Article

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Solid-Phase Horner−Emmons Synthesis of Olefins

Joseph M. Salvino,* Terence J. Kiesow, Shelley Darnbrough, and Richard Labaudiniere

Lead Discovery Department, Rhone Poulenc Rorer, 500 Arcola Road, Collegeville, Pennsylvania 19426-0107

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The Horner−Emmons condensation reaction is an attractive and versatile method to generate carbon−carbon bonds, producing olefins as products. Herein is described a study using 3 different resin bound phosphonates and 16 diverse aldehydes. To facilitate the study and to demonstrate the usefulness of this reaction for library synthesis, the protocol was semiautomated. Weighing and sample concentration were performed using the Zymark Benchmate II and Turbovap workstations, respectively. Horner−Emmons synthesis and trifluoroacetic acid cleavage from the resin were performed on a Tecan Combitec synthesis robot. The results from this study define the scope of this useful reaction for chemical library synthesis.

Introduction

Parallel synthesis on solid phase is emerging as a powerful tool in drug discovery.[1] Solid-phase synthesis simplifies the automation of chemical reactions in several ways. For example, reactions may be driven to completion by the use of excess reagents. Purification of the resin bound substrate relies simply on washing with various solvents to wash away excess reagent or solution-phase byproducts.

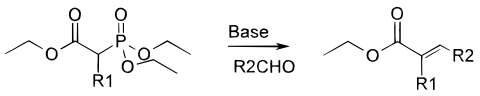
A repertoire of robust solid-phase reactions is required so that they may be applied in chemical synthesis. The main pitfall to be avoided is the generation of covalently bound impurities on the resin. This results in a mixture of desired product and undesired byproducts upon cleavage from the solid support. In this regard many new solid-phase reactions are appearing in the literature with an emphasis on product purity.

A major focus of solid-phase synthesis is to generate chemical libraries for lead discovery or lead optimization as an aid in the drug discovery process. In the optimization of a new solid-phase reaction it is clearly desired to fully understand the scope and limitations of the particular chemical reaction under study.

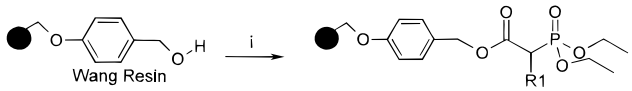
This article focuses on the optimization of a solid-phase Horner−Emmons reaction. This carbon−carbon bond-forming reaction generates acrylates, which are useful as intermediates in chemical synthesis[2] (Scheme 1).

The goal of this work was to establish reaction conditions that would prove robust enough to enable automation of the synthesis on a liquid-handling synthesis robot. It was also a goal to attempt to understand the scope of this solid-phase Horner−Emmons reaction. This article discloses the results from 48 reactions run using 3 different phosphonates and 16 different aldehydes. The aldehydes display aliphatic, aromatic, heterocyclic, and basic side chains. Product purity in the 80−90% range was desired in order to be useful for chemical library synthesis. We typically used LC-MS with UV detection at 220 nm and ^{1}H NMR to determine product purity.

Scheme 1



Scheme 2[a]



[a] Key: (i) 1-(R1)-Diethylphosphono acetic acid (6 equiv); diisopropyl carbodiimide (3 equiv), DCM, 0 °C; 30 min, then Wang resin (1 equiv), DMAP (0.2 equiv); 12 h or Wang resin (1 equiv); 1-(R1)-Diethylphosphono acetic acid (3 equiv); 2,6-dichlorobenzoyl chloride (3 equiv); pyridine (6 equiv); DMF; 25 °C; 12 h.

Discussion

The Horner−Emmons condensation is a valuable carbon−carbon bond-forming reaction used extensively in organic synthesis.[2] Exploitation of this condensation reaction in solid-phase synthesis would be valuable for chemical library synthesis.

At the onset of this work the supported Horner−Emmons condensation utilizing resin bound phosphonate was not yet reported. During the course of our investigation, two reports appeared in the literature.[3] This paper compliments these reports by expanding the scope of the reaction. Three different phosphonates were used in this study, each reacting with 16 diverse aldehydes. This article provides a general protocol useful for the solid-phase synthesis of a variety of

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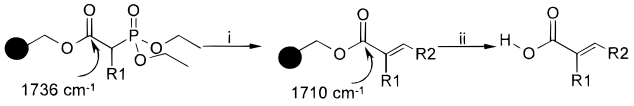
Scheme 3[a]



[a] Key: (i) lithium bis(trimethylsilyl) amide (4 equiv; 1.0 M in THF); THF; 0 °C to 25 °C, 1 h, then drain solvent, add R_2CHO (5 equiv, 0.5 M in 60% cyclohexane in THF); 2−3 days; 25 °C. (ii) 50% TFA in CH_2Cl_2; 1 h; 25 °C.

substituted acrylic acids. Detailed experimental conditions and ^{1}H NMR and IR spectra of the resin are provided to reveal the scope and limitations of this solid-phase reaction.

