Synthesis of 1-Methylbenzimidazoles from Carbonitriles

Jonas Sluiter, Jens Christoffers*

Institut für Reine und Angewandte Chemie, Carl von Ossietzky-Universität Oldenburg, 26111 Oldenburg, Germany
Fax +49(441)798 3873; E-mail: jens.christoffers@uni-oldenburg.de

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Abstract: The NaH-mediated *N*-methylbenzimidazole formation starting from carbonitriles and *N*-methyl-1,2-phenylenediamine is reported to be a procedure compatible with acid-labile acetal protective groups within the starting materials. Products were further converted in Suzuki, Sonogashira, Heck and Buchwald–Hartwig reactions.

Key words: benzimidazoles, heterocycles, carbonitriles, cross-coupling

The benzimidazole moiety is one of the privileged structures in medicinal chemistry.[1] Therefore, benzimidazoles appear quite frequently in pharmaceutical products such as Astemizole,[2] Candesartan,[3] Omeprazol,[4] and Pradaxa[5] just to name four. The heterocycle is commonly built up by condensation of *ortho*-phenylenediamine with carboxylic acids, esters, or imido esters under Brønsted or Lewis acidic conditions.[6] More flexible are two-step protocols: either condensation of the diamine with carbaldehydes and subsequent oxidation,[6] or formation of *ortho*-aminobenzamides with subsequent ring closure under acidic conditions.[7] Carbonitriles have also been applied for direct benzimidazole synthesis. Strong acids are always used in these cases in order to activate the nitrile.[8] A two-step protocol leading to benzimidazoles first converts nitriles into imido esters by nucleophilic addition of alkoxides.[9] The resulting imido esters are then condensed with the diamines. In certain cases, these two steps can be performed in one flask.[10] We were interested in the direct conversion of carbonitriles to *N*-methylbenzimidazoles under avoidance of even slightly acidic conditions, since we need to retain acetal protective groups present in our starting materials. Therefore, we aimed to develop basic reaction conditions for this condensation reaction.

As mentioned introductorily, neutral or basic reaction conditions were never been reported for the formation of benzimidazoles from *N*-methyl-1,2-phenylenediamine (**1**) and nitriles **2** (Scheme 1). With diamine **1** and cyclohexane derivative **2a** as a model system we first envisioned thermal reaction conditions without any additive or catalyst; however, heating equimolar amounts of starting materials **1** and **2a** in EtOH or toluene up to 120 °C (sealed reaction tube) did not result in the formation of benzimidazole **3a**, as monitored by GLC. When adding substoichiometric amounts of NaH (0.25 or 0.5 equiv) as a base, product **3a** was also not detectable. With one equivalent of NaH conversion of starting materials **1** and **2a** took place and was quantitative within three hours. Product **3a** was isolated after column chromatography in 90% yield (Table 1, entry 1).[11] This result could not be improved with more NaH (2 equiv gave 89% yield). Since NaH obviously deprotonated the amine **1** under these reaction conditions (which could be monitored by gas evolution), also other bases might be suitable to promote this reaction. However, when up to 2 equivalents of NaO*t*-Bu were used, no conversion of starting materials was observed. Reaction of pivalonitrile (**2b**) under the same reaction conditions gave only 33% yield of product **3b**. Yield increased to 83% when the reaction time and temperature were increased (16 h at 160 °C, entry 2). Higher temperature or larger amounts of NaH gave no further improvement. For valeronitrile (**2c**) optimal results (93% yield) were obtained at 145 °C (entry 3). Higher temperature and more NaH gave lower yields. Reaction of isobutyronitrile (**2d**) required also one equivalent of NaH to give product **3d** in 84% yield (entry 4). The isopropyl-substituted product **3d** was also isolated (29% yield) in an attempt of bisbenzimidazole formation with 2,2-dimethylmalodinitrile (**2e**, entry 5), which seems to be a result of cyanide elimination of the monoaddition product under reaction conditions. Monoaddition product **3e** of diamine **1** to dinitrile **2e** was obtained at shorter reaction time, although also with low yield (30%, entry 6). We were, though, not able to detect any bisbenzimidazole derived from dinitrile **2e**. Initial motivation for this work was the conversion of nitriles **2** with acid-labile protective groups. In particular, we were interested in the conversion of acetal-protected cyanohydrins like lactonitrile **2f**, which indeed gave benzimidazole **3f** after 15 hours at 150 °C in 60% yield (entry 7). The cleavage of the 1-ethoxyethyl (EE) group yielded quantitatively the free secondary alcohol.[12] Ethoxyethyl-protected cyanohydrin derived from cyclohexanone, compound **2g**, also yielded the corresponding benzimidazole derivative **3g**, although with lower yield (entry 8), which might be due to steric constraints caused by the quaternary center. Attempts of conversion of 3-methoxypropionitrile under the conditions introduced in this work were not fruitful, presumably this starting material decomposed by an $E1_{cb}$ process (no entry in Table 1).

