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Synthesis of 2-Thio- and 2-Oxoimidazoles via Cascade Addition−Cycloisomerization Reactions of Propargylcyanamides

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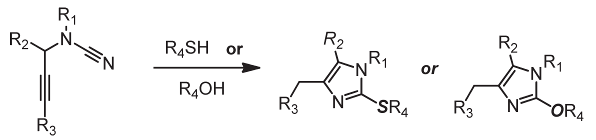


A methodology to generate 2-thio- and 2-oxoimidazoles through an addition−cyclization−isomerization reaction of propargylcyanamides with thiol and alcohol nucleophiles is described. In general, the reaction sequence allows for the rapid formation of highly substituted 2-thio- and 2-oxoimidazoles in good to excellent yields.

Both 2-thio- and 2-oxoimidazoles represent medicinally important heterocyclic scaffolds. These target substructures are central to compounds possessing inhibitory activity against HIV-1 reverse transcriptase,[1] p38 MAP kinase,[2] as well as histamine-H3 antagonists[3] (Figure 1). They have also been documented as key pharmacophores in agents for the treatment of thrombosis,[4] inflammation, and asthma.[5] The preparation of these heterocycles is usually accomplished by nucleophilic substitution of activated 2-sulfonyl-,[6] 2-nitro-,[7] or 2-haloimidazoles[8] or by the alkylation of imidazolethiones.[9] The substitution approach is often lengthy requiring multiple protecting group and oxidation manipulations, while alkylation is generally restricted to sp^3 hybridized electrophiles and can give mixtures of S/O and N alkylated products.

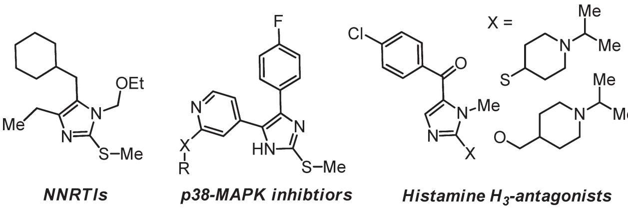
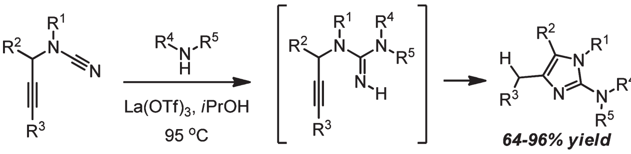


FIGURE 1. Medicinally relevant 2-thio- and 2-oxoimidazoles.

Our interest in the chemistry and biology of 2-aminoimidazoles[10] prompted us to develop a one-pot addition−hydroamination−isomerization sequence to access these related heterocycles.[11] This approach generates highly substituted 2-aminoimidazoles in just three steps by the addition of secondary amines to propargylcyanamides, as shown in Scheme 1. This reaction required the addition of a metal catalyst and it was eventually found that La(III) promotes the reaction effectively.

SCHEME 1. Addition−Hydroamination−Isomerization Sequence



We felt that the success of this methodology might be expanded to incorporate the addition of sulfur and oxygen nucleophiles to propargylcyanamides to rapidly synthesize 2-thio- and 2-oxoimidazoles.[12] This approach would obviate the need to prepare an activated imidazole for nucleophilic substitution. It would also allow for S/O building blocks to be introduced as nucleophiles, thus complementing imidazolethione alkylation. In particular it would broaden substituent diversity with the inclusion of an S/O substituent bearing an adjacent sp^2 hybridized carbon atom.

