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Synthesis of 2-(buta-1,3-diynyl)-*N*,*N*-dimethylanilines using reductive methylation step

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^{1}H and ^{13}C NMR, DEPT-135 spectra were recorded on a Bruker DPX 300 spectrometer with working frequencies of 300.13 MHz for ^{1}H nuclei and 75.5 MHz for ^{13}C nuclei and on a Bruker Avance 400 instrument with a working frequency of 400.13 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. The chemical shifts are reported with respect to the residual signal of the solvent: $CHCl_3$ in ^{1}H NMR spectra (δ 7.26) and $CDCl_3$ in ^{13}C NMR spectra (δ 77.0). The observed coupling constants (*J*, Hz) in the ^{1}H NMR spectra are measured in a first-order approximation. Mass spectra were measured on a Finnigan MAT90 instrument (electron impact (EI) ionisation with an ionising electron energy of 70 eV or ionisation by fast atom bombardment (FAB)) and on a Bruker MicroTOF instrument (electrospray ionisation (ESI)).

Melting points were determined on a Fisher−Johns Melting Point Apparatus and are uncorrected.

The reaction completeness and the purity of the products were monitored by TLC on Kieselgel 60 plates, F254, Merck. Column chromatography was carried out on Merck silica gel 60 (60–210 μm) or 60M (40–60 μm).

General methylation procedure:

A 37% aqueous solution of formaldehyde (30 mmol, 2.43 g, 2.23 ml) and $NaBH_3CN$ (4 mmol, 0.25 g) were sequentially added to a solution of *o*-iodoaniline **1a**−**d** or (buta-1,3-diynyl)aniline **7a**−**c** (1 mmol) in MeCN (5 ml) placed in a round-bottom three-necked flask no less than 100 ml in volume, then AcOH (2.5 ml) was slowly added dropwise (caution: self-heating of the reaction mixture was observed). The reaction mixture was then continuously stirred for 24 h at room temperature. The reaction was monitored by TLC. If the reaction mixture contained the starting aniline after 24 h, more formalin (10 mmol of CH_2O, 0.81 g, 0.74 ml) and $NaBH_3CN$ (4 mmol, 0.25 g) were added in succession, then AcOH (2.5 ml) was slowly added dropwise. After the starting compound and the intermediate monomethylation product disappeared (TLC monitoring, see Table 1), the reaction mixture was diluted with Et_2O (10 ml), the organic fraction was separated and washed with a saturated $NaHCO_3$ solution until the washing waters turned neutral. The organic fraction was separated and washed with water (2 × 10 ml) and an aqueous NaCl solution (10 ml), then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The product was purified by column chromatography.

Ethyl 3-iodo-4-(dimethylamino)benzoate (2a).

Was obtained from ethynyl 4-amino-3-iodobenzoate **1a** (8.18 mmol, 2.38 g), purified by column chromatography using EtOAc–hexane system (1:30) and isolated as yellow oil in 78%yield (2.03 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, 1 H, ^4J = 1.8 Hz, H-Ar), 7.96 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 1.8 Hz, H-Ar), 6.77 (d, 1 H, ^3J = 8.4 Hz, H-Ar), 4.35 (q, 2 H, ^3J = 7.2 Hz, OCH_2), 2.85 (s, 3 H, 2 × CH_3), 1.37 (t, 3 H, ^3J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 14.3 (CH_3), 44.4 (NCH_3), 61.0 (CH_2), 93.6 (IC-Ar), 119.1 (CH-Ar), 125.8 (C-Ar), 130.5 (CH-Ar), 141.9 (CH-Ar), 158.9 (C-Ar), 165.2 (C=O). HRMS ESI: $[M+H]^+$ calculated for $C_{11}H_{15}INO_2$: 320.0142; found: 320.0145.

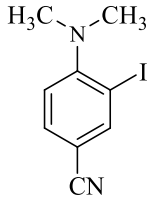
2-Iodo-*N*,*N*-dimethylaniline (2b).