Although the yield of phenyl-substituted product **3h** was good (73%) when the reaction with benzonitrile **2h** was performed at 180 °C (entry 9), the formation of *p*-bromo congener **3i** was optimal (only 65% yield) at 150 °C (entry 11), but remained unsatisfactory. Even lower was the op-

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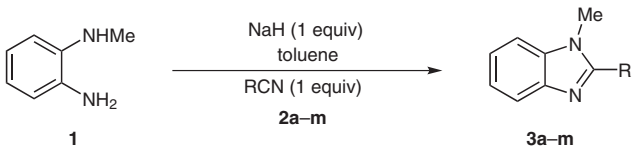


Scheme 1 Formation of *N*-methylbenzimidazoles **3** from nitriles **2**; for residues R, conditions, and yields, see Table 1

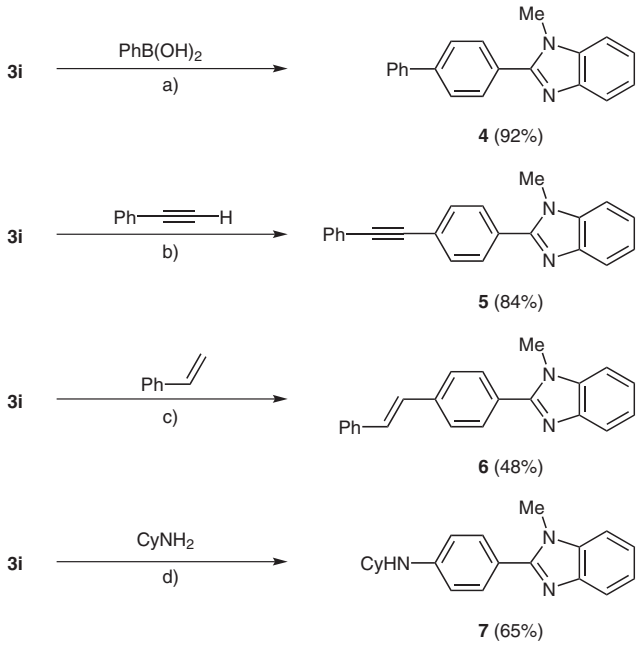
Table 1 Optimal Reaction Conditions and Yields

Entry	R	**2** (equiv)	Temp (°C)	Time (h)	**3** (yield, %)
1	Cyclohexyl	**2a** (1.0)	120	3	**3a**[13] (90)
2	*t*-Bu	**2b** (1.0)	160	16	**3b**[14] (83)
3	*n*-Bu	**2c** (1.0)	145	18	**3c** (93)
4	*i*-Pr	**2d** (1.0)	150	16	**3d**[15] (84)
5	$NCC(Me)_2$	**2e** (0.5)	160	16	**3d** (29)[a]
6	$NCC(Me)_2$	**2e** (0.5)	170	6	**3e** (30)[b]
7	MeCH(OEE)[c]	**2f**[16] (1.5)	150	15	**3f** (60)
8	c-$(CH_2)_5C(OEE)$	**2g**[17] (1.0)	160	16	**3g** (48)
9	Ph	**2h** (1.0)	180	23	**3h**[15,18] (73)[d]
10	Ph	**2h** (1.0)	170	16	**3h** (60)[e]
11	4-BrC_6H_4	**2i** (1.0)	150	16	**3i**[18a] (65)
12	4-$F_3CC_6H_4$	**2j** (1.0)	120	15	**3j**[13b] (54)
13	4-$MeOC_6H_4$	**2k**[19] (1.0)	180	6	**3k**[13b] (75)
14	2-$MeOC_6H_4$	**2l**[20] (1.0)	180	6	**3l**[21] (4)
15	2-pyridyl	**2m** (1.1)	150	16	**3m**[13b,22] (60)

