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Synthesis of imidazo[1,2-*a*]pyridines in a sequential one-pot Groebke-Blackburn modification using 2-aminopyridines, aldehydes and amines

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Herein we present a novel synthetic procedure for the synthesis of imidazo[1,2-*a*]pyridines in a modified Groebke-Blackburn fashion. In a sequential three-step one-pot protocol the commercially hardly available isocyanide-component is formed *in situ* using standard reagents. Cyclization to the desired products can be afforded in the same reaction mixture. The absent need of isolation of the isocyanide in this protocol eases its handling considerably and workup is only needed to finally furnish the imidazo[1,2-*a*]pyridines *via* column chromatography. This protocol is a convenient way to more diverse libraries of imidazo[1,2-*a*]pyridines extending the functionality of the Groebke-Blackburn synthesis.

1. Introduction

Isocyanide based multicomponent reactions are regularly employed methods to synthesize highly diverse organic structures for compound libraries in medicinal chemistry. These reactions got even more in focus with the emergence of parallel synthesis and combinatorial chemistry. Famous name reactions like the Ugi-, Passerini- or Biginelli-reaction come alongside the Groebke-Blackburn reaction, which is used for the synthesis of imidazo[1,2-*a*]pyridines (Groebke et al. 1998; Blackburn et al. 1998; Bienaymé and Bouzid 1998).

Imidazo[1,2-*a*] pyridines are privileged structures for novel synthetic drug molecules and incorporated in the marketed drugs zolpidem (Ambien®) and minodronic acid (Recalbon®). Furthermore this core structure can be found in a variety of compounds in clinical and preclinical studies with indications including gastric and heart diseases as well as viral diseases. (Devi et al. 2015). Depending on their substitution pattern imidazo[1,2-*a*]pyridines show biological activity for example as inhibitors of reverse transcriptase (Elleder et al. 2012), 5-lipoxygenase (Hieke et al. 2012) or topoisomerase II (Baviskar et al. 2011) and exhibit a wide range of antibacterial effects (Devi et al. 2015).

A lot of research has been invested in maximizing the yield of the Groebke-Blackburn reaction using acidic catalysts like zinc chloride, microwave assistance or ionic liquids (Rousseau et al. 2007; Ireland et al. 2003; Shaabani et al. 2006). But one big disadvantage in these isocyanide-based reactions lies in the isocyanide part of the three components. These molecules have a limited commercial availability, which leads to a reduced chemical diversity, or high synthetic effort, when isocyanides are prepared separately (El Kaim et al. 2009). Because of their characteristic smell, it is favourable to reduce the time of handling in reaction protocols, especially the need to isolate and purify the isocyanides.

There are several ways of preparing isocyanides from other functional groups: e.g. from alkyl halides *via* silver cyanide,

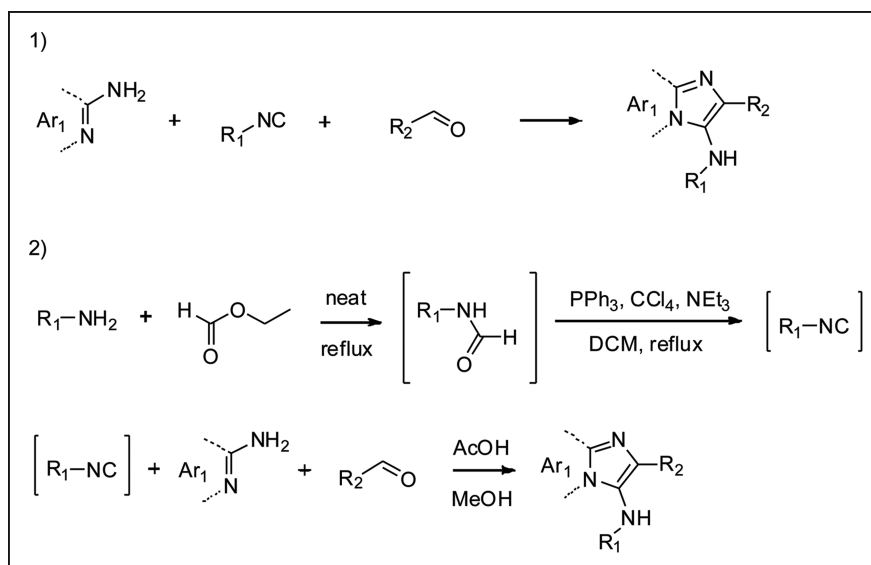
using TMSCN/silver salts or from amines via formation of formates and dehydration using common reagents like POCl₃ (El Kaim et al. 2009; Kitano et al. 2006; Lacerda et al. 2009). Another interesting approach to isocyanides has been found by Bossio et al. (1993), who utilized PPh₃, CCl₄ and NEt₃ in refluxing DCM for dehydration of the respective formates. Furthermore convertible isocyanides were used to overcome the limited diversity of the amine side chain of the imidazo[1,2-*a*]pyridines (Krasavin et al. 2008; Guchhait and Madaan 2010). But all protocols include multiple steps to afford the desired imidazo[1,2-*a*]pyridines and therefore a certain amount of time and material. Progress was made by Guchhait et al. (2013), who converted amines to isocyanides *in situ* using TsCl and DABCO and then generated the desired imidazo[1,2-*a*]pyridines in one-pot fashion.

