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Synthesis and Reactivity of β-Methoxymethyl Enecarbamates

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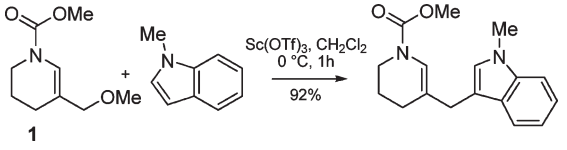
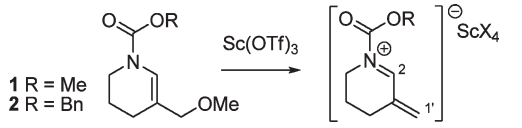


β-Methoxymethyl enecarbamates (e.g., **1**) have been prepared in a single step from α-methoxy carbamates. In the presence of a mild Lewis acid, compound **1** underwent substitution with a variety of nucleophiles including indoles, electron-rich aromatics, silyl enol ethers, and 2-trimethylsilyloxyfuran.

Enecarbamates are a class of stable enamines that are important building blocks for construction of a range of nitrogen heterocycles. With a relatively nucleophilic C3-terminus, enecarbamates are known to engage in "electrophile driven" β-substitution reactions.[1] Additionally, the endocyclic π-system displays typical olefin-like reactivity, hence haloetherification,[2a,b] cyclopropanation,[2c] redox,[2d−g] and palladium mediated[2h] reactions are also possible. Owing to their versatility and ease of synthesis, typically by elimination of methanol from an α-methoxycarbamate,[2a] enecarbamates possess great potential for the construction of functionalized heterocycles. The industrial significance of this class of molecules was recently highlighted by the manufacture of a proline-like enecarbamate on a scale exceeding 100 kg.[3]

During the course of our investigations into iminium ion catalyzed Diels−Alder cycloadditions we disclosed a novel method for the synthesis of **1** and **2**.[4] β-Substitution of the enecarbamate with a methoxymethyl group facilitates a complementary mode of electrophilic reactivity dominated by the formation of a conjugated iminium ion (Scheme 1).

SCHEME 1. Conjugated *N*-Acyliminium Cation Formation



Despite the fact that *endocyclic* analogues of this conjugated iminium ion have proven synthetically useful,[5,6] the synthesis and reactivity of *exocyclic* α,β-unsaturated *N*-acyliminium ions remains relatively unexplored with the exception of a single publication by our group relating to cycloaddition chemistry.[4]

We herein report a significantly improved method for the synthesis of β-methoxymethyl enecarbamates **1** and **2** and explore their subsequent Lewis acid catalyzed reactions with a range of nucleophiles.

In a previous report[4] we detailed an approach to **1** whereby hemiaminal **3**, formed by electrochemical oxidation of **4**,[7] underwent methylenation using Pihko's organocatalytic procedure[8] to afford open chain enal **5**. Subsequent Lewis acid mediated cyclization afforded the stable[9] adduct **1**, in which the exocyclic disubstituted olefin had migrated to an endocyclic trisubstituted position in conjugation with the carbamate function (Scheme 2). The regioisomeric *N*,*O*-acetal **6** was not observed under the reaction conditions.[10]

Although the aforementioned synthesis of **1** proved adequate for our cycloaddition studies,[4] the apparent synthetic utility of this intermediate (vide infra) prompted us to search for an alternative, higher yielding preparative method. It was

(1) (a) Shono, T. *Tetrahedron* **1984**, *40*, 811–850. (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y. *Tetrahedron Lett.* **1982**, *23*, 1201–1204. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697–6703.

(2) (a) Matsumura, Y.; Terauchi, J.; Yamamoto, T.; Konno, T.; Shono, T. *Tetrahedron* **1993**, *49*, 8503–8512. (b) Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. *J. Org. Chem.* **1987**, *52*, 536–541. (c) Arenare, L.; Decaprariis, P.; Marinozzi, M.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1994**, *35*, 1425–1426. (d) Backenstrass, F.; Streith, J.; Tschamber, T. *Tetrahedron Lett.* **1990**, *31*, 2139–2142. (e) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255–3258. (f) Oppolzer, W.; Bochet, C. G. *Tetrahedron Lett.* **1995**, *36*, 2959–2962. (g) Lei, A. W.; Chen, M.; He, M. S.; Zhang, X. M. *Eur. J. Org. Chem.* **2006**, 4343–4347. (h) Hallberg, A.; Nilsson, K. *J. Org. Chem.* **1990**, *55*, 2464–2470.