[a] Product **3d** with R = *i*-Pr.
[b] Monoaddition product **3e** with R = $NCC(Me)_2$.
[c] EE = 1-ethoxyethyl.
[d] Scale: 2 mmol.
[e] Scale: 50 mmol, refluxing mesitylene.

timal yield of *p*-trifluoromethyl derivative **3j** (54%, entry 12), which was obtained at comparatively low temperature of 120 °C. Whereas results for *p*-methoxybenzonitrile (**2k**) were as good as for R = Ph (75%, entry 13), the *ortho*-substituted congener **2l** resulted in only 4% yield of product **3l** (entry 14), which could be due to steric effects. The yield of pyridine derivative **3m** (60%, entry 15) was satisfying. *p*-Nitrobenzonitrile was consumed in the reaction, but afforded a mixture of several not fully identified products (no entry in Table 1). All reactions discussed so far were performed on a 1–2 mmol scale with toluene as solvent in a tightly closed reaction flask. In order to show the feasibility of this method, the reaction of benzonitrile (**2h**) was scaled up to 50 mmol in refluxing mesitylene (ca. 170 °C) and gave 60% yield of product **3g** (entry 10).[23]

p-Bromophenyl-substituted benzimidazole **3i** was submitted to four cross-coupling reactions in order to check a potential point of diversification. Suzuki coupling with $PhB(OH)_2$ was performed with Na_2PdCl_4 and cataCXium FSulf as precatalyst[24] and gave biphenyl-substituted benzimidazole **4** with 92% yield (Scheme 2).[25] Disodium tetrachloropalladate (Na_2PdCl_4) and cataCXium FBu were the precatalyst[26] for Sonogashira coupling with PhC≡CH, which gave product **5** with 84% yield.[27] This compound has very recently been reported to be a PDE 4-inihibitor.[28] Stilbene derivative **6** was obtained with 48% yield in the Heck reaction with styrene and $Pd(OAc)_2$–Ph_3P[29] as precatalyst.[30] The olefinic coupling constant in the ^1H NMR spectrum clearly indicated *E*-configuration of product **6**. Finally, Buchwald–Hartwig amination with $CyNH_2$ and $Pd(OAc)_2$–BINAP[31] as precatalyst gave secondary aryl amine **7** in 65% yield.[32]



Scheme 2 Cross-coupling reactions of *p*-bromophenyl-substituted benzimidazole **3i**. *Reagents and conditions*: (a) Na_2PdCl_4 (1.3 mol%), cataCXium Fsulf (1.5 mol%), K_2CO_3 (3 equiv), $PhB(OH)_2$ (1.1 equiv), H_2O, *n*-BuOH, 16 h, 100 °C; (b) Na_2PdCl_4 (1.6 mol%), cataCXium FBu (2.3 mol%), CuI (2.5 mol%), phenylacetylene (1.2 equiv), *i*-$PrNH_2$, 16 h, 100 °C; (c) $Pd(OAc)_2$ (10 mol%), Ph_3P (24 mol%), Et_3N (4 equiv), styrene (2 equiv), DMF, 16 h, 100 °C; (d) $Pd(OAc)_2$ (5 mol%), BINAP (7.5 mol%), NaO*t*-Bu (1.7 equiv), $CyNH_2$ (1.3 equiv), toluene, 16 h, 85 °C.

In summary, formation of benzimidazole derivatives from 1,2-phenylenediamines and carboxylic acid derivatives including carbonitriles commonly require acidic reaction conditions, which are not compatible with acid-labile protective groups such as acetals. We have reported herein on the first benzimidazole synthesis starting from carbonitriles under basic reaction conditions. The protocol requires a stoichiometric amount of NaH. The reaction proceeds in toluene in a tightly closed reaction vial at 120–180 °C on a mmol scale or alternatively in refluxing mesitylene on a larger scale within 3 to 23 hours. A broad

range of aliphatic and aromatic including heteroaromatic carbonitriles was investigated. After optimization of reaction time and temperature for every single substrate yields in the range of 50–93% can be obtained. Importantly, this method is fully compatible with acid-labile ethoxyethyl-protected cyanohydrins. The *p*-bromophenyl-substituted product can be further converted in cross-couplings such as Suzuki, Sonogashira, Heck, and Buchwald–Hartwig reactions.

