Selenium-Based Safety-Catch Linker: Solid-Phase Synthesis of Vinyl-Substituted Oxadiazoles and Triazoles

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Vinyl-substituted oxadiazoles and triazoles were prepared through hydrazinolysis, acylation, cyclocondensation, and elimination of selenium resins. The polystyrene-supported resins used here not only facilitate separation of products but also serve as a pro-vinyl safety-catch linker.

Introduction

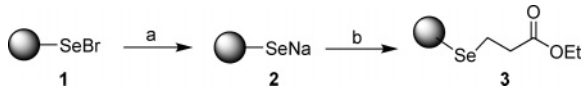
The preparation of diverse libraries of organic compounds is an important facet of modern drug discovery programs.[1] One of the most commonly employed methods in library production is solid phase organic synthesis (SPOS).[2] Because substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents, the field of solid-phase heterocyclic chemistry has rapidly expanded for the preparation of pharmaceutically useful heterocyclic compounds.[3]

Vinyl-substituted heterocycles have a highly reactive terminal double bond and are easily polymerized because the double bond is directly connected with an electron-withdrawing group (heterocycle).[4] As a result, such compounds are seldom reported in solid-phase synthesis because of the lack of diversity and stability, although vinyl-substituted heterocycles show interesting biological properties,[5] such as antiallergic, antibacterial, and anti-HIV activity.

In the search for alternative strategies to solve this problem, we turned our attention toward a polymer-supported selenium resin. We reasoned that the facile selenoxide syn elimination of the polymer-bound phenylseleno group could be used to mask a vinylic functionality, thus serving as a pro-vinyl safety-catch linker.[6]

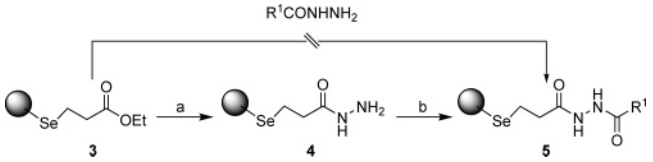
The first organoselenium resin[7] was reported in 1976, and until 1998, Nicolaou[8] and Ruhland[9] reported the development of organoselenium resins independently as convenient linkers for their versatile reactivities and easy cleavages. Recently, others[10] and our research group[11] have been interested in the preparation of heterocycle libraries from organoselenium resins. Herein, we present our investigation of the applicability of the SPOS methodology for the preparation of vinyl-substituted oxadiazoles and triazoles with the advantages of straightforward operation, lack of odor, stability, and good resulting purity of the product.

Scheme 1[a]



[a] Reagents and conditions: (a) $NaBH_4$, THF/DMF, room temp, 10 h; (b) $ClCH_2CH_2COOEt$, room temp, 5 h.

Scheme 2[a]



[a] Reagents and conditions: (a) $NH_2NH_2H_2O$, CH_3OH, 24 h; (b) R^1COCl, pyridine, CH_2Cl_2, 0 °C, then room temp, 12 h.

Results and Discussion

Resin-bound ethyl propionate **3** was prepared by treatment of a THF/DMF-swollen suspension of resin **1** (dark-red resin; Se, 1.25 mmol g^{-1})[8] with $NaBH_4$ for 10 h,[12] followed by treatment with ethyl 3-chloropropionate for another 5 h. FT-IR showed a strong carbonyl absorption at 1734 cm^{-1}, and prolonging the reaction time didn't increase this value. The minimum loading of COOH for resin **3** was determined by acid−base titration[11a] to be 1.20 mmol g^{-1} (Scheme 1).

With resin **3** in hand, we investigated the acylhydrazination reaction. Since the direct reaction of resin **3** and acylhydrazine didn't occur, a two-step reaction was adopted. First, resin **3** was reacted with hydrazine hydrate in MeOH for 24 h to obtain resin **4** (FT-IR showed a band at 1640 cm^{-1}, with disappearance of the band at 1734 cm^{-1}). Second, resin **4** was reacted with acyl chloride smoothly, and the FT-IR spectra of resin **5** showed that the band of the strong carbonyl absorption moved to about 1590 cm^{-1} because of the conjugative effect (Scheme 2).

We began our cyclocondensation reaction to synthesize 1,2,4-triazole by following the conditions that Su[13] et al. had recently devised, but there was very little conversion in the solid-phase reaction, even when 10 equiv of primary amines was used. Further investigation showed that the cyclocondensation reaction proceeded smoothly when arylphos-

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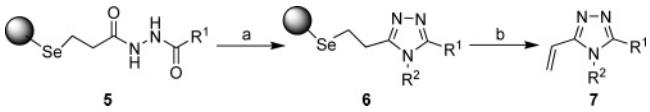
Scheme 3[a]



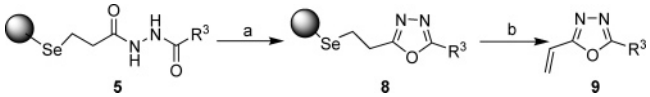
[a] Reagents and conditions: (a) $R^2-N=P-NH-R^2$, *o*-dichlorobenzene, ref, 4 h; (b) H_2O_2, THF, 0 °C, 10 min, then room temp, 1.5 h.

Table 1. Synthesis of the Vinyl-Substituted 1,2,4-Trizoles

product	R^1	R^2	yield (%)[a]	purity (%)[b]
7a	CH_3	C_6H_5	65	90
7b	CH_3	3-$CH_3C_6H_4$	61	92
7c	CH_3	2,4-$(CH_3)_2C_6H_3$	51	89
7d	CH_3	4-ClC_6H_4	60	89
7e	CH_3	3-$CH_3OC_6H_4$	61	90
7f	CH_3	α-naphthalenyl	53	85
7g	C_6H_5	C_6H_5	63	87
7h	C_6H_5	4-$CH_3C_6H_4$	61	91
7i	C_6H_5	3-$CH_3C_6H_4$	61	90
7j	C_6H_5	4-ClC_6H_4	59	94
7k	C_6H_5	3-$CH_3OC_6H_4$	57	89
7l	C_6H_5 CH_2	2-$CH_3C_6H_4$	54	89
7m	C_6H_5 CH_2	2,4-$(CH_3)_2C_6H_3$	55	93
7n	C_6H_5 CH_2	4-ClC_6H_4	59	91
7o	C_6H_5 CH_2	3-$CH_3OC_6H_4$	61	89
7p	4-$CH_3OC_6H_4$	C_6H_5	64	92
7q	4-$CH_3OC_6H_4$	3-$CH_3C_6H_4$	60	89
7r	4-$CH_3OC_6H_4$	2,4-$(CH_3)_2C_6H_3$	56	85
7s	4-$CH_3OC_6H_4$	4-ClC_6H_4	61	90
7t	*n*-C_6H_{13}	C_6H_5	69	93
7u	*n*-C_6H_{13}	4-$CH_3C_6H_4$	67	91
7v	*n*-C_6H_{13}	2,4-$(CH_3)_2C_6H_3$	60	88
7w	*n*-C_6H_{13}	4-ClC_6H_4	62	90
7x	*i*-C_3H_7	3-$CH_3C_6H_4$	59	86
7y	*i*-C_3H_7	2,4-$(CH_3)_2C_6H_3$	49	92
7z	*i*-C_3H_7	4-ClC_6H_4	58	89

[a] Yield of the crude products based on the loading of the resin **3**. [b] Purity of the crude products was determined by HPLC (λ = 254 nm).

