JOC*Note*

Zinc-Mediated Allylation and Alkylation of Aminals in the Presence of TMSCl and Diisopropylamine

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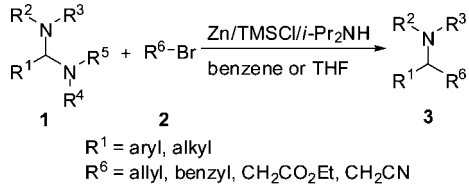
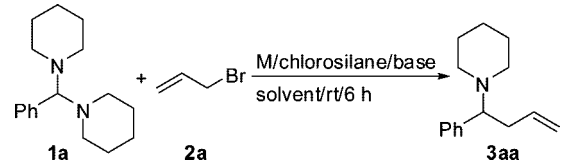


18 examples 46-89% yield

An alkylation of aminals with organozinc reagents derived from allyl bromide, benzyl bromide, α-bromoacetate, and α-bromonitrile proceeded efficiently in the presence of TMSCl and diisopropylamine. This reaction system was applied to the synthesis of an antispasmodic: butaverine.

Nucleophilic additions to carbonyl compounds and imines with organometallic reagents are important for syntheses of functionalized alcohols and amines. Among them, addition using organozinc reagents based on Barbier- and Reformatsky-type reactions is a useful method in organic synthesis because the organozinc reagents are readily prepared in situ from the corresponding alkyl bromide, such as allyl bromide and α-bromoacetate, in the presence of zinc.[1,2] Moreover, the organozinc reagents show a much lower reactivity. Consequently, they show higher chemoselectivity than their lithium and magnesium counterparts. Several synthetic methods using these reactions have been developed, giving homoallyl alcohols and β-hydroxy esters from the corresponding aldehydes and ketones. Furthermore, imines are used as substrates in the same manner.

TABLE 1. Influence of Bases, Metals, Chlorosilanes, and Solvents on Allylation of 1a[a]



entry	M	chlorosilane	base	solvent	yield (%)[b]
1	Zn	TMSCl	none	benzene	31
2	Zn	none	none	benzene	0
3	Zn	TMSCl	*i*-Pr_2NH	benzene	86
4[c]	Zn	TMSCl	*i*-Pr_2NH	benzene	65
5[d]	Zn	TMSCl	*i*-Pr_2NH	benzene	70
6	Zn	TMSCl	Et_3N	benzene	80
7	Zn	TMSCl	pyridine	benzene	—[e]
8	Zn	TMSCl	Na_2CO_3	benzene	69
9	Zn	TMSCl	K_2CO_3	benzene	80
10	Zn	TMSCl	NaOH	benzene	70
11	Mn	TMSCl	*i*-Pr_2NH	benzene	0
12	In	TMSCl	*i*-Pr_2NH	benzene	68
13	Sn	TMSCl	*i*-Pr_2NH	benzene	0
14	Sm[f]	TMSCl	*i*-Pr_2NH	benzene	0
15	Zn	TESCl	*i*-Pr_2NH	benzene	68
16	Zn	TBSCl	*i*-Pr_2NH	benzene	28
17	Zn	$SiCl_4$	*i*-Pr_2NH	benzene	78
18	Zn	TMSCl	*i*-Pr_2NH	toluene	59
19	Zn	TMSCl	*i*-Pr_2NH	Et_2O	72
20	Zn	TMSCl	*i*-Pr_2NH	THF	80
21	Zn	TMSCl	*i*-Pr_2NH	CH_3CN	trace
22	Zn	TMSCl	*i*-Pr_2NH	DMF	32

[a] Reaction conditions: **1a** (2.0 mmol), **2a** (6.0 mmol), Zn (6.0 mmol), TMSCl (6.0 mmol), base (12.0 mmol), solvent (10 mL), rt, 6 h, under N_2. [b] Isolated yield. [c] **2a** (3.0 mmol), Zn (3.0 mmol), TMSCl (3.0 mmol), *i*-Pr_2NH (6.0 mmol). [d] **2a** (4.0 mmol), Zn (4.0 mmol), TMSCl (4.0 mmol), *i*-Pr_2NH (8.0 mmol). [e] The complex mixture was obtained. [f] A small piece of I_2 was added to activate Sm.

