3-Substituted Phthalic Acid Derivatives by Sonogashira Coupling Reaction

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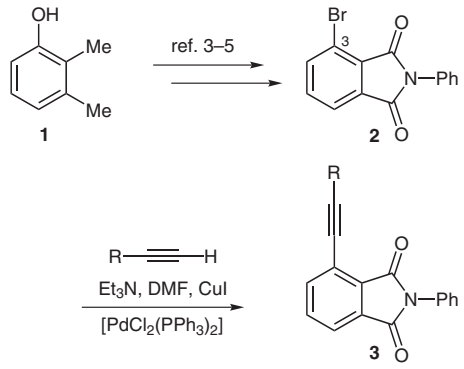
Dedicated to Prof. Dr. Gerhard Erker on the occasion of his 60th birthday

Abstract: Phthalic acid derivatives with carbon substituents in position 3 are easily accessible by Sonogashira coupling reaction of the corresponding bromo derivative. For reasonable conversions the phthaloyl moiety is masked as the *N*-phenylphthalimide, which can smoothly be converted into other phthalic acid derivatives.

Key words: alkynes, palladium, cross-coupling, heterocycles, phthalic acid

Supramolecular affinity molecules with a highly convergent hydrogen bonding pattern, such as triphenylene acetals, represent powerful molecular recognition systems.[1] For the design of more elaborate and well pre-organized hydrogen-bonding donors that would provide suitable solubility in organic solvents, 3-alkyl-substituted phthalic acid derivatives were envisaged as valuable synthetic intermediates. Only a few architectures derived from 4-substituted phthalic acid are well described,[2] while no direct and reliable synthesis for the 3-substituted congeners has been reported.

We have developed a facile and reliable sequence to the desired structures starting from *N*-phenylphthalimide **2** (Scheme 1). This compound is readily prepared from xylenol (**1**) by a known sequence that includes conversion into the bromo derivative at elevated temperatures,[3] permanganate-mediated oxidation to 3-bromophthalic acid,[4] and finally phthaloyl imide formation under standard conditions.[5]



Scheme 1

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Table 1 Palladium-Catalyzed Conversions of **2**

Entry	R	Equiv of alkyne	Product	Yield (%)
1	*n*-Hex	1.5	**3a**	91
2	Bu	1.5	**3b**	92
3	*t*-Bu	1.5 5.0	**3c**	39 88
4	Ph	1.5	**3d**	71
5	Si(*i*-Pr)$_3$	1.5 5.0	**3e**	54 82
6	3-pyridyl	5.0	**3f**	55
7	2-pyridyl	5.0	**3g**	18
8	4-MeOC$_6$H$_4$	1.5	**3h**	98
9	(CH$_2$)$_4$OH	5.0	**3i**	53
10	(CH$_2$)$_2$OH	5.0	**3j**	64
11	(CH$_2$)$_2$OCO-*t*-Bu	5.0	**3k**	90

For the installation of fragments with sp^2 or sp hybridized carbon centers in position 3, palladium-catalyzed cross-coupling reactions were evaluated.[6] Initially, the dibenzyl ester **4** (Figure 1) was regarded as an ideal substrate since simultaneous deprotection and removal of multiple bonds in the side chain should occur by hydrogenolysis. Using Heck-type or Sonogashira coupling reactions, simple alkenyl and alkynyl substituents could be introduced only with prolonged reaction times and in very poor yields. Most probably, the oxidative insertion into the C–Br bond is accompanied by coordination to an oxygen on the adjacent carbonyl group. The formation of a five-membered ring system stabilizes the intramolecular species, thus, almost no turnover is possible. However, masking the phthalic acid as an imide improves the situation tremendously. The formation of two five-membered rings fused to a planar benzene core is not favored and consequently the catalytic reaction proceeds.

