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Bond Rotation Dynamics of *N*-Cycloalkenyl-*N*-benzyl α-Haloacetamide Derivatives

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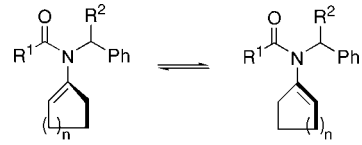

Barriers to rotation of the *N*-alkenyl bond in a series of *N*-cycloalkenyl-*N*-benzyl α-haloacetamide derivatives have been measured by variable-temperature NMR experiments. The barriers range from 10 to 18 kcal/mol, depending on ring size and on substituents on the cycloalkene and the amide. The observed trends aid in the design of substituent combinations that provide resolvable enantiomers or diastereomers at ambient temperature. The compounds undergo 4-*exo* and 5-*endo* radical cyclizations at rates that may be faster or slower than the estimated rate of *N*-alkenyl bond rotation in the derived radicals, depending on the substituents.

Introduction

Though still usually classified as disfavored, 5-*endo* radical cyclizations are increasingly recognized as invaluable synthetic transformations in certain settings.[1] The most widely used class of 5-*endo* cyclizations is that of radicals derived from α-haloenamides.[2−5] Such radicals can also provide products of 4-*exo* cyclization, another disfavored pathway, if substitution patterns dictate. Reactions have been conducted by tin hydride and atom transfer methods (among others) and produce reduced, isomerized, or oxidized products depending on the reaction conditions and the nature of the precursor.[5] Figure 1 shows representative examples of a 5-*endo* tin hydride cyclization by Ishibashi and co-workers (**1a** → **3**)[2a] and 5-*endo* (**4b** → **6**) and 4-*exo* (**7** → **9**) atom transfer cyclizations by Clark and co-workers.[3a] Related cyclizations to make larger rings are known, and the functionalized lactam products from such reactions are useful in alkaloid synthesis.[6]

Rotational features of amides can dictate the success or failure of their radical cyclizations,[7] and we commented on the importance of the amide N−CO bond in a recent mechanistic analysis of radicals like **2**.[5] Figure 2 shows rotations of both the amide N−CO bond and the *N*-alkenyl bond of typical radical precursor **1**. Comparable rotations are available to the derived radical **2**. It is evident that radicals like **2** can only cyclize as the *E*-rotamer of the amide N−C═O bond. In the *Z*-rotamer, the radical cannot reach the alkene. So the amide bond rotation dynamics of both the radical precursor and the radical are important in such cyclizations. Fortunately, enamides typically prefer the *E*-rotamer,[8] so their radicals are formed in a geometry that is predisposed to cyclize.

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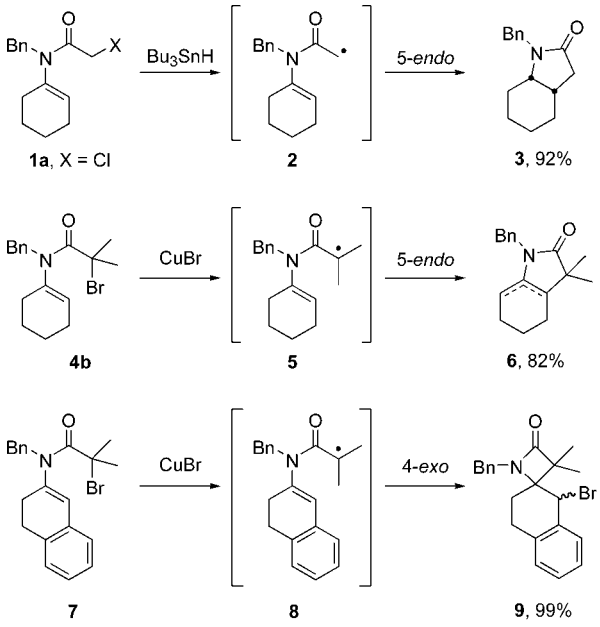

FIGURE 1. Typical 5-*endo* and 4-*exo* radical cyclizations of α-haloenamides.