One of the key aspects to this chemistry is the rapid preparation of the propargylcyanamide precursors (Table 1). The propargylcyanamides (**2a**−**d**) used in this study were prepared in two steps by a iminium−acetylide three-component coupling (3-CC) to give the propargylamines **1a**−**d**.[13] Cleavage of the tertiary amine with cyanogen bromide gave the propargylcyanamides **2a**−**d** with cleavage of the

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(5) Fenske, D. C.; Kuo, E. A.; Tully, W. R. U.S. Patent 4,810,828, **1989**.
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(7) Goldamn, P.; Wuest, J. D. *J. Am. Chem. Soc.* **1981**, *103*, 6224.
(8) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Synthesis* **1999**, 1613.
(9) For representative examples see: (a) Tweit, R. C.; Kreider, E. M.; Muir, R. D. *J. Med. Chem.* **1973**, *16*, 1161. (b) Anderson, W. K.; Bhattacharjee, D.; Houston, D. M. *J. Med. Chem.* **1989**, *32*, 119. (c) Theoclitou, M.-E.; Delaet, N. G. J.; Robinson, L. A. *J. Comb. Chem.* **2002**, *4*, 315.
(10) Sullivan, J. D.; Giles, R. L.; Looper, R. E. *Curr. Bioact. Compd.* **2009**, *5*, 39.
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(12) A conceptually related sequence has been reported for the addition of H_2S to allenylthioureas to generate imidazolethiones: Devan, B.; Rajagopalan, K. *Tetrahedron Lett.* **1994**, *35*, 1585.
(13) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (c) Aschwanden, P.; Stephenson, C. R. J.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437.

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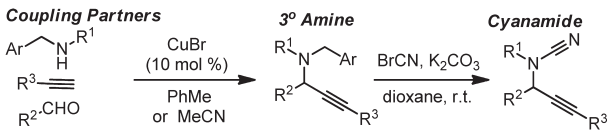
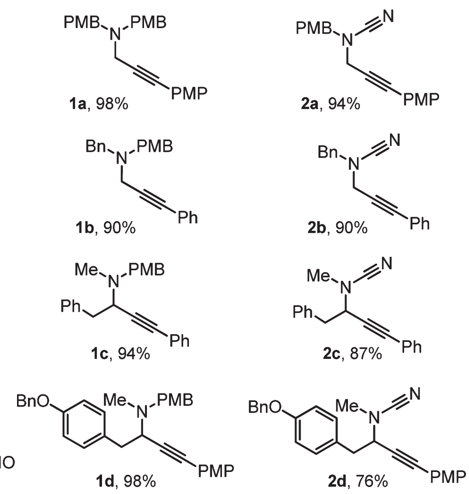
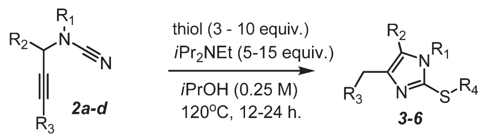
TABLE 1. Synthesis of Propargylcyanamides

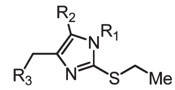
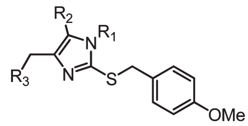
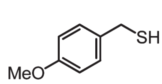
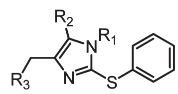
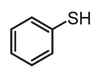
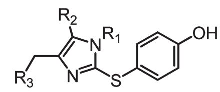
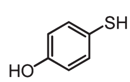




Coupling Partners	3° Amine	Cyanamide
PMB_2NH; PMP—≡; HCHO	**1a**, 98%	**2a**, 94%
PMBNHBn; Ph—≡; HCHO	**1b**, 90%	**2b**, 90%
PMBNMe; Ph—≡; $PhCH_2CHO$	**1c**, 94%	**2c**, 87%
PMBNMe; PMP—≡; 4-BnOPhCH_2CHO	**1d**, 98%	**2d**, 76%

TABLE 2. Scheme 2 Synthesis of 2-Thioimidazoles



Entry	cyanamide	thiol	2-thioimidazole	R_1	R_2	R_3	Yield
							
1	**2a**	Me⌒SH	**3a**	PMB	H	PMP	67%
2	**2b**		**3b**	Bn	H	Ph	77%
3	**2c**		**3c**	Me	Bn	Ph	93%
4	**2d**		**3d**	Me	*p*-BnOBn	PMP	82%
							