Compared to the methods used for carbonyl compounds and imines, several reports describe acetals and aminals; in particular, the applications for aminals have remained an attractive research area because functionalized amines are prepared directly in one step.[3−5] Herein, we report an alkylation of aminals with organozinc reagents based on Barbier- and Reformatsky-type reaction. This reaction proceeded smoothly in the presence of TMSCl and diisopropylamine, affording the corresponding functionalized amines.

Our initial experiments were carried out in the reaction of benzaldehyde-derived aminal **1a** with allylzinc bromide as a model substrate at room temperature (Table 1). When 1,1′-benzylidenedipiperidine (**1a**) and allyl bromide (**2a**) were stirred for 6 h in the presence of zinc and TMSCl, the corresponding homoallylamine **3aa** was obtained in 31% yield along with unreacted benzaldehyde (entry 1). For this reaction, the addition of TMSCl was extremely important: formation of **3aa** was not observed at all in the absence of TMSCl (entry 2). These facts suggest that TMSCl would likely activate not only zinc metal

(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., FlemingI., Eds.; Pergamon: Oxford, UK, 1991; Vol 1, pp 211−229.

(2) (a) Ocampo, R.; Dolbier, W. R. *Tetrahedron* **2004**, *60*, 9325–9374. (b) Rathke, M. W., Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., FlemingI., Eds.; Pergamon: Oxford, UK, 1991; Vol. 1, pp 277−299. (c) Fürstner, A. *Synthesis* **1989**, 571–590.

(3) References for acetals using Barbier- and Reformatsky-type reaction, see: (a) Surendra, K.; Krishnaveni, N. S.; Rao, K. R. *Tetrahedron Lett.* **2006**, *47*, 2133–2136. (b) Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett.* **2003**, *44*, 5579–5582. (c) Tanaka, H.; Nakahata, S.; Watanabe, H.; Zhao, J. F.; Kuroboshi, M.; Torii, S. *Inorg. Chim. Acta* **1999**, *296*, 204–207. (d) Maeda, H.; Shono, K.; Ohmori, H. *Chem. Pharm. Bull.* **1994**, *42*, 1808–1812. (e) Tanaka, H.; Yamashita, S.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 1721–1724.

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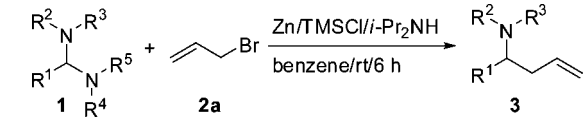
but also the aminal substrate.[6] We next examined the influence of several typical bases on the reaction of **1a** because the recovery of benzaldehyde was considered to be attributed to the interaction of **1a** with zinc chloride or zinc bromide generated in situ. As expected, the yield of **3aa** increased dramatically when diisopropylamine base was used (entry 3). For this reaction, the amounts of reagents are important: the use of 1.5 or 2.0 mol equiv amounts of reagents (**2a**, Zn, TMSCl, and *i*-Pr_2NH) against **1a** resulted in the moderate yield of **3aa** (entries 4 and 5).[7] Other typical bases were also effective, except pyridine, giving **3aa** in moderate to good yields (entries 6−10).

We also found that zinc was more effective than other metals. Surprisingly, no allylation took place with manganese, tin, and samarium, except indium (entries 11−14). Furthermore, this allylation was affected by the substituent bearing silyl chloride. As expected, both sterically hindered TESCl and TBSCl impeded the reaction to give **3aa** in low to moderate yields (entries 15 and 16). The use of tetrachlorosilane, which may be expected to work as a strong Lewis acid, led to **3aa** in good yield (entry 17). Moreover, the formation of **1a** is also achieved in THF and Et_2O, in which a Barbier-type reaction took place, giving **3aa** in 80% and 72% yields, respectively (entries 18−22).