Scheme 4[a]



[a] Reagents and conditions: (a) phosphorus oxychloride, ref, 12 h; (b) H_2O_2, THF, 0 °C, 10 min, then room temp, 1.5 h.

phazoanilide ($Ar-N=P-NH-Ar$)[14] was used. After the selenoxide syn elimination of resin **6**, the triazoles **7** can be obtained in moderate yield with good purity regardless of R^1 and R^2 (in products **7**) being alkyl or aryl with an electron-donating group or an electron-withdrawing group (Scheme 3). The results are described in Table 1.

In addition to arylphosphazoanilide, resin **5** can also perform cyclocondensation itself with elimination of the water to form 1,3,4-oxadiazole.[15] In the presence of phosphorus oxychloride, the cyclocondensation reaction of resin **5** was carried out smoothly to form resin **8**, followed by selenoxide syn elimination to obtain vinyl-substituted 1,3,4-oxazole **9** in a moderate yield with good purity (Scheme 4). The results are summarized in Table 2.

To expand the diversity of this method, Porco's two-step one-pot condensation was performed because it was also one of the most useful and powerful tools in organic chemistry.[16]

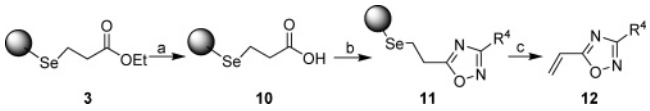
Thus, resin **3** was treated with LiOH to give the corresponding resin **10** almost quantitatively, and the reaction was also monitored by FT-IR, which showed a strong peak for the carbonyl absorption at 1694 cm^{-1}. Resin **10** was also found to react smoothly with amidoxime and DCC through Porco's two-step one-pot condensation to furnish resin **11** (FT-IR spectra showed a band at 1653 cm^{-1}, with disappearance of the band at 1694 cm^{-1}), which was followed by selenoxide syn elimination to obtain vinyl-substituted 1,2,4-oxazole **12** in a moderate yield with good purity (Scheme 5). The results are summarized in Table 3.

Table 2. Synthesis of the Vinyl-Substituted 1,3,4-Oxadiazoles

product	R^3	yield (%)[a]	purity (%)[b]
9a	CH_3	67	94
9b	C_6H_5	66	88
9c	$CH_2C_6H_5$	63	91
9d	4-$CH_3OC_6H_4$	64	90
9e	*n*-C_6H_{13}	61	92
9f	*i*-C_3H_7	57	89

[a] Yield of the crude products based on the loading of the resin **3**. [b] Purity of the crude products was determined by HPLC (λ = 254 nm).

Scheme 5[a]



[a] Reagents and conditions: (a) LiOH, THF, H_2O, room temp, 24 h; (b) DCC, $R^4C(NH_2)=NOH$, 1,4-dioxane, 50 °C, 15 h, then 95 °C, 5 h; (c) H_2O_2, THF, 0 °C, 10 min, then room temp, 1.5 h.

Table 3. Synthesis of the Vinyl-Substituted 1,2,4-Oxadiazoles

product	R^4	yield (%)[a]	purity (%)[b]
12a	C_6H_5	62	89
12b	4-$CH_3C_6H_4$	60	92
12c	4-$CH_3OC_6H_4$	58	94
12d	2-ClC_6H_4	53	88
12e	3-BrC_6H_4	57	91
12f	4-BrC_6H_4	60	93
12g	4-ClC_6H_4	61	91
12h	4-FC_6H_4	56	86

[a] Yield of the crude product based on the loading of the resin **3**. [b] Purity of the crude product was determined by HPLC (λ = 254 nm).

In all these reactions, the polystyrene-supported resins not only facilitate separation of products but also serve as a pro-vinyl safety-catch linker (the protective group of the terminal double bond during the reaction and finally released through facile selenoxide syn elimination).

Conclusions

In summary, we developed efficient solid-phase parallel synthetic routes to vinyl-substituted oxadiazoles and 1,2,4-triazoles using polymer-supported selenium resin. The advantages of these methods include straightforward operation, lack of odor, stability, and high purity of the product.

Experimental Section

General Methods. The starting materials were obtained from commercial suppliers and were used without further purification. THF and 1,4-dioxane were distilled from sodium/benzophenone immediately prior to use. Polystyrene (H 1000, 100−200 mesh, cross-linked with 1% divinylbenzene) was used for the preparation of the selenenyl bromide resin (1.25 mmol of Br g^{-1}), according to the procedure described by Nicolaou and co-workers,[10] and was purchased from commercial sources (Nankai University). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance spectrometer, using $CDCl_3$ as the solvent and TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on a Agilent 5975 inert mass selective detector. Infrared spectra were recorded on a Bruker Vector 22 spectrometer. Elemental analyses were performed on a Flash EA1112 instrument. HPLC was performed on an Agilent 1100 (column, Eclipse XDB-C18 5 μm, 4.6 × 150 mm; mobile phase, 50/20/30 THF/MeOH/H_2O (v/v); flow rate, 1.0 mL min^{-1}; detector, UV 254 nm). The samples were further purified by TLC for ^{1}H NMR, ^{13}C NMR, and microanalysis.

Typical Procedure for the Preparation of Arylphosphazoanilide (Ar−N═P−NH−Ar). Phosphorus trichloride (15 mmol) was slowly dropped into a solution or suspension of the amine (78 mmol) in 100 mL of toluene. The mixture was stirred for 1.5 h at the reflux temperature. After completion of the reaction, the reaction mixture was filtered, and the filter cake was washed with hot toluene (30 mL × 2). The filtrate was evaporated to dryness under vacuum and further purified via ethanol recrystallization to obtain the products; the yield was 60−70%.

