JOC*Note*

Lewis Base-Promoted Hydrosilylation of Cyclic Malonates: Synthesis of β-Substituted Aldehydes and γ-Substituted Amines

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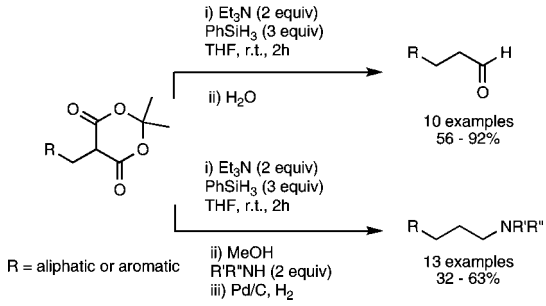
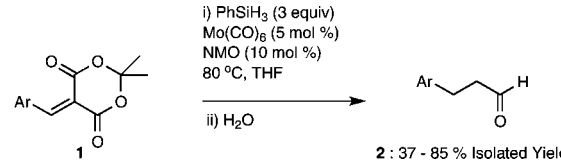


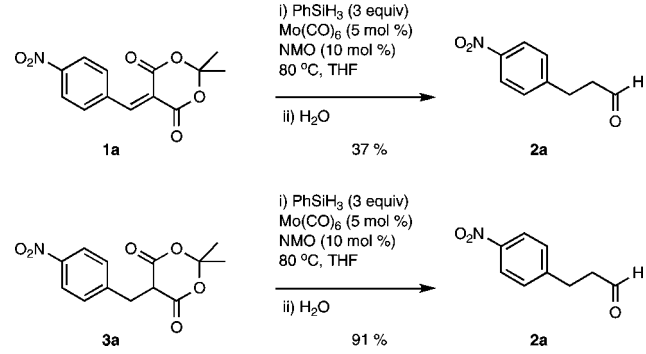
The Lewis base-promoted hydrosilylation of cyclic malonates provides a convenient synthesis of β-substituted aldehydes. No over-reduction to the primary alcohol is observed as the aldehyde functionality is protected until a subsequent hydrolysis step. The utility of the method is demonstrated in a number of examples and further in the synthesis of γ-substituted propylamines in a one-pot hydrosilylation/reductive amination process.

Aldehydes are indispensable functional groups in organic chemistry and a variety of methods have been developed for their synthesis.[1] A desirable approach to the chemoselective synthesis of aldehydes involves the direct reduction of carboxylic acid derivatives with metal hydrides.[2] However, this strategy can be capricious with some substrates lacking reactivity and the over-reduction to the corresponding alcohol a common drawback. Perhaps the most commonly used reducing agent for the synthesis of aldehydes is diisobutylaluminum hydride (DIBAL-H), although like the majority of alkylaluminium compounds, DIBAL-H ignites upon prolonged exposure to air and reacts violently with water.[3] Alternative methods for the efficient synthesis of aldehydes are of obvious importance to synthetic chemists. In this context we have recently reported the use of tandem molybdenum-catalyzed hydrosilylations in the synthesis of β-aryl aldehydes from benzylidene Meldrum's acid derivatives.[4] We proposed the reaction proceeded via an α-oxoketene intermediate formed after an initial molybdenum-catalyzed conjugate reduction and elimination of acetone. Subsequent hydrosilylation of the α-oxoketene and hydrolysis yielded the desired aldehydes in moderate to good yields (Scheme 1). No over-reduction to the primary alcohol was observed as the aldehyde functionality is protected until hydrolysis.

SCHEME 1. Molybdenum-Catalyzed Conjugate Reduction−Hydrosilylation



SCHEME 2. Molybdenum-Catalyzed Reduction of Cyclic Malonates



Interestingly, from our studies we observed that, under the molybdenum-catalyzed reductive conditions, 3-(4-nitrophenyl)-propanal (**2a**) was formed in 91% yield from 2,2-dimethyl-5-(4-nitrobenzyl)-1,3-dioxane-4,6-dione (**3a**) after thermal cycloreversion as opposed to 37% from the relevant benzylidene Meldrum's acid derivative (Scheme 2). For the deactivated substrate **1a**, the limitation of the tandem process was clearly the conjugate reduction step and not the reduction of the cyclic malonate.