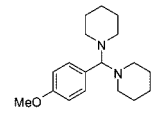
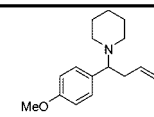
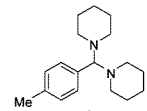
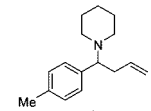
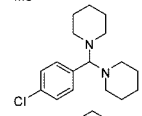
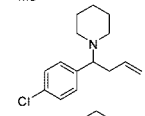
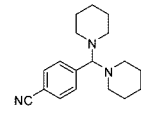
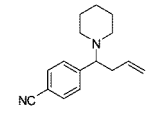
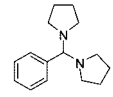
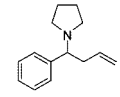
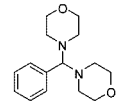
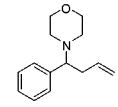
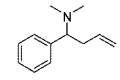
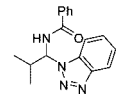
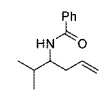
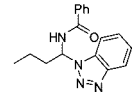
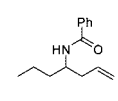
The reaction system with TMSCl and diisopropylamine was useful for other aminal derivatives (Table 2). Similar treatment of aminals **1** gave the corresponding homoallylamines **3** in moderate to good yields (entries 1−5). Although the formation of homoallylamine took place slightly in the case of **1g** derived from morpholine, this problem was circumvented by the treatment of **1g** at 50 °C for 24 h (entry 6). In dimethyl derivative **1h**, the product was purified by Kugelrohr distillation because dimethyl derivatives **3ha** decomposed during purification on silica gel columns (entry 7). The allylation of aliphatic aminals (**1i** and **1j**)[8] proceeded efficiently in THF rather than benzene because of their poor solubility in benzene (in benzene: **3ia** 56%, **3ja** 30%, respectively, entries 8 and 9).

This reaction procedure is applicable to several highly reactive alkyl bromides. The results are presented in Table 3. Treatment of **1a** with **2b** or **2c** at room temperature for 6 h gave the corresponding homoallylamines (**3ab** and **3ac**) in moderate to good yields (entries 1 and 2).[9] The crotyl derivatives (**2d** and **2e**) were also used in this reaction, which displayed no marked stereoselectivity (entries 3 and 4).[9] The reaction of **1a** took place in the case of benzyl bromide (**2f**) to give **3af** in 46% yield (entry 5). The use of α-bromoacetate (**2g**) and α-bromonitrile (**2h**), a Reformatsky-type reaction, does not present a problem, giving the corresponding β-amino ester (**3ag**) and β-amino nitrile (**3ah**) in 68% and 52% yields, respectively (entries 6 and 7).

TABLE 2. Reaction of 1 with Allylzinc Bromide in the Presence of TMSCl and *i*-Pr_2NH[a]



1 **2a** **3**

entry	1		3		yield (%)[b]
1		**1b**		**3ba**	83
2		**1c**		**3ca**	80
3		**1d**		**3da**	66
4		**1e**		**3ea**	60
5		**1f**		**3fa**	77
6		**1g**		**3ga**	52[c]
7		**1h**		**3ha**	quant[d]
8		**1i**		**3ia**	77[e]
9		**1j**		**3ja**	89[e]

[a] Reaction conditions: **1** (2.0 mmol), **2a** (6.0 mmol), Zn (6.0 mmol), TMSCl (6.0 mmol), *i*-Pr_2NH (12.0 mmol), benzene (10 mL), rt, 6 h, under N_2. [b] Isolated yield. [c] The reaction was carried out at 50 °C for 24 h. [d] Product (**3ha**) was purified by Kugelrohr distillation. [e] THF was used instead of benzene.

Recently, β-amino acids have been shown to have biologically important properties and have been used as intermediates in natural product syntheses.[10] We finally achieved direct access to β-amino carbonyl derivatives from aminals.

Our direct access to β-amino ester from aminal was applied to the synthesis of butaverine (**3ai**), which is an antispasmodic agent bearing a β-amino ester.[11] For example, the preparation of **1a** in the presence of alumina and subsequent reaction of **1a** with *n*-propyl α-bromoacetate under these reaction conditions afforded **3ai** in 66% yield in two steps from benzaldehyde (Scheme 1). Reportedly, butaverine (**3ai**) had been synthesized

(4) References for aminals and related compounds using Barbier- and Reformatsky-type reaction, see: (a) Katritzky, A. R.; Manju, K.; Singh, S. K.; Meher, N. K. *Tetrahedron* **2005**, *61*, 2555–2581. (b) Tan, C. Y. K.; Wainman, D.; Weaver, D. F. *Bioorg. Med. Chem.* **2003**, *11*, 113–122. (c) Wang, X.; Li, J.; Zhang, Y. *Synth. Commun.* **2003**, *33*, 3575–3582. (d) Katritzky, A. R.; Shobana, N.; Harris, P. A. *Tetrahedron Lett.* **1991**, *32*, 4247–4248.