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(11) **2-Cyclohexyl-1-methyl-1*H*-benzimidazole (3a)**
Diamine **1** (244 mg, 2.00 mmol), NaH (80.0 mg, 60% dispersion in mineral oil, 2.00 mmol), and abs. toluene (1.0 mL) were successively added to nitrile **2a** (218 mg, 2.00 mmol). The mixture was stirred for 3 h at 120 °C in a tightly closed reaction vial, then completely transferred on top of a column (SiO_2), and chromatographed (hexane–EtOAc, 1:1; R_f = 0.32) to give the title compound **3a** (384 mg, 1.79 mmol, 90%) as a light brown solid, mp 102 °C (lit.[13a] 104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30–1.48 (m, 3 H), 1.74–2.03 (m, 7 H), 2.84 (tt, *J* = 3.5, 11.6 Hz, 1 H), 3.74 (s, 3 H), 7.20–7.31 (m, 3 H), 7.72–7.77 (m, 1 H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 25.82 (CH_2), 26.32 (2 CH_2), 29.52 (CH_3), 31.46 (2 CH_2), 36.33 (CH), 108.80 (CH), 119.27 (CH), 121.66 (CH), 121.87 (CH), 135.64 (C), 142.55 (C), 159.00 (C) ppm. IR (ATR): ν = 3173 (w), 3052 (w), 2929 (s), 2851 (m), 1730 (m), 1615 (m), 1506 (m), 1441 (s), 1278 (m), 1239 (m), 842 (m), 736 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 214 (14) [M$^+$], 159 (100). HRMS (CI, isobutane): *m/z* calcd for $C_{14}H_{19}N_2$: 215.1548; found: 215.1548 [M + H$^+$]. Anal. Calcd for $C_{14}H_{18}N_2$ (214.31): C, 78.46; H, 8.47; N, 13.07. Found: C, 78.40; H, 8.55; N, 13.05.
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(23) **1-Methyl-2-phenyl-1*H*-benzimidazole (3h)**
Diamine **1** (6.1 g, 50 mmol), NaH (2.0 g, 60% dispersion in mineral oil, 50 mmol) and abs. mesitylene (10 mL) were successively added to nitrile **2h** (5.2 g, 50 mmol). The mixture was heated to reflux for 16 h (inner temp ca. 170 °C, oil bath 210 °C). After cooling to ambient temperature, the mixture was filtered through SiO_2 (1 cm), the residue washed with CH_2Cl_2 (5 mL), and the combined filtrates evaporated. The residue was chromatographed (SiO_2, hexane–EtOAc, 1:1; R_f = 0.34) to give the title compound **3a** (6.2 g, 30 mmol, 60%) as a light yellow solid, mp 91 °C (lit.[18b] 92–93 °C). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 31.57 (CH_3), 109.54 (CH), 119.76 (CH), 122.33 (CH), 122.67 (CH), 128.58 (2 CH), 129.35 (2 CH), 129.63 (CH), 130.16 (C), 136.51 (C), 142.91 (C), 153.70 (C) ppm. All other data were in accordance with the literature.[18b]
(24) cataCXium FSulf = dicyclohexyl{2-sulfo-9-[3-(4-sulfophenyl)propyl]-9-fluorenyl}phosphonium hydrogensulfate; for use in Suzuki reactions, see: (a) Fleckenstein, C. A.; Plenio, H. *Green Chem.* **2007**, *9*, 1287. (b) Fleckenstein, C. A.; Plenio, H. *Chem. Eur. J.* **2007**, *13*, 2701.
(25) **2-(Biphenyl-4-yl)-1-methyl-1*H*-benzimidazole (4)**
A mixture of bromophenyl compound **3i** (91 mg, 0.32 mmol, 1.0 equiv), $PhB(OH)_2$ (42 mg, 0.35 mmol, 1.1 equiv), Na_2PdCl_4 (1.2 mg, 4.2 μmol, 1.3 mol%), cataCXium Fsulf (3.3 mg, 4.5 μmol, 1.5 mol%), and K_2CO_3 (131 mg, 945 μmol, 3 equiv) was placed in a Schlenk tube and twice evacuated and flushed with N_2. Degassed H_2O (0.5 mL) and BuOH (0.5 mL) were added, and the resulting mixture was stirred for 16 h at 100 °C. Subsequently, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (5 mL). The combined organic layers were dried ($MgSO_4$), and after filtration, the solvent was evaporated and the residue chromatographed (SiO_2, hexane–EtOAc = 1:1, R_f = 0.48) to give the title compound **4** (82 mg, 0.29 μmol, 92%) as a yellow solid, mp 164 °C. ^{1}H NMR (500 MHz,