Was obtained from 2-iodoaniline **1b** (0.91 mmol, 0.2 g), purified by column chromatography using EtOAc–hexane system (1:10) and isolated as yellow oil in 97% yield (0.215 g). The spectral characteristics of the resulting compound match literature data.[1]

Methyl 3-iodo-4-(dimethylamino)benzoate (2c).

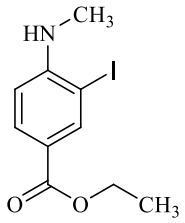
Was obtained from methyl 4-amino-3-iodobenzoate **1c** (0.91 mmol, 0.2 g), purified by column chromatography using EtOAc–hexane system (1:30) and isolated as yellow oil in 82% yield (2.35 g). The spectral characteristics of the resulting compound match literature data.[2]

3-Iodo-4-(dimethylamino)benzonitrile (2d).



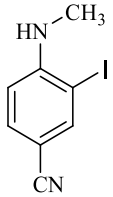
Was obtained from 4-amino-3-iodobenzonitrile **1d** (0.16 mmol, 0.04 g), purified by column chromatography using EtOAc–hexane system (1:5) and isolated as yellow oil in 39% yield (0.017 g). The spectral characteristics of the product match literature data.[3]

Ethyl 3-iodo-4-(methylamino)benzoate (3a).



Was obtained from ethynyl 4-amino-3-iodobenzoate **1a** (0.69 mmol, 0.20 g), purified by column chromatography using EtOAc–hexane system (1:30) and isolated as yellow solid in 38% yield (0.08 g). M.p. = 82–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (d, 1 H, ^4J = 2.1 Hz, H-Ar), 7.91 (dd, 1 H, ^3J = 8.7 Hz, ^4J = 2.1 Hz, H-Ar), 6.77 (d, 1 H, ^4J = 8.7 Hz, H-Ar), 4.70 (br.s, 1 H, NH), 4.31 (q, 2 H, ^3J = 7.2 Hz, OCH_2), 2.94 (s, 3 H, CH_3), 1.36 (t, 3 H, ^3J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 30.7 (CH_3), 60.5 (CH_2), 83.3 (IC-Ar), 108.3 (CH-Ar), 120.0 (C-Ar), 131.5 (CH-Ar), 140.5 (CH-Ar), 151.3 (C-Ar), 165.6 (C=O); HRMS ESI: $[M+H]^+$ calculated for $C_{10}H_{13}INO_2$: 305.9985; found: 305.9985.

3-Iodo-4-(methylamino)benzonitrile (3d).



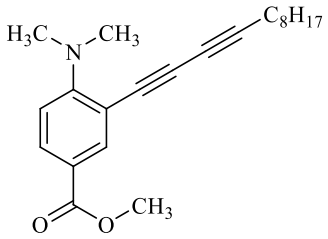
Was obtained from 4-amino-3-iodobenzonitrile **1d** (0.16 mmol, 0.04 g), purified by column chromatography using EtOAc–hexane system (1:5) and isolated as beige solid in 27% yield (0.01 g). M.p. = 110–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (d, 1 H, ^4J = 1.8 Hz, H-Ar), 7.49 (dd, 1 H, ^3J = 8.7 Hz, ^4J = 1.8

Hz, H-Ar), 6.49 (d, 1 H, ^3J = 8.7 Hz, H-Ar), 4.80 (br.s, 1 H, NH), 2.94 (d, 3 H, ^3J = 3.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.6 (CH_3), 83.1 (IC-Ar), 100.2 (C-Ar), 108.8 (CH-Ar), 118.7 (C-Ar), 133.8 (CH-Ar), 142.1 (CH-Ar), 151.1 (C-Ar); HRMS ESI: $[M+H]^+$ calculated for $C_8H_8IN_2$: 258.9727; found: 258.9727.