(5) For recently selected examples using Barbier- and Reformatsky-type reaction, see: (a) Petrini, M.; Profeta, R.; Righi, P. *J. Org. Chem.* **2002**, *67*, 4530–4535. (b) Choucair, B.; Leon, H.; Mire, M. A.; Lebreton, C.; Mosset, P. *Org. Lett.* **2000**, *2*, 1851–1853. (c) Saidi, R. M.; Khalaji, R. H.; Ipaktschi, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, *1*, 1983–1986.

(6) Picotin, G.; Miginiac, P. J. *Org. Chem.* **1987**, *52*, 4796–4798.

(7) The silylated amines (*N*-trimethylsilylpiperidine and *N*-trimethylsilyldiisopropylamine) and allylated piperidine (3-piperidino-1-propene) were observed by GC-MS, which were removed by hydrolysis and evaporation. In contrast, allylated diisopropylamine was not observed.

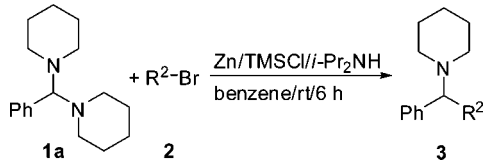
(8) Aminals (**1i** and **1j**) were prepared according to a modified procedure of a known method, see: Katritzky, A. R.; Drewniak, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2339–2344.

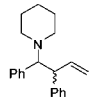
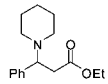
(9) No regioisomer was detected from ^1H NMR of crude product.

(10) Juaristi, E. *Enantioselective Synthesis of β-amino Acids*, Wiley-VCH: New York, 1997.

(11) (a) Cerbai, G.; Di Paco, G. F. *Boll. Chim. Farm.* **1966**, *105*, 45–53. (b) Pacheco, H.; Dreux, M.; Beauvillain, A. *Bull. Soc. Chim. Fr.* **1962**, 1379–1387. (c) Pollard, C. B.; Mattson, G. C. *J. Am. Chem. Soc.* **1956**, *78*, 4089–4090.

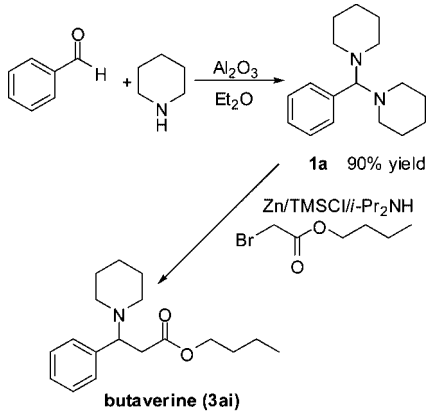
TABLE 3. Reaction of 1a with Organozinc Reagents in the Presence of TMSCl and *i*-Pr_2NH[a]



entry	R^2-Br	2	product	3	yield (%)[b]
1		**2b**		**3ab**	68
2		**2c**		**3ac**	82
3		**2d**		**3ad**	66 syn/anti = 39/61[c]
4		**2e**		**3ae**	66 syn/anti = 45/55[c]
5		**2f**		**3af**	46
6		**2g**		**3ag**	68
7		**2h**		**3ah**	52

[a] Reaction conditions: **1a** (2.0 mmol), **2** (6.0 mmol), Zn (6.0 mmol), TMSCl (6.0 mmol), *i*-Pr_2NH (12.0 mmol), benzene (10 mL), rt, 6 h, under N_2. [b] Isolated yield. [c] Determined with ^1H NMR.