(3) Yu, J. R.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B. *Tetrahedron Lett.* **2005**, *46*, 4011–4013.

(4) O'Connor, P. D.; Korber, K.; Brimble, M. A. *Synlett* **2008**, 1036–1038.

(5) (a) Matsumura, Y.; Minato, D.; Onomura, O. *J. Organomet. Chem.* **2007**, *692*, 654–663. (b) Onomura, O.; Kanda, Y.; Nakamura, Y.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2002**, *43*, 3229–3231. (c) Onomura, O.; Kanda, Y.; Imai, E.; Matsumura, Y. *Electrochim. Acta* **2005**, *50*, 4926–4935.

(6) (a) Zou, Y.; Che, Q.; Snider, B. B. *Org. Lett.* **2006**, *8*, 5605–5608. (b) Kim, J.; Thomson, R. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3104–3106.

(7) (a) Finkelstein, M.; Ross, S. D. *Tetrahedron* **1972**, *28*, 4497–4502. (b) Cedheim, L.; Eberson, L.; Helgée, B.; Nyberg, K.; Servin, R.; Sternerup, H. *Acta Chem. Scand. B* **1975**, *29*, 617–621. (c) Nyberg, K.; Servin, R. *Acta Chem. Scand. B* **1976**, *30*, 640–642. (d) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264–4268. (e) Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. *J. Org. Chem.* **1987**, *52*, 536–541. (f) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176. (g) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, *63*, 206–212.

(8) Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538–2541.

(9) The methylenated adducts **1**, **2**, and **13** were stable for at least a month when stored below 0 °C. However, prolonged storage resulted in gradual decomposition.

(10) Gas phase density functional calculations performed at the B3LYP/6-31+G(d)//B3LYP/6-31+G(d) level support the conclusion that **1** is thermodynamically favored over **6** with a Boltzmann distribution of 98:2 based on unscaled zeropoint corrected electronic energies at 298 K (ΔE = 9.78 kJ/mol). See the Supporting Information for computational details.

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SCHEME 2. Electrochemical Routes to β-Methoxymethyl Enecarbamates

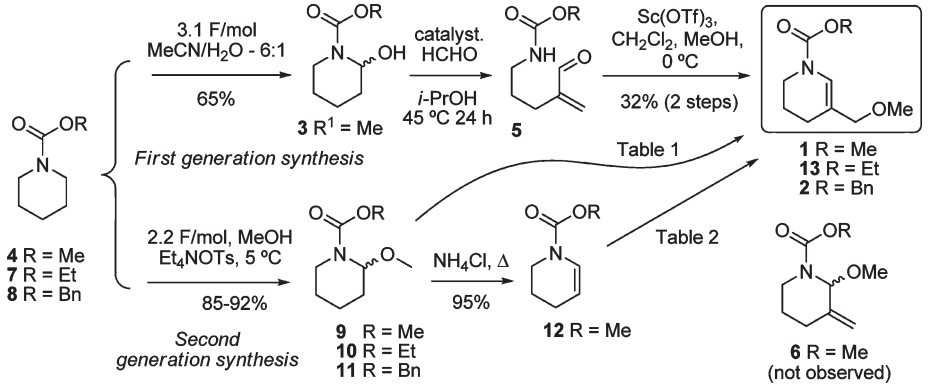
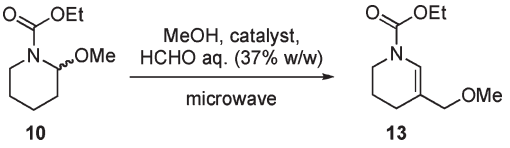


TABLE 1. β-Alkoxymethyl Enecarbamate Synthesis Optimization[a]



entry	R	MeOH (equiv)	catalyst (ratio)[b]	mol % cat.	temp (°C)	time	yield (%)[c]
1	Et	6	pip/pro (1:1)	20	25	2 days	0
2	Et	6	pip/pro (1:1)	20	130	1 h	61
3	Et	6	pyrr/pro (1:1)	20	130	1 h	55
4	Et	6	pip/pro (1:1)	100	130	1 h	24
5	Et	6	pip/pro (1:1)	3	130	1 h	17
6	Et	6	pip/pro (3:2)	20	130	1 h	47
7	Et	6	pip/pro (2:3)	20	130	1 h	56
8	Et	4	pip/pro (1:1)	20	130	1 h	40
9	Et	8	pip/pro (1:1)	20	130	1 h	54
10	Et	40	pip/pro (1:1)	20	130	1 h	10

[a]In a typical reaction 200−800 mg of starting material was reacted with 1.5 equiv of 37% (w/w) aqueous formaldehyde and heated with microwave irradiation in a 10 mL CEM Discovery microwave vessel. [b]Catalysts were prepared as stock solutions of a 1:1 mixture of either piperidine (pip) or pyrrolidine (pyrr) and propionic acid (pro). [c]Isolated yields after silica gel chromatography.

felt that the direct alkoxymethylation of enecarbamate **12** with an oxonium ion derived from formaldehyde would offer the best chance of success.

