



Copper-Free Sonogashira coupling in water with an amphiphilic resin-supported palladium complex

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ABSTRACT

The palladium-catalyzed coupling reaction of aryl halides with terminal alkynes, the Sonogashira coupling, took place in water under copper-free conditions by use of an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported palladium-phosphine complex to give the corresponding aryl-substituted alkynes in high yields. The PS-PEG resin-supported palladium catalyst was recovered by simple filtration and reused four times without any loss of catalytic activity.

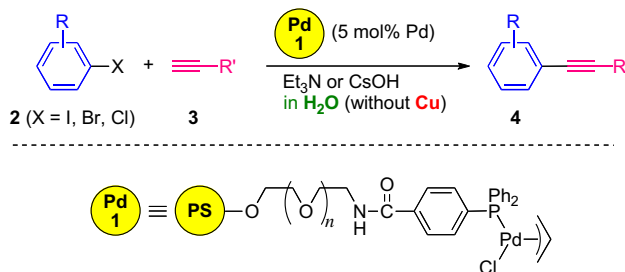
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1. Introduction

The palladium-catalyzed coupling of an aryl halide with a terminal alkyne, the Sonogashira coupling,¹ is recognized as the most successful method for forming an *sp-sp*² carbon–carbon bond. Since its discovery by Sonogashira and co-workers in 1975, considerable research has been devoted to the synthetic application of the reaction as well as to improving its efficiency.² One of the major problems associated with it lies in the reaction conditions where the use of both a palladium catalyst and a copper reagent (co-catalyst) is frequently required to promote the reaction, resulting in contamination of the coupling products with metal residue. In addition, it has been well-documented that the Sonogashira coupling often suffers from the Glaser-type oxidative dimerization of the alkyne substrate³ as a side reaction in the presence of a Cu(I) co-catalyst. Recently, quite a few reports addressing these problems have appeared, in which the coupling is carried out with an immobilized palladium catalyst and/or under copper-free conditions.^{4,5}

However, given the increasing concern about green and safe chemical processes, it is not surprising that the development of water-based organic transformations has become a burgeoning area of research.^{6,7} If the Sonogashira coupling were performed in water with an immobilized catalyst under copper-free conditions,⁸ the reaction system would represent a clean, green, and safe application of the coupling in what may be considered an ideal chemical process.

We have recently developed amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG)⁹ resin-supported transition metal catalysts, which promote various catalytic transformations,¹⁰ including the palladium-catalyzed π -allylic substitution, cross-coupling reaction, and the Heck reaction, smoothly in water under heterogeneous conditions.¹¹ Our continuing interest in the catalytic utility of PS-PEG resin-supported palladium complexes led us to examine the Sonogashira coupling in water with the PS-PEG-Pd complex under copper-free conditions.¹² We report herein our results demonstrating that the Sonogashira coupling of various aryl halides with terminal acetylenes proceeds in water in the presence of a palladium complex of an amphiphilic PS-PEG resin-bound triarylphosphine ligand under copper-free conditions (Scheme 1).



Scheme 1. Sonogashira coupling in water.

2. Results and discussion

2.1. Coupling conditions

Upon screening reaction conditions for the copper-free Sonogashira coupling in water with the polymeric palladium **1**, we

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found that the reaction efficiency was greatly enhanced by the base employed. Thus, the coupling of iodobenzene (**2a**) and phenylacetylene (**3a**) was carried out in water with the polymeric catalyst **1** (5 mol % to Pd) at 40 °C for 6 h in the presence of 3 equiv of base. The reaction mixture was filtered and the recovered resin beads were rinsed with a small portion of water and extracted with EtOAc to give diphenylacetylene (**4a**). The most effective base proved to be triethylamine as seen in the representative results summarized in Table 1. The coupling with sodium bicarbonate, sodium carbonate, potassium carbonate, and cesium carbonate gave **4a** in <2%, 12%, 12%, and 7% yield, respectively (entries 1–4). The coupling reaction in aqueous potassium hydroxide afforded **4a** in 26% yield (entry 5). Of inorganic bases examined, cesium hydroxide was identified to be an effective base to promote the Sonogashira coupling, which improved the coupling performance to afford diphenylacetylene (**4a**) in 58% yield under otherwise the identical conditions (entry 6). Organic amines were found to promote the Sonogashira coupling smoothly in water. Thus, the reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a 63% yield of **4a** under similar conditions (entry 7). When triethylamine was used, the chemical yield of **4a** increased significantly, resulting in the quantitative formation of the coupling product **4a** (entry 8).