General procedure of Pd/Cu-catalysed coupling:

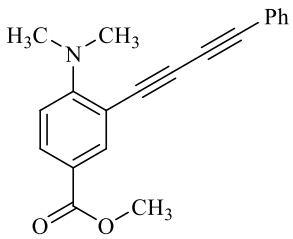
Bis(triphenylphosphine)palladium dichlorde (0.05 mmol, 0.035 g), PPh_3 (0.1 mmol, 0.026 g), DIPA (4 mmol, 0.53 g) and buta-1,3-diyne [3 mmol or 3.5 mmol (for alchohols)] were successively added to a solution of a iodoarene (1 mmol) in DMF (10 ml, 0.1 M). The reaction mixture was heated to 40 °C and stirred for 40–60 min in a flow of argon, then CuI (0.15 mmol, 0.028g) was added. The reaction mixture was stirred at 40 °C until the starting iodoarene disappeared (18 h, TLC monitoring), cooled, diluted with EtOAc and successively washed with saturated aqueous solutions of NH_4Cl, H_2O, and brine. The combined aqueous fractions were extracted with EtOAc. The combined organic fractions were repeatedly washed with NH_4Cl, H_2O and brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the reaction product was purified by column chromatography.

Methyl 3-(dodeca-1,3-diyn-1-yl)-4-(dimethylamino)benzoate (5a).



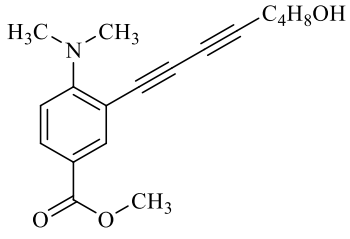
Was obtained from aniline **2c** (0.16 mmol, 0.05 g) and dodeca-1,3-diyne **4a** (0.49 mmol, 0.079 g), purified by column chromatography using EtOAc–hexane system (1:30) and isolated as orange oil in 43% yield (0.024 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, 1 H, ^4J = 2.1 Hz, H-Ar), 7.83 (dd, 1 H, ^3J = 8.8 Hz, ^4J = 2.1 Hz, H-Ar), 6.76 (d, 1 H, ^3J = 8.8 Hz, H-Ar), 3.85 (s, 3 H, OCH_3), 3.10 (s, 6 H, 2 × CH_3), 2.36 (t, 2 H, ^3J = 6.9 Hz, CH_2), 1.53–1.61 (m, 2 H, CH_2), 1.25–1.41 (m, 10 H, 5 × CH_2), 0.88 (t, 3 H, ^3J = 6.4 Hz, CH_3).

Methyl 4-(dimethylamino)-3-(4-phenylbuta-1,3-diyn-1-yl)benzoate (5b).



Was obtained from aniline **2c** (0.21 mmol, 0.065 g) and 4-phenylbuta-1,3-diyne **4b** (0.64 mmol, 0.08 g), purified by column chromatography using EtOAc–hexane system (1:100) and isolated as yellow oil in 48% yield (0.03 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H, H-Ar), 7.86 (d, 1 H, ^3J = 8.7 Hz, H-Ar), 7.17–7.44 (m, 5 H, 5 × H-Ar), 6.78 (d, 1 H, ^3J = 8.7 Hz, H-Ar), 3.77 (s, 3 H, OCH_3), 3.05 (s, 6 H, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.8 (2 × CH_3), 61.8 (CH_3), 74.1 (C≡), 78.9 (C≡), 80.6 (C≡), 82.8 (C≡), 109.5 (C-Ar), 115.1 (CH-Ar), 120.1 (C-Ar), 121.9 (C-Ar), 128.4 (2 × CH-Ar), 129.1 (CH-Ar), 131.4 (CH-Ar), 132.4 (2 × CH-Ar), 138.1 (CH-Ar), 157.9 (C-Ar), 166.38 (C=O); HRMS ESI: $[M+H]^+$ calculated for $C_{20}H_{18}NO_2$: 304.1333; found: 304.1336.

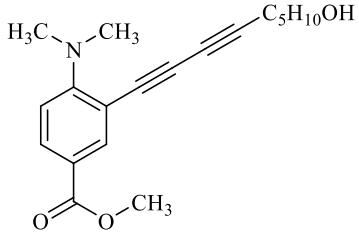
Methyl 3-(8-hydroxyocta-1,3-diyn-1-yl)-4-(dimethylamino)benzoate (5c).



