 16.6 (CH_3), 14.5 (CH_3).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{14}H_{13}FN_3O_2$: 274.0986; found: 274.0984.

Ethyl 2-Methyl-1,3a,4,9-tetraazabenz[*e*]indene-3-carboxylate (10)

Starting from **1** (100 mg, 0.59 mmol) and 2-bromopyridine-3-carbaldehyde (121 mg, 0.65 mmol), compound **10** was obtained as a white solid (40 mg, 26%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.22 (dd, *J* = 4.6, 1.5 Hz, 1 H), 8.87 (s, 1 H), 8.28 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.72 (dd, *J* = 8.2, 4.6 Hz, 1 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 2.82 (s, 3 H), 1.47 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9 (C=O), 155.9 (CH), 150.1, 144.8 (CH), 140.9, 137.9, 135.1 (CH), 124.8 (CH), 118.8, 118.1, 60.9 (CH_2), 16.7 (CH_3), 14.4 (CH_3).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{13}H_{13}N_4O_2$: 257.1033; found: 257.1031.

Ethyl 2,6-Dimethylimidazo[2,1-*a*]phthalazine-3-carboxylate (11)

Starting from **1** (100 mg, 0.59 mmol) and 1-(2-bromophenyl)ethanone (130 mg, 0.65 mmol), compound **11** was obtained as a white solid (11 mg, 7%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 8.0 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.88–7.86 (m, 1 H), 7.78–7.74 (m, 1 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 2.92 (s, 3 H), 2.76 (s, 3 H), 1.45 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (C=O), 152.2, 148.6, 138.4, 132.7 (CH), 129.9 (CH), 125.8 (CH), 124.5, 123.3 (CH), 117.1, 60.5 (CH_2), 20.1 (CH_3), 16.5 (CH_3), 14.4 (CH_3).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{15}H_{16}N_3O_2$: 270.1237; found: 270.1235.

Methyl Imidazo[2,1-*a*]phthalazine-3-carboxylate (12)

Starting from methyl 3-amino-3*H*-imidazole-4-carboxylate (100 mg, 0.71 mmol, new reference for calculation of all additional reagents) and 2-bromobenzaldehyde (**2**; 144 mg, 0.78 mmol), compound **12** was obtained as a white solid (40 mg, 25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1 H), 8.64 (dd, *J* = 8.1, 0.8 Hz, 1 H), 8.29 (s, 1 H), 7.99–7.93 (m, 2 H), 7.84–7.79 (m, 1 H), 3.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (C=O), 146.7 (CH), 140.1, 138.6 (CH), 133.6 (CH), 130.3 (CH), 127.7 (CH), 125.3, 123.1 (CH), 120.5, 51.9 (CH_3).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{12}H_{10}N_3O_2$: 228.0767; found: 228.0766.

Ethyl 3-Methylimidazo[2,1-*a*]phthalazine-2-carboxylate (13)

Starting from ethyl 1-amino-5-methyl-1*H*-imidazole-4-carboxylate (100 mg, 0.59 mmol) and **2** (120 mg, 0.65 mmol), compound **13** was obtained as a white solid (67 mg, 45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 8.0 Hz, 1 H), 8.68 (s, 1 H), 7.90–7.85 (m, 2 H), 7.73–7.69 (m, 1 H), 4.50 (q, *J* = 7.2 Hz, 2 H), 2.89 (s, 3 H), 1.48 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (C=O), 147.7, 144.8 (CH), 137.1, 132.3 (CH), 129.1 (CH), 126.5 (CH), 123.4, 122.1, 121.9 (CH), 116.3, 59.7 (CH_2), 15.4 (CH_3), 13.4 (CH_3).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O_2$: 256.1080; found: 256.1078.

Benzimidazo[2,1-*a*]phthalazine (14)

Starting from benzimidazol-1-ylamine (100 mg, 0.75 mmol, new reference for calculation of all additional reagents) and **2** (153 mg, 0.83 mmol), compound **14** was obtained as a beige solid (51 mg, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 7.4 Hz, 1 H), 8.61 (s, 1 H), 8.08 (d, *J* = 7.4 Hz, 1 H), 7.99 (d, *J* = 8.1 Hz, 1 H), 7.91–7.87 (m, 2 H), 7.79–7.74 (m, 1 H), 7.55–7.45 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5 (CH), 142.1, 141.4, 133.0 (CH), 131.5, 130.7 (CH), 127.8 (CH), 125.5, 125.1 (CH), 124.6, 123.9 (CH), 123.1 (CH), 120.0 (CH), 111.2 (CH).

HRMS (APCI$^+$): *m/z* [M + H]$^+$ calcd for $C_{14}H_{10}N_3$: 220.0869; found: 220.0867.

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