5	**2a**		**4a**	PMB	H	PMP	82%
6	**2b**		**4b**	Bn	H	Ph	71%
7	**2c**		**4c**	Me	Bn	Ph	97%
8	**2d**		**4d**	Me	*p*-BnOBn	PMP	53%
							
9	**2a**		**5a**	PMB	H	PMP	83%
10	**2b**		**5b**	Bn	H	Ph	91%
11	**2c**		**5c**	Me	Bn	Ph	94%
12	**2d**		**5d**	Me	*p*-BnOBn	PMP	87%
							
13	**2a**		**6a**	PMB	H	PMP	74%
14	**2b**		**6b**	Bn	H	Ph	64%
15	**2c**		**6c**	Me	Bn	Ph	77%
16	**2d**		**6d**	Me	*p*-BnOBn	PMP	78%

intermediate cyanoammonium salt at the activated benzylic position of the PMB group.[14]

We initially investigated the addition of neutral thiols to initiate the addition−cyclization−isomerization sequence. While we observed formation of **3a** after heating a solution of the propargylcyanamide **2a** with ethanethiol, only ~5% of the propargylcyanamide had been converted to the desired 2-thioimidazole after 24 h at 150 °C. The poor electrophilic nature of *N*,*N*-dialkylcyanamides suggested that a Lewis acid catalyst or an anionic species would be required to effect addition to the cyanamide.[15,16] In contrast to the addition of amines to propargylcyanamides, La(III) did not catalyze product formation.[11] This was worrisome as we had previously noted that the propargylcyanamides undergo isomerization to the allenecyanamides under basic conditions, resulting in decomposition/polymerization. Thus it was questionable if thiolate anions ($pK_a \approx 8-11$)[17] would be capable of isomerizing the propargylcyanamides. Fortunately, the addition of 5 equiv of Hunig's base in the reaction mixture led to complete consumption of the propargylcyanamide after only 12 h at 120 °C to give 2-ethylthioimidazole **3a** in 67% yield (Table 2, entry 1). Treatment of the other cyanamides under the same conditions gave comparative results (entries 2−4). Benzylic thiols also gave the 2-thioimidazoles in moderate to good yields (Table 2, entries 5−8). Thiophenols are also competent partners in this reaction sequence (Table 2, entries 9−12) and react chemoselectively in the presence of phenols (Table 2, entries 13−16).

For experimental convenience we were using an excess of thiol in the addition−cyclization−isomerization sequence; however, we found that the use of dithiols in the presence of 1.5 equiv of cyanamide per thiol was capable of producing bis-2-thioimidazoles **7a** and **7b** in good yields (Scheme 2).

Since we had noted that isopropanol was a noncompetitive solvent for the La(III) catalyzed addition of amines to cyanamides, it was not surprising to observe that they were not competent nucleophiles in the addition−cycloisomerization sequence under neutral conditions.[11] Also, we had previously observed that sterically hindered alkoxides (KO*t*Bu in THF) quantitatively isomerized propargylcyanamides to the allenecyanamides in ~10 min at 0 °C. Due to the increased basicity of alkoxides relative to thiolates, which could favor isomerization over addition to the cyanamide, we were pessimistic that phenoxides or alkoxides