Was obtained from aniline **2c** (11.0 mmol, 3.36 g) and octa-5,7-diyn-1-ol **4c** (38.5 mmol, 4.7 g), purified by column

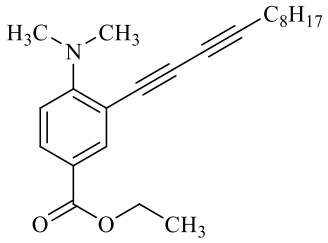
chromatography using EtOAc–hexane system (1:3) and isolated as yellow oil in 82% yield (2.6 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, 1 H, ^4J = 2.2 Hz, H-Ar), 7.82 (dd, 1 H, ^3J = 8.8 Hz, ^4J = 2.2 Hz, H-Ar), 6.75 (d, 1 H, ^3J = 8.8 Hz, H-Ar), 3.84 (s, 3 H, OCH_3), 3.68 (t, 2 H, ^3J = 5.8 Hz, CH_2), 3.08 (s, 6 H, 2 × CH_3), 2.42 (t, 2 H, ^3J = 6.5 Hz, CH_2), 1.61–1.78 (m, 4 H, 2 × CH_2), 1.51 (br.s, 1 H, OH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 19.5 (CH_2), 24.6 (CH_2), 31.7 (CH_2), 42.8 (2 × CH_3), 51.8 (CH_3), 62.2 (CH_2), 65.6 (C≡), 73.7 (C≡), 79.4 (C≡), 85.5 (C≡), 110.0 (C-Ar), 115.1 (CH-Ar), 120.1 (C-Ar), 131.1 (CH-Ar), 138.0 (CH-Ar), 158.0 (C-Ar), 166.3 (C=O); HRMS FAB: $[M+H]^+$ calculated for $C_{18}H_{22}NO_3$: 300.1595; found: 300.1598.

Methyl 3-(9-hydroxynona-1,3-diyn-1-yl)-4-(dimethylamino)benzoate (5d).



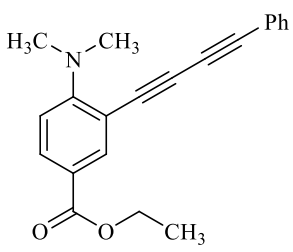
Was obtained from aniline **2c** (0.57 mmol, 0.175 g) and nona-6,8-diyn-1-ol **4d** (0.0 mmol, 0.27 g), purified by column chromatography using EtOAc–hexane system (1:3) and isolated as yellow oil in 61% yield (0.11 g). The spectral characteristics of the product match literature data.[4]

Ethyl 3-(dodeca-1,3-diyn-1-yl)-4-(dimethylamino)benzoate (6a).



Was obtained from aniline **2a** (0.85 mmol, 0.27 g) and dodeca-1,3-diyne **4a** (2.53 mmol, 0.41 g), purified by column chromatography using EtOAc–hexane system (1:20) and isolated as yellow oil in 79% yield (0.24 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, 1 H, ^4J = 2.0 Hz, H-Ar), 7.84 (dd, 1 H, ^3J = 8.8 Hz, ^4J = 2.0 Hz, H-Ar), 6.77 (d, 1 H, ^3J = 8.8 Hz, H-Ar), 4.32 (q, 2 H, ^3J = 7.2 Hz, OCH_2), 3.09 (s, 6 H, 2 × CH_3), 2.37 (t, 2 H, ^3J = 6.8 Hz, CH_2), 1.53–1.61 (m, 2 H, CH_2), 1.28–1.43 (m, 13 H, 5 × CH_2, $OCH_2C\mathit{H}_3$), 0.89 (t, 3 H, ^3J = 6.4 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.1 (CH_3), 14.4 (CH_3), 19.7 (CH_2), 22.6 (CH_2), 28.3 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.8 (CH_2), 42.8 (2 × CH_3), 60.6 (CH_2), 65.3 (C≡), 73.6 (C≡), 79.6 (C≡), 86.2 (C≡), 110.3 (C-Ar), 115.2 (CH-Ar), 120.7 (C-Ar), 131.1 (CH-Ar), 137.9 (CH-Ar), 158.0 (C-Ar), 165.8 (C=O); HRMS ESI: $[M+H]^+$ calculated for $C_{23}H_{32}NO_2$: 354.2428; found: 354.2427.