It is known that α-oxoketenes can be accessed from 5-monoalkyl Meldrum's acid derivatives by using an amine base to enolize the cyclic malonate, which then undergoes cycloreversion eliminating acetone and revealing the α-oxoketene.[5] It has also been established that Lewis bases can activate silanes enabling new processes for organic synthesis.[6] Of particular relevance is the Lewis base activation of trichlorosilane for the reduction of ketones, imines, and reductive aldol reactions.[7] In this paper we report the Lewis base-promoted hydrosilylation

* To whom correspondence should be addressed.

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.;Wiley-VCH: New York, 1999. (b) Aldehydes In *Science of Synthesis*; Brückner, R., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2006; Vol. 25, Chapter 25.1−25.9, pp 1−897.

(2) For a recent comprehensive review, see: Harcken, C. *Science of Synthesis*; Brückner, R., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2006; Vol. 25, Chapter 25.1.4; pp 65−136.

(3) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361–2364. (b) Luly, J. R.; Hsiao, C. N.; Bamaung, N.; Plattner, J. J. *J. Org. Chem.* **1988**, *53*, 6109–6112.

(4) Frost, C. G.; Hartley, B. C. *Org. Lett.* **2007**, *9*, 4259–4261.

(5) Sato, M.; Ban, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689–6692.

(6) (a) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727–1747. (b) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

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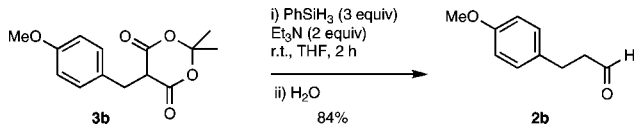
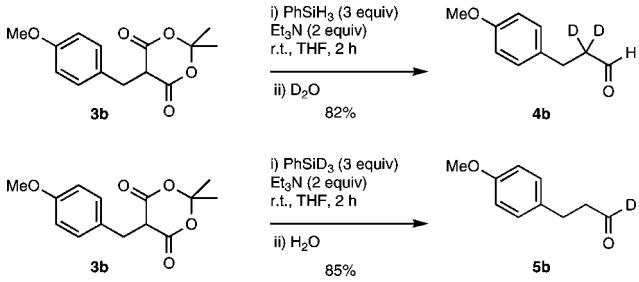
SCHEME 3. Triethylamine-Promoted Reduction of Cyclic Malonates



SCHEME 4. Triethylamine-Promoted Reduction of Cyclic Malonates



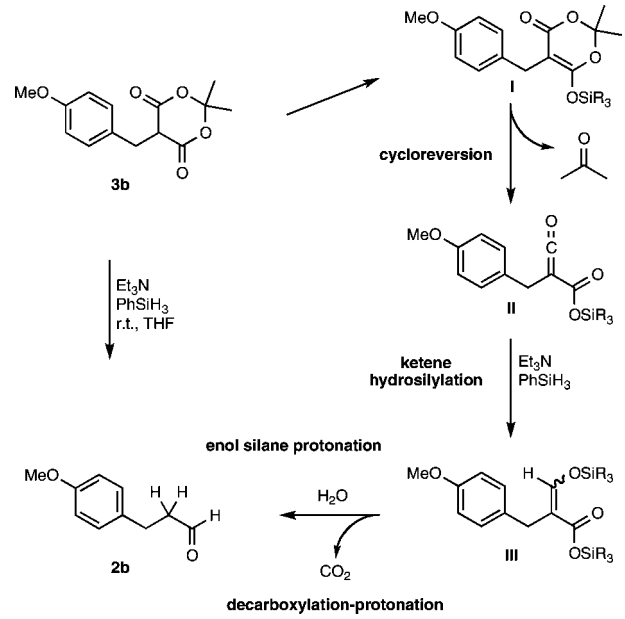
of cyclic malonates to provide a convenient synthesis of β-substituted aldehydes and γ-substituted propylamines.