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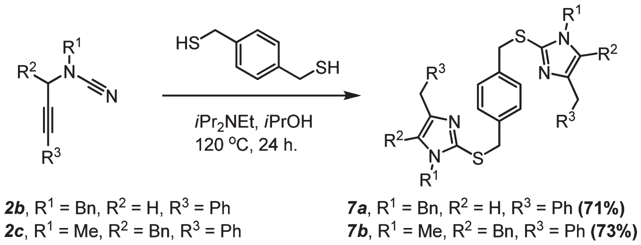
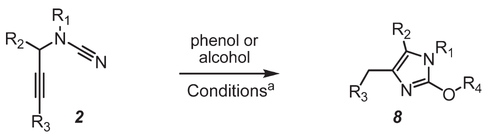
(15) Snider, B. B.; O'Hare, S. M. *Tetrahedron Lett.* **2001**, *42*, 2455.
(16) Dalby, K. N.; Jencks, W. P *J. Chem. Soc., Perkin Trans. 2* **1997**, 1555.
(17) (a) Pascal, I.; Tarbell, D. S. *J. Am. Chem. Soc.* **1957**, *79*, 6015. (b) Kreevoy, M. M.; Harper, E. T.; Duvall, R. E.; Wilgus, H. S. III; Ditsch, L. T. *J. Am. Chem. Soc.* **1960**, *82*, 4899.

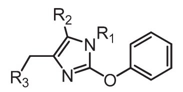
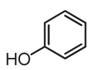
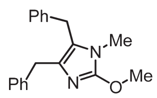
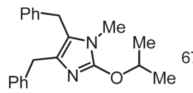
SCHEME 2. Synthesis of Bis-2-thioimidazoles



would be competent nucleophiles in this chemistry. Contrary to our assumptions, treatment of cyanamide **2a** with phenol in the presence of K_2CO_3 successfully delivered the 2-phenoxyimidazole (**8a**) in 77% yield (Table 3, entry 1). Toluene proved to be the best solvent for temperature considerations.

TABLE 3. Synthesis of 2-Oxoimidazoles



Entry	cyanamide	conditions^a	alcohol	2-oxoimidazole		R_1	R_2	R_3	Yield
									
1	**2a**	*A*		**8a**		PMB	H	PMP	77%
2	**2c**	*A*		**8b**		Me	Bn	Ph	76%
3	**2d**	*A*		**8c**		Me	*p*-BnOPh	PMP	62%
4	**2c**	*B*	MeOH	**8d**					72%
5	**2c**	*C*							82%
6	**2c**	*C*	*i*PrOH	**8e**					67%

We then pressed our nucleophile choice to alkoxides and were quite surprised to see that MeOH and Huning's base gave the methoxyimidazole **8d** in 72% yield (Table 3, entry 4). The use of K_2CO_3 worked equally as well to promote the reaction (entry 5). We were quite surprised to see that *i*PrOH, the solvent choice for the La(III) catalyzed amine addition–hydroamination–isomerization manifold, delivered the 2-isopropoxyimidazole **8e** in 67% yield with the addition of K_2CO_3 (entry 6).

In conclusion we have developed optimal conditions for the addition of both alkyl and aryl thiols and alcohols to propargylcyanamides. Subsequent cycloisomerization delivers the 2-thio- or 2-oxoimidazoles in good yields. The fact that equimolar KO*t*Bu decomposes the substrates but catalytically generated nucleophiles (e.g., K_2CO_3/*i*PrOH) are competent partners suggests that thio- or oxo-nucleophiles with a $pK_a < \sim 18$ should be tolerated under these conditions. Interestingly La(III) does not influence the reaction of thio- or oxo-nucleophiles with propargylcyanamides, suggesting a unique catalytic role for La(III) in the addition–hydroamination–isomerization sequence with amines. Studies to elucidate this mechanistic difference are currently underway and will be reported in due course.