Typical Procedure for the Preparation of Resin-Bound Ethyl Propionate 3. Under a positive pressure of nitrogen, to a suspension of the swollen resin **1** (1.0 g, 1.25 mmol of Br g^{-1}) in anhydrous THF/DMF (10/3 mL) was added $NaBH_4$ (2.5 mmol). After the mixture was stirred for 10 h at room temperature, ethyl 3-chloropropionate (5.0 mmol) was added, and the mixture was stirred for 5.0 h at the room temperature. The resin was collected on a filter and washed successively with H_2O (20 mL × 2), THF (10 mL × 2), acetone (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 1), THF/H_2O (2:1) (10 mL × 1), THF (10 mL × 2) and CH_2Cl_2 (10 mL × 2), and then dried under vacuum overnight to afford resin **3**.

Typical Procedure for the Preparation of the Substituted Acid *N′*-(3-Resin-Bound-propionyl)-hydrazide 5. Under a positive pressure of nitrogen, hydrazine hydrate 85% (48 mmol) was added to a suspension of the swollen polystyrene resin **3** (1.0 g) in methanol (15 mL). The mixture was stirred at reflux temperature for 24 h. The resin was collected by filtration, washed with H_2O (20 mL × 3), THF (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 2), and then dried at 35 °C under vacuum to afford resin **4**.

Anhydrous pyridine (2.4 mmol) was added to a suspension of the swollen resin **4** in anhydrous CH_2Cl_2 (15 mL), and 1.2 mmol of acyl chloride in anhydrous CH_2Cl_2 (3 mL) was dropped into the mixture at 0 °C; then the reaction mixture was stirred for 12 h at the room temperature. The resin was collected by filtration, washed with hot H_2O (20 mL × 2), hot THF (10 mL × 3), hot DMF (10 mL × 3), hot THF (10 mL × 3), hot DMSO (10 mL × 3), THF (10 mL × 2), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), and CH_2Cl_2 (10 mL × 1), and then dried at 40 °C in a vacuum overnight to afford resin **5**.

Typical Procedure for the Preparation of the Substituted 1,2,4-Trizoles (Products 7a−z). Under a positive pressure of nitrogen, arylphosphazoanilide (1.8 mmol) was added to a suspension of the swollen resin **5** (0.6 mmol functional group) in 1,2-dichlorobenzene (15 mL). The mixture was stirred for 4 h at reflux. Resin **6** was collected by filtration and washed with DMF (10 mL × 3), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 1), acetone (10 mL × 2), THF (10 mL × 1), CH_3OH (10 mL × 2), and THF (10 mL × 1).

The washed resin **6** was suspended in THF (15 mL), and 30% (aq) H_2O_2 (0.5 mL) was added; the mixture was stirred for 10 min at 0 °C, followed by an additional 1.5 h at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (25 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **7**. Further purification was via flash chromatography with *n*-hexanes−acetone (1:1 v/v) as the eluent for ^{1}H NMR, ^{13}C NMR, and microanalysis.

7a. White solid. mp: 157−159 °C. ^{1}H NMR ($CDCl_3$): δ 7.60−7.56 (3H, m), 7.26−7.24 (2H, m), 6.31−6.23 (1H, m), 6.12−6.08 (1H, m), 5.46−5.43 (1H, m), 2.31 (3H, s). ^{13}C NMR ($CDCl_3$): δ 152.1, 151.8, 133.7, 130.0, 129.8, 127.0, 121.4, 120.9, 10.9. MS: *m*/*z* 185 (M^+, 100). IR: ν_{max} (cm^{-1}) 3050, 1638, 1599, 1525, 1502, 1430, 941, 786, 761, 701. Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.26; H, 6.12%; N, 22.62%.

7b. Low-point solid. ^{1}H NMR ($CDCl_3$): δ 7.46−7.03 (4H, m), 6.30−6.23 (1H, m), 6.14−6.09 (1H, m), 5.45−5.42 (1H, m), 2.45 (3H, s), 2.30 (3H, s). ^{13}C NMR ($CDCl_3$): δ 151.9, 151.6, 140.2, 133.5, 130.4, 129.6, 127.3, 123.9, 121.0, 120.9, 21.0, 10.8. MS: *m*/*z* 199 (M^+, 100). IR: ν_{max} (cm^{-1}) 3049, 2925, 1610, 1496, 1458, 1431, 1394, 937, 852, 759, 701. Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.58; N, 21.09%. Found: C, 72.27; H, 6.69; N, 21.04%.

7c. White solid. mp: 100−102 °C. ^{1}H NMR ($CDCl_3$): δ 7.16−6.95 (3H, m), 6.21−6.14 (1H, m), 5.89−5.84 (1H, m), 5.33−5.30 (1H, m), 2.36 (3H, s), 2.15 (3H, s); 1.89 (3H, s). ^{13}C NMR ($CDCl_3$): δ 151.8, 151.7, 140.4, 135.0, 132.1, 130.0, 128.1, 127.2, 121.1, 120.6, 21.0, 16.9, 10.5. MS: *m*/*z* 213 (M^+, 100). IR: ν_{max} (cm^{-1}) 3044, 2923, 1511, 1428, 1011, 931, 881, 848, 607. Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70%. Found: C, 73.25; H, 7.12; N, 19.63%.

7d. White solid. mp: 165−167 °C. ^{1}H NMR ($CDCl_3$): δ 7.53 (2H, d, J = 8.0 Hz), 7.20 (2H, d, J = 8.0 Hz), 6.24−6.17 (1H, m), 6.09−5.42 (2H, m), 2.26 (3H, s). ^{13}C NMR ($CDCl_3$): δ 151.9, 151.6, 136.0, 132.1, 130.3, 128.3, 121.8, 120.5, 10.9. MS: *m*/*z* 219 (M^+, 100). IR: ν_{max} (cm^{-1}) 3057, 1526, 1497, 1429, 1090, 1013, 931, 842, 755, 566. Anal.

Calcd for $C_{11}H_{10}ClN_3$: C, 60.14; H, 4.59; N, 19.13%. Found: C, 60.17; H, 4.62; N, 19.17%.

7e. White solid. mp: 145−147 °C. ^{1}H NMR ($CDCl_3$): δ 7.48−7.44 (1H, m), 7.09−7.06 (1H, m), 6.82−6.80 (1H, m), 6.75−6.74 (1H, m), 6.29−6.24 (1H, m), 6.14−6.09 (1H, m), 5.46−5.43 (1H, m), 3.86 (3H, s), 2.31 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.7, 152.1, 151.9, 134.8, 130.9, 121.5, 120.9, 119.2, 115.3, 113.0, 55.6, 11.0. MS: *m*/*z* 215 (M^+, 100). IR: ν_{max} (cm^{-1}) 3056, 3007, 2930, 1607, 1492, 1458, 1429, 1281, 1220, 1048, 1022, 938, 841. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52%. Found: C, 66.89; H, 6.15; N, 19.55%.