Initially, the hydrosilylation of 5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**3b**) was examined in the presence of various Lewis bases and organosilanes. We were pleased to note that when **3b** was exposed to a mixture of triethylamine and phenylsilane in THF followed by hydrolysis the desired aldehyde **2b** was obtained in good yield, 84% (Scheme 3). No aldehyde was observed when less reactive silanes were employed (Et_3SiH, $(EtO)_2MeSiH$, and PMHS) and only a low conversion (<10%) was achieved with trichlorosilane. Similarly, no reaction was detected in the absence of amine base. Using substoichiometric amounts of triethylamine led to lower conversions to product (49% with 0.5 equiv). 4-(*N*,*N*-Dimethylamino)pyridine (DMAP) and *N*-methylmorpholine *N*-oxide (NMO) provided similar results to triethylamine. Other amines proved less effective in this reaction while *N*,*N*-dimethylformamide, dimethyl sulfoxide, triphenylphosphine, and K_2CO_3 all gave no conversion to product.[8]

We propose that triethylamine has two roles in this process: first, substrate deprotonation leading to α-oxoketene formation, and second, the activation of phenylsilane enabling ketene hydrosilylation.

To gain insight into the reaction mechanism, isotopic labeling studies were carried out with deuterium as both an electrophile and a nucleophile (Scheme 4). Reaction of Meldrum's acid derivative **3b** with phenylsilane followed by hydrolysis with deuterium oxide afforded the α,α′-dideuteriated product **4b**. The use of trideuteriophenylsilane followed by water led to the formation deuterioaldehyde **5b** with no other deuterium incorporation being observed. These observations are consistent with the mechanism shown in Scheme 5. First, addition of triethylamine gives silyl ketene acetal **I**, which undergoes cycloreversion to reveal the α-oxoketene **II**. Ketene hydrosilylation occurs giving enol silane **III**, which remains in solution until decarboxylative protonation occurs (as confirmed by evolution of CO_2 detected by limewater test) releasing the aldehyde product.

SCHEME 5. Ketene Hydrosilylation Mechanistic Proposal



To probe the scope of the triethylamine-promoted reduction of cyclic malonates, a range of 5-monoalkyl Meldrum's acid derivatives were prepared and subjected to the reaction conditions (Table 1).[9]

Pleasingly, good substrate scope was observed, with both aromatic and aliphatic substituents being tolerated. Of particular note is the selective reduction of cyclic malonate **3f** containing an alkene (entry 6) and the synthesis of chiral amino aldehyde **2g** (entry 7) derived from *N*-Boc-L-proline. The use of tandem or domino chemical transformations in a one-pot, multiple-step organic synthesis can increase efficiency by avoiding repeated isolation and purification processes.[10] We were intrigued by the possibility of utilizing the aldehyde functionality generated by the reduction of cyclic malonates in further transformations. In this context, we set out to develop a one-pot reductive amination procedure to form γ-substituted propylamines directly from 5-monoalkyl Meldrum's acid derivatives **3**.[11] The triethylamine-promoted hydrosilylation of **3** followed by treatment with methanol reveals the aldehyde functionality in situ. The imine formed on addition of the relevant amine (Scheme 6, **6a**−**g**)

(7) (a) Kobayashi, S.; Yasuda, M.; Hachiya, I. *Chem. Lett.* **1996**, 407–408. (b) Iwasaki, F.; Onomura, O.; Mishima, K.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **1999**, *40*, 7507–7511. (c) Iwasaki, F.; Onomura, O.; Mishima, K.; Kanematsu, T.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2001**, *42*, 2525–2527. (d) Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *8*, 999–1001. (e) Wang, Z.; Cheng, M.; Wu, P.; Wei, S.; Sun, J. *Org. Lett.* **2006**, *8*, 3045–3048. (f) Malkov, A. V.; Stoncius, S.; MacDougall, K. N.; Mariani, A.; McGeoch, G. D.; Kocovsky, P. *Tetrahedron* **2006**, *62*, 264–284. (g) Sugiura, M.; Sata, N.; Kotani, S.; Nakajima, M. *Chem. Commun.* **2008**, 4309–4311.