2.2. Substrate tolerance

The heterogeneous aquacatalytic copper-free Sonogashira coupling was examined with a variety of haloarenes under the reaction conditions identified above and exhibited wide substrate tolerance. Representative results are summarized in Table 2. The coupling of iodobenzene (**2a**) with phenylacetylene took place smoothly in water at 40 °C in the presence of 3 equiv of Et₃N and 5 mol % palladium of the PS-PEG resin-supported π -allylpalladium-triaryl-phosphine complex **1** to give a quantitative yield of diphenylacetylene (**4a**) (Table 2, entry 1). The Sonogashira coupling of *p*-methoxyiodobenzene (**2b**) and *p*-methyliodobenzene (**2c**) bearing electron donating groups at their *para*-positions gave the corresponding biarylacetylenes **4b** and **4c** in 62% and 92% yield, respectively (Table 2, entries 2 and 3). *p*-(Trifluoromethyl)iodobenzene (**2d**), *p*-acetoxyiodobenzene (**2e**), and *p*-(methoxy-carbonyl)iodobenzene (**2f**) having electron deficient aromatic rings also underwent the Sonogashira coupling with phenylacetylene under similar conditions to afford the

corresponding biarylacetylenes **4d**, **4e**, and **4f** in 100%, 81%, and 85% yield, respectively (Table 2, entries 4, 5, and 6). The coupling of *meta*- and *ortho*-substituted iodobenzenes **2g–j** having *meta*-methyl, *meta*-chloro, *ortho*-methyl, and *ortho*-chloro groups, took place with phenylacetylene to give the corresponding products **4g–j** in 90%, 91%, 83%, and 87% yield, respectively (entries 7–10). Coupling of 1-iodonaphthalene (**2k**) and **3a** under the aqueous copper-free conditions gave naphthylphenylacetylene **4k** in 73% yield (entry 11). The coupling reactions of the bromoarenes **2n–q** with **3a** were carried out at a higher reaction temperature (refluxing water) to give the corresponding biarylacetylenes in 69–87% isolated yield (entries 13–15), although the electron-rich bromoarene **2m** showed lower reactivity under similar conditions. It should be noted that the coupling reactions of the chloroarenes **2r** and **2s** also took place in water under similar copper-free conditions (entries 16 and 17), though the reactivity was much lower than their iodo and bromo counterparts, **2e**, **2f**, and **2p**.

Cesium hydroxide was found to promote the Sonogashira coupling of terminal acetylenes bearing aliphatic carboxylic acid groups more efficiently than triethylamine, though the optimal base-substrate combination is not well-rationalized. Thus, the coupling of iodobenzene (**2a**) with 6-heptynoic acid (**3b**) with the polymeric catalyst **1** in water was complete within 6 h at 60 °C by using CsOH to give an 83% isolated yield of 6-phenyl-6-heptynoic acid (**4m**), while the coupling product **4m** was obtained in 35% yield with triethylamine (entry 18 vs entry 19). The reactivity of alkyne carboxylic acids decreased as their hydrophobicity decreased. Thus, pentynoic acid (**3c**) and propiolic acid (**3d**) reacted with **2a** under similar conditions to give **4n** and **4p** in 68% and 58% yield, respectively (entries 20 and 21).

2.3. Recycling experiments

The recyclability of the PS-PEG resin-supported Pd catalyst **1** was examined for the Sonogashira coupling of iodobenzene (**2a**) and phenylacetylene (**3a**). Thus, after the first reaction, which gave a quantitative yield of the coupling product **4a** (Table 2, entry 1), the catalyst beads were recovered and successively subjected to a second through a fifth run of the coupling under the same conditions to afford **4a** in 92%, 81%, 92%, and 87% yield, respectively, (Scheme 2) during which hardly any palladium residue could be detected by ICP-AES analysis from the aqueous or organic filtrates.

3. Conclusion

In conclusion, we have developed a clean, green, and safe protocol for the Sonogashira coupling of aryl iodides and bromides with terminal acetylenes using a PS-PEG resin-supported palladium catalyst to give various biarylacetylene derivatives. This catalyst was recovered and reused four times without any loss of catalytic activity.