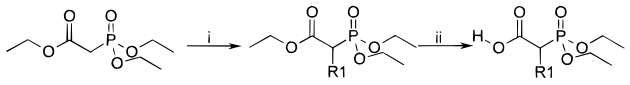
Wang resin was chosen as the solid support for this study. Wang resin is commercially available, and substrates are conveniently cleaved using 50% trifluoroacetic acid in dichloromethane (DCM). Thus, diethylphosphonoacetic acid was loaded to Wang resin either by a preformed symmetric anhydride or via a 2,6-dichlorobenzoic acid anhydride.[4] Loading of the phosphonate could be determined by phosphorus elemental analysis. However, we found it convenient to confirm loading by cleaving a known weight of the resin and determining the weight of the recovered phosphonoacetic acid. The phosphonate-loaded resin also showed a strong carbonyl stretch near 1735 cm^{-1} corresponding to the ester carbonyl stretch. Typically Wang resin [0.7 mequiv/g] yielded approximately 0.5−0.6 mequiv/g of ester (Scheme 2).

Solution-phase Horner−Emmons condensations use basic reaction conditions. Typical conditions would be to use potassium *tert*-butoxide in tetrahydrofuran (THF) or lithium bis(trimethylsilyl)amide in THF. Mild conditions employ lithium bromide and triethylamine in acetonitrile.[5]

Converting these conditions to the solid phase posed several problems. Under strongly basic conditions the desired product was hydrolyzed from the resin during the reaction, resulting in low yield of desired product. Using the mild reaction conditions, particularly for α-substituted phosphonates, the reaction did not proceed to completion.

It was necessary to suppress the hydrolysis of the resin ester linkage, yet have conditions basic enough to drive the reaction to completion. After consideration of the problem, reaction conditions were found that proved to be quite general. Thus the resin bound phosphonate anion was generated in 100% THF at 0 °C by addition of an excess of the strong base lithium bis(trimethylsilyl)amide. The reaction mixture was allowed to warm to room temperature for about 1 h. Then excess base was drained from the resin under an inert atmosphere. A solution of the aldehyde dissolved in 60% cyclohexane in THF was then added to the resin bound anion. The reasoning behind this solvent mixture was that the less polar solvent mixture should suppress ester hydrolysis, while allowing the Horner−Emmons condensation to proceed. FT-IR was used to monitor the progress of the reaction. The reaction was completed over a 2 day period. The diagnostic carbonyl stretch at 1736 cm^{-1} had shifted to 1710 cm^{-1}, indicating the presence of an α,β-unsaturated ester. After workup and cleavage from the resin under acidic conditions the olefin product was obtained in good to excellent yield, with excellent purity by LC-MS and ^{1}H NMR (Scheme 3). Thus it was found that the use of the less polar solvent mixture combined with draining off the excess base stabilized the resin linkage toward hydrolysis.

Scheme 4[a]



[a] Key: (i) NaH (2 equiv); R1−Br (2 equiv); THF; 0 °C, 30 min, then reflux 4 h, then rt overnight. (ii) LiOH (excess); THF; 0 °C; 24 h.

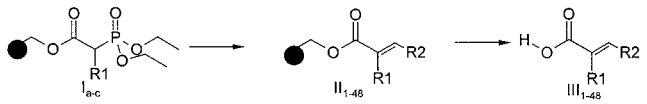
To expand the scope of the synthesis, an attempt was made to alkylate the resin bound diethylphosphonate. However, we were not sucessful in cleanly alkylating the phosphonate while attached to the resin. Therefore custom α-substituted phosphonates were synthesized by a solution-phase route, purified, and then loaded to the resin via an anhydride (Scheme 4).

To facilitate the synthesis of the 48 examples used in this study, the synthesis was performed using a Tecan Combitec organic synthesis robot. TECAN US supplied the reaction block and the automation software used. Three phosphonates and 16 aldehydes were used in this study to generate 48 acrylic acids. The three phosphonates were loaded on the resin on large scale. The three different resins were then weighted out into 16 different reaction vessels each.

The 16 aldehydes were prepared as 0.5 M solutions in 60% cyclohexane in THF. The lithium bis(trimethylsilyl)-amide (1.0 molar in THF) was used as purchased from the Aldrich Chemical company. The system solvents used were HPLC grade, and anhydrous THF was purchased from Aldrich and placed on the deck of the robot in a septum-sealed bottle. The robot dispensed anhydrous THF to the reaction vessels, followed by the solution of base (1.0 M in THF) as they sat on the deck of the robot in an ice bath. The reaction block was then manually moved to an orbital shaker and agitated for 1 h at ambient temperature. The reaction block was then placed back on the instrument. The vessels were then drained, and solutions of the aldehydes were dispensed to their respective reaction vessel. The reaction block was then moved to an orbital shaker and agitated for 2−3 days at ambient temperature. Workup of the reaction on the robot consisted of draining the vessels and washing the resin with THF, 20% aqueous DMF, DMF, THF, and then DCM. A total of about 20 washes were needed to remove all the impurities in the resin matrix. The resin was then sampled for single-bead FT-IR analysis. The diagnostic carbonyl shift is a qualitative means of determining if the reaction has gone to completion.