2. Investigations, results and discussion

Herein we present a novel method using PPh₃, CCl₄ and NEt₃ to form the isocyanides as intermediates and proceed to the imidazo[1,2-*a*]pyridines in one pot without the need of transient work-up and using common, non-expensive reagents. The use of amines as starting materials leads to a wide range of isocyanides, which usually cannot be purchased, are expensive or have to be prepared including all obstacles mentioned before.

In a medicinal chemistry approach to new biologically active imidazo[1,2-*a*]pyridines, we decided to elongate the amine side chain from a screening hit, which incorporated a benzyl moiety at position R₁ (Table 1). Furthermore substituents at the *para*-position should be introduced.

For method development we have chosen to use a solvent-free formation of formates from the respective amine to ease the choice of solvent for the following steps. The reaction was carried out in a slight excess of ethyl formate which is suitable as reactant and solvent at the same time. Poorly soluble or voluminous amines have been readily converted into the respective formates using slight amounts of ethanol as a co-solvent.



Scheme 1: Groebke-Blackburn synthesis (1) and the presented one-pot protocol (2) in comparison.

Table 1: Proof of concept synthesis

	Amine (R ₁ -NH ₂)	Yield (%)
1		11
2		25
3		20
4		7
5		11

I) Amine (1 eq), Ethyl formate (1,1 eq), neat, 3h, reflux
 II) PPh₃ (1.2 eq), CCl₄ (1 eq), NEt₃ (1 eq), DCM, 4h, reflux
 III) Aminopyridine (0.5 eq), Aldehyde (0.5 eq), AcOH, MeOH/DCM 1:1, 48h, rt

Isocyanide formation was carried out using a dehydration procedure employing PPh₃, CCl₄ and NEt₃ in DCM. The use of POCl₃ could have led to side-reactions in the following three-component step due to the reactivity of (excess) POCl₃ and its by-products.

In the last part of the sequence the reagents for the three-component cyclization (aldehyde, aminopyridine) were added to the reaction mixture and the solvent was adjusted to a 1:1 DCM/methanol ratio. Acetic acid was used in excess to set the pH to an appropriate level for imine formation and the equivalents of aminopyridine and aldehyde were adjusted to the reported yield for isocyanide formation using CCl₄, PPh₃ and NEt₃. (Bossio et al. 1993) With this method we were able to synthesize several imidazo[1,2-*a*]pyridines as a proof of concept with moderate yields (see Table 1). The introduction of para-substituents like a methoxy- or ethyl ester group was tolerated (compounds **4** and **5**).

To improve this first approach, reaction parameters were evaluated and optimized, especially regarding reaction times, equivalents and temperatures. We used the benzyl reference compound of Table 1, that could be easily synthesized *via* the

standard Groebke-Blackburn protocol (Groebke et al. 1998) from the commercially available benzyl isocyanide with a yield of 62% (crude, after column chromatography).