7f. Pale yellow solid. mp: 141−143 °C. ^{1}H NMR ($CDCl_3$): δ 8.08−8.00 (2H, m), 7.65−7.60 (2H, m), 7.57−7.53 (1H, m), 7.42−7.20 (2H, m), 6.16−6.00 (2H, m), 5.34−5.31 (1H, m), 2.20 (3H, s). ^{13}C NMR ($CDCl_3$): δ 152.9, 152.7, 134.3, 130.7, 130.1, 129.8, 128.6, 128.4, 127.4, 125.7, 125.4, 121.6, 121.4, 120.8, 10.8. MS: *m*/*z* 235 (M^+, 100). IR: ν_{max} (cm^{-1}) 3423, 3063, 2926, 1597, 1521, 1469, 1072, 957, 811, 780. Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86%. Found: C, 76.60; H, 5.61; N, 17.79%.

7g. White solid. mp: 113−115 °C. ^{1}H NMR ($CDCl_3$): δ 7.52−7.50 (3H, m), 7.42−7.40 (2H, m), 7.35−7.20 (5H, m), 6.31−6.29 (2H, m), 5.53−5.50 (1H, m). ^{13}C NMR ($CDCl_3$): δ 154.0, 153.1, 134.4, 130.0, 129.8, 129.6, 128.4, 128.3, 127.6, 126.7, 122.3, 120.6. MS: *m*/*z* 247 (M^+, 100). IR: ν_{max} (cm^{-1}) 3062, 1595, 1497, 1469, 1447, 1427, 1079, 780, 698. Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99%. Found: C, 77.66; H, 5.38; N, 16.96%.

7h. White solid. mp: 106−108 °C. ^{1}H NMR ($CDCl_3$): δ 7.44 (2H, d, J = 8.8 Hz), 7.33−7.25 (5H, m), 7.10 (2H, d, J = 8.8 Hz), 6.33−6.26 (2H, m), 5.53−5.50 (1H, m), 2.44 (3H, s). ^{13}C NMR ($CDCl_3$): δ 154.1, 153.3, 140.0, 131.7, 130.6, 129.5, 128.4, 128.3, 127.3, 126.8, 122.2, 120.7, 21.2. MS: *m*/*z* 261 (M^+, 100). IR: ν_{max} (cm^{-1}) 2918, 2849, 1631, 1515, 1469, 1448, 1429, 1392, 830, 758, 692. Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08%. Found: C, 78.15; H, 5.84; N, 16.01%.

7i. Low-point solid. ^{1}H NMR ($CDCl_3$): δ 7.44−7.24 (7H, m), 7.02−7.00 (2H, m), 6.30−6.28 (2H, m), 5.52−5.49 (1H, m), 2.38 (3H, s). ^{13}C NMR ($CDCl_3$): δ 153.8, 153.1, 140.2, 134.2, 130.5, 129.7, 129.4, 128.3, 128.1, 127.8, 126.7, 124.5, 122.0, 120.6, 21.1. MS: *m*/*z* 261 (M^+, 100). IR: ν_{max} (cm^{-1}) 3024, 2920, 1607, 1591, 1491, 1468, 979, 928, 848, 797, 778, 757, 699. Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08%. Found: C, 78.09; H, 5.87; N, 16.04%.

7j. White solid. mp: 158−160 °C. ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, d, J = 8.4 Hz), 7.40−7.26 (5H, m), 7.19 (2H, d, J = 8.4 Hz), 6.33−6.22 (2H, m), 5.55−5.52 (1H, m). ^{13}C NMR ($CDCl_3$): δ 153.7, 152.8, 135.7, 132.6, 130.1, 129.6, 128.7, 128.4, 128.2, 126.2, 122.5, 120.1. MS: *m*/*z* 281 (M^+, 100). IR: ν_{max} (cm^{-1}) 3090, 3066, 1493, 1468, 1427, 1092, 1009, 933, 844, 756, 700. Anal. Calcd for $C_{16}H_{12}ClN_3$: C, 68.21; H, 4.29; N, 14.91%. Found: C, 68.18; H, 4.27; N, 14.99%.

7k. White solid. mp: 81−83 °C. ^{1}H NMR ($CDCl_3$): δ 7.47−7.39 (2H, m), 7.35−7.33 (1H, m), 7.30−7.26 (3H, m), 7.06−7.04 (1H, m), 6.83−6.80 (1H, m), 6.73−6.72 (1H, m), 6.34−6.32 (2H, m), 5.56−5.53 (1H, m), 3.79 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.7, 153.9, 153.1, 135.4, 130.8, 129.6, 128.4, 128.3, 126.7, 122.4, 120.6, 119.8, 115.4, 113.4, 55.6. MS: *m*/*z* 277 (M^+, 100). IR: ν_{max} (cm^{-1}) 3423, 3065, 2925, 2852, 1602, 1493, 1466, 1430, 1228, 1025, 696. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15%. Found: C, 73.56; H, 5.51; N, 15.18%.

7l. White solid. mp: 70−72 °C. ^{1}H NMR ($CDCl_3$): δ 7.40−7.37 (1H, m), 7.27−7.19 (2H, m), 7.12−7.06 (3H, m), 6.95−6.91 (1H, m), 6.83−6.81 (2H, m), 6.19−6.11 (1H, m), 5.94−5.90 (1H, m), 5.35−5.32 (1H, m), 4.03−3.85 (2H, m), 1.50 (3H, s). ^{13}C NMR ($CDCl_3$): δ 153.8, 152.2, 136.1, 135.0, 132.3, 131.3, 130.2, 128.6, 128.2, 127.7, 127.2, 126.7, 121.0, 120.9, 31.4, 16.5. MS: *m*/*z* 275 (M^+, 100). IR: ν_{max} (cm^{-1}) 3035, 2924, 1499, 1458, 1440, 1016, 935, 769, 721, 697, 584. Anal. Calcd for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26%. Found: C, 78.60; H, 6.27; N, 15.13%.