The products were then cleaved from the resin using 50% trifluoroacetic acid (TFA) in DCM on the Tecan Combitec. A custom Benchmate II compatible 5 × 10 position rack was defined on the deck of the robot. This enabled the use of the Zymark Benchmate II workstation and the Zymark Turbovap workstation to be interfaced for sample weighing and concentration, respectively.[6] Thus after the resin was incubated in the TFA mixture for about 1 h, the 48 solutions were transferred to the pre-tared test tubes contained in the Benchmate II compatible rack. The rack was placed in the Zymark Turbovap for nitrogen blow-down to concentrate the samples. The samples were chased with a 1 mL portion of DCM then re-evaporated, to ensure complete removal of the

Table 1



compd	R1	IR resin C=O stretch of **II**	R2[a]	% yield of **III**[b]	purity of **III** (*A*% at UV_{220})	compd	R1	IR resin C=O stretch of **II**	R2[a]	% yield of **III**[b]	purity of III (*A*% at UV_{220})
I_a	Et	1733				**24**	$Ph(CH_2)_3$-	1708	H	>95	86
I_b	$Ph(CH_2)_3$-	1733				**25**	$Ph(CH_2)_3$-	1708	I	>95	97
I_c	H	1737				**26**	$Ph(CH_2)_3$-	1704	J	>95	91
1	Et	1707	A	75	81	**27**	$Ph(CH_2)_3$-	1704	K	62	76
2	Et	1704	B	>95	92	**28**	$Ph(CH_2)_3$-	1705	L	>95	93
3	Et	1711	C	>95	95	**29**	$Ph(CH_2)_3$-	1706	M	68	73
4	Et	1699	D	55	85	**30**	$Ph(CH_2)_3$-	1705	N	>95	80
5	Et	1703	E	>95	95	**31**	$Ph(CH_2)_3$-	1702	O	>95	95
6	Et	1708	F	>95	95	**32**	$Ph(CH_2)_3$-	1702	P	80	83
7	Et	1706	G	>95	85	**33**	H	1712	A	>95	76
8	Et	1709	H	>95	90	**34**	H	1711	B	>95	87
9	Et	1708	I	>95	96	**35**	H	1717	C	>95	93
10	Et	1705	J	>95	97	**36**	H	1706	D	74	48
11	Et	1704	K	69	77	**37**	H	1708	E	>95	90
12	Et	1706	L	>95	95	**38**	H	1711	F	>95	75
13	Et	1707	M	73	50	**39**	H	1708	G	>95	50
14	Et	1705	N	>95	93	**40**	H	1712	H	>95	85
15	Et	1703	O	>95	81	**41**	H	1714	I	>95	70
16	Et	1703	P	86	80	**42**	H	1711	J	>95	81
17	$Ph(CH_2)_3$-	1707	A	94	93	**43**	H	1708	K	67	90
18	$Ph(CH_2)_3$-	1705	B	>95	88	**44**	H	1711	L	>95	85
19	$Ph(CH_2)_3$-	1711	C	>95	89	**45**	H	1711	M	84	74
20	$Ph(CH_2)_3$-	1699	D	72	87	**46**	H	1711	N	>95	76
21	$Ph(CH_2)_3$-	1703	E	>95	88	**47**	H	1711	O	>95	75
22	$Ph(CH_2)_3$-	1708	F	>95	82	**48**	H	1711	P	74	89
23	$Ph(CH_2)_3$-	1707	G	>95	90						

[a] See Table 2. [b] Yields were estimated by weight assuming an initial loading of 0.5 mmol/g for **I_{a-c}**.

TFA solution. The samples after evaporation were weighed using the Zymark Benchmate II workstation, allowing the percent yield calculation and determination of exact weight of sample. ^{1}H NMR and LC-MS were used to analyze the reaction set. These data along with the single-bead FT-IR spectrum and weight give an accurate evaluation of the reaction in terms of scope and limitations of inputs that are tolerated.

A variety of aldehydes containing aliphatic, aromatic, and basic functionality were successfully employed in this study (Tables 1 and 2). For unsubstituted phosphonates, the trans product (the ester carbonyl is trans to the aldehyde R group) is the major product, in most cases better than 9:1. Bulky α-substitution of the phosphonate affected the trans:cis ratio, giving more cis product. The main limitation of the reaction was that if a substituted phosphonate was used which could assist in the hydrolysis of the resin ester linkage, low yields were obtained. This could be observed by loss of the ester carbonyl signal near 1735 cm^{-1} in the FT-IR spectrum.