$CDCl_3$): δ = 3.87 (s, 3 H), 7.29–7.34 (m, 2 H), 7.35–7.40 (m, 2 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.62–7.67 (m, 2 H), 7.71–7.76 (m, 2 H), 7.81–7.87 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 31.70 (CH_3), 109.57 (CH), 119.75 (CH), 122.42 (CH), 122.74 (CH), 127.08 (2 CH), 127.26 (2 CH), 127.78 (CH), 128.86 (2 CH), 128.94 (C), 129.77 (2 CH), 136.61 (C), 140.09 (C), 142.40 (C), 142.93 (C), 153.40 (C) ppm. IR (ATR): ν = 3031 (w), 2925 (w), 1463 (m), 1375 (m), 1325 (m), 1005 (m), 850 (m), 765 (m), 737 (s), 690 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 284 (98) [M^+], 283 (100), 179 (10), 152 (10), 78 (12), 77 (29). HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{16}N_2$: 284.1313; found: 284.1313 [M^+].

(26) cataCXium FBu = (9-butyl-9-fluorenyl)dicyclohexylphosphonium tetrafluoroborate; for use in Sonogashira reactions, see ref. 24a

(27) **1-Methyl-2-[4-(phenylethynyl)phenyl]-1*H*-benzimidazole (5)**[28]
A suspension of bromophenyl compound **3i** (91 mg, 0.32 mmol, 1 equiv), phenylacetylene (38 mg, 0.38 mmol, 1.2 equiv), Na_2PdCl_4 (1.5 mg, 5.1 μmol, 1.6 mol%), cataCXium FBu (3.6 mg, 7.2 μmol, 2.3 mol%), and CuI (1.5 mg, 7.8 μmol, 2.5 mol%) in *i*-$PrNH_2$ (1.0 mL) was stirred under an inert atmosphere for 16 h at 100 °C. Subsequently, all volatile materials were removed in vacuo, the residue dissolved in CH_2Cl_2 (5 mL), and washed with H_2O (2 × 3 mL). The organic layer was dried (Na_2SO_4), and after filtration, the solvent was evaporated. Chromatography of the residue (SiO_2; hexane–EtOAc, 2:1; R_f = 0.29) gave the title compound **5** (81 mg, 0.26 mmol, 84%) as a light yellow solid, mp 152 °C (lit.[28] 153–155 °C). ^1H NMR (500 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 7.26–7.37 (m, 6 H), 7.50–7.57 (m, 2 H), 7.63–7.68 (m, 2 H), 7.71–7.77 (m, 2 H), 7.79–7.86 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 31.63 (CH_3), 88.71 (C), 91.27 (C), 109.58 (CH), 119.75 (CH), 122.47 (CH), 122.77 (C), 122.87 (CH), 124.62 (C), 128.31 (2 CH), 128.48 (CH), 129.20 (2 CH), 129.68 (C), 131.57 (2 CH), 131.70 (2 CH), 136.56 (C), 142.86 (C), 152.83 (C) ppm. IR (ATR): ν = 3058 (w), 2950 (w), 2216 (w), 1457 (m), 1437 (m), 1381 (m), 1329 (m), 1249 (m), 1103 (m), 1007 (m), 919 (m), 840 (s), 740 (s), 730 (s), 690 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 308 (100) [M^+], 307 (80), 203 (23), 176 (12), 154 (12). HRMS (EI, 70 eV): *m/z* calcd for $C_{22}H_{16}N_2$: 308.1313; found: 308.1313 [M^+].