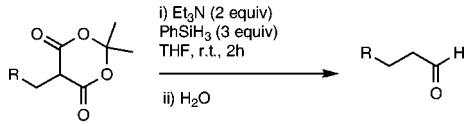
(8) In the conversion of **3b** to **2b** with $PhSiH_3$ (3 equiv) at room temperature a range of Lewis bases (0.5 equiv) were tested. After 2 h the reactions were quenched with water and the ^1H NMR conversions were as follows: triethylamine (49%), 4-(*N*,*N*-dimethylamino)pyridine (49%), *N*-methylmorpholine *N*-oxide (45%), *N*,*N*-diisopropylethylamine (40%), 1,8-diazabicyclo[5.4.0]undec-7-ene (30%), *N*,*N*-dimethylformamide (0%), dimethyl sulfoxide (0%), and triphenylphosphine (0%).

(9) For the synthesis of 5-monoalkyl Meldrum's acid derivatives, see: (a) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203–5205. (b) Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Sartori, G. *Green Chem.* **2001**, *3*, 173–174. (c) Frost, C. G.; Penrose, S. D.; Lambshead, K.; Raithby, P. R.; Warren, J. E.; Gleave, R. *Org. Lett.* **2007**, *9*, 2119–2122.

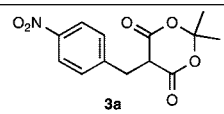
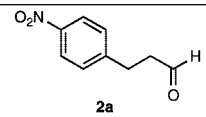
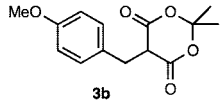
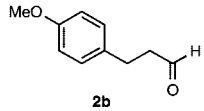
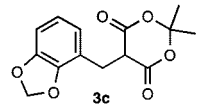
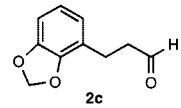
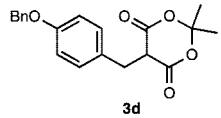
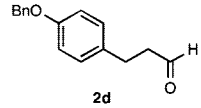
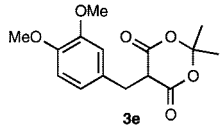
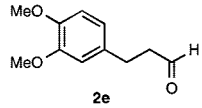
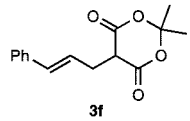
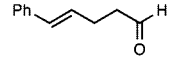
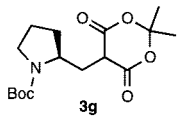
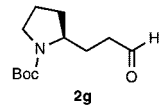
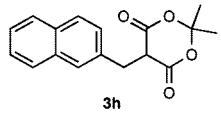
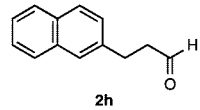
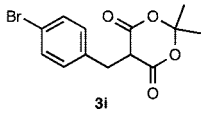
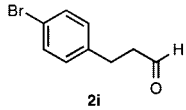
(10) For recent accounts of tandem or domino organic reactions, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1–21. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (d) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477–1489.

(11) Tripathi, R. P.; Verma, S. S.; Pandey, J.; Tiwari, V. K. *Curr. Org. Chem.* **2008**, *12*, 1093–1115.

TABLE 1. Triethylamine-Promoted Reduction of Cyclic Malonates

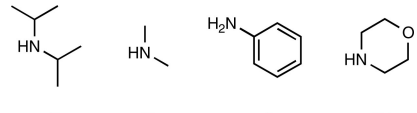


3a-j **2a-j**

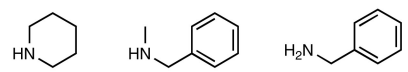
entry	substrate	product[a]	yield (%)[b]
1	 **3a**	 **2a**	92
2	 **3b**	 **2b**	84
3	 **3c**	 **2c**	78
4	 **3d**	 **2d**	74[c]
5	 **3e**	 **2e**	61
6	 **3f**	 **2f**	80
7	 **3g**	 **2g**	75
8	 **3h**	 **2h**	65
9	 **3i**	 **2i**	56

[a] Reaction conditions: **3** (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, rt, 2 h. [b] Isolated yields. [c] Reaction was stirred for 4 h.