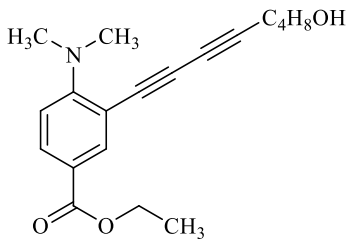
Ethyl 4-(dimethylamino)-3-(4-phenylbuta-1,3-diyn-1-yl)benzoate (6b).



Was obtained from aniline **2a** (0.44 mmol, 0.14 g) and 4-phenylbuta-1,3-diyne **4b** (1.32 mmol, 0.17 g), purified by column chromatography using EtOAc–hexane system (1:7) and isolated as yellow oil in 86%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, 1 H, ^4J = 2.1 Hz, H-Ar), 7.87 (dd, 1 H, ^3J = 8.7 Hz, ^4J = 2.1 Hz, H-Ar), 7.51–7.54 (m, 2 H, 2 × H-Ar), 7.32–7.38 (m, 3 H, 3 × H-Ar), 6.78 (d, 1 H, ^3J = 9.0 Hz, H-Ar), 4.33 (q, 2 H, ^3J = 7.2 Hz, OCH_2), 3.14 (s, 6 H, 2 × CH_3), 1.37 (t, 3 H, ^3J = 7.2 Hz, $OCH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 42.8 (2 × CH_3), 60.6 (OCH_2), 74.2 (C≡), 78.9 (C≡), 80.6 (C≡), 82.8 (C≡), 109.5 (C-Ar), 115.1 (CH-Ar), 120.5 (C-Ar), 121.9 (C-

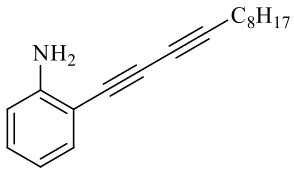
Ar), 128.4 (2 × CH-Ar), 129.1 (CH-Ar), 131.5 (CH-Ar), 132.4 (2 × CH-Ar), 138.0 (CH-Ar), 157.9 (C-Ar), 165.8 (C=O); HRMS EI: $[M]^+$ calculated for $C_{21}H_{19}NO_2$: 317.1416; found: 317.1418.

Ethyl 3-(8-hydroxyocta-1,3-diynyl)-4-(dimethylamino)benzoate (6c).



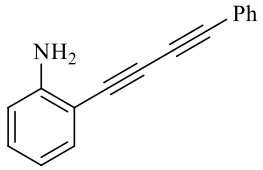
Was obtained from aniline **2a** (18.0 mmol, 5.74 g) and octa-5,7-diyn-1-ol **4c** (63.0 mmol, 7.69 g), purified by column chromatography using EtOAc–hexane system (1:3) and isolated as yellow oil in 79% yield (4.43 g). The spectral characteristics of the product match literature data.[4]

2-(Dodeca-1,3-diyn-1-yl)aniline (7a).



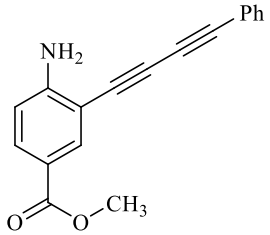
Was obtained from aniline **1b** (1.0 mmol, 0.22 g) and dodeca-1,3-diyn **4a** (3.0 mmol, 0.48 g), purified by column chromatography using EtOAc–hexane system (1:50 → 1:10) and isolated as orange oil in 89% yield (0.17 g). The spectral characteristics of the product match literature data.[5]

2-(4-Phenylbuta-1,3-diyn-1-yl)aniline (7b).



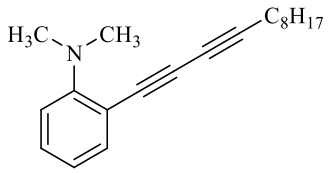
Was obtained from aniline **1b** (7.31 mmol, 1.6 g) and 4-phenylbuta-1,3-diyne **4b** (21.9 mmol, 2.76 g), purified by column chromatography using EtOAc–hexane system (1:30) and isolated as yellowish solid in 73% yield (1.17 g). The spectral characteristics of the product match literature data.[6,7]

Methyl 4-amino-3-(4-phenylbuta-1,3-diyn-1-yl)benzoate (7c).