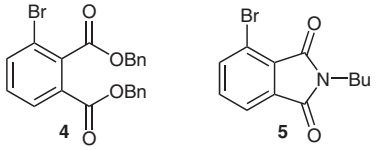
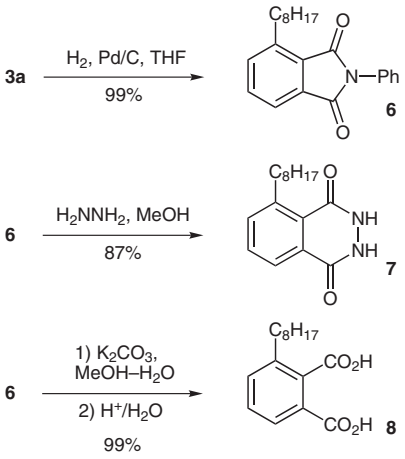


Figure 1 Alternative starting materials to **2** that have been tested

Both imides **2** and **5** work equally well. However, the *N*-phenyl imide is preferred since the subsequent transformations are easier to perform. In an initial screening process, investigation of the common Sonogashira protocols and various palladium/ligand combinations showed that a simple palladium(II) precursor and triphenylphosphine can be used.[7]

Employing simple terminal alkynes with a slight excess of reagent resulted in very good conversions (Table 1, entries 1 and 2), whereas increasing steric demand required a pronounced excess of alkyne (entry 3). When the alkyne component became less electron rich, the conversions were significantly lower. This is exemplified by phenylacetylene as substrate, which gave reduced, but still satisfying, yields (entry 4). Silyl-protected acetylene underwent an even slower transformation, which could be compensated by using an excess of reagent (entry 5). The electronic nature of the acetylenic reaction partner strongly influences the catalysis; 3-ethynylpyridine underwent the transformation in good yields, whereas the much more electron-deficient 2-ethynylpyridine provided a poor 18% yield (entries 6 and 7). Consequently, an extremely electron-rich substrate like 4-ethynylanisole led to superb results (entry 8). This Sonogashira coupling reaction process reached its limits with propiolic acid and derivatives thereof, where only traces of the desired products were detected by GC/MS techniques. The robust nature of the catalytic transformation is shown by the successful conversion of hydroxylated alkynes. But-1-yn-4-ol afforded slightly better yields than the higher homologue hex-1-yn-6-ol probably because it is less prone to intramolecular coordination (entries 9 and 10). However, the yield of the palladium-catalyzed coupling reaction significantly improved when the hydroxy group was protected (entry 11).

Compounds **3** represent valuable synthetic intermediates that offer a variety of chemical transformations (Scheme 2). The triple bond can be smoothly reduced to furnish the corresponding alkyl-substituted derivative, e.g. hydrogenation of **3a** to give **6**. As anticipated, the *N*-phenyl imides exhibit rewarding reactivity. Compound **6** can be transformed into the phthalazine-1,4-dione **7**. Hydrolysis of **7** under mild conditions yields the phthalic acid **8**. A variety of substituted phthalic acid derivatives has successfully been tested as potent analogues of common drugs, e.g. thalidomide.[8]



Scheme 2

In conclusion, phthalic acid derivatives with carbon substituents in position 3 can be prepared by a Sonogashira coupling reaction. The transformation depends on the electronic nature of the acetylenic component. Electron-deficient substituents result in inferior conversion, which can be compensated by using an excess of the acetylenic component.

All reagents used were of analytical grade. Solvents for extractions and column chromatography were of technical quality and were distilled prior to use. Column chromatography was performed on silica gel (particle size 63–200 μm, Merck, Darmstadt, Germany) eluting with mixtures of cyclohexane and EtOAc. TLC was performed on silica gel 60 F_{254} on glass (Merck, Darmstadt, Germany). Melting points were determined on a melting point apparatus SMP3 (Stuart Scientific, Watford Herts, UK) and are uncorrected. Microanalysis was performed using a Vario EL III (Elementar-Analysensysteme, Hanau, Germany). NMR spectra were recorded on a Bruker DPX 300 or DPX 400 (Analytische Messtechnik, Karlsruhe, Germany) using TMS as internal standard or residual $CHCl_3$ with δ = 7.26 for ^{1}H NMR, and δ = 77.0 for ^{13}C NMR spectroscopy. MS spectra were obtained on a MAT95XL (Finnigan, Bremen, Germany) employing EI and performing HRMS.