While α-alkoxycarbamates have been obtained from *N*-acyl lactams by hydride reduction,[11] in the present work, a simple electrochemical method was adopted. Toward this end, the anodic α-oxidation of **4**, **7**, and **8** with the Ross−Eberson−Nyberg procedure[5] afforded high yields of *N*,*O*-acetals **9**−**11**. The high-yielding conversion of **9** to **12** was next accomplished by NH_4Cl mediated elimination.[12] Unfortunately, subsequent direct alkylation of **12** with either paraformaldehyde or dimethoxymethane under acidic anhydrous conditions failed to facilitate the desired transformation to **1**, instead heterodimerization of the starting material was observed.[13] After some degree of experimentation it was found that microwave irradiation[14] of **12** under aqueous organocatalytic conditions did furnish the desired adduct **1**. Interestingly, the same reaction conditions, when applied to *N*,*O*-acetals **9**−**11**, also resulted in direct conversion of the starting material to β-methoxymethyl enecarbamates **1**, **13**, and **2** after only 1 h at 130 °C. This result initially seemed surprising considering the similarity of the reaction conditions to those employed in the conversion of **3** to **5**.[8]

To obtain a greater understanding of the conversion of *N*,*O*-acetals to β-methoxymethyl enecarbamates, further optimization was carried out (Table 1). By systematically varying the nature of the catalyst and loading (Table 1 entries 2−7), and the methanol-to-formalin ratio (Table 1, entries 8−10), the yield after silica gel chromatography was optimized to approximately 60%.

Although the exact methanol:formalin:starting material ratio did not seem critical, biphasic reactant combinations invariably afforded poor yields and it was therefore deemed necessary to use sufficient methanol to afford a homogeneous reaction mixture.

Having optimized the methoxymethylation step (Table 1), the versatility of the reaction was next assessed by changing the alcohol component. In this case *N*,*O*-acetals **9**−**11** were unsuitable substrates because the additional equivalent of

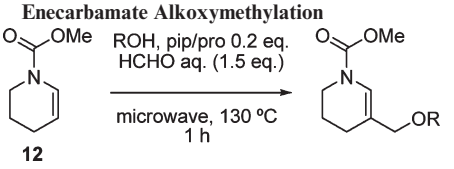
(11) (a) Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77–82. (b) Altman, K. W. *Tetrahedron Lett*. **1993**, *34*, 7721–7724. (c) Dieter, R. K.; Sharma, R. R. J. *Org. Chem*. **1996**, *61*, 4180–4184.

(12) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett*. **1987**, *28*, 4073–4074.

(13) The homo- and heterodimerization of enecarbamates has been reported; see ref 3 and: Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem*. **1999**, *64*, 6646–6652.

(14) Conventional heating gave significant amounts of starting material **12** and *N*,*O*-acetal **9** byproduct. Microwave-assisted organocatalytic Mannich reactions have been described, see: (a) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem*. **2007**, *72*, 1417–1424. (b) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Mol. Diversity* **2003**, *7*, 135–144.

TABLE 2. Enecarbamate Alkoxymethylation



12

entry	R	product	yield (%)[a]
1	Me	**1**	52
2	Et	**14**	33
3	CF_3CH_2	**15**	23
4	*i*-Pr	**16**	19
5	*t*-Bu	na	0

[a]Isolated yield after silica gel chromatography.

methanol contained within the starting material complicated the outcome of the reaction by forming mixtures of alkoxy- and methoxymethylenated products. To circumvent this problem enecarbamate **12** was reacted with various alcohols under optimized conditions (Table 2).

Less sterically hindered alcohols, e.g., ethanol and 2,2,2-trifluoroethanol, afforded the corresponding adducts **14** and **15** in better yield compared to using more sterically demanding alcohols (isopropanol and *tert*-butanol). The scope of the alkoxymethylation is currently limited to piperidine starting materials as acyclic or pyrrolidine derived substrates failed to cleanly form adducts under the reaction conditions.