7m. White solid. mp: 110−112 °C. ^{1}H NMR ($CDCl_3$): δ 7.13−7.05 (5H, m), 6.90−6.81 (3H, m), 6.21−6.14 (1H, m), 5.97−5.93 (1H, m), 5.37−5.34 (1H, m), 4.03−3.87 (2H, m), 2.40 (3H, s), 1.50 (3H, s). ^{13}C NMR ($CDCl_3$): δ 153.8, 152.2, 140.2, 135.5, 135.0, 131.8, 129.5, 128.6, 128.0, 127.7, 127.3, 126.6, 120.9, 120.8, 31.2, 21.0, 16.4. MS: *m*/*z* 289 (M^+, 100). IR: ν_{max} (cm^{-1}) 3030, 2922, 1506, 1450, 1016, 938, 827, 727, 585. Anal. Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52%. Found: C, 78.80; H, 6.65; N, 14.55%.

7n. White solid. mp: 114−116 °C. ^{1}H NMR ($CDCl_3$): δ 7.39 (2H, d, J = 8.4 Hz), 7.17−7.15 (3H, m), 6.94−6.91 (2H, m), 6.90 (2H, d, J = 8.4 Hz), 6.22−6.08 (2H, m), 5.46−5.43 (1H, m), 4.02 (2H, s). ^{13}C NMR ($CDCl_3$): δ 153.7, 152.4, 135.9, 135.2, 131.7, 129.8, 128.7, 128.4, 128.3, 126.8, 122.0, 120.4, 31.1. MS: *m*/*z* 294 (100), 295 (M^+). IR: ν_{max} (cm^{-1}) 3093, 3030, 1495, 1436, 1091, 848, 741, 568. Anal. Calcd for $C_{17}H_{14}ClN_3$: C, 69.03; H, 4.77; N, 14.21%. Found: C, 68.98; H, 4.81; N, 14.23%.

7o. White solid. mp: 95−97 °C. ^{1}H NMR ($CDCl_3$): δ 7.35−7.27 (1H, m), 7.18−7.16 (3H, m), 7.02−6.95 (3H, m), 6.60−6.58 (1H, m), 6.35−6.34 (1H, m), 6.27−6.10 (2H, m), 5.45−5.42 (1H, m), 4.03 (2H, s), 3.64 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.3, 153.9, 152.5, 135.7, 134.3, 130.4, 128.6, 128.4, 126.7, 121.7, 120.8, 119.5, 116.1, 112.6, 55.3, 31.4. MS: *m*/*z* 290 (100), 291 (M^+). IR: ν_{max} (cm^{-1}) 3095, 3028, 2906, 1495, 1440, 1091, 1031, 850, 745, 733. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42%. Found: C, 74.26; H, 5.92; N, 14.38%.

7p. White solid. mp: 112−114 °C. ^{1}H NMR ($CDCl_3$): δ 7.53−7.51 (3H, m), 7.34 (2H, d, J = 8.8 Hz), 7.22−7.20 (2H, m), 6.78 (2H, d, J = 8.8 Hz), 6.28−6.26 (2H, m), 5.50−5.47 (1H, m), 3.75 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.3, 153.7, 152.6, 134.2, 129.8, 129.6, 129.5, 127.4, 121.7, 120.5, 118.7, 113.6, 55.0. MS: *m*/*z* 277 (M^+, 100). IR: ν_{max} (cm^{-1}) 3059, 2936, 2838, 1613, 1499, 1468, 1437, 1254, 1179, 1030, 836, 776, 701, 594. Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15%. Found: C, 73.52; H, 5.51; N, 15.23%.

7q. White solid. mp: 113−115 °C. ^{1}H NMR ($CDCl_3$): δ 7.40−7.31 (2H, m), 7.37 (2H, d, J = 8.8 Hz), 7.01−7.00 (2H, m), 6.79 (2H, d, J = 8.8 Hz), 6.28−6.26 (2H, m), 5.49−5.46 (1H, m), 3.75 (3H, s), 2.39 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.2, 153.5, 152.6, 140.1, 134.1, 130.3, 129.5, 129.4, 127.7, 124.4, 121.5, 120.6, 118.9, 113.6, 54.9, 21.0. MS:

m/*z* 291 (M^+, 100). IR: ν_{max} (cm^{-1}) 2931, 2839, 1612, 1465, 1253, 1180, 1030, 840, 795. Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42%. Found: C, 74.16; H, 5.93; N, 14.49%.

7r. White solid. mp: 147−150 °C. ^1H NMR ($CDCl_3$): δ 7.41 (2H, d, J = 8.8 Hz), 7.17−7.07 (3H, m), 6.79 (2H, d, J = 8.8 Hz), 6.25−6.10 (2H, m), 5.43−5.41 (1H, m), 3.74 (3H, s), 2.41 (3H, s), 1.88 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.2, 153.2, 152.4, 140.1, 134.9, 132.0, 130.6, 128.6, 128.0, 127.5, 121.0, 120.5, 119.0, 113.6, 54.8, 20.8, 16.9. MS: *m*/*z* 305 (M^+, 100). IR: ν_{max} (cm^{-1}) 2928, 2840, 1612, 1503, 1465, 1440, 1254, 1180, 1031, 836. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76%. Found: C, 74.66; H, 6.22; N, 13.87.

7s. White solid. mp: 139−141 °C. ^1H NMR ($CDCl_3$): δ 7.51 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 7.19 (2H, d, J = 8.4 Hz), 6.81 (2H, d, J = 8.4 Hz), 6.30−6.21 (2H, m), 5.53−5.49 (1H, m), 3.76 (3H, s). ^{13}C NMR ($CDCl_3$): δ 160.5, 153.6, 152.5, 135.6, 132.8, 130.1, 129.7, 128.8, 122.2, 120.3, 118.5, 113.8, 55.1. MS: *m*/*z* 311 (M^+, 100). IR: ν_{max} (cm^{-1}) 3057, 2934, 2840, 1613, 1495, 1469, 1438, 1254, 1179, 1092, 1030, 839, 731. Anal. Calcd for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48%. Found: C, 65.53; H, 4.57; N, 13.55%.

7t. Low-point solid. ^1H NMR ($CDCl_3$): δ 7.60−7.57 (3H, m), 7.25−7.22 (2H, m), 6.29−6.22 (1H, m), 6.10−6.06 (1H, m), 5.44−5.41 (1H, m), 2.62−2.58 (2H, m), 1.65−1.57 (2H, m), 1.28−1.18 (6H, m), 0.84−0.81 (3H, m). ^{13}C NMR ($CDCl_3$): δ 155.3, 151.9, 133.7, 129.9, 129.7, 127.1, 121.2, 120.9, 31.0, 28.6, 27.1, 24.8, 22.2, 13.8. MS: *m*/*z* 184 (100), 255 (M^+). IR: ν_{max} (cm^{-1}) 3052, 2955, 2928, 2857, 1597, 1501, 1431, 1013, 928, 780, 757, 698. Anal. Calcd for $C_{16}H_{21}N_3$: C, 75.26; H, 8.29; N, 16.46%. Found: C, 75.29; H, 8.36; N, 16.35%.