3-Bromo-*N*-phenylphthalimide (2)[5]

3-Bromophthalic anhydride[4] (9.0 g, 40 mmol) was dissolved in pyridine (20 mL). Aniline (3.7 mL, 40 mmol) was added and the soln was heated to reflux for 4 h. The mixture was poured onto ice (300 mL) and the off-white precipitate was extracted with Et_2O (2 × 200 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by crystallization (MeOH, 50 mL). The product was obtained as fine yellowish crystals; yield: 9.8 g (81%); mp 187 °C (Lit.[5] 185 °C); R_f = 0.54 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.48 (m, 3 H, Ph), 7.52–7.57 (m, 2 H, Ph), 7.76–7.81 (m, 1 H, Phth), 7.94–7.97 (m, 1 H, Phth), 8.04–8.07 (m, 1 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.4 (Phth), 122.6 (Phth), 127.3 (Ph), 128.1 (Ph), 128.7 (Ph), 128.9 (Phth), 131.6 (Phth), 134.0 (Ph), 135.8 (Phth), 138.8 (Phth), 164.9 (CO), 165.4 (CO).

MS (EI): *m*/*z* (%) = 301/303 (16) $[M]^+$, 257/259 (35), 223 (10) $[M - Br]^+$.

Anal. Calcd for $C_{14}H_8BrNO_2$: C, 55.66; H, 2.67; N, 4.64. Found: C, 55.77; H, 2.74; N, 4.64.

Sonogashira Coupling Reactions; General Procedure[7a]

Under inert and anhyd conditions a 10-mL Schlenk vessel was charged with 3-bromo-*N*-phenylphthalimide (**2**, 302 mg, 1.0 mmol). The starting material was dissolved in a mixture of Et_3N–DMF (1:1, 4 mL). The corresponding acetylene derivative (1.5 mmol or 5.0 mmol), CuI (2.0 mg, 1 mol%), and $PdCl_2(PPh_3)_2$ (21 mg, 3 mol%) were then added to the soln, which was stirred at 80 °C for 16 h. The mixture was fractioned between aq 10-wt% citric acid soln (20 mL) and EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4) and the solvent was evaporated. The products were purified by column chromatography or crystallization.

3-(Oct-1-ynyl)-*N*-phenylphthalimide (3a)
Phthalimide **3a** was prepared according to the general procedure using oct-1-yne (0.22 mL, 1.5 mmol). The crude product was purified by crystallization (MeOH, 5 mL). The product was obtained as colorless crystals; yield: 302 mg (91%); mp 225 °C; R_f = 0.50 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7.0 Hz, 3 H, CH_3), 1.30–1.34 (m, 4 H, alkyl), 1.45–1.52 (m, 2 H, alkyl), 1.64–1.71 (m, 2 H, C≡CCH_2CH_2), 3.14 (t, J = 7.2 Hz, 2 H, C≡CCH_2), 7.38–7.52 (m, 5 H, Ph), 7.66–7.74 (m, 2 H, Phth), 7.83–7.85 (m, 1 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 18.8 (CH_2), 21.8 (CH_2), 27.6 (CH_2), 27.7 (CH_2), 30.6 (CH_2), 76.2 (C≡C), 98.5 (C≡C), 119.9 (Phth), 122.3 (Phth), 127.3 (Ph), 127.9 (Ph), 128.6 (Ph), 130.3 (Phth), 131.7 (Phth), 132.2 (Ph), 134.2 (Phth), 137.9 (Phth), 165.4 (CO), 165.0 (CO).