Conclusion

Thus in summary, the Horner−Emmons synthesis of olefins has been completed using a solid-phase approach. Aliphatic, aromatic, and basic aldehydes react to give products, most showing a purity in the 80−95% range with yields between 70 and 95%. Efficient tools have been used to couple sample weighing, synthesis, and evaporation for a streamlined semiautomated process to produce these valuable compounds for screening or further synthetic manipulation.

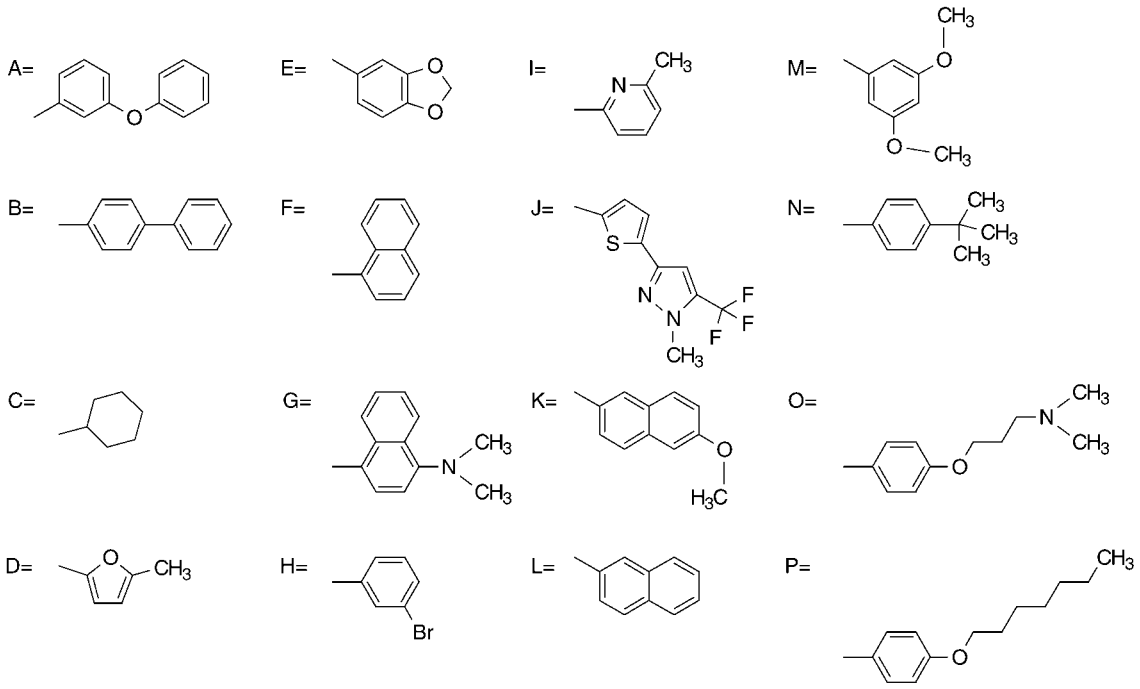
Experimental Section

General. Solvents used were EM Science HPLC grade unless specified otherwise. The following abbreviations were used: DCM = dichloromethane, DMF = dimethylformamide, THF = tetrahydrofuran, TFA = trifluoroacetic acid. ^{1}H NMR spectra were recorded on a 300 MHz ARX Bruker spectrometer in $CDCl_3$ unless otherwise stated. Mass spectra were recorded on Finnigan 4500 EI and Sciex API 3 IS spectrometers.

2-(Diethoxyphosphoryl)-5-phenyl-ethyl Pentanoate. Sodium hydride (6.25 g; 60% dispersion in mineral oil, 0.156 mol) was stirred in anhydrous THF (500 mL) at 0 °C under nitrogen. Triethyl phosphonaoacetate (30.97 mL; 0.156 mol) was added via syringe over a period of 10 min. The mixture was stirred for 30 min at 0 °C, forming a yellow solution. 1-Bromo-3-phenyl propane (62.12 g; 0.31 mol) was added. The mixture was allowed to warm to room temperature and then heated to reflux for 4 h. TLC revealed the reaction to be complete. The solution was allowed to cool to room temperature and was stirred overnight. The mixture was partitioned between 500 mL of aqueous ammonium chloride and 500 mL of diethyl ether. The aqueous layer was extracted twice more with 500 mL of ether. All organic layers were combined and washed twice with 400 mL of water and once with 400 mL saturated aqueous sodium chloride.