Experimental Section

Typical Procedure for the Preparation of Propargylamines. *N*,*N*-Bis(4-methoxybenzyl)-3-(4-methoxyphenyl)prop-2-yn-1-amine (1a). To a 100 mL round-bottomed flask containing a magnetic stir bar was added bis(4-methoxybenzyl)amine (PMB_2NH) (3.73 g, 14.5 mmol, 1.0 equiv), 37% aqueous solution of formaldehyde (6.54 g, 6.00 mL, 80.6 mmol, 5.6 equiv), 4-methoxyphenyl acetylene (2.02 g, 15.3 mmol, 1.06 equiv), CuBr (0.209 g, 1.45 mmol, 0.1 equiv), and MeCN (45 mL). The reaction mixture was allowed to stir at room temperature for 24 h. The reaction mixture was filtered through a plug of Celite before the solvent was removed under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 5.7 × 15 cm column, eluting with 20% ethyl acetate/hexanes. The product containing fractions were combined and then concentrated under reduced pressure to give propargylamine **1a** (5.77 g, 98% yield) as a light yellow oil. R_f 0.49 (35% ethyl acetate /hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (ddd, J = 9.5, 2.5, 2.0 Hz 2H), 7.35 (ddd, J = 8.4, 2.9, 1.8 Hz 4H), 6.90–6.86 (m, 6H), 3.81 (s, 6H), 3.83 (s, 3H), 3.80 (s, 6H), 3.67 (s, 2H), 3.43 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 159.0, 133.4, 131.3, 130.5, 115.8, 114.2, 113.9, 85.8, 83.2, 57.1, 55.6, 55.5, 42.0. ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: (2 × 55.4); CH_2: 57.0, 41.8; CH_1: 133.3, 132.3, 131.1, 114.0, 113.8; CH_0: 158.9, 85.8, 83.2. IR (neat): 2933, 2834, 1607, 1509, 1463, 1291, 1246, 1172, 1106, 1034, 832, 668 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{28}NO_3$ m/z (M + H) 402.2069, obsd 402.2055.

Typical Procedure for the Preparation of Propargylcyanamides. *N*-(4-Methoxybenzyl)-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)cyanamide (2a). To a 250 mL round-bottomed flask containing a magnetic stir bar was added propargylamine **1a** (5.030 g, 12.5 mmol, 1.0 equiv), 3 M solution of CNBr in CH_2Cl_2 (8.40 mL, 25.1 mmol, 2.0 equiv), K_2CO_3 (3.916 g, 28.33 mmol, 2.3 equiv), and dioxane (125 mL). The reaction mixture was allowed to stir at rt for 24 h before being quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL). The reaction mixture was diluted in CH_2Cl_2 (100 mL) and water (50 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 5.7 × 15 cm column, eluting with 20% ethyl acetate/hexanes. The product containing fractions were combined and then concentrated under reduced pressure to give cyanamide **2a** (3.608 g, 94% yield) as a light yellow oil. R_f 0.40 (35% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.26 (s, 2H), 3.92 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.3, 160.2, 133.6, 130.7, 126.0, 117.7, 114.5, 114.4, 114.3, 114.2, 87.2, 80.1, 55.6, 55.5, 54.3, 41.1. ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.6, 55.5; CH_2: 54.3, 41.1; CH_1: 133.6, 130.7, 114.5, 114.3; CH_0: 160.3, 160.2, 126.0, 117.7, 114.5, 114.4, 87.2, 80.1. IR (neat): 2931, 2836, 1721, 1643, 1612, 1585, 1512, 1491, 1453, 1407, 1359, 1302, 1247, 1223, 1175, 1145, 1107, 1078, 1034, 905 822, 758, 696 cm^{-1}. HRMS (ESI) calcd for m/z $C_{19}H_{18}N_2NaO_2$ (M + Na) 329.1266, obsd 329.1263.