SCHEME 1. Synthesis of Butaverine (3ai) Using the Alkylation of 1a with Reformatsky Reagent

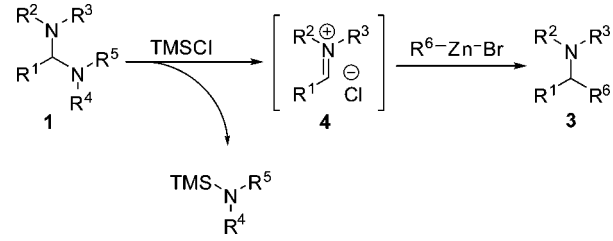


by Michael addition of piperidine to *n*-propyl cinnamate; unfortunately, the yield of **3ai** was not quite satisfactory.[12] Finally, our developed method has some advantages for synthesis of butaverine.

Although the detailed pathway is not clear for this alkylation of **1** with organozinc reagents, the alkylation seems to be

(12) In previous reports, butaverine was obtained by Michael addition of piperidine to *n*-propyl cinnamate in 20−50% yields, see ref 11.

SCHEME 2. Plausible Reaction Pathways for Alkylation of 1 with Organozinc Reagents



triggered by the activation of **1** with chlorosilane: the chlorosilane serves as an activator of not only zinc metal but also aminal, generating an iminium salt intermediate (**4**) and silylated amine (Scheme 2). Then, the reaction of **4** with organozinc reagent leads to the alkylated product **3**.

In conclusion, our study demonstrated the alkylation of aminals with organozinc reagents derived from allyl bromide, benzyl bromide, α-bromoacetate, and α-bromonitrile. This reaction proceeded efficiently in the presence of TMSCl and diisopropylamine. Furthermore, this reaction system is applicable to the synthesis of butaverine, which is well-known as an antispasmodic agent. Further detailed studies of aminals are in progress.

Experimental Section

Representative Procedure for Homoallylamines (3). To a suspension of zinc (392 mg, 6.0 mmol) in benzene (10 mL) was added allyl bromide (6.0 mmol) followed by diisopropylamine (1.7 mL, 12 mmol) and **1** (2.0 mmol) at room temperature under nitrogen atmosphere. After cooling in an ice−water bath, chlorotrimethylsilane (761 μL, 6.0 mmol) was added to the mixture in one portion. The reaction mixture was stirred for 10 min in an ice bath, and then allowed to warm to room temperature. After the mixture was stirred for 6 h at room temperature, aqueous NaOH (1N, 30 mL) was added. The mixture was then stirred for an additional 30 min, during which zinc hydroxide precipitated. The resulting suspension was filtered in suction, and the filtered solid was washed with ether (3 × 10 mL). The ethereal solution was separated and washed with aqueous NaOH (1N, 30 mL), water (30 mL), and brine (30 mL). After drying over Na_2SO_4, and subsequent evaporation, the residue was purified with column chromatography on silica gel (30 g; eluent, CH_2Cl_2/MeOH = 100:0, 98:2, 96:4, 94:6, 92:8, 90:10, 100 mL × each). The results are presented in Tables 1, 2, and 3.

Representative Procedure for Homoallylamide (3ia and 3ja). The same procedure as that described above was followed except that benzene was replaced by THF, because aminals (**1i** and **1j**) did not dissolve enough in benzene. After the mixture was stirred for 6 h at room temperature, the reaction mixture was poured into saturated NH_4Cl (30 mL). The mixture was extracted with ether (2 × 30 mL), and the combined organic extract was washed with aqueous NaOH (1 N, 30 mL), water (30 mL), and brine (30 mL). After drying over Na_2SO_4, and subsequent evaporation, the residue was purified with column chromatography on silica gel (30 g; eluent, haxane/AcOEt = 75:25, 300 mL). The results are presented in Table 2.

Representative Procedure for β-Amino Derivatives (3af, 3ag, and 3ah). The same procedure as that described above was followed except that allyl bromide was replaced by benzyl bromide (713 μL, 6.0 mmol), ethyl α-bromoacetate (662 μL, 6.0 mmol), or α-bromonitrile (400 μL, 6.0 mmol). In the case of ethyl α-bromoacetate, workup was performed by the addition of saturated $NaHCO_3$ (30 mL) instead of aqueous NaOH to prevent possible de-esterification. The results are presented in Table 3.