The organic layer was dried over magnesium sulfate and evaporated to afford a dark yellow oil. Purification was achieved via filtration through a silica gel plug, eluting with

Table 2. Structures of R2 in Table 1



petrol/ethyl acetate 9:1. Pure product (28.3 g; 53% yield) was recovered as a colorless oil. ^{1}H NMR: δ 1.25 (m, 9H); 1.5−2.1 (m, 4H); 2.55 (t, 2H); 2.9 (dd, 1H); 4.15 (m, 6H); 7.1−7.3 (m, 5H). MS: (M^+) m/z = 342.

2-(Diethoxyphosphoryl)-5-phenyl Pentanoic Acid. Phosphonate ester (56.5 g; 0.165 mol) was stirred in a 900 mL solvent mixture (1:1:1) of methanol, THF, and water. Solution cooled to 0 °C. Lithium hydroxide (6.93 g; 0.165 mol) was added, and the resulting yellow solution was allowed to warm to room temperature and stir overnight. TLC analysis of the subsequent pink solution indicated that the reaction was complete. The solution was concentrated to near dryness and then partitioned between 800 mL of water and 500 mL of diethyl ether. The organic layer was discarded, and the aqueous layer was acidified with 1 N HCl. The aqueous layer was extracted 3 times with 500 mL of diethyl ether. The combined organic extracts were washed with 200 mL of saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated to afford 40.1 g (77% yield) of a pale yellow oil. ^{1}H NMR: δ 1.3 (t, 6H); 1.6−2.1 (m, 4H); 2.65 (t, 2H); 3.0 (dd, 1H); 4.15 (sept, 4H); 7.1−7.3 (m, 5H). MS: (M^+) m/z = 314.

Phosphonate Loading. Wang resin (**Ia**) (Advanced Chem Tech; 40 g; 1.09 mmol/g loading; 43.6 mmol) was placed in a 2 L three-neck round-bottom flask and swelled with 400 mL of DMF for 20 min. An overhead stirrer was attached to provide gentle stirring. Added in succession was diethylphosphonoacetic acid (21 mL; 130.8 mmol), anhydrous pyridine (22 mL; 261.6 mmol), and 2,6-dichlorobenzoyl chloride (19 mL, 130.8 mmol). The solution was stirred at ambient temperature for 12 h; during that time the reaction mixture turned an orange color. The resin was then filtered and washed with DMF, THF, DCM, and MeOH. Each wash solvent addition was approximately 400 mL, and each washing step was repeated 5−8 times. The resin was dried in vacuo overnight at 25 °C.

Resins **Ib** and **Ic** were prepared in an analogous manner as above.

Horner−Emmons Reaction and Cleavage from the Resin. Compound 35. Phosponate-loaded Wang resin (**Ia**) (0.2 g; ca. 0.9 mmol/g loading; 0.18 mmol) was swelled with 3.0 mL of anhydrous THF for 15 min. The reaction vessel was then cooled to 0 °C, and lithium bis(trimethylsilyl)amide (0.72 mL; 1 M in THF; 0.72 mmol) was added to the reaction mixture. The solution was agitated at 0 °C for 10 min and then shaken on an orbital shaker for an additional 30 min at ambient temperature. Approximately 2 mL of THF was removed from the reaction vessel by filtration, and cyclohexane carboxaldehyde (1.8 mL; 0.5 M in anhydrous 60% cyclohexane in THF; 0.90 mmol) was added. The reaction vessel was shaken on an orbital shaker at ambient temperature for 3 days, after which the resin was washed with THF, 20% aqueous DMF, DMF, THF, and DCM. Each solvent addition was approximately 5.0 mL, and each washing step was repeated 8−10 times. The resin was then dried in vacuo. Several resin beads were used for IR analysis (C═O stretch at 1717 cm^{-1}). 50% TFA in DCM containing 0.5% water (3 mL) was added to the reaction vessel. The reaction vessel was incubated at ambient temperature for 30−60 min, after which the reaction mixture was filtered and the solvent evaporated by nitrogen blow-down, to yield 140 mg (0.9 mmol; 99% yield) of the β-cyclohexane acrylic acid product. ^{1}H NMR: δ 1.3 (m, 5H); 1.7 (m, 5H); 2.2 (m, 1H); 5.8 (d, 1H); 7.0 (dd, 1H). MS: [M − H]$^-$ m/z = 153, A% (UV_{220}) = 93%.

The following compounds were synthesized using the above protocol on a TECAN Combitec organic synthesis robot utilizing a reaction block supplied by TECAN US, Inc.

Compound 1. ^{1}H NMR: δ 1.1 (t, 3H); 2.5 (q, 2H); 6.7−7.5 (m, 9H); 7.8 (s, 1H). MS: [M − H]$^-$ m/z = 267, A% (UV_{220}) = 81%.

Compound 2. ^{1}H NMR: δ 1.3 (t, 3H); 2.8−2.9 (q, 2H);

7.3−7.8 (m, 9H); 7.1 and 7.9 (s, 1H). MS: $[M - H]^-$ m/z = 251, $A\%$ (UV_{220}) = 92%.