MS (EI): *m*/*z* (%) = 331 (16) $[M]^+$, 302 (4) $[M - C_2H_5]^+$, 274 (20) $[M - C_4H_9]^+$, 261 (100) $[M - C_5H_{10}]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{21}NO_2$: 331.1572; found: 331.1572.

3-(Hex-1-ynyl)-*N*-phenylphthalimide (3b)
Phthalimide **3b** was prepared according to the general procedure using hex-1-yne (0.17 mL, 1.5 mmol). The crude product was purified by crystallization (MeOH, 5 mL). The product was obtained as off-white crystals; yield: 279 mg (92%); mp 105 °C; R_f = 0.63 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.4 Hz, 3 H, CH_3), 1.47–1.56 (m, 2 H, alkyl), 1.63–1.70 (m, 2 H, alkyl), 2.53 (t, J = 7.2 Hz, 2 H, C≡CCH_2), 7.37–7.52 (m, 5 H, Ph), 7.65–7.73 (m, 2 H, Phth), 7.82–7.84 (m, 1 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (CH_3), 19.5 (CH_2), 22.0 (CH_2), 30.4 (CH_2), 76.0 (C≡C), 99.7 (C≡C), 121.7 (Phth), 122.4 (Phth), 126.6 (Ph), 128.0 (Ph), 129.0 (Ph), 130.5 (Phth), 131.6 (Phth), 132.3 (Ph), 133.7 (Phth), 138.4 (Phth), 166.0 (CO), 166.5 (CO).

MS (EI): *m*/*z* (%) = 303 (12) $[M]^+$, 288 (4) $[M - CH_3]^+$, 274 (16) $[M - C_2H_5]^+$, 261 (100) $[M - C_3H_6]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{17}NO_2$: 303.1259; found: 303.1268.

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62. Found: C, 78.78; H, 5.72; N, 4.59.

3-(3,3-Dimethylbut-1-ynyl)-*N*-phenylphthalimide (3c)
Phthalimide **3c** was prepared according to the general procedure using 3,3-dimethylbutyne (0.62 mL, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 9:1). The product was obtained as colorless crystals; yield: 267 mg (88%); mp 180 °C; R_f = 0.75 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *t*-Bu), 7.37–7.52 (m, 5 H, Ph), 7.65–7.73 (m, 2 H, Phth), 7.82–7.84 (m, 1 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [$C(CH_3)_3$], 30.6 (CH_3), 76.0 (C≡C), 107.3 (C≡C), 121.8 (Phth), 122.3 (Phth), 126.8 (Ph), 128.1 (Ph), 129.1 (Ph), 130.6 (Phth), 131.6 (Phth), 132.3 (Ph), 133.6 (Phth), 138.2 (Phth), 166.0 (CO), 166.6 (CO).

MS (EI): *m*/*z* (%) = 303 (88) $[M]^+$, 288 (100) $[M - CH_3]^+$, 211 (16) $[M - CH_3 - Ph]^+$, 169 (44) $[M - C_4H_9 - Ph]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{17}NO_2$: 303.1259; found: 303.1260.

***N*-Phenyl-3-(phenylethynyl)phthalimide (3d)**
Phthalimide **3d** was prepared according to the general procedure using phenylacetylene (0.16 mL, 1.5 mmol). The crude product was purified by crystallization (MeOH, 5 mL). The product was obtained as colorless crystals; yield: 230 mg (71%); mp 185 °C; R_f = 0.57 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.54 (m, 8 H, Ph), 7.66–7.68 (m, 2 H, PhH), 7.72–7.76 (m, 1 H, Phth), 7.84–7.90 (m, 2 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.6 (C≡C), 97.3 (C≡C), 120.8 (Phth), 122.2 (Ph), 122.9 (Phth), 126.6 (Ph), 128.1 (Ph), 128.4 (Ph), 129.1 (Ph), 129.3 (Ph), 130.6 (Phth), 131.6 (Phth), 132.1 (Ph), 132.4 (Ph), 133.8 (Phth), 137.8 (Phth), 165.9 (CO), 166.4 (CO).