As can be seen in Table 2 the unoptimized, proof of concept method (PoC) yielded 37% for this derivative. Reduction of reaction time of step I (approach 1) led to a significantly lower yield and it has been noticed, that it is crucial to evaporate the formed EtOH and excess ethyl formate since the yield dips to 10-15% if not done so. Elongation of the reaction time of step II increased the yield slightly, but not the abbreviation of step II to 2 h (3 and 5). Excess of the reagents CCl₄/PPh₃/NEt₃ (4) led to a strongly reduced yield, possibly due to side reactions or insufficient imine formation because of the excess NEt₃. Handling the one-pot procedure in one solvent was not possible for either DCM or MeOH (2 and 6) and the original method using DCM at first and then a 1:1 mixture with MeOH proved to be ideal. The absent formation of isocyanide using MeOH in step II proves again that protic solvents are not tolerated in this step. Higher equivalents of aminopyridine and aldehyde in approach number 7 led to a comparable yield absolutely, but not relatively. This leads to the conclusion, that the conversion of the formate

Table 2: Evaluation of reaction parameters

	Step I			Step II			Step III						Yield ^a
	Amine	Ethyl-formate	Time	CCl ₄ PPh ₃ NEt ₃	Solvent	Time	Amino-pyridine	Alde-hyde	AcOH	Solvent	Time	Temp	
	eq	eq	h	eq		h	eq	eq	eq		h	°C	%
PoC	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	rt	37
1	1	1.1	1	1;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	rt	8
2	1	1.1	3	1;1.2;1	MeOH	4	0.5	0.5	1.5	MeOH	48	rt	-
3	1	1.1	3	1;1.2;1	DCM	2	0.5	0.5	1.5	MeOH/DCM	48	rt	13
4	1	1.1	3	2;2.4;2	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	rt	3
5	1	1.1	3	1;1.2;1	DCM	24	0.5	0.5	1.5	MeOH/DCM	48	rt	42
6	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	1.5	DCM	48	rt	-
7	1	1.1	3	1;1.2;1	DCM	4	1	1	1.5	MeOH/DCM	48	rt	21
8	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	17	reflux	12
9	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	40	38
10	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	3	MeOH/DCM	48	rt	29
11	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	0	MeOH/DCM	48	rt	-
12 ^b	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	rt	58
13 ^c	1	1.1	3	1;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	rt	-
14	1	1.1	3	-;1.2;1	DCM	4	0.5	0.5	1.5	MeOH/DCM	48	rt	-

^a respective to aminopyridine/aldehyde; crude, after column chromatography
^b premixed aminopyridine/aldehyde/AcOH in MeOH
^c CCl₄ substituted by CCl₃

to the isocyanide is not quantitative, as expected from former works (Bossio et al. 1993).

Abbreviation of step III to 17 h and raising the temperature to reflux furnished considerably less product (8) and therefore it was not possible to reduce the reaction time of step III. Slight warming of the reaction mixture did not lead to higher yield (9) and higher equivalents of AcOH did also not change the output considerably (10). Nevertheless it could be proven, that there is a dependence on an AcOH-buffered solvent, considering there was no yield for evaluation number 11. It was also not possible to substitute CCl₄ for CCl₃ or completely since there was no product detectable in these approaches (13 and 14). Interestingly it could be shown, that premixing the aminopyridine and aldehyde in glacial acetic acid and dry methanol (to promote imine formation) is beneficial for the method leading to a yield of 58% (12). This output is comparable to the yield of the standard Groebke-Blackburn reaction for this compound (62%), although in the presented one-pot-procedure three reaction steps were passed. In conclusion we present a novel procedure for the synthesis of imidazo[1,2-*a*]pyridines in one-pot, extending the functionality of the Groebke-Blackburn protocol. The intermediate formation of the isocyanide bypasses most of the deterring odor and makes the challenging isolation and purification of isocyanides unnecessary. Furthermore this protocol saves time and effort and enhances the scope of this reaction, when using amines as precursors. This protocol is a convenient way to more diverse libraries of imidazo[1,2-*a*]pyridines regarding the amine side chain.