Was obtained from aniline **1c** (2.0 mmol, 0.55 g) and 4-phenylbuta-1,3-diyne **4b** (5.95 mmol, 0.75 g), purified by column chromatography using EtOAc–hexane system (1:5) and isolated as colourless solid in 52% yield (0.28 g). M.p. = 125–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, 1 H, ^4J = 2.1 Hz, H-Ar), 7.83 (dd, 1 H, ^3J = 8.4 Hz, ^4J = 2.1 Hz, H-Ar), 7.52–7.55 (m, 2 H, 2 × H-Ar), 7.35–7.40 (m, 3 H, 3 × H-Ar), 6.68 (d, 1 H, ^3J = 8.7 Hz, H-Ar), 4.73 (br.s, 2 H, NH_2), 3.86 (s, 3 H, OCH_3).

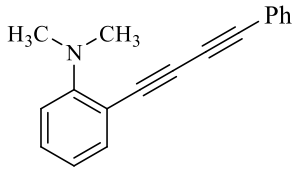
3-(Dodeca-1,3-diyn-1-yl)-*N*,*N*-dimethylaniline (8a).



Was obtained from aniline **7a** (0.78 mmol, 0.2 g), purified by column chromatography using EtOAc–cyclohexane system (1:99) and isolated as orange oil in 69% yield (0.15 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.89 (m, 2 H, H-Ar), 7.20–7.26 (m, 1 H, H-Ar),

7.43 (dd, 1 H, ^{3}J = 7.7 Hz, ^{4}J = 1.5 Hz, H-Ar), 2.94 (s, 6 H, 2 × CH_3), 2.37 (t, 2 H, ^{3}J = 7.0 Hz, CH_2), 1.53–1.60 (m, 2 H, CH_2), 1.28–1.47 (m, 10 H, 5 × CH_2), 0.89 (t, 3 H, ^{3}J = 6.4 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.1 (CH_3), 19.7 (CH_2), 22.6 (CH_2), 28.3 (CH_2), 28.9 (CH_2), 29.06 (CH_2), 29.14 (CH_2), 31.8 (CH_2), 43.5 (2 × CH_3), 65.4 (C≡), 73.9 (C≡), 79.5 (C≡), 85.9 (C≡), 113.7 (C-Ar), 116.8 (CH-Ar), 120.3 (CH-Ar), 129.7 (CH-Ar), 135.4 (CH-Ar), 156.1 (C-Ar). HRMS (EI): calculated for $C_{20}H_{17}N$: 281.2143. Found: 281.2146**.**

***N,N*-Dimethyl-2-(4-phenylbuta-1,3-diyn-1-yl)aniline (8b).**



Was obtained from aniline **7b** (0.37 mmol, 0.08 g), purified by column chromatography using EtOAc–hexane system (1:20) and isolated as yellowish solid in 78% yield (0.07 g). M.p. = 64–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.54 (m, 2 H, 2 × H-Ar), 7.47–7.49 (m, 1 H, H-Ar), 7.32–7.36 (m, 3 H, 3 × H-Ar), 7.25–7.29 (m, 1 H, H-Ar), 6.84–6.91 (m, 2 H, 2 × H-Ar), 2.89 (s, 6 H, 2 × CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 43.6 (2 × CH_3), 74.4 (C≡), 78.9 (C≡), 81.0 (C≡), 82.6 (C≡), 113.1 (C-Ar), 116.8 (CH-Ar), 120.2 (CH-Ar), 122.1 (C-Ar), 128.4 (2 × CH-Ar), 129.0 (CH-Ar), 130.1 (CH-Ar), 132.4 (2 × CH-Ar), 135.4 (CH-Ar), 156.2 (C-Ar). HRMS (EI): calculated for $C_{18}H_{14}N$: 244.1126**.** Found: 244.1125**.**

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