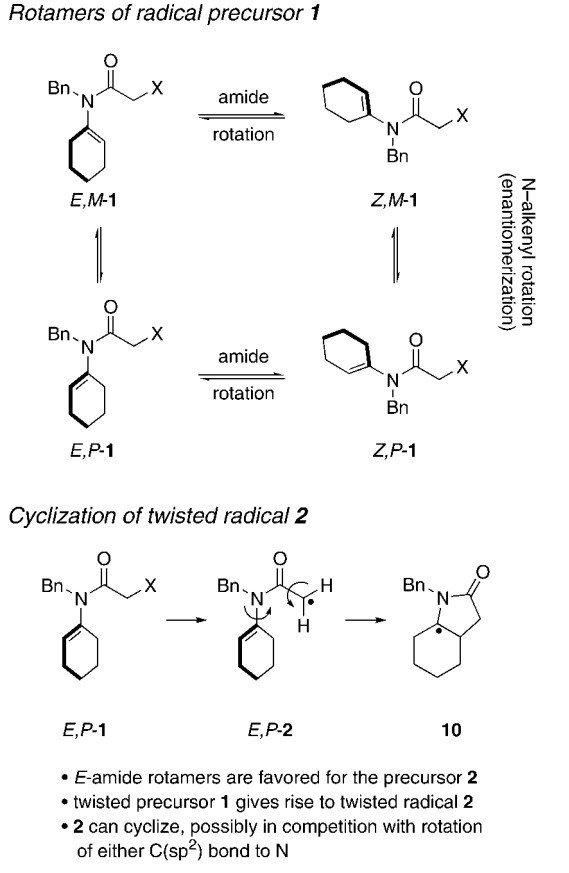

FIGURE 2. Rotamers of radical precursor **1** and cyclizations of derived radical **2**.

Less evident but perhaps equally important are the rotational features of the *N*-alkenyl bond. Conventional drawings of enamide radicals like those in Figure 1 convey the mistaken impression that 5-*endo* cyclizations may be difficult or even impossible because the radical and alkene orbitals seem to be parallel and do not overlap. Intuition suggests that twisting must occur to reach a transition state, and this is confirmed by calculations.[4] We suggest that a key reason for the success of such cyclizations is that the radicals are already twisted in the ground state, as shown in Figure 2. Indeed, cyclizations of radicals like **2** occur not by twisting away from planarity, as suggested by the flat structure in Figure 1, but toward planarity, as shown by *E*,*P*-**2** in Figure 2.

In other words, both the radicals and the radical precursors are axially chiral and exist as atropisomers.[9] For example, an angle of 74° is observed for the *N*-alkenyl bond in the X-ray crystal structure of *N*-cyclohexenyl-α-chloroacetamide **1a** (X = Cl).[5] In this respect, *N*-acylenamides resemble acetanilides, which are also known to be twisted and reach angles of 70−90° if one or both of the ortho substituents are not hydrogen.[10] If rotation barriers are high enough, then the axial chirality of suitable acetanilides can be retained or transferred in a diverse set of asymmetric reactions.[11] By analogy, chirality transfer could also be possible for enamides, depending on whether cyclization is faster than *N*-alkenyl bond rotation.

To better contemplate the prospects of chirality transfer in radical or other reactions of enamides, a basic understanding of their rotation dynamics is needed. Ahlbrecht and co-workers described rotation barriers of several acyclic enamides and related molecules in 1979.[8] Here we report variable-temperature (VT) NMR experiments that provide rotation barriers of a complementary series of α-haloenamides with *N*-cycloalkenyl substituents. Taken together, the past and new results provide a quantitative footing that can be used to design axially chiral enamides that are stable at ambient temperatures or that undergo onward reactions that are faster (or slower) than bond rotations.

Results and Discussion

The experiments were initiated with *N*-benzyl-*N*-cyclohexenyl α-chloroacetamide **1a** and the analogous bromide **1b** and iodide **1c** as part of a comprehensive mechanistic study of the cyclizations of the derived radicals.[5] Iodide **1c** was dissolved in $CDCl_3$ with a small amount of tetramethylsilane for use as a chemical shift and line width standard. ^{1}H NMR spectra were recorded at temperature intervals in the range of 215−297 K. Portions of these spectra are shown in Figure 3, while Figure 4 shows the rotation process for **1c** with the protons relevant for the analysis.