Synthesis of Butaverine (3ai) Using Alkylation of 1a with Organozinc Reagents. To a suspension of zinc (392 mg, 6.0 mmol)

in benzene (10 mL) was added *n*-butyl α-bromoacetate[13] (867 μL, 6.0 mmol) followed by diisopropylamine (1.7 mL, 12 mmol) and **1a** (2.0 mmol) at room temperature under nitrogen atmosphere. After cooling in an ice−water bath, chlorotrimethylsilane (761 μL, 6.0 mmol) was added to the mixture in one portion. The reaction mixture was stirred for 10 min in an ice bath and then allowed to warm to room temperature. After the mixture was stirred for 6 h at room temperature, saturated $NaHCO_3$ (30 mL) was added. The mixture was then stirred for an additional 30 min. Then the resulting suspension was filtered in suction, and the filtered solid was washed with ether (3 × 10 mL). The ethereal solution was separated and washed with saturated $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL). After drying over Na_2SO_4, and evaporation, the residue was purified with column chromatography on silica gel (30 g; eluent, CH_2Cl_2/MeOH = 100:0, 98:2, 96:4, 94:6, 92:8, 90:10, 100 mL × each). Pure butaverine was obtained in 74% yield (427 mg, 1.49 mmol).

4-Phenyl-4-piperidino-1-butene (3aa): colorless oil; IR (neat) ν_{max} 2933, 1639, 1446, 1111, 991, 914, 758, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, 2H, J = 7.3, 7.3 Hz), 7.24 (d, 1H, J = 7.3 Hz), 7.21 (d, 2H, J = 7.3 Hz), 5.67−5.56 (m, 1H), 4.96 (dd, 1H, J = 17.0, 3.7 Hz), 4.89 (dd, 1H, J = 10.5, 3.7 Hz), 3.39 (dd, 1H, J = 9.3, 5.3 Hz), 2.66 (ddd, 1H, J = 14.5, 7.0, 5.3 Hz), 2.57 (ddd, 1H, J = 14.5, 9.3, 7.5 Hz), 2.36−2.33 (m, 4H), 1.59−1.48 (m, 4H), 1.35 (ddd, 2H, J = 15.0, 7.5, 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 136.1, 128.8, 127.8, 126.8, 116.0, 70.2, 51.2, 37.1, 26.3, 24.6; MS (EI) *m*/*z* (%) 175 (17), 174 ([M − C_3H_5], 100), 91 (56); HRMS (ESI) calcd for $C_{15}H_{22}N_1$ 216.1752 $[M + H]^+$, found 216.1746.

4-Benzoylamino-5-methyl-1-hexene (3ia): white solid; mp 109.0−110.2 °C; IR (KBr) ν_{max} 3322, 3069, 2964, 1636, 1546, 1322, 1289, 1152, 914, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75−7.73 (m, 2H), 7.50−7.47 (m, 1H), 7.42 (dd, 2H, J = 7.5, 7.5 Hz), 5.91 (br, 1H), 5.83 (dddd, 1H, J = 17.2, 10.2, 7.1, 7.1 Hz), 5.10 (dd, 1H, J = 17.2, 1.6 Hz), 5.07 (dd, 1H, J = 10.2, 1.6 Hz), 4.09 (ddd, 1H, J = 7.8, 6.1, 5.0 Hz), 2.40 (ddd, 1H, J = 12.8, 7.1, 5.0 Hz), 2.26 (ddd, 1H, J = 12.8, 7.8, 7.1 Hz), 1.92−1.83 (m, 1H), 0.99 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 135.1, 134.8, 131.3, 128.5, 126.7, 117.6, 53.9, 36.6, 31.5, 19.3, 18.2; MS (EI) *m*/*z* (%) 176 ([M − C_3H_5], 17), 105 (100), 77 (35), 51 (10); HRMS (ESI) calcd for $C_{14}H_{20}N_1O_1$ 218.1545 $[M + H]^+$, found 218.1549.

(13) Preparation of butyl α-bromoacetate, see: Zhu, X.-F.; Schaffrer, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977–2980.

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Supporting Information Available: Experimental details, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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