Compound 3. ^{1}H NMR: δ 0.9−1.1 (t, 3H); 1.1−1.5 (m, 6H); 1.6−1.8 (m, 4 H); 2.2−2.4 (q, 2H); 2.8−3.1 (m, 1H); 5.5 and 6.7 (d, 1H). MS: $[M - H]^-$ m/z = 181, $A\%$ (UV_{220}) = 95%.

Compound 4. ^{1}H NMR: δ 1.1 (t, 3H); 2.4 (s, 3H); 2.8 (q, 2H); 6.1 (s, 1H); 6.6 (s, 1H); 7.5 (s, 1H). MS: $[M + H]^+$ m/z = 181, $A\%$ (UV_{220}) = 85%.

Compound 5. ^{1}H NMR: δ 1.2 (t, 3H); 2.6 (q, 2H); 6.1 (s, 2H); 6.8 (d, 1H); 7.0 (d, 2H); 8.8 (s, 1H). MS: $[M + H]^+$ m/z = 221, $A\%$ (UV_{220}) = 95%.

Compound 6. ^{1}H NMR: δ 1.0−1.4 (t, 3H); 2.4−2.7 (q, 3H); 7.4−7.7 (m, 4H); 7.8−8.0 (m, 3H); 8.4 (s, 1H). MS: $[M-H]^-$ m/z = 225, $A\%$ (UV_{220}) = 95%.

Compound 7. ^{1}H NMR: δ 1.0−1.3 (t, 3H); 2.4−2.6 (q, 2H); 3.4 (s, 6H); 7.4−8.4 (m, 7H). MS: $[M + H]^+$ m/z = 270, $A\%$ (UV_{220}) = 85%.

Compound 8. ^{1}H NMR: δ 1.2 (t, 3H); 2.5 (q, 2H); 7.2−7.6 (m, 4H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 253, $A\%$ (UV_{220}) = 90%.

Compound 9. ^{1}H NMR: δ 1.1−1.4 (t, 3H); 2.5−2.7 (m, 2H); 2.7 and 2.9 (s, 3H); 6.8 and 7.8 (s, 1H); 7.4−8.3 (m, 3H). MS: $[M + H]^+$ m/z = 192, $A\%$ (UV_{220}) = 96%.

Compound 10. ^{1}H NMR: δ 1.2 (t, 3H); 2.7 (q, 2H); 4.1 (s, 3H); 6.7 (s, 1H); 7.2 (s, 1H); 7.9 (s, 1H). MS: $[M + H]^+$ m/z = 331, $A\%$ (UV_{220}) = 97%.

Compound 11. ^{1}H NMR (CD_3OD): δ 1.2 (t, 3H); 2.6 (q, 2H); 3.9 (s, 3H); 6.6−8.0 (m, 7H). MS: $[M - H]^-$ m/z = 255, $A\%$ (UV_{220}) = 77%.

Compound 12. ^{1}H NMR: δ 1.2 (t, 3H); 2.7(q, 2H); 7.5 (m, 3H); 7.8 (m, 4H); 8.0 (s, 1H). MS: $[M - H]^-$ m/z = 225, $A\%$ (UV_{220}) = 95%.

Compound 13. ^{1}H NMR: δ 1.2 (t, 3H); 1.7 (q, 2H); 3.9 (s, 6H); 6.5 (s, 1H); 6.6 (s, 2H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 235, $A\%$ (UV_{220}) = 50%.

Compound 14. ^{1}H NMR: δ 1.2 (t, 3H); 1.3 (s, 9H); 2.6 (q, 2H); 7.4−7.6 (m, 4H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 231, $A\%$ (UV_{220}) = 93%.

Compound 15. ^{1}H NMR: δ 1.2 (t, 3H); 2.3 (m, 2H); 2.5 (q, 2H); 2.8 (s, 6H); 3.2, (t, 2H); 4.1 (t, 2H); 6.9 (d, 2H); 7.4 (d, 2H); 7.7 (s, 1H). MS: $[M + H]^+$ m/z = 278, $A\%$ (UV_{220}) = 81%.

Compound 16. ^{1}H NMR: δ 0.9 (t, 3H); 1.0−1.9 (m, 13H); 1.8 (q, 2H); 4.0 (t, 2H); 6.9 (d, 2H); 7.5 (d, 2H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 290, $A\%$ (UV_{220}) = 80%.

Compound 17. ^{1}H NMR: δ 1.8 (m, 2H); 2.4−2.7 (m, 4H); 6.9−7.1 (m, 14 H); 7.7 (s, 1H). MS: $[M - H]^-$ m/z = 357, $A\%$ (UV_{220}) = 93%.