3. Experimental

3.1. General procedure for proof of concept

The respective amine (4 mmol, 1 eq) and ethyl formate (4.4 mmol, 1.1 eq) are refluxed for 3 h. After 5 min of evaporation of the volatile reaction products by opening the reaction apparatus, 10 ml of dry DCM are added as

well as PPh₃ (4.8 mmol, 1.2 eq), NEt₃ (4 mmol, 1 eq) and CCl₄ (4 mmol, 1 eq). The apparatus is charged with argon and the mixture refluxed for 4 h. After cooling to room temperature, 10 ml of dry methanol, the respective 2-aminopyridine (2 mmol, 0.5 eq), aldehyde (2 mmol, 0.5 eq) and glacial acetic acid (6 mmol, 1.5 eq) are added. After 48 h the formation of imidazo[1,2-*a*]pyridine is controlled by TLC and several grams of silica gel are added to the reaction mixture. After evaporating to dryness on a rotavapor, the loaded silica gel is worked up by column chromatography (hexane/ethyl acetate 10:1, 5:1, 3:1 and 1:1) to furnish the desired product.

3.2. General optimized procedure

The respective amine (4 mmol, 1 eq) and ethyl formate (4.4 mmol, 1.1 eq) are refluxed for 3 h. After 5 min of evaporation of the volatile reaction products by opening the reaction apparatus, 10 ml of dry DCM are added as well as PPh₃ (4.8 mmol, 1.2 eq), NEt₃ (4 mmol, 1 eq) and CCl₄ (4 mmol, 1 eq). The apparatus is charged with argon and the mixture refluxed for 4 h. After cooling to room temperature, a premixed solution (30 min) of 10 ml dry methanol, the respective 2-aminopyridine (2 mmol, 0.5 eq), aldehyde (2 mmol, 0.5 eq) and glacial acetic acid (6 mmol, 1.5 eq) is added. After 48 h at 40 °C the formation of imidazo[1,2-*a*]pyridine is controlled by TLC and several grams of silica gel are added to the reaction mixture. After evaporating to dryness on a rotavapor, the loaded silica gel is worked up by column chromatography (hexane/ethyl acetate 10:1, 5:1, 3:1 and 1:1) to furnish the desired product.

3.3. Standard Groebke-Blackburn protocol

(Groebke et al. 1998) The respective amine (1 eq) and aldehyde (1 eq) are solved in glacial acetic acid (2 eq) and 10 ml of dry methanol. The isocyanide (1 eq) is added and the mixture is stirred for 48 h. Then several grams of silica gel are added and the mixture evaporated to dryness. The loaded silica gel is worked up by column chromatography (hexane/ethyl acetate 10:1, 5:1, 3:1 and 1:1) to furnish the desired product.

3.4. Compound characteristics

3.4.1. 6-Methyl-N-(2-phenylethyl)-2-(thiophen-2-yl)imidazo[1,2-*a*]pyridin-3-amine (1)

Yield: 71 mg (11%), colourless needles, mp: 140,4 °C. IR (KBr): 3259, 3063, 3024, 2909, 2852, 1581, 1510, 1493, 1450, 1410, 1338, 1200, 1030, 805, 733, 706, 695 cm⁻¹. ¹H NMR (500.18 MHz, DMSO) δ [ppm] = 2.23 (s, 3

H), 2.85–2.88 (t, 2 H), 3.18–3.21 (quartet, 2 H), 4.79–4.82 (t, 1 H), 7.01–7.03 (dd, $J=9.1$, 1.6 Hz, 1 H), 7.07–7.08 (t, 1 H), 7.21–7.25 (m, 3 H), 7.28–7.31 (t, 2 H), 7.33–7.35 (d, $J=9.1$ Hz, 1 H), 7.44–7.45 (dd, $J=5.1$, 1.1 Hz, 1 H), 7.48–7.49 (dd, $J=3.6$, 1.1 Hz, 1 H), 7.73 (s, 1 H). ^{13}C NMR (125.77 MHz, DMSO) δ [ppm]=18.25, 36.98, 49.32, 116.38, 120.93, 121.10, 123.63, 125.17, 125.52, 126.52, 127.48, 128.23, 128.71, 129.35, 131.33, 138.27, 140.00, 140.32. ESI: m/z (%)=334.5 (100, $[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{S}$: C, 72.04; H, 5.74; N, 12.60; S, 9.62. Found: C, 71.91; H, 5.71; N, 12.96; S, 9.86.