4. Experimental section

4.1. General methods

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P₂O₅. Water was deionized with a Millipore system as Milli-Q grade. NMR spectra were recorded on a JEOL JNM-LA 500 spectrometer (500 MHz for ¹H and 125 MHz for ¹³C). ¹H and ¹³C NMR spectra were recorded in CDCl₃ at 25 °C. Chemical shifts were reported in ppm referenced to an internal tetramethylsilane standard for ¹H NMR. Chemical shifts

Table 1
Effect of Base on the Sonogashira coupling of Iodobenzene with Phenylacetylene using Polymeric Catalyst **1** in water^a

Entry	Bases	Yield of 4a
1	Na ₂ CO ₃	<2%
2	Na ₂ CO ₃	12%
3	K ₂ CO ₃	12%
4	Cs ₂ CO ₃	7%
5 ^b	KOH	26%
6 ^b	CsOH	58%
7	DBU	63%
8	Et ₃ N	99%

^a All reactions were carried out with iodobenzene (**2a**, 0.4 mmol), phenylacetylene (**3a**, 0.8 mmol), base (1.2 mmol) in the presence of PS-PEG resin-supported palladium–phosphine complex **1** (5 mol % Pd) in 3.0 mL of H₂O at 40 °C for 6 h under nitrogen, unless otherwise noted.

^b Reaction for 12 h.

Table 2
Sonogashira coupling of aryl halides and 1-alkynes with triethylamine and polymeric catalyst **1** in water^a

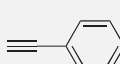
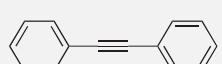
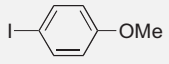
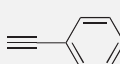
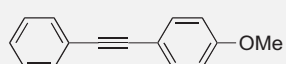
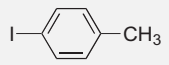
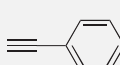
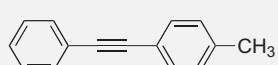
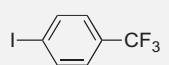
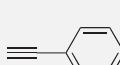
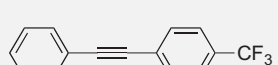
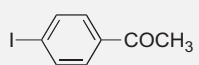
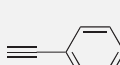
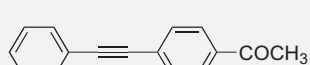
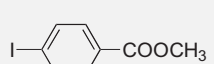
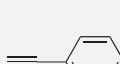
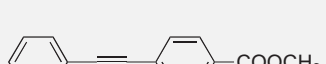
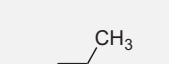
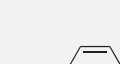
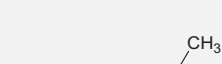
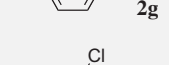
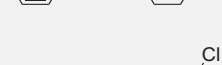
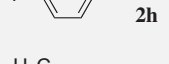
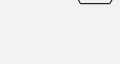
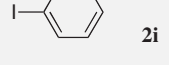
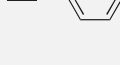
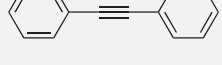
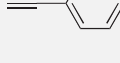
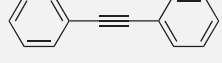
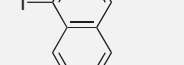
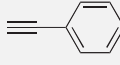
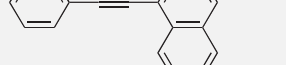
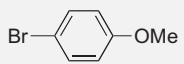
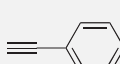
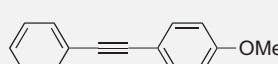
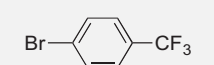
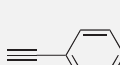
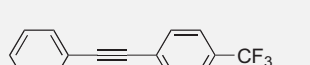
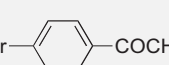
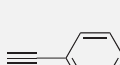
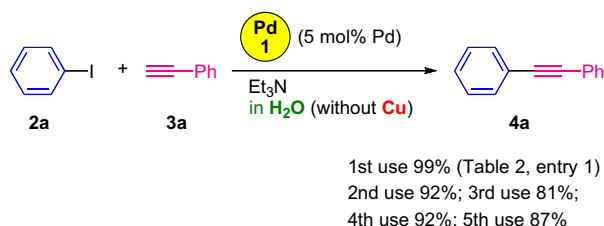
Entry	Aryl halide (2)	1-alkyne (3)	Temp (°C)	Time (h)	Product (4)	Yield (%)
1	 2a	 3a	40	6	 4a	99
2	 2b	 3a	40	6	 4b	62
3	 2c	 3a	40	6	 4c	99
4	 2d	 3a	40	6	 4d	99
5	 2e	 3a	40	6	 4e	81
6	 2f	 3a	40	6	 4f	85
7	 2g	 3a	40	6	 4g	90
8	 2h	 3a	40	6	 4h	91
9	 2i	 3a	40	6	 4i	83
10	 2j	 3a	40	6	 4j	87
11	 2k	 3a	40	6	 4k	73
12	 2m	 3a	100	24	 4b	25
13	 2n	 3a	100	24	 4d	87
14	 2p	 3a	100	24	 4e	81
15	 2q	 3a	100	24	 4k	69