Consistent with the expectation that **1c** was mainly the *E*-amide rotamer in solution, its NMR spectrum at 297 K showed one singlet apiece for the benzyl methylene group and the methylene group α to the amide. As the sample was cooled, decoalescence of the benzyl and α-amide proton resonances occurred. At 215 K, the benzyl protons gave rise to mutually coupled doublets (J = 14.6 Hz) at 5.04 and 4.22 ppm. Similarly, the α-amide protons gave rise to doublets (J = 9.3 Hz) at 3.99 and 3.79 ppm. The variable-temperature ^{1}H NMR spectra of chloride **1a** and bromide **1b** are shown in the Supporting Information, and these displayed temperature-dependent decoalescences and couplings similar to those of **1c**.

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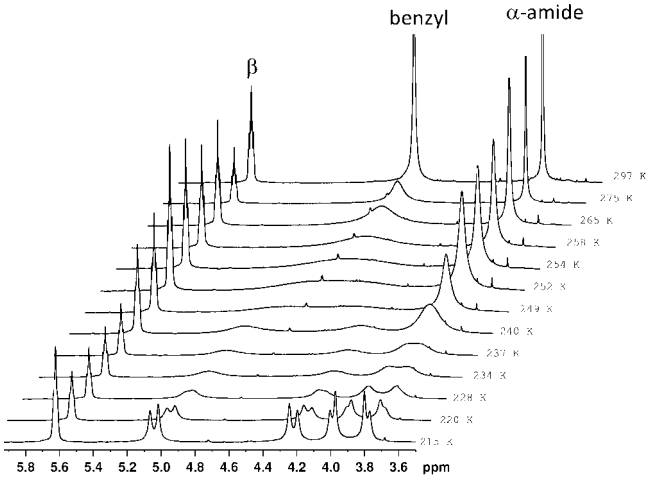
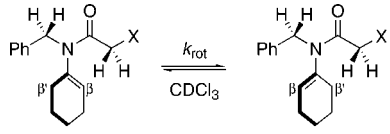


FIGURE 3. Expansion of the ^{1}H NMR spectra of **1c** at 215−297 K.



	X	k_{rot} at 298 K	$\Delta G^{\ddagger}$
1a	Cl	8.5 x 10^3 s^{-1}	12.1 kcal/mol
1b	Br	1.6 x 10^4 s^{-1}	11.7 kcal/mol
1c	I	1.1 x 10^4 s^{-1}	11.9 kcal/mol

FIGURE 4. *N*-Alkenyl rotation of **1a**−**c** with diastereotopic protons.

This behavior is not consistent with standard amide N−CO bond rotation since such a process should cause all signals to double and should not cause geminal protons to become diastereotopic. Instead, the results are consistent with existence of largely a single *E*-amide rotamer in solution. The decoalescences are caused by slowing of the *N*-cyclohexenyl bond rotation, which reveals the diastereotopicity of the pairs of geminal protons.

Using the WINDNMR 7.1 line-shape analysis program[12] to analyze the benzyl peaks of **1a**−**c**, we determined the rotational rate constant k_{rot} at each temperature *T*. The standard Eyring plots for chloride **1a**, bromide **1b**, and iodide **1c** are shown in Figure 5. The three lines nearly coincide, showing that the dynamics of the molecules are similar. The activation barriers at 298 K ($\Delta G^{\ddagger}$) were also similar: 12.1 kcal/mol for **1a**, 11.7 kcal/mol for **1b**, and 11.9 kcal/mol for **1c**. The activation enthalpies and entropies were calculated in the standard way and are shown in Table 1. To assess solvent effects, the barriers for **1b** were also determined in toluene-d_8 (entry 3, 11.1 kcal/mol) and methanol-d_4 (entry 4, 11.6 kcal/mol).

We next extended the studies to the series of eight α-bromoisobutenamides shown in Figure 6. Most of these precursors undergo 5-*endo* cyclizations,[3] the exception being **7**, which prefers 4-*exo* cyclization (see Figure 1). The 300 MHz NMR spectra of **1a**−**c** at room temperature were simple, and peak broadening and decoalescence were only observed upon cooling. Only in hindsight did we notice that the benzyl methylene singlets were slightly broadened at rt. In contrast, the rt spectra of the amides in Figure 6 exhibited a range of different behaviors. For example, the benzylic protons of **4a** were sharp