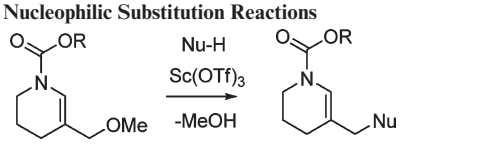
A likely mechanism for the transformations illustrated in Tables 1 and 2 may involve initial hydrolysis of the *N*,*O*-acetal, or enecarbamate, to an open chain aldehyde that undergoes a Mannich-type reaction with formaldehyde.[15] The open chain enal (i.e. **5**) then cyclizes to form an α,β-unsaturated *N*-acyliminium intermediate (cf. Scheme 1) that reacts with the alcohol present. The product distribution from the reaction is the likely result of a thermodynamic equilibrium in which alkoxymethylenated adducts are the predominant species.

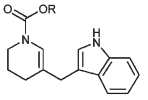
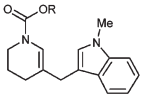
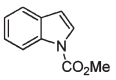
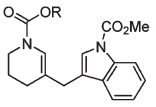
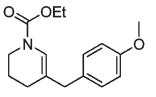
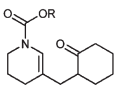
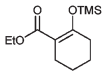
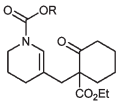
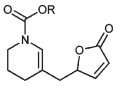
Having previously demonstrated that β-methoxymethyl enecarbamates **1** and **2** react as active dienophiles in a limited range of Diels–Alder cycloadditions,[4] it was decided to examine their reactivity with a range of readily available nucleophiles such as indoles and silyl enol ethers (Table 3).

Pleasingly, nucleophilic substitution reactions proceeded in high yields in the presence of a Lewis acid. Reactive enol ether and indole nucleophiles underwent smooth reaction in dichloromethane at 0 °C catalyzed by scandium triflate, while anisole required the use of $BF_3 \cdot Et_2O$ as a catalyst. In general, prolonged reaction times generally resulted in decomposition. While the putative α,β-unsaturated *N*-acyliminium ion intermediate (Scheme 1) is an ambident electrophile, nucleophilic substitution of **1**, **2**, and **13** takes place at the sterically unencumbered exocyclic carbon to give thermodymanic products.[16]

In summary a novel method for the construction of β-alkoxymethyl enecarbamates starting from either cyclic *N*,

TABLE 3. Nucleophilic Substitution Reactions



Entry	Nucleophile	Product		R	Yield (%)[c]
1			**17**	Me	85[a]
2			**18**	Bn	90[a]
3			**19**	Me	92[a]
4			**20**	Bn	90[a]
5			**21**	Et	13[a]
6			**22**	Et	11[b,d]
7			**23**	Me	83[a]
8			**24**	Bn	96[a]
9			**25**	Me	81[a]
10			**26**	Me	65[a]
11			**27**	Bn	75[a]

[a]CH_2Cl_2, $Sc(OTf)_3$ (5 mol %), 0 °C for 2 h. [b]CH_2Cl_2, $BF_3 \cdot Et_2O$ (1 equiv), −78 to 0 °C for 1 h. [c]Isolated yield after silica gel flash chromatography. [d]Isolated with an inseparable impurity.

O-acetals or unfunctionalized enecarbamates has been demonstrated. The acetal or enecarbamate starting materials are easily prepared and purified by distillation and their conversion proceeds under mild, and near solvent-free conditions using inexpensive commercially available reagents. The β-methoxymethyl enecarbamates thus prepared extended the scope of reactions occurring via generation of the *N*-acyliminium ion[17] by forming novel adducts with a variety of electron-rich nucleophiles. Given the potential for asymmetric hydrogenation,[18] β-alkylated enecarbamates prepared herein also provide useful heterocyclic building blocks for the future synthesis of enantiopure pharmaceuticals and natural products.

(15) (a) Casas, J.; Sunden, H.; Cordova, A. *Tetrahedron Lett*. **2004**, *45*, 6117–6119. (b) Herrera, R. P.; Monge, D.; Martin-Zamora, E.; Fernandez, R.; Lassaletta, J. M. *Org. Lett*. **2007**, *9*, 3303–3306. (c) Mase, N.; Inoue, A.; Nishio, M.; Takabe, K. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3955–3958.

(16) The C1′ alkylated adduct of **1** with anisole (cf. adduct **22**) is predicted be thermodynamically favored over the C2 adduct by 37.7 kJ/mol based on unscaled zero-point corrected electronic energies at 298 K. See the Experimental Section for computational details.