7u. Oil. ^1H NMR ($CDCl_3$): δ 7.38 (2H, d, J = 7.6 Hz), 7.12 (2H, d, J = 7.6 Hz), 6.29−6.22 (1H, m), 6.09−6.05 (1H, m), 5.42−5.39 (1H, m), 2.61−2.57 (2H, m), 2.47 (3H, s), 1.66−1.58 (2H, m), 1.31−1.17 (6H, m), 0.84−0.79 (3H, m). ^{13}C NMR ($CDCl_3$): δ 155.3, 151.9, 139.8, 130.9, 130.4, 126.8, 120.9, 120.8, 31.0, 28.5, 27.0, 24.7, 22.1, 21.0, 13.7. MS: *m*/*z* 198 (100), 269 (M^+). IR: ν_{max} (cm^{-1}) 3037, 2955, 2928, 2857, 1516, 1444, 1011, 827, 757. Anal. Calcd for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; N, 15.60%. Found: C, 75.69; H, 8.65; N, 15.66%.

7v. Oil. ^1H NMR ($CDCl_3$): δ 7.18−6.98 (3H, m), 6.23−6.16 (1H, m), 5.90−5.85 (1H, m), 5.33−5.30 (1H, m), 2.49−2.39 (5H, m), 1.91 (3H, s), 1.60−1.56 (2H, m), 1.26−1.17 (6H, m), 0.80−0.77 (3H, m). ^{13}C NMR ($CDCl_3$): δ 155.3, 151.7, 140.3, 135.1, 132.1, 130.0, 128.0, 127.3, 121.1, 120.4, 31.1, 28.6, 27.0, 24.7, 22.2, 21.0, 17.0, 13.8. MS: *m*/*z* 226 (100), 283 (M^+). IR: ν_{max} (cm^{-1}) 2955, 2927, 2858, 1507, 1443, 1013, 926, 829, 759. Anal. Calcd for $C_{18}H_{25}N_3$: C, 76.28; H, 8.89; N, 14.83%. Found: C, 76.14; H, 8.98; N, 14.88%.

7w. Low-point solid. ^1H NMR ($CDCl_3$): δ 7.57 (2H, d, J = 8.4 Hz), 7.22 (2H, d, J = 8.4 Hz), 6.27−6.20 (1H, m), 6.12−6.07 (1H, m), 5.47−5.44 (1H, m), 2.60−2.56 (2H, m), 1.65−1.58 (2H, m), 1.29−1.18 (6H, m), 0.85−0.82 (3H, m). ^{13}C NMR ($CDCl_3$): δ 155.2, 151.9, 135.9, 132.2, 130.2, 128.5, 121.6, 120.6, 31.1, 28.6, 27.1, 24.8, 22.2, 13.8. MS: *m*/*z* 218 (100), 289 (M^+). IR: ν_{max} (cm^{-1}) 3053, 2956, 2928, 2857, 1496, 1430, 1092, 1010, 844. Anal. Calcd for $C_{16}H_{20}ClN_3$: C, 66.31; H, 6.96; N, 14.50%. Found: C, 66.24; H, 7.00; N, 14.55%.

7x. White solid. mp: 59−61 °C. ^1H NMR ($CDCl_3$): δ 7.40−7.28 (2H, m), 6.97 (2H, s), 6.20−5.95 (2H, m), 5.41−5.30 (1H, m), 2.77−2.74 (1H, m), 2.38 (3H, s), 1.21 (3H, s), 1.19 (3H, s). ^{13}C NMR ($CDCl_3$): δ 159.6, 151.8, 140.1, 133.6, 130.4, 129.5, 127.7, 124.3, 120.9, 120.8, 29.0, 24.8, 21.0. MS: *m*/*z* 212 (100), 227 (M^+). IR: ν_{max} (cm^{-1}) 3022, 2973, 2930, 2871, 1607, 1494, 1445, 1098, 933, 800, 702. Anal. Calcd for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49%. Found: C, 74.05; H, 7.60; N, 18.35%.

7y. Low-point solid. ^1H NMR ($CDCl_3$): δ 7.21−7.03 (3H, m), 6.26−6.19 (1H, m), 5.91−5.86 (1H, m), 5.36−5.32 (1H, m), 2.71−2.64 (1H, m), 2.42 (3H, s), 1.94 (3H, s), 1.28−1.24 (6H, m). ^{13}C NMR ($CDCl_3$): δ 159.6, 151.6, 140.3, 135.2, 132.1, 130.1, 128.0, 127.5, 121.2, 120.5, 24.9, 21.4, 21.0, 20.7, 17.0. MS: *m*/*z* 226 (100), 241 (M^+). IR: ν_{max} (cm^{-1}) 2972, 2928, 2871, 1506, 1438, 1097, 1012, 928, 826. Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.65; H, 7.94; N, 17.41%. Found: C, 74.69; H, 8.00; N, 17.31%.

7z. White solid. mp: 67−69 °C. ^1H NMR ($CDCl_3$): δ 7.54 (2H, d, J = 8.0 Hz), 7.19 (2H, d, J = 8.0 Hz), 6.22−6.14 (1H, m), 6.05−6.01 (1H, m), 5.42−5.39 (1H, m), 2.78−2.75 (1H, m), 1.25−1.20 (6H, m). ^{13}C NMR ($CDCl_3$): δ 159.5, 151.9, 136.0, 132.3, 130.2, 128.7, 121.7, 120.6, 25.0, 21.1. MS: *m*/*z* 232 (100), 247 (M^+). IR: ν_{max} (cm^{-1}) 3090, 3054, 2973, 2931, 1496, 1438, 1091, 1009, 844, 505. Anal. Calcd for $C_{13}H_{14}ClN_3$: C, 63.03; H, 5.70; N, 16.96%. Found: C, 63.10; H, 5.72; N, 16.92%.

Typical Procedure for the Preparation of the Substituted 1,3,4-oxadiazoles (Products 9a−f). Resin **5** (0.6 mmol functional group) and 25 mL of phosphorus oxychloride was refluxed for 12 h under a nitrogen atmosphere. After completion of the reaction, resin **8** was collected by filtration and washed with DMF (10 mL × 1), THF (10 mL × 1), DMSO (10 mL × 1), THF (10 mL × 1), THF/H_2O (2:1) (10 mL × 2), THF (10 mL × 2), H_2O (10 mL × 2), THF (10 mL × 1), acetone (10 mL × 1), THF (10 mL × 2).