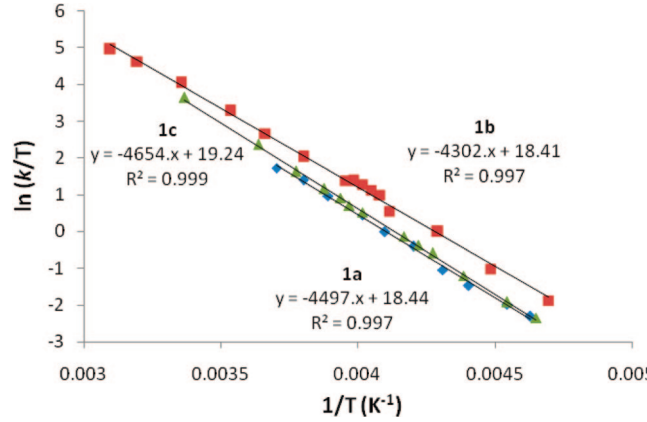


FIGURE 5. Eyring plot of VT NMR data of **1a** (diamonds), **1b** (squares), and **1c** (triangles).

singlets at room temperature, so only cooling was required, while those of **11** were already a well-resolved pair of doublets, so only heating was needed. The other compounds were in between, with more or less broad (in some cases, extremely broad) resonances, so samples were both cooled and heated. Enamide **12** has an additional stereocenter, so its rotamers are diastereomers, not enantiomers. The equilibrium constant for the two diastereomers **12** is about 2, and we did not attempt to assign the structure of the major rotamer.

To extend the temperature range for data collection in both directions, we used toluene-d_8 as the solvent for this series of variable-temperature experiments. The spectra are gathered in the Supporting Information along with the derived Eyring plots. The benzylic protons were well-resolved from other resonances in every case, so we made these the focal points of the line-shape analyses.

Table 1 lists the rate constants at room temperature and the activation parameters for all the substrates. Among the interesting comparisons, notice that cyclohexenamide **4b** with a quaternary carbon on the acyl group has a barrier of 13.3 kcal/mol (entry 7). This is more than 1 kcal/mol higher than the barriers of halides **1a**−**c** with a secondary carbon on the acyl group (entries 1−5). Varying the ring size of the cycloalkenyl group (**4b**−**e**, entries 7−10) does not have much effect on the barrier (12.4−13.5 kcal/mol), except when the ring shrinks to five-membered **4a** (entry 6, 10.0 kcal/mol). Presumably, as the ring is pinned back by its decreasing size, the barrier goes down. Adding a methyl substituent on the *N*-benzyl group to give phenethyl analogue **12** boosts the barrier by about 1 kcal/mol (entry 13).

With an sp^3-hybridized atom (CH_2) at the β'-position of the enamide, 2-tetralone analogue **7** rather closely resembles cyclohexamide **4b**, though its rotation barrier at 11.7 kcal/mol is reduced by about 1.6 kcal/mol (entry 11). In contrast, with an sp^2-hybdrized atom at the β'-position (aromatic C), 1-tetralone enamide **11** is more related to an anilide than a cyclohexenamide. It has the highest rotation barrier observed at 18 kcal/mol (entry 12), though this is surely due primarily to the fact that it is also the only compound in the series to have a non-hydrogen substituent (the phenyl ring of the tetralone) in the β'-position. Indeed, only the beginnings of coalescence were observed in the high-temperature spectra for **11**, so its barrier measurement may not be as accurate as the others.

Though β-tetralone-derived enamide **7** is closely related to cyclohexenamide **4b**, its barrier to rotation is about 1.6 kcal/

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TABLE 1. ***N*-Alkenyl Bond Rotation Rates and Activation Parameters from Variable-Temperature NMR Experiments**

entry	substrate	temp range	sol[a]	k_{rot} 298 K (s^{-1})	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (cal/mol K)	$\Delta G^{\ddagger}_{298}$ (kcal/mol)
1	**1a**	297−215 K	C	8.49×10^3	8.9	−10.6	12.1
2	**1b**	323−213 K	C	1.58×10^4	8.5	−10.6	11.7
3	**1b**	323−193 K	T	4.54×10^4	8.1	−10.0	11.1
4	**1b**	298−213 K	M	1.96×10^4	8.2	−11.3	11.6
5	**1c**	270−216 K	C	1.12×10^4	9.2	−9.0	11.9
6	**4a**	290−186 K	T	3.11×10^5	8.0	−6.6	10.0
7	**4b**	311−233 K	T	1.06×10^3	11.3	−6.6	13.3
8	**4c**	350−250 K	T	7.35×10^2	11.8	−5.7	13.5
9	**4d**	341−230 K	T	3.09×10^3	11.4	−4.3	12.7
10	**4e**	341−230 K	T	4.88×10^3	11.4	−3.5	12.4
11	**7**	313−203 K	T	1.77×10^4	9.8	−6.3	11.7
12	**11**	379−341 K	T	4.08×10^{-1}	11.9	−20.4	18.0
13	**12**[b]	350−271 K	T	1.83×10^2	12.7	−5.4	14.4
				3.64×10^2	12.7	−4.0	14.0

[a] C is $CDCl_3$, T is $C_6D_5CD_3$, M is CD_3OD. [b] Rotamers are diastereomers, so forward and reverse rates were determined.