SCHEME 6. Amines Used in Reductive Amination



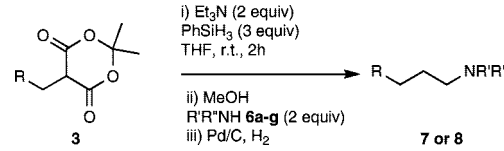
6a **6b** **6c** **6d**



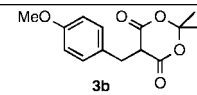
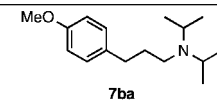
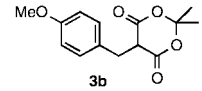
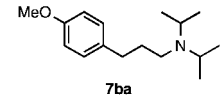
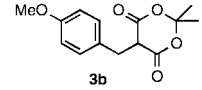
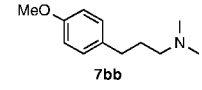
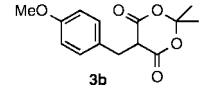
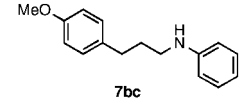
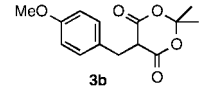
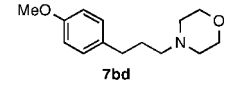
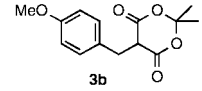
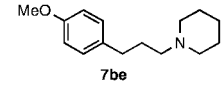
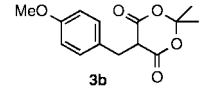
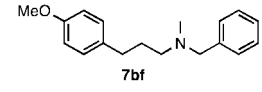
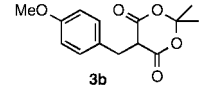
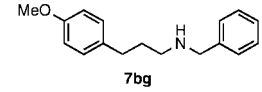
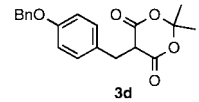
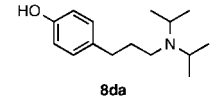
6e **6f** **6g**

was then reduced as illustrated in Table 2. Both Pd/C with molecular hydrogen and $NaBH(OAc)_3$ afforded the desired

TABLE 2. Reductive Amination of Cyclic Malonates



3 **7 or 8**

entry	substrate	product[a]	yield (%)[b]
1	 **3b**	 **7ba**	63
2	 **3b**	 **7ba**	31[c]
3	 **3b**	 **7bb**	52
4	 **3b**	 **7bc**	48
5	 **3b**	 **7bd**	41
6	 **3b**	 **7be**	50
7	 **3b**	 **7bf**	52
8	 **3b**	 **7bg**	37
9	 **3d**	 **8da**	57
10	**3e**	**7ea**	56
11	**3g**	**7ga**	61
12	**3h**	**7ha**	41
13	**3d**	**7da**	32[c]

[a] Reaction conditions: **3** (1 equiv), phenylsilane (3 equiv), triethylamine (2 equiv), THF, rt, 2 h, MeOH, R′R″NH **6** (2 equiv), rt, 0.5 h, Pd/C, H_2 (1 atm), rt, 16 h. [b] Isolated yields. [c] Imine reduction carried out with $NaBH(OAc)_3$ (2 equiv).

products although higher yields were observed with the catalytic method (entries 1 and 2). The method was tolerant of both primary and secondary amines (entries 7 and 8), chiral substrates (entry 11), and sterically hindered reactants (entry 12). Interestingly, either of the products **8da** and **7da** could be obtained

selectively from cyclic malonate **3d** by switching the hydrogen source (entries 9 and 13). The isolated yields were reasonable for this challenging, one-pot, multistep process.