Table 2 (continued)

Entry	Aryl halide (2)	1-alkyne (3)	Temp (°C)	Time (h)	Product (4)	Yield (%)
16			100	24		22
17			100	24		13
18 ^b			60	12		83
19			60	12		35
20 ^b			60	12		68
21 ^b			60	12		58

^a All reactions were carried out with Ar-X (2; 0.4 mmol), acetylene (3; 0.8 mmol), and triethylamine (1.2 mmol) in the presence of the polystyrene-poly(ethylene glycol)-supported palladium-phosphine complex **1** in 3.0 mL of H₂O at 40–100 °C for 6–24 h under nitrogen.

^b CsOH was used instead of Et₃N.



Scheme 2. Recycling experiments.

of ¹³C NMR were given relative to CDCl₃ as an internal standard (δ 77.0 ppm). Mass spectral data were measured on an Agilent 6890 GC/5973 N MS detector (GC–MS); the abbreviation ‘bp’ is used to denote the base peak. IR analysis was performed on a JASCO FTIR-460.

4.2. Materials

PS–PEG-supported catalyst **1** was prepared from PS–PEG amino-resin (Tenta Gel S NH₂, average diameter 90 μm, 1% divinylbenzene cross-linked, average graft length=68 units, loading value of amino residue 0.31 mmol/g; purchased from RAPP POLYMER) according to the reported procedure.^{10b}

4.3. Palladium-catalyzed Sonogashira coupling with phenylacetylene; typical procedure

To a mixture of the polymeric catalyst **1** (64 mg, 0.020 mmol) and iodobenzene (**2a**; 81.6 mg, 0.40 mmol) in H₂O (3.0 mL) was added phenylacetylene (**3a**; 81.7 mg, 0.80 mmol) and triethylamine (121 mg, 1.20 mmol). The reaction mixture was shaken at 40 °C for 6 h and filtered. The recovered resin beads were rinsed with H₂O and extracted three times with EtOAc (6 mL). The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (5 mL).

The combined EtOAc extracts were washed with brine (2 mL), dried over MgSO₄, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (hexane–EtOAc, 100:1) to give 95.0 mg (quantitative yield) of diphenylacetylene **4a**.

4.4. Spectral and analytical data for the arylacetylenes **4**

4.4.1. Diphenylacetylene (**4a**). ¹H NMR (CDCl₃) δ 7.55–7.51 (m, 4H), 7.36–7.29 (m, 6H); ¹³C NMR (CDCl₃) δ 131.5, 128.3, 128.2, 123.2, 89.4. MS (EI): *m/z* (rel%) 178 (bp, M⁺), 152 (24). IR (ATR): (cm^{−1}) ν 3062, 1598, 1491. CAS registry number: 64666-02-0.

4.4.2. 1-(*p*-Methoxyphenyl)-2-phenylacetylene (**4b**). ¹H NMR (CDCl₃) δ 7.55–7.46 (m, 4H), 7.35–7.29 (m, 3H), 6.88 (d, *J*=8.1 Hz, 2H), 3.83 (s, 3H); ¹³C NMR (CDCl₃) δ 159.6, 133.0, 131.4, 128.3, 127.9, 123.5, 115.3, 113.9, 89.3, 88.0, 55.3. MS (EI): *m/z* (rel%) 208 (bp, M⁺), 165 (76), 139 (27). IR (ATR): (cm^{−1}) ν 3010, 2214, 1604, 1592, 1508, 1458, 1246. CAS registry number: 7380-78-1.