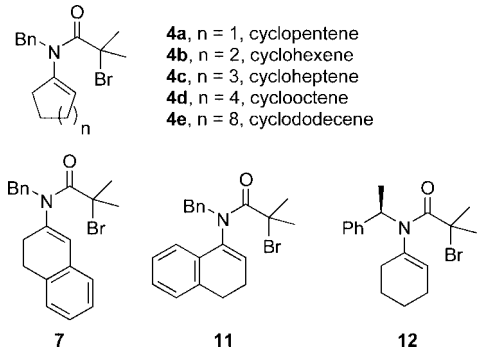

FIGURE 6. Structures of α-haloenamides studied by VT NMR.

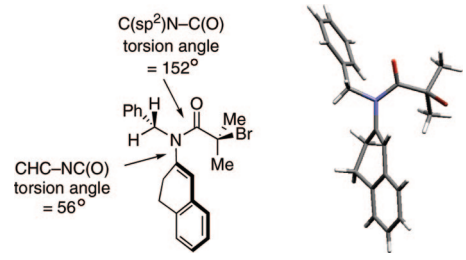

FIGURE 7. X-ray crystal structure of **7**.

mol lower (compare entries 7 and 11). Seeking insight into this difference, we crystallized **7** and solved the X-ray structure. This exhibited several interesting features that are summarized in Figure 7. The torsion angle of the key *N*-alkenyl bond is only 56°. This is smaller than usually observed for related anilides[9] and for enamide **1a**.[5] Perhaps the additional overlap of the nitrogen lone pair through the alkene to the fused phenyl ring reduces both the twist angle and the rotation barrier compared to **1b** and **4b**. In addition, the amide is not completely planar.[13] For example, the sum of the bond angles to nitrogen is not 360° but 356.9°, and the torsion angle of the amide C−N bond to the cycloalkene is not 180° but is only 152°. So the partial rehybridization of N from sp^2 toward sp^3 may also reduce the rotation barrier.

None of the enamides in this study has a barrier to *N*-alkenyl bond rotation that is high enough to provide for separation of rotamers at room temperature. However, the trends of the past and present results with enamides show parallels to the more well studied anilides.[9,10] By analogy, it should be generally

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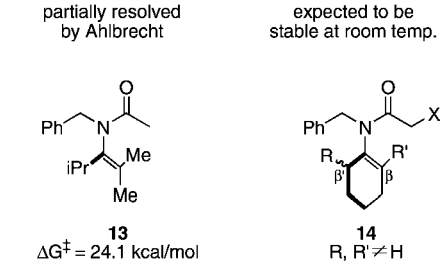

FIGURE 8. Designing resolvable *N*-cycloalkenyl amides.

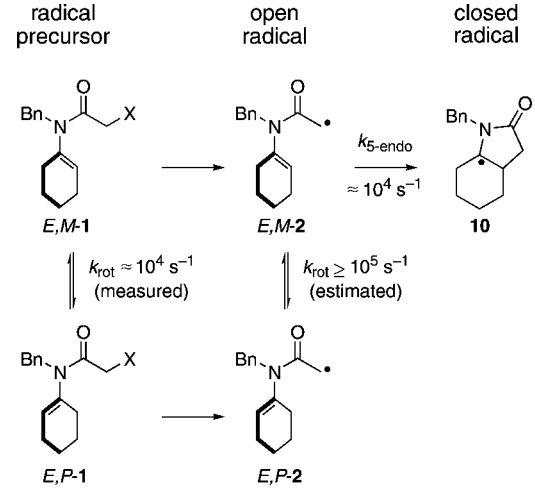

FIGURE 9. Comparing rate constants for onward reactions of radical **2**. Cyclization competes with rotation.

possible to design resolvable enamides simply by changing the hydrogen substituents on the β- and β′-carbons to non-hydrogen ones. Indeed, Ahlbrecht and co-workers partially resolved compound **13** (Figure 8) about 30 years ago and measured its rotation barrier at about 25 kcal/mol. A similarly substituted cyclic analogue such as **14** will probably have a higher rotation barrier (because the β′ substituent is not freely rotating) and be in the range (≥26−27 kcal/mol) that allows for convenient handling at room temperature.