MS (EI): *m*/*z* (%) = 323 (100) $[M]^+$, 295 (50), $[M - CO]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{13}NO_2$: 323.0946; found: 323.0945.

***N*-Phenyl-3-[(triisopropylsilyl)ethynyl]phthalimide (3e)**
Phthalimide **3e** was prepared according to the general procedure using ethynyltriisopropylsilane (1.12 mL, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 9:1). The product was obtained as off-white crystals; yield: 332 mg (82%); mp 98 °C; R_f = 0.77 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17–1.18 (m, 21 H, *i*-Pr), 7.37–7.53 (m, 5 H, Ph), 7.67–7.72 (m, 1 H, Phth), 7.81–7.90 (m, 2 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3 [$CH(CH_3)_2$], 18.6 (CH_3), 100.8 (C≡C), 101.1 (C≡C), 120.7 (Phth), 123.0 (Phth), 126.7 (Ph), 128.1 (Ph), 129.1 (Ph), 131.0 (Phth), 131.6 (Phth), 132.4 (Ph), 133.6 (Phth), 139.1 (Phth), 165.3 (CO), 166.5 (CO).

MS (EI): *m*/*z* (%) = 403 (8) $[M]^+$, 388 (8) $[M - CH_3]^+$, 360 (100) $[M - C_3H_7]^+$.

HRMS (EI): *m*/*z* $[M - C_3H_7]^+$ calcd for $C_{22}H_{22}NO_2Si$: 360.1420; found: 360.1424.

Anal. Calcd for $C_{25}H_{29}NO_2Si$: C, 74.40; H, 7.24; N, 3.47. Found: C, 74.09; H, 7.16; N, 3.46.

***N*-Phenyl-3-(3-pyridylethynyl)phthalimide (3f)**
Phthalimide **3f** was prepared according to the general procedure using 3-ethynylpyridine (0.51 mL, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 3:1). The product was obtained as yellowish crystals; yield: 178 mg (55%); mp 187 °C; R_f = 0.26 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.25 (m, 1 H, Py), 7.31–7.47 (m, 5 H, Ph), 7.67–7.72 (m, 1 H, Phth), 7.78–7.81 (m, 1 H, Phth), 7.84–7.87 (m, 1 H, Phth), 7.85–7.89 (m, 1 H, Py), 8.51–8.53 (m, 1 H, Py), 8.78–8.79 (m, 1 H, Py).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 87.5 (C≡C), 93.5 (C≡C), 119.5 (Py), 119.9 (Phth), 123.1 (Py), 123.5 (Phth), 126.6 (Ph), 128.2 (Ph), 129.1 (Ph), 130.9 (Phth), 131.4 (Phth), 132.5 (Ph), 134.0 (Phth), 137.8 (Phth), 139.1 (Py), 149.5 (Py), 152.5 (Py), 165.8 (CO), 166.6 (CO).

MS (EI): *m*/*z* (%) = 324 (100) $[M]^+$, 296 (28) $[M - CO]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{12}N_2O_2$: 324.0899; found: 324.0895.