The washed resin **8** was suspended in THF (15 mL), and 30% (aq) H_2O_2 (0.5 mL) was added, the mixture was stirred for 10 min at 0 °C, followed by an additional 1.5 h at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (25 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **9**. Further purification was via flash chromatography with *n*-hexanes−EtOAc (1/1−2/1 v/v) as the eluent for ^1H NMR, ^{13}C NMR, and microanalysis.

9a. Oil. ^1H NMR ($CDCl_3$): δ 6.69−6.62 (1H, m), 6.19−5.73 (2H, m), 2.52 (3H, s). ^{13}C NMR ($CDCl_3$): δ 163.9, 163.3, 124.5, 119.9, 11.0. MS: *m*/*z* 110 (M^+, 100). IR: ν_{max} (cm^{-1}) 2926, 2854, 1720, 1580, 1529, 1237, 978, 769. Anal. Calcd for $C_5H_6N_2O$: C, 54.54; H, 5.49; N, 25.44%. Found: C, 54.47; H, 5.54; N, 25.50%.

9b. Oil. ^1H NMR ($CDCl_3$): δ 8.11−8.09 (2H, m), 7.57−7.51 (3H, m), 6.84−6.77 (1H, m), 6.39−5.86 (2H, m). ^{13}C

NMR ($CDCl_3$): δ 164.2, 163.6, 131.9, 129.1, 127.0, 124.9, 123.8, 120.1. MS: *m/z* 172 (M^+, 100). IR: ν_{max} (cm^{-1}) 3066, 2925, 1611, 1550, 1524, 1485, 1450, 978, 726, 704. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27%. Found: C, 69.71; H, 4.72; N, 16.30%.

9c. Oil. ^1H NMR ($CDCl_3$): δ 7.36−7.26 (5H, m), 6.69−6.61 (1H, m), 6.19−5.72 (2H, m), 4.19 (2H, s). ^{13}C NMR ($CDCl_3$): δ 164.7, 163.9, 133.5, 128.7, 128.6, 127.3, 124.7, 119.6, 31.5. MS: *m/z* 91 (100), 186 (M^+). IR: ν_{max} (cm^{-1}) 3032, 2926, 1567, 1527, 1496, 1030, 980, 944, 729, 695. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04%. Found: C, 70.98; H, 5.45; N, 14.98%.

9d. White solid. mp: 80−82 °C. ^1H NMR ($CDCl_3$): δ 7.84 (2H, d, J = 9.2 Hz), 6.85 (2H, d, J = 9.2 Hz), 6.67−6.59 (1H, m), 6.19−5.68 (2H, m), 3.71 (3H, s). ^{13}C NMR ($CDCl_3$): δ 163.6, 162.7, 161.9, 128.2, 124.0, 119.5, 115.6, 114.0, 55.0. MS: *m/z* 135 (100), 202 (M^+). IR: ν_{max} (cm^{-1}) 3071, 2988, 2953, 2843, 1885, 1641, 1526, 1269, 1088, 1021, 939, 769, 698, 521. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85%. Found: C, 65.28; H, 5.05; N, 13.81%.

9e. Oil. ^1H NMR ($CDCl_3$): δ 6.64−6.57 (1H, m), 6.13−5.5.68 (2H, m), 2.79−2.75 (2H, m), 1.75−1.68 (2H, m), 1.34−1.21 (6H, m), 0.82−0.78 (3H, m). ^{13}C NMR ($CDCl_3$): δ 166.7, 163.7, 124.4, 120.1, 31.3, 28.7, 26.5, 25.4, 22.5, 14.0. MS: *m/z* 110 (100), 180 (M^+). IR: ν_{max} (cm^{-1}) 2957, 2931, 2859, 1571, 1528, 1027, 980, 940, 766. Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54%. Found: C, 66.59; H, 9.01; N, 15.48%.

9f. Oil. ^1H NMR ($CDCl_3$): δ 6.64−6.57 (1H, m), 6.23−6.09 (1H, m), 5.77−5.67 (1H, m), 3.14−3.07 (1H, m), 1.32 (3H, s), 1.31 (3H, s). ^{13}C NMR ($CDCl_3$): δ 170.3, 163.4, 124.1, 119.8, 26.1, 19.8. MS: *m/z* 55 (100), 138 (M^+). IR ν_{max} (cm^{-1}): 2978, 2938, 2879, 1567, 1529, 1013, 981, 943, 774. Anal. Calcd for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28%. Found: C, 60.91; H, 7.33; N, 20.21%.

Typical Procedure for the Preparation of the Resin-Bound Propionic Acid 10. Under a positive pressure of nitrogen, 5 mL of H_2O and LiOH (2.4 mmol) was added to a suspension of the swollen resin **3** (1.0 g) in THF (20 mL). The mixture was stirred at room temperature for 24 h. Resin 10 was collected by filtration, washed with THF (10 mL × 1), H_2O (20 mL × 2), THF (10 mL × 1), THF/H_2O (2/1) (10 mL × 2), THF (10 mL × 1), H_2O (20 mL × 2), THF (10 mL × 2), CH_2Cl_2 (10 mL × 2), and then dried at 40 °C in a vacuum.

Typical Procedure for the Titration of Carboxylate of Resin 10. Titration was effected by treatment of 0.5 g of resin **10** with an excess of *n*-BuLi in benzene and back-titration with 0.1 N HCl. Resin **10** was found to contain around 1.20 mmol of functional group per gram.

Typical Procedure for the Preparation of the Substituted 1,2,4-oxadiazoles (Products 12a−h). Under a positive pressure of nitrogen, DCC (1.5 mmol) was added to a suspension of the swollen resin 10 (0.6 mmol functional group) in anhydrous 1,4-dioxane (20 mL). The mixture was stirred at 50 °C for 3 h; then amidoxime (2.1 mmol) was added. The mixture was stirred at 50 °C for 12 h and then at 95 °C for 5 h. Resin **11** was collected by filtration and washed with hot DMF (10 mL × 2), hot EtOH (10 mL × 2), hot THF (10 mL × 2), hot EtOH (10 mL × 2), hot THF (10 mL × 2), hot EtOH (10 mL × 2), and hot THF (10 mL × 2).