Typical Procedure for the Preparation of 2-Thioimidazoles. Preparation of 2-(Ethylthio)-1,4-bis(4-methoxybenzyl)-1*H*-imidazole (3a). To a 15 mL high-pressure tube containing a magnetic stir bar was added cyanamide **2a** (0.107 g, 0.347 mmol, 1.0 equiv), ethanethiol (0.216 g, 260 μL, 3.47 mmol, 10.0 equiv), *N*,*N*-diisopropylethylamine (0.674 g, 910 μL, 5.21 mmol, 15.0 equiv), and isopropanol (2 mL). The high-pressure tube was then sealed and placed in a preheated 120 °C oil bath. After 24 h at 120 °C, the high pressure was removed from the oil bath, which was then left to cool to rt. The crude reaction mixture was diluted in CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 2.5 × 15 cm column, eluting with 35% ethyl acetate/hexanes (w/3% triethylamine). The product containing fractions were combined and then concentrated under reduced pressure to give 2-thioimidazole **3a** (0.086 g, 67% yield) as a light yellow oil. R_f 0.24 (35% ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.42 (s, 1H), 4.96 (s, 2H), 3.80 (s, 2H), 3.73 (s, 6H), 2.94 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.3, 158.0, 143.5, 140.5, 132.2, 130.0, 128.9, 128.7, 118.3, 114.3, 113.8 (2 × 55.4), 49.7, 34.4, 29.5, 15.7. DEPT ^{13}C NMR ($CDCl_3$, 125 MHz): δ CH_3: (2 × 55.4), 15.7; CH_2: 49.7, 34.4, 29.5; CH_1: 130.0, 128.7, 118.3, 114.3, 113.8; CH_0: 159.3, 158.0, 143.5, 140.5, 132.2, 128.9. IR (neat): 2931, 2834, 1612, 1584, 1512, 1453, 1300, 1247, 1176, 1106, 1034, 794 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{24}N_2O_2S$ m/z (M + H) 369.1637, obsd 369.1641.

Typical Procedure for the Preparation of 2-Oxoimidazoles. 1,4-Bis(4-methoxybenzyl)-2-phenoxy-1*H*-imidazole (8a). In a 15 mL high-pressure tube containing a magnetic stir bar was added cyanamide **2a** (0.120 g, 0.392 mmol, 1.0 equiv), phenol (0.111 g, 0.1.18 mmol, 3.0 equiv), K_2CO_3 (0.271 g, 1.96 mmol, 5.0 equiv), and toluene (1.5 mL). The high-pressure tube was then sealed and placed in a preheated 150 °C oil bath. After 24 h at 150 °C, the high pressure was removed from the oil bath, which was then left to cool to rt. The crude reaction mixture was diluted in CH_2Cl_2 (50 mL) and water (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The organic extract was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the material was accomplished by flash column chromatography on a 2.5 × 15 cm column, eluting with 350 mL of 25% ethyl acetate/hexanes (w/1% triethylamine). The product containing fractions were combined and then concentrated under reduced pressure to give 2-oxoimidazole **8a** (0.121 g, 77% yield) as a light yellow oil. R_f 0.43 (40% ethyl acetate/hexane w/1% triethylamine). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dd, J = 7.3, 8.8 Hz, 2H), 7.20−7.14 (m, 4H), 7.13−7.07 (m, 3H), 6.84−6.81 (m, 4H), 6.13 (s, 1H), 4.82 (s, 2H), 3.77 (s, 3H), 3.77 (s, 3H), 3.76 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.4, 158.1, 155.7, 148.8, 137.9, 132.1, 130.1, 129.8, 129.1, 128.7, 124.1, 118.1, 114.3, 113.9, 112.3, 55.4, 55.4, 47.8, 34.7. ^{13}C DEPT NMR ($CDCl_3$, 125 MHz): δ CH_3: 55.4, 55.4; CH_2: 47.8, 34.7; CH_1: 130.1, 129.8, 129.1, 124.1, 118.1, 114.3, 113.9, 112.3 . IR (neat): 2933, 2834, 1611, 1587, 1509, 1476, 1299, 1240, 1204, 1174, 1030, 807, 755, 687 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{25}N_2O_3$ m/z (M + H) 401.1865, obsd 401.1860.

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Supporting Information Available: Experimental details and ^{1}H, ^{13}C, and ^{13}C DEPT NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.