***N*-Phenyl-3-(2-pyridylethynyl)phthalimide (3g)**
Phthalimide **3g** was prepared according to the general procedure using 2-ethynylpyridine (0.51 mL, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 3:2). The product was obtained as yellowish crystals; yield: 58 mg (18%); mp 144 °C; R_f = 0.21 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.24 (m, 2 H, Ph), 7.38–7.39 (m, 1 H, Py), 7.43–7.52 (m, 3 H, Ph), 7.65–7.70 (m, 2 H, Py), 7.72–7.76 (m, 1 H, Phth), 7.90–7.92 (m, 1 H, Phth), 8.59 (m, 1 H, Phth), 8.62 (m, 1 H, Py).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.1 (C≡C), 80.8 (C≡C), 119.6 (Phth), 123.7 (Phth), 126.6 (Ph), 128.1 (Py), 128.3 (Ph), 129.1 (Ph), 131.4 (Phth), 132.4 (Phth), 134.0 (Phth), 136.2 (Py), 136.3 (Ph), 138.2 (Phth), 141.8 (Py), 142.4 (Py), 150.3 (Py), 165.7 (CO), 166.2 (CO).

MS (EI): *m*/*z* (%) = 324 (100) $[M]^+$, 296 (28) $[M - CO]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{12}N_2O_2$: 324.0899; found: 324.0899.

3-[(4-Methoxyphenyl)ethynyl]-*N*-phenylphthalimide (3h)

Phthalimide **3h** was prepared according to the general procedure using 4-ethynylanisole (0.19 mL, 1.5 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 3:1). The product was obtained as yellow crystals; yield: 347 mg (98%); mp 134 °C; R_f = 0.39 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, CH_3), 6.89 (d, *J* = 8.8 Hz, 2 H, anisyl), 7.39–7.54 (m, 5 H, Ph), 7.61 (d, *J* = 8.8 Hz, 2 H, anisyl), 7.70–7.74 (m, 1 H, Phth), 7.81–7.88 (m, 2 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (CH_3), 83.7 (C≡C), 97.8 (C≡C), 114.1 (anisyl), 114.3 (anisyl), 121.3 (Phth), 122.5 (Phth), 126.7 (Ph), 128.1 (Ph), 129.1 (Ph), 130.3 (Phth), 131.6 (Phth), 132.4 (Phth), 133.8 (Ph and anisyl), 137.6 (Phth), 160.5 (anisyl), 166.1 (CO), 166.5 (CO).

MS (EI): *m*/*z* (%) = 353 (100) $[M]^+$, 310 (20) $[M - CH_3 - CO]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{15}NO_3$: 353.1052; found: 353.1049.

3-(6-Hydroxyhex-1-ynyl)-*N*-phenylphthalimide (3i)

Phthalimide **3i** was prepared according to the general procedure using hex-5-yn-1-ol (0.55 mL, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 3:2). The product was obtained as colorless crystals; yield: 169 mg (53%); mp 142 °C; R_f = 0.14 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73–1.84 (m, 4 H, alkyl), 2.57 (t, *J* = 6.6 Hz, 2 H, CH_2OH), 3.69 (t, *J* = 6.0 Hz, 2 H, C≡CCH_2), 7.36–7.52 (m, 5 H, Ph), 7.64–7.73 (m, 2 H, Phth), 7.82–7.84 (m, 1 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_2), 24.5 (CH_2), 31.7 (CH_2), 62.2 (CH_2OH), 76.4 (C≡C), 99.1 (C≡C), 121.5 (Phth), 122.5 (Phth), 126.6 (Ph), 128.1 (Ph), 129.0 (Ph), 130.6 (Phth), 131.5 (Phth), 132.2 (Ph), 133.8 (Phth), 138.3 (Phth), 166.1 (CO), 166.4 (CO).

MS (EI): *m*/*z* (%) = 319 (44) $[M]^+$, 274 (100) $[M - C_2H_4OH]^+$, 261 (40) $[M - C_3H_6O]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{17}NO_3$: 319.1208; found: 319.1212.