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(30) **(*E*)-1-Methyl-2-[4-(2-phenylethenyl)phenyl]-1*H*-benzimidazole (6)**
A mixture of bromophenyl compound **3i** (60 mg, 0.21 mmol, 1 equiv), freshly distilled styrene (44 mg, 0.42 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.0 mg, 21 μmol, 0.1 equiv), Ph_3P (14 mg, 51 μmol, 0.24 equiv), Et_3N (85 mg, 0.84 mmol, 4.0 equiv), and abs. DMF (3.0 mL) was stirred for 16 h at 100 °C under an inert atmosphere. Subsequently, all volatile materials were removed in vacuo, the residue dissolved in CH_2Cl_2 (5 mL), and washed with H_2O (2 × 3 mL). The organic layer was dried (Na_2SO_4), and after filtration, the solvent was evaporated. Chromatography of the residue (SiO_2; hexane–EtOAc, 2:1; R_f = 0.27) gave the title compound **6** (31 mg, 0.10 mmol, 48%) as a light yellow solid, mp 150 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 7.15 (d, *J* = 16.3 Hz, 1 H), 7.21 (d, *J* = 16.3 Hz, 1 H), 7.23–7.34 (m, 3 H), 7.33–7.41 (m, 3 H), 7.50–7.56 (m, 2 H), 7.60–7.68 (m, 2 H), 7.72–7.79 (m, 2 H), 7.80–7.87 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 31.74 (CH_3), 109.56 (CH), 119.74 (CH), 122.45 (CH), 122.76 (CH), 126.63 (4 CH), 127.67 (CH), 127.97 (CH), 128.71 (2 CH), 129.01 (C), 129.68 (2 CH), 130.17 (CH), 136.62 (C), 136.90 (C), 138.68 (C), 142.91 (C), 153.40 (C) ppm. IR (ATR): ν = 3025 (w), 2953 (w), 1461 (m), 1379 (m), 1326 (m), 960 (m), 821 (s), 741 (s), 688 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 310 (100) [M^+], 309 (75). HRMS (EI, 70 eV): *m/z* calcd for $C_{22}H_{18}N_2$: 310.1470; found: 310.1470 [M^+].

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(32) **2-[4-(Cyclohexylamino)phenyl]-1-methyl-1*H*-benzimidazole (7)**
A suspension of $Pd(OAc)_2$ (3.0 mg, 11 μmol, 5.0 mol%) and *rac*-BINAP (7.0 mg, 11 μmol, 7.5 mol%) in abs. toluene (1.5 mL) was stirred for 5 min at 23 °C under an inert atmosphere. Bromophenyl compound **3i** (60 mg, 0.21 mmol, 1 equiv), $CyNH_2$ (27 mg, 0.27 mmol, 1.3 equiv), and NaO*t*-Bu (34 mg, 0.36 mmol, 1.7 equiv) were added, and the resulting mixture was stirred for 16 h at 85 °C. Subsequently, it was diluted with CH_2Cl_2 (5 mL) and washed with sat. $NaHCO_3$ solution (5 mL). The organic layer was dried ($MgSO_4$), and after filtration, the solvent was evaporated. Chromatography of the residue (SiO_2; hexane–EtOAc, 1:2; R_f = 0.44) gave the title compound **7** (42 mg, 0.14 mmol, 65%) as a light yellow solid, mp 145 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.13–1.29 (m, 3 H), 1.32–1.46 (m, 2 H), 1.62–1.70 (m, 1 H), 1.73–1.83 (m, 2 H), 2.01–2.13 (m, 2 H), 3.25–3.39 (m, 1 H), 3.77–3.93 (m, 4 H), 6.63–6.69 (m, 2 H), 7.23–7.28 (m, 2 H), 7.29–7.34 (m, 1 H), 7.54–7.60 (m, 2 H), 7.74–7.80 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 24.89 (2 CH_2), 25.78 (CH_2), 31.74 (CH_3), 33.24 (2 CH_2), 51.40 (CH), 109.23 (CH), 112.51 (2 CH), 117.80 (C), 119.20 (CH), 121.97 (CH), 122.00 (CH), 130.65 (2 CH), 136.61 (C), 142.97 (C), 148.49 (C), 154.62 (C) ppm. IR (ATR): ν = 3335 (w), 3055 (w), 2928 (m), 2853 (m), 1608 (s), 1542 (m), 1456 (s), 1379 (m), 1323 (m), 1180 (m), 1006 (m), 888 (s), 828 (m), 814 (m), 743 (s), 731 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 305 (100) [M^+], 304 (16), 263 (12), 262 (62), 222 (14), 131 (10). HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{23}N_3$: 305.1892; found: 305.1892 [M^+].