(17) *N*-Acyliminium cyclizations are used extensively for the construction of heterocyclic ring systems; see: (a) Marson, C. M.; Pink, J. H.; Smith, C. *Tetrahedron Lett*. **1995**, *36*, 8107–8110. (b) Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem*. **1985**, *50*, 3243–3245. (c) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc*. **1981**, *103*, 1172–1176. (d) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc*. **1981**, *103*, 4645–4646. (e) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc*. **1987**, *109*, 7914–7915.

(18) The asymmetric hydrogenation of β-acyl enecarbamates has been demonstrated, see: Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem*. **2006**, *19*, 4343–4347.

Experimental Section

General Procedure for the Conversion of Piperidine Carbamate *N*,*O*-Acetals to *β*-Methoxymethyl Enecarbamates: Methyl 5-(Methoxymethyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (1). A 10 mL CEM pressure vessel equipped with a stirrer bar was charged with *N*,*O*-acetal **9** (2.03 g, 11.0 mmol), 37% (w/w) formalin (1.40 g, 17.3 mmol), methanol (2.31 g, 72.1 mmol), and a 1:1 mixture of pyrrolidine and propionic acid (306 mg, 2.11 mmol). The stirred mixture was heated in a CEM Discover microwave reactor (max power 100 W) to 130 °C for 1 h. After the reaction was quenched with saturated $NaHCO_3$, the aqueous layer was extracted with EtOAc (3 × 40 mL) and the pooled organic fractions were washed with brine and dried over $MgSO_4$ and the solvent was evaporated in vacuo to give a yellow oil. The UV active crude product was further purified by silica gel chromatography, eluting with hexane/EtOAc 10:1 to give the title compound (1.20 g, 59%) as a colorless oil: IR (film) 2928, 1714, 1673, 1446, 1354, 1178 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)[19] δ (ppm) 6.95 and 6.82 (s, 1H, H6), 3.86−3.81 (m, 2H, H1′), 3.76 (s-br, 3H, H2‴), 3.61−3.53 (m, 2H, H2), 3.28 and 3.26 (s-br, 3H, H1″), 2.10−2.06 (m, 2H, H3), 1.88−1.81 (m, 2H, H4); ^{13}C NMR (100 MHz, $CDCl_3$)[19] δ (ppm) 154.1 and 153.6 (C1‴), 124.0 and 123.4 (C6), 115.3 and 115.0 (C5), 75.1 (C1′), 57.1 and 56.9 (C1″), 52.8 (C2‴), 42.0 and 41.8 (C2), 23.0 and 22.7 (C4), 21.3 and 21.2 (C3); HRMS (ESI) exact mass calcd for $C_9H_{16}NO_3$ 186.1130 (MH^+), found 186.1134.

(19) Dynamic NMR effects due to hindered rotation about the CO−N bond.

General Procedure for the Nucleophilic Substitution of *β*-Alkoxymethyl Enecarbamates: Methyl 5-((1*H*-Indol-3-yl)-methyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (17). To a stirred solution of **1** (87 mg, 461 μmol) and indole (121 mg, 1.03 μmol) in CH_2Cl_2 (4 mL) at 0 °C was added $Sc(OTf)_3$ (3.0 mg, 6.1 μmol). After being stirred at 0 °C for 1 h the reaction was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2 (3 × 20 mL), dried over $MgSO_4$, and evaporated to give the title compound as a colorless oil that was further purified by silica gel chromatography eluting with hexane/EtOAc 7:1 to afford the title compound as a colorless oil (108 mg, 85%): IR (film) 2952, 1682, 1455, 1316 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6, 60 °C) δ (ppm) 10.62 (s-br, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.14−7.13 (m, 1H), 7.15−7.17 (m, 2H), 7.04−6.97 (m, 1H), 6.77 (s, 1H), 3.70 (s, 3H), 3.53−3.48 (m, 2H), 3.45 (s, 2H), 2.04−1.98 (m, 2H), 1.81−1.72 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, 60 °C) δ (ppm) 153.7 (C), 137.2 (C), 128.0 (C), 123.6 (CH), 121.3 (CH), 120.8 (CH), 119.1 (C), 118.9 (CH), 118.7 (CH), 112.7 (C), 111.9 (CH), 52.9 (CH_3), 42.2 (CH_2), 31.2 (CH_2), 25.2 (CH_2), 22.0 (CH_2); HRMS (EI) exact mass calcd for $C_{16}H_{18}N_2O_2$ 270.1368 (M^+), found 270.1362.

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Supporting Information Available: Spectroscopic data for all products and Cartesian coordinates for computed structures with electronic and zero point energy. This material is available free of charge via the Internet at http://pubs.acs.org.