3.4.2. 6-Methyl-N-(3-phenylpropyl)-2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-amine (2)

Yield: 174 mg (25%), beige needles, mp: 145.4 °C. IR (KBr): 3217, 3057, 3022, 2922, 2923, 2890, 2855, 1592, 1449, 1338, 1251, 1199, 1125, 1030, 849, 804, 714, 695 cm^{-1} . ^1H NMR (500.18 MHz, DMSO) δ [ppm]=1.82–1.88 (quintet, 2 H), 2.23 (s, 3 H), 2.66–2.70 (t, 2 H), 2.97–3.01 (quartet, 2 H), 4.79–4.82 (t, 1 H), 7.03–7.05 (dd, $J=9.1$, 1.6 Hz, 1 H), 7.11–7.12 (t, 1 H), 7.14–7.18 (m, 3 H), 7.24–7.27 (t, 2 H), 7.36–7.38 (d, $J=9.2$ Hz, 1 H), 7.45–7.47 (dd, $J=5.1$, 1.0 Hz, 1 H), 7.61–7.61 (dd, $J=3.6$, 1.0 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (125.77 MHz, DMSO) δ [ppm]=18.31, 32.58, 33.13, 47.15, 116.51, 120.94, 121.24, 123.65, 125.24, 125.86, 126.18, 127.49, 128.17, 128.72, 128.74, 131.39, 138.32, 140.05, 142.33. ESI: m/z (%)=348.4 (100, $[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{S}$: C, 72.59; H, 6.09; N, 12.09; S, 9.23. Found: C, 72.61; H, 6.03; N, 12.12; S, 9.54.

3.4.3. 6-Methyl-N-(4-phenylbutyl)-2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-amine (3)

Yield: 141 mg (20%), gray solid, mp: 119.3 °C. IR (KBr): 3230, 3073, 3025, 2935, 2885, 2858, 2811, 1593, 1496, 1476, 1449, 1409, 1384, 1337, 1251, 1200, 801, 742, 714, 698 cm^{-1} . ^1H NMR (500.18 MHz, DMSO) δ [ppm]=1.57–1.65 (m, 4 H), 2.31 (s, 3 H), 2.51–2.55 (t, 2 H), 2.98–3.99 (quartet, 2 H), 4.73 (t, 1 H), 7.03–7.05 (dd, $J=9.1$, 1.6 Hz, 1 H), 7.11–7.13 (t, 1 H), 7.15–7.16 (m, 3 H), 7.24–7.27 (t, 2 H), 7.36–7.37 (d, $J=9.1$ Hz, 1 H), 7.46–7.47 (dd, $J=5.1$, 1.0 Hz, 1 H), 7.61–7.61 (dd, $J=3.6$, 1.1 Hz, 1 H), 8.03 (s, 1 H). ^{13}C NMR (125.77 MHz, DMSO) δ [ppm]=18.32, 29.06, 30.45, 35.52, 47.52, 116.49, 120.96, 121.18, 123.60, 125.21, 125.97, 126.10, 127.44, 128.13, 128.67, 128.75, 131.35, 138.36, 140.02, 142.58. ESI: m/z (%)=363.0 (100, $[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{S}$: C, 73.09; H, 6.41; N, 11.62; S, 8.87. Found: C, 73.25; H, 6.10; N, 11.66; S, 8.87.