4.4.3. 1-Phenyl-2-(*p*-tolyl)acetylene (**4c**). ¹H NMR (CDCl₃) δ 7.52 (dd, *J*=8.1, 1.9 Hz, 2H), 7.43 (d, *J*=8.1 Hz, 2H), 7.38–7.30 (m, 3H), 7.15 (d, *J*=7.8, 2H), 2.36 (s, 3H); ¹³C NMR (CDCl₃) δ 138.3, 134.8, 131.5, 131.4, 129.1, 128.3, 128.0, 127.7, 120.1, 89.5, 21.5. MS (EI): *m/z* (rel%) 192 (bp, M⁺), 165 (27), 39 (21). IR (ATR): (cm^{−1}) ν 3052, 3029, 2215, 1594, 1509, 1441, 1380. CAS registry number: 185817-85-0.

4.4.4. 1-Phenyl-2-(*p*-trifluoromethylphenyl)acetylene (**4d**). ¹H NMR (CDCl₃) δ 7.62 (dd, *J*=14.1, 8.2 Hz, 4H), 7.56–7.54 (m, 2H), 7.37 (m, 3H); ¹³C NMR (CDCl₃) δ 132.5, 131.8, 131.7, 129.8 (q, *J*=33.1 Hz, 1C), 128.8, 128.4, 126.4 (q, *J*=272 Hz, 1C), 125.2 (q, *J*=272 Hz, 1C), 122.5, 91.7, 87.9. MS (EI): *m/z* (rel%) 246 (73, M⁺), 176 (43), 98 (bp), 75 (49), 51 (46). IR (ATR): (cm^{−1}) ν 3080, 2219, 1508. CAS registry number: 370-99-0.

4.4.5. 1-(*p*-Acetoxyphenyl)-2-phenylacetylene (**4e**). ¹H NMR (CDCl₃) δ 7.94 (d, *J*=8.3 Hz, 2H), 7.61 (d, *J*=8.3 Hz, 2H), 7.57–7.52 (m, 2H), 7.45–7.36 (m, 3H), 2.62 (s, 3H); ¹³C NMR (CDCl₃) δ 197.0, 136.1, 131.7,

131.6, 128.8, 128.4, 128.2, 122.6, 92.7, 88.5, 26.3. MS (EI): m/z (rel%) 220 (76, M^+), 205 (92), 176 (bp), 151, (35). IR (ATR): (cm^{-1}) ν 2915, 1716, 1603, 1507, 1456. CAS registry number: 1942-31-0.

4.4.6. 1-(*p*-Methoxycarbonylphenyl)-2-phenylacetylene (**4f**). ^1H NMR (CDCl_3) δ 8.02 (d, $J=8.5$ Hz, 2H), 7.59 (d, $J=8.5$ Hz, 2H), 7.57–7.53 (m, 2H), 7.38–7.36 (m, 3H), 3.93 (s, 3H); ^{13}C NMR (CDCl_3) δ 166.5, 131.7, 131.4, 129.5, 129.4, 128.7, 128.4, 127.9, 122.6, 92.4, 88.6, 52.9. MS (EI): m/z (rel%) 236 (80, M^+), 205 (bp), 176 (91), 151 (34). IR (ATR): (cm^{-1}) ν 2949, 2217, 1718, 1606, 1508, 1455, 1374, 1280. CAS registry number: 42497-80-3.

4.4.7. 1-Phenyl-2-(*m*-tolyl)acetylene (**4g**). ^1H NMR (CDCl_3) δ 7.51 (d, $J=5.8$ Hz, 2H), 7.35–7.28 (m, 5H), 7.21 (t, $J=7.5$ Hz, 1H), 7.12 (d, $J=7.5$ Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (CDCl_3) δ 137.9, 132.1, 131.5, 129.3, 128.6, 128.2, 128.1, 123.3, 122.9, 89.5, 89.0, 21.1. MS (EI): m/z (rel%) 192 (bp M^+), 165 (13), 115 (5). IR (ATR): (cm^{-1}) ν 3003, 2919, 1492. CAS registry number: 14635-91-7.

4.4.8. 1-(*m*-Chlorophenyl)-2-phenylacetylene (**4h**). ^1H NMR (CDCl_3) δ 7.46–7.43 (m, 3H), 7.34–7.32 (m, 1H), 7.29–7.27 (m, 3H), 7.23–7.16 (m, 2H); ^{13}C NMR (CDCl_3) δ 134.1, 131.6, 131.4, 129.6, 129.5, 128.5, 128.4, 128.3, 124.9, 122.7, 90.5, 87.8. MS (EI): m/z (rel%) 212 (bp, M^+), 176 (46), 151 (13). IR (ATR): (cm^{-1}) ν 3055, 1490. CAS registry number: 51624-34-1.