Finally, it is also interesting to compare the rate constants for rotation of radical precursors with the rate constants for cyclization of the derived radicals to deduce which process is faster, cyclization or rotation. This is already possible for one class of radical **2**, shown in Figure 9. In round numbers, the rate constant for cyclization of radical **2** at 298 K is about 10^4 M^{-1} s^{-1}.[4] Remarkably, this is essentially the same as the rate

constant for rotation of the radical precursors **1a**−**c**.[14] Assuming that the radical **2** has a similar rotation barrier to the precursor **1**,[15] radical **2** partitions between direct cyclization and rotation prior to cyclization. Rate constants for cyclization are not known for the other radicals derived from the halides in this study. However, the lowest possible rate constants for successful radical cyclizations under these conditions are in the range of 10^3 s^{-1}. So the radicals derived from **11** and probably also **12** cyclize faster than they rotate.

Conclusions

Barriers to rotation of the *N*-alkenyl bond in a series of *N*-cycloalkenyl-*N*-benzyl α-haloacetamide derivatives have been measured by variable-temperature NMR experiments. The barriers are all significant and range from 10 to 18 kcal/mol, depending on ring size and on substituents on the cycloalkene and the amide. The trends are qualitatively similar to those observed for anilide derivatives, so it is now possible to design substituent combinations that will provide resolvable enantiomers or diastereomers at ambient temperature. The compounds undergo 4-*exo* and 5-*endo* radical cyclizations at rates that may be faster or slower than the estimated rate of *N*-alkenyl bond rotation in the derived radicals, depending on the nature of the substituents that are present.

Experimental Section

Representative Procedure for Synthesis of Enamides 4a−e, 7, 11, and 12. Benzyl-2-bromo-*N*-(cyclopent-1-enyl)-2-methylpropionamide (4a): Benzylamine (30 mmol) was added to the cyclopentanone (30 mmol) in toluene (20 mL), and the mixture was stirred under reflux in a Dean−Stark apparatus for 6 h. The solvent was removed in vacuo to give the crude imine that was used in the next step without further purification. The crude imine (9 mmol) was dissolved in dry toluene (50 mL) and cooled to 0 °C. 2-Bromoisobutyryl bromide (9 mmol) was added dropwise, followed by the slow addition of *N*,*N*-diethylaniline (9 mmol). The reaction was then stirred for 4 h at room temperature then added to water (50 mL). The layers were separated, and the organic layer was washed with 10% HCl (10 mL). After drying over $MgSO_4$, the solvent was removed in vacuo to give a crude residue that was purified by column chromatography: yield (60%); clear oil; R_f (3:1 petroleum ether/EtOAc) 0.83; IR (film)/cm^{-1} υ_{max} 2932, 2850, 1633, 1496, 1464, 1453, 1392, 1365, 1173, 1108, 729, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (5H, m), 5.53 (1H, m), 4.62 (2H, s), 2.39 (2H, m), 2.22 (2H, m), 1.94 (6H, s), 1.85 (2H, q, $J = 7.5$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9, 142.6, 137.9, 130.3, 128.7, 128.3, 127.5, 58.3, 52.4, 33.6, 32.3, 30.5, 22.4; ESI *m*/*z* 344 ([M] + Na) 322, 242, 91; found $(MNa)^+$, 344.0620, $C_{16}H_{20}BrNO$ requires $(MNa)^+$, 344.0626; found C, 57.1; H, 6.1; N, 4.0; $C_{16}H_{20}BrNO$ requires C, 56.8; H, 6.0; N, 4.1.

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Supporting Information Available: Procedures of synthesis and characterization data of **4a**−**e**, **7**, **11**, and **12**, general methods for VT NMR experiments, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Support for this assumption comes from anilide rotation barriers; see ref 9, Table 3. Compounds with alkyl substituents on the acyl group have similar rotation barriers to compounds with alkenyl substituents. Here, the sp^2 alkenyl group is a model for a radical.