3.4.4. N-[(4-Methoxyphenyl)methyl]-6-methyl-2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-amine (4)

Yield: 51 mg (7%), light yellow solid, mp: 172.4 °C. IR (KBr): 3215, 3076, 2947, 2909, 2837, 1609, 1589, 1582, 1508, 1473, 1408, 1341, 1248, 1240, 1196, 1171, 1027, 840, 809, 799, 752, 575, 565 cm^{-1} . ^1H NMR (500.18 MHz, DMSO) δ [ppm]=2.22 (s, 3 H), 3.72 (s, 3 H), 4.05–4.06 (d, $J=6.2$ Hz, 2 H), 5.13 (t, 1 H), 6.84–6.86 (d, $J=8.6$ Hz, 2 H), 6.99–7.01 (dd, $J=9.1$, 1.6 Hz, 1 H), 7.12–7.13 (t, 1 H), 7.26–7.28 (d, $J=8.5$ Hz, 2 H), 7.32–7.34 (d, $J=9.1$ Hz, 1 H), 7.47–7.48 (dd, $J=5.1$, 1.0 Hz, 1 H), 7.60–7.61 (dd, $J=3.6$, 1.1 Hz, 1 H), 7.83 (s, 1 H). ^{13}C NMR (125.77 MHz, DMSO) δ [ppm]=18.20, 50.89, 55.52, 114.06, 116.32, 120.82, 121.17, 123.68, 125.32, 125.54, 127.45, 128.13, 130.06, 131.68, 132.36, 138.26, 140.10, 158.94. ESI: m/z (%)=350.4 (100, $[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{OS}$: C, 68.74; H, 5.48; N, 12.02; S, 9.18. Found: C, 68.36; H, 5.37; N, 12.27; S, 9.48.

3.4.5. Ethyl-4-(2-[(6-methyl-2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl)amino]ethyl)benzoate (5)

Yield: 53 mg (11%), yellow-orange needles, mp: 145.5 °C. IR (KBr): 3273, 2983, 2901, 2857, 1707, 1585, 1510, 1410, 1339, 1276, 1199, 1175, 1122, 1104, 1022, 806, 757, 688 cm^{-1} . ^1H NMR (500.18 MHz, DMSO) δ [ppm]=1.30–1.33 (t, 3 H), 2.20 (s, 3 H), 2.94–2.95 (t, 2 H), 3.24–3.26 (quartet, 2 H), 4.29–4.33 (quartet, 2 H), 4.83 (t, 1 H), 7.00–7.02 (dd, $J=9.1$, 1.6 Hz, 1 H), 7.05–7.06 (t, 1 H), 7.32–7.34 (d, $J=9.1$ Hz, 1 H), 7.38–7.40 (d, $J=8.2$ Hz, 2 H), 7.44–7.47 (m, 2 H), 7.67 (s, 1 H), 7.88–7.89 (d, $J=8.3$ Hz, 2 H). ^{13}C NMR (125.77 MHz, DMSO) δ [ppm]=14.68, 18.16, 36.89, 48.83, 61.01, 116.39, 120.88, 121.06, 123.64, 125.21, 125.35, 127.48, 128.16, 128.25, 129.54, 129.74, 131.49, 138.27, 140.02, 146.26. ESI: m/z (%)=406.8 (100, $[\text{M}+\text{H}]^+$). Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$: C, 68.12; H, 5.72; N, 10.36; S, 7.91. Found: C, 68.04; H, 5.86; N, 10.08; S, 8.14.

3.4.6. N-Benzyl-6-methyl-2-(thiophen-2-yl)imidazo[1,2-a]pyridin-3-amine (6, Table 2, entry 12)

Yield (crude): 370 mg (58%), yellow solid, mp: 197.0 °C. IR (KBr): 3212, 3075, 3021, 2953, 2920, 1588, 1477, 1451, 1408, 1379, 1341, 1252, 1196, 1080, 848, 839, 799, 757, 701, 575 cm^{-1} . ^1H NMR (500.18 MHz, DMSO) δ [ppm]=2.22 (s, 3 H), 4.12–4.13 (d, $J=6.3$ Hz, 2 H), 5.21–5.24 (t, 1 H), 7.00–7.02 (dd, $J=9.1$, 1.6 Hz, 1 H), 7.12–7.13 (t, 1 H), 7.23–7.26 (t, 1 H), 7.29–7.35 (m, 3 H), 7.37–7.39 (d, $J=7.0$ Hz, 2 H), 7.47–7.48 (dd, $J=5.1$, 1.0 Hz, 1 H), 7.61–7.62 (dd, $J=3.6$, 1.0 Hz, 1 H), 7.86 (s, 1 H). ^{13}C NMR (125.77 MHz, DMSO) δ [ppm]=18.22, 51.47, 116.33, 120.89, 121.16, 123.72, 125.37, 125.49, 127.50, 127.53, 128.14, 128.68, 128.80, 131.69, 138.21, 140.12, 140.37. ESI: m/z (%)=320.2 (100, $[\text{M}+\text{H}]^+$).

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