The washed resin **11** was suspended in THF (15 mL), and 30% (aq) H_2O_2 (0.5 mL) was added; the mixture was stirred for 10 min at 0 °C, followed by 1.5 h at room temperature. The mixture was filtered, and the resin was washed with CH_2Cl_2 (15 mL × 2). The filtrate was washed with H_2O (25 mL × 2), dried over $MgSO_4$, and evaporated to dryness under vacuum to obtain the crude products **12**. Further purification was via flash chromatography with *n*-hexanes−EtOAc (12/1−16/1 v/v) as the eluent for ^1H NMR, ^{13}C NMR, and microanalysis.

12a. Oil. ^1H NMR ($CDCl_3$): δ 8.12−8.09 (2H, m), 7.51−7.47 (3H, m), 6.81−6.57 (2H, m), 6.01−5.99 (1H, m). ^{13}C NMR ($CDCl_3$): δ 174.3, 168.6, 131.1, 128.7, 128.6, 127.3, 126.6, 120.4. MS: *m/z* 119 (100), 172 (M^+). IR: ν_{max} (cm^{-1}) 3071, 2926, 1647, 1543, 1446, 1360, 958, 912, 770, 707. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27%. Found: C, 69.70; H, 4.72; N, 16.33%.

12b. Oil. ^1H NMR ($CDCl_3$): δ 7.99 (2H, d, J = 8.0 Hz), 7.29 (2H, d, J = 8.0 Hz), 6.78−6.71 (1H, m), 6.59−5.96 (2H, m), 2.40 (3H, s). ^{13}C NMR ($CDCl_3$): δ 174.2, 168.6, 141.4, 129.4, 128.5, 127.2, 123.8, 120.5, 21.4. MS: *m/z* 133 (100), 186 (M^+). IR: ν_{max} (cm^{-1}) 3321, 3034, 2924, 2852, 1613, 1541, 1477, 1415, 1357, 786. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04%. Found: C, 70.98; H, 5.45; N, 14.95%.

12c. White solid. mp: 49−51 °C. ^1H NMR ($CDCl_3$): δ 8.05−8.02 (2H, m), 7.00−6.98 (2H, m), 6.78−6.71 (1H, m), 6.59−5.96 (2H, m), 3.86 (3H, s). ^{13}C NMR ($CDCl_3$): δ 174.1, 168.3, 161.8, 128.9, 128.4, 120.5, 119.1, 114.1, 55.2. MS: *m/z* 202 (M^+, 100). IR: ν_{max} (cm^{-1}) 3005, 2935, 2840, 1613, 1541, 1476, 1423, 1357, 1255, 1109, 841, 789. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85%. Found: C, 65.24; H, 5.03; N, 13.88%.

12d. Oil. ^1H NMR ($CDCl_3$): δ 7.93−7.91 (1H, m), 7.54−7.52 (1H, m), 7.45−7.36 (2H, m), 6.82−6.75 (1H, m), 6.62−6.58 (1H, m), 6.03−6.00 (1H, m). ^{13}C NMR ($CDCl_3$): δ 173.9, 167.4, 133.3, 131.6, 131.5, 130.8, 128.9, 126.8, 125.9, 120.2. MS *m/z* 153 (100), 206 (M^+). IR: ν_{max} (cm^{-1}) 3068, 2926, 2854, 1645, 1542, 1469, 1345, 1056, 956, 765, 738. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56%. Found: C, 58.08; H, 3.38; N, 13.59%.

12e. White solid. mp: 61−63 °C. ^1H NMR ($CDCl_3$): δ 8.27−8.26 (1H, m), 8.05−8.02 (1H, m), 7.65−7.63 (1H, m), 7.38−7.34 (1H, m), 6.80−6.73 (1H, m), 6.63−6.01 (2H, m). ^{13}C NMR ($CDCl_3$): δ 174.6, 167.5, 134.1, 130.33, 130.31, 129.1, 128.6, 125.8, 122.8, 120.3. MS: *m/z* 250 (M^+, 100), 252 (M + 2, 97). IR: ν_{max} (cm^{-1}) 2924, 1644, 1541, 1469, 1398, 1358, 955, 786, 727, 678. Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16%. Found: C, 47.80; H, 2.84; N, 11.19%.

12f. White solid. mp: 69−71 °C. ^1H NMR ($CDCl_3$): δ 7.96 (2H, d, J = 8.8 Hz), 7.61 (2H, d, J = 8.8 Hz), 6.78−6.70 (1H, m), 6.60−5.98 (2H, m). ^{13}C NMR ($CDCl_3$): δ 174.6, 167.9, 132.1, 129.0, 128.8, 125.7, 125.6, 120.3. MS: *m/z* 250 (M^+, 100), 252 (M + 2, 97). IR: ν_{max} (cm^{-1}) 3075, 2925, 1917, 1673, 1537, 1403, 1355, 1007, 957, 840, 787,

671. Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16%. Found: C, 47.89; H, 2.85; N, 11.10%.

12g. White solid. mp: 57−59 °C. ^{1}H NMR ($CDCl_3$): δ 8.02−8.00 (2H, m), 7.45−7.43 (2H, m), 6.77−6.70 (1H, m), 6.59−6.55 (1H, m), 6.00−5.97 (1H, m). ^{13}C NMR ($CDCl_3$): δ 174.5, 167.8, 137.3, 129.1, 128.9, 128.6, 125.2, 120.3. MS: *m*/*z* 153 (100), 206 (M^+). IR: ν_{max} (cm^{-1}) 3063, 2926, 1917, 1541, 1469, 1412, 1092, 983, 960, 837, 787, 501. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56%. Found: C, 58.02; H, 3.50; N, 13.60%.

12h. White solid. mp: 42−44 °C. ^{1}H NMR ($CDCl_3$): δ 8.12−8.07 (2H, m), 7.19−7.14 (2H, m), 6.79−6.71 (1H, m), 6.60−5.98 (2H, m). ^{13}C NMR ($CDCl_3$): δ 174.4, 167.8, 164.5 (J = 249.4 Hz), 129.5 (J = 8.7 Hz), 128.8, 122.9 (J = 3.1 Hz), 120.3, 116.0 (J = 22.0 Hz). MS: *m*/*z* 149 (100), 190 (M^+). IR: ν_{max} (cm^{-1}) 3063, 2926, 1920, 1608, 1473, 1420, 1214, 963, 845, 788, 515. Anal. Calcd for $C_{10}H_7FN_2O$: C, 63.16; H, 3.71; N, 14.73%. Found: C, 63.09; H, 3.75; N, 14.79%.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra of all the products and parts of HPLC spectra of **7a**, **7f**, **7g**, **7j**, **7k**, **7m**, **7y**, **9b**, **9d**, **12a**, **12f**, **12h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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