3-(4-Hydroxybut-1-ynyl)-*N*-phenylphthalimide (3j)

Phthalimide **3j** was prepared according to the general procedure using but-3-yn-1-ol (0.38 mL, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 3:2). The product was obtained as colorless crystals; yield: 186 mg (64%); mp 160 °C; R_f = 0.19 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.73 (t, *J* = 5.7 Hz, 2 H, CH_2OH), 3.87 (t, *J* = 5.7 Hz, 2 H, C≡CCH_2), 7.40–7.52 (m, 5 H, Ph), 7.69–7.71 (m, 2 H, Phth), 7.83–7.88 (m, 1 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.4 (CH_2), 60.7 (CH_2OH), 78.2 (C≡C), 99.7 (C≡C), 121.0 (Phth), 122.8 (Phth), 126.6 (Ph), 128.2 (Ph), 129.0 (Ph), 131.0 (Phth), 131.3 (Phth), 132.1 (Ph), 134.0 (Phth), 137.2 (Phth), 166.3 (CO), 166.7 (CO).

MS (EI): *m*/*z* (%) = 291 (16) $[M]^+$, 260 (100) $[M - CH_2OH]$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{13}NO_3$: 291.0895; found: 291.0890.

***N*-Phenyl-3-[4-(pivaloyloxy)but-1-ynyl]phthalimide (3k)**

Phthalimide **3k** was prepared according to the general procedure using but-3-ynyl 2,2-dimethylpropanoate[9] (771 mg, 5.0 mmol). The crude product was purified by column chromatography (cyclohexane–EtOAc, 4:1). The product was obtained as a glassy solid; yield: 338 mg (90%); R_f = 0.40 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (s, 9 H, *t*-Bu), 2.85 (t, *J* = 6.9 Hz, 2 H, CH_2O), 4.33 (t, *J* = 6.9 Hz, 2 H, C≡CCH_2), 7.36–7.51 (m, 5 H, Ph), 7.64–7.71 (m, 2 H, Phth), 7.83–7.86 (m, 1 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (CH_2), 27.1 (CH_3), 38.7 [$C(CH_3)_3$], 61.7 (CH_2O), 77.1 (C≡C), 94.5 (C≡C), 120.8 (Phth), 122.7 (Phth), 126.5 (Ph), 128.0 (Ph), 129.0 (Ph), 130.7 (Phth), 131.5 (Phth), 132.3 (Ph), 133.7 (Phth), 138.2 (Phth), 165.7 (CO), 166.3 (CO), 178.1 (Pv).

MS (EI): *m*/*z* (%) = 375 (2) $[M]^+$, 273 (100) $[M - C_5H_{10}O_2]^+$, 245 (10) $[M - C_7H_{14}O_2]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{23}H_{21}NO_4$: 375.1471; found: 375.1473.

3-Octyl-*N*-phenylphthalimide (6)

3-(Oct-1-ynyl)-*N*-phenylphthalimide (**3a**, 6.66 g, 20.0 mmol) was dissolved in THF (50 mL). 10% Pd/C (212 mg, 50% moisture) was added and the suspension was stirred under a H_2 atmosphere for 3 d. The catalyst was removed by filtration through a pad of Celite, which was thoroughly washed with CH_2Cl_2. The solvents were evaporated. The product was dried under high vacuum and obtained as colorless crystals; yield: 6.64 g (99%); mp 59 °C; R_f = 0.74 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 3 H, CH_3), 1.27–1.45 (m, 10 H, alkyl), 1.64–1.74 (m, 2 H, alkyl), 3.14 (t, *J* = 7.8 Hz, 2 H, ArCH_2), 7.37–7.51 (m, 5 H, Ph), 7.54–7.56 (m, 1 H, Phth), 7.63–7.68 (m, 1 H, Phth), 7.78–7.80 (m, 1 H, Phth).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 31.0 (CH_2), 31.5 (CH_2), 31.8 (CH_2), 121.4 (Phth), 126.6 (Ph), 127.9 (Ph), 129.0 (Ph), 131.7 (Phth), 132.4 (Ph), 133.9 (Phth), 135.9 (Phth), 143.8 (2 × Phth), 167.3 (CO), 167.8 (CO).