In conclusion, we have developed an efficient synthesis of β-aryl aldehydes from 5-monoalkyl Meldrum's acid derivatives employing a Lewis base-promoted hydrosilylation reaction. A mechanism is proposed that suggests the reaction proceeds via the hydrosilylation of a key ketene intermediate. The reaction can tolerate a broad range of functionality to deliver functionalized products in good yields. This convenient methodology has been applied to the synthesis of γ-substituted propylamines in a one-pot reductive amination process.

Experimental Section

Representative Procedure for Triethylamine-Promoted Reduction of Cyclic Malonates. To a solution of 5-alkyl Meldrum's acid derivative **3** (0.5 mmol) in tetrahydrofuran was added triethylamine (139 μL, 1 mmol) followed by phenylsilane (185 μL, 1.5 mmol). The resulting solution was stirred for 2 h at room temperature. Water (0.5 mL) was added to the solution, which was then stirred for 15 min. The reaction mixture was dissolved in diethyl ether (50 mL) and washed with water (2 × 50 mL) then with brine (50 mL). The organic phase was extracted, dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography to give the desired product.

3-(4-Methoxyphenyl)propanal (2b):[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.7 Hz, Ar), 6.82 (2H, d, J = 8.7 Hz, Ar), 3.77 (3H, s, OCH_3), 3.72 (1H, t, J = 4.9 Hz, CH), 3.44 (2H, d, J = 4.9 Hz, CH_2), 1.72 (3H, s, CH_3), 1.48 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.9, 159.1, 131.4, 129.4, 114.3, 105.6, 55.6, 48.7, 31.86, 28.9, 27.8; HRMS (ESI) calcd for $C_{14}H_{15}O_5$ $[M - H]^-$ m/z 263.0919, found m/z 263.0912.

Representative Procedure for One-Pot Reductive Aminations of Cyclic Malonates. To a solution of 5-substituted Meldrum's acid derivative **3** (0.5 mmol) in tetrahydrofuran (3 mL) was added triethylamine (139 μL, 1 mmol) followed by phenylsilane (185 μL, 1.5 mmol). The reaction mixture was stirred for 2 h at room temperature. Methanol (1 mL) was added to the reaction mixture, which was then stirred for 15 min before amine **6** was added (1 mmol), followed by an additional hour of stirring. Palladium on activated carbon (50 mg) was added and hydrogen gas bubbled through the solution. The reaction mixture was left for 16 h. The reaction mixture was then passed through a pad of Celite and concentrated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and washed with 1 M $HCl_{(aq)}$ (3 × 25 mL). The aqueous phase was basified with 1 M $NaOH_{(aq)}$ and washed with DCM (3 × 50 mL). The combined organic phase was dried over $MgSO_4$ and concentrated in vacuo.

1-(3-(4-Methoxyphenyl)propyl)piperidine (7be): $\nu_{(max)}$ (neat)/cm^{-1} 3009, 2938, 2855, 2804, 2769, 2068, 1613, 1584, 1513, 1466, 1442, 1377, 1351, 1300, 1245, 1217, 1177, 1153, 117, 1103, 1038, 808, 753, 699, 667; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (2H, d, J = 8.7 Hz, Ar), 6.81 (2H, d, J = 8.7 Hz, Ar), 3.77 (3H, s, OCH_3), 2.56 (2H, t, J = 7.9 Hz, CH_2), 2.38−2.28 (6H, m), 1.79 (2H, quin, J = 7.9 Hz, CH_2), 1.58 (4H, quin, J = 5.7 Hz, CH_2), 1.46−1.38 (2H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.1, 134.8, 129.6, 114.1, 59.3, 55.6, 55.0, 33.4, 29.3, 26.4, 24.9; HRMS (ESI) calcd for $C_{15}H_{24}NO$ $[M + H]^+$ m/z 234.1858, found m/z 234.1857.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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