4.4.9. 1-Phenyl-2-(*o*-tolyl)acetylene (**4i**). ^1H NMR (CDCl_3) δ 7.44–7.39 (m, 3H), 7.25–7.21 (m, 3H), 7.12–7.10 (m, 2H), 7.08–7.04 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (CDCl_3) δ 166.5, 131.7, 131.4, 129.5, 129.4, 128.7, 128.4, 127.9, 122.6, 92.4, 88.6, 52.9. MS (EI): m/z (rel%) 192 (bp, M^+), 165 (27), 115 (11). IR (ATR): (cm^{-1}) ν 3055, 2919, 1600, 1492. CAS registry number: 14309-60-5.

4.4.10. 1-(*o*-Chlorophenyl)-2-phenylacetylene (**4j**). ^1H NMR (CDCl_3) δ 7.57–7.55 (m, 3H), 7.53–7.50 (m, 1H), 7.34–7.32 (m, 3H), 7.22–7.18 (m, 2H); ^{13}C NMR (CDCl_3) δ 135.9, 133.2, 131.7, 129.2, 128.6, 128.3, 126.4, 123.1, 122.8, 94.5, 86.2. MS (EI): m/z (rel%) 212 (bp, M^+), 176 (38), 151 (11). IR (ATR): (cm^{-1}) ν 3057, 1491, 1468. CAS registry number: 10271-57-5.

4.4.11. 1-(1-Naphthyl)-2-phenylacetylene (**4k**). ^1H NMR (CDCl_3) δ 8.44 (d, $J=8.3$ Hz, 1H), 7.83 (ddd, $J=13.2$, 13.2, 4.9 Hz, 2H), 7.75 (d, $J=7.1$ Hz, 1H), 7.64 (d, $J=7.3$ Hz, 2H), 7.58 (t, $J=7.3$ Hz, 1H), 7.52 (t, $J=7.3$ Hz, 1H), 7.44 (t, $J=7.6$ Hz, 1H), 7.39–7.34 (m, 3H); ^{13}C NMR (CDCl_3) δ 133.1, 131.7, 131.6, 130.3, 128.7, 128.4, 128.3, 128.2, 128.2, 126.7, 126.4, 126.1, 125.2, 125.2, 94.3, 87.5. MS (EI): m/z (rel%) 228 (bp, M^+), 202 (6), 113 (13). IR (ATR): (cm^{-1}) ν 3055, 1488, 1396. CAS registry number: 4044-57-9.

4.4.12. 7-Phenyl-6-heptynoic acid (**4m**). ^1H NMR (CDCl_3) δ 11.1 (br s, 1H), 7.39–7.38 (m, 2H), 7.28–7.26 (m, 3H), 2.46–2.41 (m, 4H), 1.85–1.79 (m, 2H), 1.73–1.65 (m, 2H); ^{13}C NMR (CDCl_3) δ 179.8, 131.5, 128.2, 127.6, 123.8, 89.4, 81.0, 33.5, 28.0, 23.8, 19.1. MS (EI): m/z (rel%) 202 (9, M^+), 142 (6), 129 (77), 115 (bp). IR (KBr s): (cm^{-1}) ν 3298, 3041, 1709. CAS registry number: 49769-28-0.

4.4.13. 5-Phenyl-4-pentynoic acid (**4n**). ^1H NMR (CDCl_3) δ 11.2 (br s, 1H), 7.40–7.38 (m, 2H), 7.28–7.26 (m, 3H), 2.74–2.70 (m, 4H); ^{13}C NMR (CDCl_3) δ 178.0, 131.6, 128.2, 127.9, 123.3, 87.5, 81.3, 33.4, 15.0. MS (EI): m/z (rel%) 174 (43, M^+), 146 (bp), 128 (81), 115 (93). IR (KBr): (cm^{-1}) ν 3278, 3021, 1703. CAS registry number: 3350-92-3.

4.4.14. 3-Phenyl-2-propionic acid (**4p**). ^1H NMR (CDCl_3) δ 11.1 (br s, 1H), 7.62 (d, $J=7.0$ Hz, 2H), 7.48 (t, $J=7.0$ Hz, 1H), 7.40 (t, $J=7.0$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 182.8, 133.2, 131.0, 128.6, 119.1, 88.8, 79.9.

MS (EI): m/z (rel%) 146 (9, bp), 128 (72), 115 (63), 115 (72). IR (KBr): (cm^{-1}) ν 3288, 3003, 1706. CAS registry number: 637-44-5.

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