MS (EI): *m*/*z* (%) = 335 (100) $[M]^+$, 264 (20) $[M - C_5H_{11}]^+$, 250 (90) $[M - C_6H_{13}]^+$, 237 (64) $[M - C_7H_{14}]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{25}NO_2$: 335.1885; found: 335.1886.

Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.66; H, 7.18; N, 4.17.

5-Octyl-2,3-dihydrophthalazine-1,4-dione (7)

3-Octyl-*N*-phenylphthalimide (**6**, 6.64 g, 19.8 mmol) was dissolved in MeOH (50 mL). Aq hydrazine hydrate soln (80 wt%, 1.44 mL, 29.7 mmol) was added and the soln was heated to reflux for 16 h. The volatile components were removed and the remaining mixture was fractioned between aq 10-wt% citric acid soln (200 mL) and CH_2Cl_2 (200 mL). The organic layer was washed with brine (50 mL) and dried ($CaCl_2$) and the solvent was evaporated. The crude product was purified by crystallization (MeOH, 50 mL). The product was obtained as colorless crystals; yield: 4.72 g (87%); mp 98 °C; R_f = 0.39 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.25–1.42 (m, 10 H, alkyl), 1.59–1.69 (m, 2 H, alkyl), 3.06 (t, *J* = 7.6 Hz, 2 H, ArCH_2), 4.13 (s, 2 H, NH), 7.46–7.48 (m, 1 H, Phth), 7.55–7.60 (m, 1 H, Phth), 7.65–7.70 (m, 1 H, Phth).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 30.9 (CH_2), 31.3 (CH_2), 31.8 (CH_2), 121.1 (Phth), 126.5 (Phth), 130.8 (Phth), 133.7 (Phth), 135.6 (Phth), 143.4 (Phth), 166.5 (CO), 167.3 (CO).

MS (EI): *m*/*z* (%) = 274 (100) $[M]^+$, 258 (40) $[M - O]^+$, 243 (50) $[M - NCO]^+$, 189 (60) $[M - C_6H_{13}]^+$, 161 (44) $[M - C_8H_{17}]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{22}N_2O_2$: 274.1681; found: 274.1682.

3-Octylphthalic Acid (8)

3-Octyl-*N*-phenylphthalimide (**6**, 337 mg, 1.0 mmol) was dissolved in MeOH (5 mL). K_2CO_3 (691 mg, 5.0 mmol) and H_2O (0.5 mL) were added and the suspension was stirred at 50 °C for 2 d. The solvent was evaporated and H_2O (20 mL) was added to the mixture, which was subsequently cooled in an ice bath while it was adjusted to pH 1 using concd HCl. The aqueous soln was extracted with EtOAc (2 × 20 mL). The combined organic fractions were washed with brine and dried (Na_2SO_4) and the solvent was evaporated. The product was obtained as colorless crystals; yield: 276 mg (99%); mp 101 °C; R_f = 0.0 (cyclohexane–EtOAc, 3:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.73–0.81 (m, 3 H, CH_3), 1.08–1.17 (m, 12 H, alkyl), 2.43–2.44 (m, 2 H, Ar-CH_2), 7.30–7.42 (m, 2 H, Phth), 7.64–7.68 (m, 1 H, Phth).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.1 (CH_3), 22.2 (CH_2), 27.2 (CH_2), 28.7 (CH_2), 31.2 (CH_2), 31.4 (CH_2), 32.7 (CH_2), 35.6 (CH_2), 128.7 (Phth), 130.0 (Phth), 133.3 (Phth), 136.2 (Phth), 139.3 (Phth), 144.2 (Phth), 167.3 (CO), 170.0 (CO).

MS (EI): *m*/*z* (%) = 278 (100) $[M]^+$, 260 (49) $[M - H_2O]^+$, 161 (44) $[M - C_8H_{17}]^+$.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.22; H, 7.84.

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