Compound 18. ^{1}H NMR: δ 1.9 (m, 2H); 2.5 (t, 2H); 2.7 (t, 2H); 7.2−7.7 (m, 14H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 342, $A\%$ (UV_{220}) = 88%.

Compound 19. ^{1}H NMR: δ 0.9−1.3 (m, 4H); 1.5−1.9 (m, 8H); 2.2 (t, 2H); 2.7 (t, 2H); 3.1 (m, 1H); 5.8 (d, 1H); 7.2−7.4 (m, 5H). MS: $[M - H]^-$ m/z = 271, $A\%$ (UV_{220}) = 89%.

Compound 20. ^{1}H NMR: δ 1.8 (m, 2H); 2.2 (s, 3H); 2.7 (m, 4H); 6.1 (s, 1H); 6.4 (s, 1H); 7.2 (m, 5H); 7.5 (s, 1H). MS: $[M - H]^-$ m/z = 269, $A\%$ (UV_{220}) = 87%.

Compound 21. ^{1}H NMR: δ 1.8 (m, 2H); 2.6 (dd, 2H); 2.7 (t, 2H); 6.0 (s, 2H); 6.8 (m, 3H); 7.3 (m, 5H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 309, $A\%$ (UV_{220}) = 88%.

Compound 22. ^{1}H NMR: δ 1.9 (m, 2H); 1.5 (m, 4H); 7.1−7.7 (m, 9H); 7.8−7.9 (m, 3H); 8.3 (s, 1H). MS: $[M - H]^-$ m/z = 315, $A\%$ (UV_{220}) = 82%.

Compound 23. ^{1}H NMR: δ 1.8 (m, 2H); 2.4 (m, 2H); 2.6 (t, 2H); 3.4 (s, 6H); 7.0−7.4 (m, 7H); 7.6−7.8 (m, 2H); 8.0 (d, 1H); 8.2 (s, 1H); 8.4 (d, 1H). MS: $[M - H]^-$ m/z = 358, $A\%$ (UV_{220}) = 90%.

Compound 24. ^{1}H NMR: δ 1.9 (m, 2H); 2.5 (m, 2H); 2.7 (t, 2H); 7.2−7.6 (m, 9H); 7.7 (s, 1H). MS: $[M - H]^-$ m/z = 343, $A\%$ (UV_{220}) = 86%.

Compound 25. ^{1}H NMR: δ 1.9 (m, 2H); 2.5 (m, 2H); 2.7−2.8 (m, 5H); 6.6 (s, 1H); 7.2−7.4 (m, 7H); 8.9 (s, 1H). MS: $[M - H]^-$ m/z = 280, $A\%$ (UV_{220}) = 97%.

Compound 26. ^{1}H NMR: δ 1.9 (m, 2H); 2.8 (m, 4H); 4.0 (s, 3H); 6.77 (s, 1H); 7.3 (m, 7H); 7.9 (s, 1H). MS: $[M - H]^-$ m/z = 419, $A\%$ (UV_{220}) = 91%.

Compound 27. ^{1}H NMR (CD_3OD): δ 1.9 (m, 2H); 2.5−2.8 (m, 4H); 3.9 (s, 3H); 6.6−7.7 (m, 12H). MS: $[M - H]^-$ m/z = 345, $A\%$ (UV_{220}) = 76%.

Compound 28. ^{1}H NMR: δ 2.0 (m, 2H); 2.7 (m, 4H); 6.9−8.0 (m, 13H). MS: $[M - H]^-$ m/z = 315, $A\%$ (UV_{220}) = 93%.

Compound 29. ^{1}H NMR: δ 1.9 (m, 2H); 2.7 (m, 4H); 3.8 (s, 6H); 6.4 (s, 1H); 6.5 (s, 2H); 7.2−7.4 (m, 5H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 325, $A\%$ (UV_{220}) = 73%.

Compound 30. ^{1}H NMR: δ 1.3 (s, 9H); 1.9 (m, 2H); 2.6 (m, 2H); 2.7 (m, 2H); 7.3 (m, 9H); 7.8 (s, 1H). MS: $[M - H]^-$ m/z = 321, $A\%$ (UV_{220}) = 80%.

Compound 31. ^{1}H NMR: δ 1.9 (m, 2H); 2.3 (m, 2H); 2.6 (m, 2H); 2.8 (t, 2H); 2.9 (s, 6H); 3.3 (m, 2H); 4.1 (t, 2H); 6.8 (d, 2H); 7.3 (m, 7H); 7.7 (s, 1H). MS: $[M + H]^+$ m/z = 368, $A\%$ (UV_{220}) = 95%.

Compound 32. ^{1}H NMR: δ 0.9 (t, 3H); 1.3 (m, 8H); 1.7 (m, 2H); 1.9 (m, 2H); 2.5 (m, 2H); 2.7 (m, 2H); 3.9 (t, 2H); 6.8 (d, 2H); 7.2 (m, 7H); 7.7 (s, 1H). MS: $[M - H]^-$ m/z = 379, $A\%$ (UV_{220}) = 83%.

Compound 33. ^{1}H NMR: δ 6.4 (d, 1H); 7.1−7.5 (m, 9H); 7.8 (d, 1H). MS: $[M - H]^-$ m/z = 239, $A\%$ (UV_{220}) = 76%.

Compound 34. ^{1}H NMR (CD_3OD): δ 6.6 (d, 1H); 7.4 (m, 3H); 7.7 (m, 7H). MS: $[M - H]^-$ m/z = 223, $A\%$ (UV_{220}) = 87%.

Compound 36. ^{1}H NMR: δ 2.3 (s, 3H); 6.1 (s, 1H); 6.3 (d, 1H); 6.7 (s, 1H); 7.5 (d, 1H). MS: $[M - H]^-$ m/z = 151, $A\%$ (UV_{220}) = 48%.

Compound 37. ^{1}H NMR (CD_3OD): δ 6.0 (s, 2H); 6.3 (d, 1H); 6.9 (d, 1H); 7.2 (d, 1H); 7.3 (s, 1H); 7.6 (d, 1H). MS: $[M - H]^-$ m/z = 191, $A\%$ (UV_{220}) = 90%.

Compound 38. ^{1}H NMR (CD_3OD): δ 6.6 (d, 1H); 7.6 (m, 3H); 7.9 (m, 3H); 8.2 (d, 1H); 8,5 (d, 1H). MS: $[M - H]^-$ m/z = 197, $A\%$ (UV_{220}) = 75%.

Compound 39. ^{1}H NMR: δ (2:1 trans and cis mixtures) 3.2 and 3.4 (s, 6H); 6.3 and 6.5 (d, 1H); 7.4−8.3 (m, 6H); 8.4 and 8.6 (d, 1H). MS: $[M + H]^+$ m/z = 242, $A\%$ (UV_{220}) = 50%.

Compound 40. ^{1}H NMR: δ 6.6 (d, 1H); 7.4 (dd, 1H); 7.5 (d, 1H); 7.6 (d, 1H); 7.8 (m, 2H). MS: $[M - H]^-$ m/z = 225, A% (UV_{220}) = 85%.

Compound 41. ^{1}H NMR: δ (mixture trans and cis) 2.6 and 2.8 (s, 3H); 6.4 (d, 1H); 7.6 (m, 3H); 7.8 (d, 1H). MS: $[M + H]^+$ m/z = 164, A% (UV_{220}) = 70%.

Compound 42. ^{1}H NMR: δ 4.1 (s, 3H); 6.3 (d, 1H); 6.7 (s, 1H); 7.2 (d, 1H); 7.4 (d, 1H); 7.9 (d, 1H). MS: $[M + H]^+$ m/z = 229, A% (UV_{220}) = 81%.

Compound 43. ^{1}H NMR: δ 3.9 (s, 3H); 6.5 (d, 1H); 6.6−8.0 (m, 7H). MS: $[M + H]^+$ m/z = 229, A% (UV_{220}) = 90%.

Compound 44. ^{1}H NMR (CD_3OD): δ 6.6 (d, 1H); 7.5 (m, 2H); 7.6−8.0 (m, 6H). MS: $[M + H]^+$ m/z = 199, A% (UV_{220}) = 85%.

Compound 45. ^{1}H NMR: δ 3.8 (d, 6H); 6.4 (d, 1H); 6.5 (s, 1H); 6.6 (s, 2H); 7.8 (d, 1H). MS: $[M - H]^-$ m/z = 207, A% (UV_{220}) = 74%.

Compound 46. ^{1}H NMR: δ 1.3 (s, 9H); 6.4 (d, 1H); 7.4 (d, 2H); 7.5 (d, 2H); 7.8 (d, 1H). MS: $[M + H]^+$ m/z = 205, A% (UV_{220}) = 76%.

Compound 47. ^{1}H NMR: δ 2.3 (m, 2H); 3.0 (s, 6H); 3.3 (m, 2H); 4.1 (t, 2H); 6.3 (d, 1H); 6.9 (d, 2H); 7.5 (d, 2H); 7.7 (d, 1H). MS: $[M + H]^+$ m/z = 250, A% (UV_{220}) = 75%.

Compound 48. ^{1}H NMR: δ 0.8 (t, 3H); 1.4 (m, 8H); 1.8 (m, 2H); 4.0 (t, 2H) 6.3 (d, 1H); 6.9 (d, 2H); 7.5 (d, 2H); 7.8 (d, 1H). MS: $[M + H]^+$ m/z = 263, A% (UV_{220}) = 89%.

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Supporting Information Available. Copies of the ^{1}H NMR and MS spectra of the products and IR spectra of the resins are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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