A NEW APPROACH TO 5-ARYLPYRROLIDIN-2-ONES *VIA* 5-*ENDO*-TRIG RADICAL CYCLIZATION OF α-HALO- OR α-THIO-SUBSTITUTED *N*-(1-ARYLETHENYL)ACETAMIDES†

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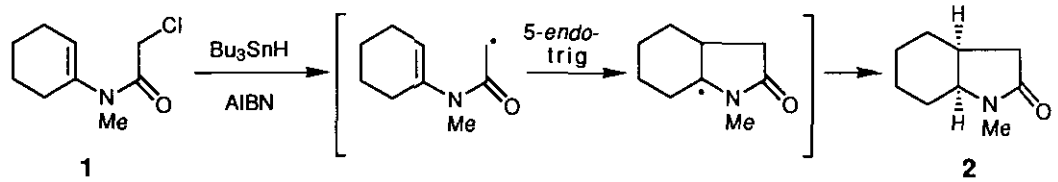
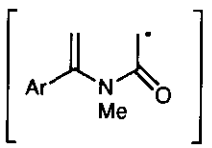
Abstract — *N*-(1-Phenylethenyl)carbamoylmethyl radicals generated by tributyltin hydride-mediated cleavage of carbon-halogen or carbon-sulfur bond underwent smooth cyclization in a "disfavored" 5-*endo*-trig manner to give 5-phenylpyrrolidin-2-one. This method was applied to the synthesis of (±)-cotinine.

In a previous paper,[1] we reported the first example of the so-called "disfavored" 5-*endo*-trig cyclization[2] of the carbamoylmethyl radicals generated from α-chloro-*N*-ethenylacetamides (*e.g.*, **1**) which provides a new route to the five-membered lactams (*e.g.*, **2**).



†This paper is dedicated to Professor Emeritus Masatomo Hamana of Kyushu University on the occasion of his 75th birthday.

Our interests in this area led to examine the behavior of the *N*-(1-arylethenyl)carbamoylmethyl radical (**3**) in the hope that a short entry to the alkaloids such as nicotine (**4**)[3] and codonopsinine (**5**)[4] might result. Here we report a new approach to the 5-arylpyrrolidin-2-ones by using the 5-*endo*-trig radical cyclization. An application of this method to a synthesis of cotinine (**12**), a metabolite of nicotine, is also described.



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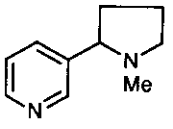

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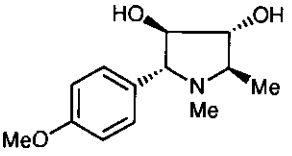

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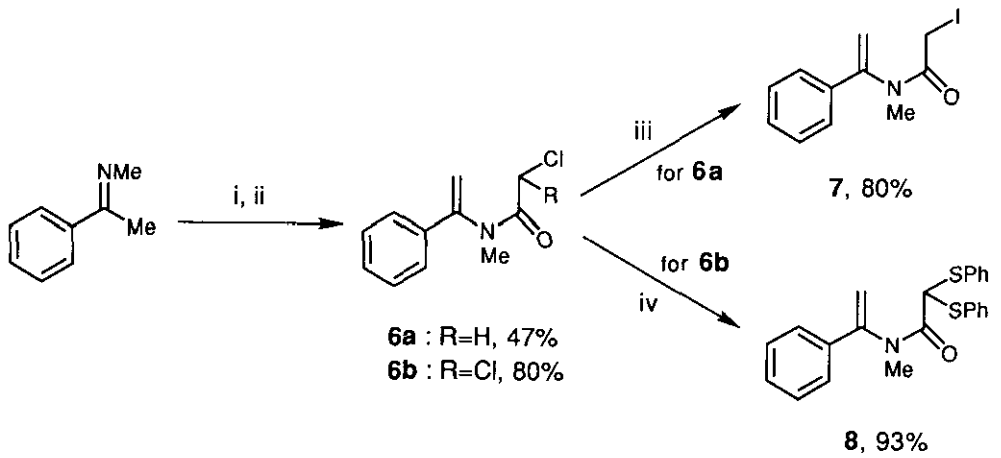
The radical precursors (**6a**) and (**6b**) were easily prepared by treatment of acetophenone *N*-methylimine with the corresponding acid chlorides in methylene chloride at 0 °C followed by addition of saturated sodium bicarbonate solution in 47 and 80% yields, respectively. The enamides (**7**) and (**8**) were synthesized from **6a** and **6b** as shown in Scheme 1.[5]



Scheme 1. *Reagents and conditions:* i, RClCHCOCl (R=H or Cl), CH_2Cl_2; ii, sat. $NaHCO_3$; iii, NaI, MeCN; iv, PhSNa (2.2 equiv.), EtOH.

These substrates thus obtained were treated with tributyltin hydride (TBTH) and a catalytic amount of AIBN in boiling toluene by using our usual technique.[6] The results are summarized in Table 1.

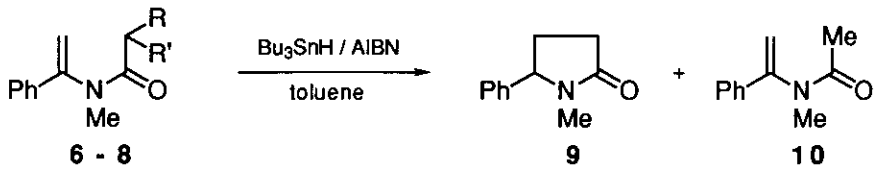


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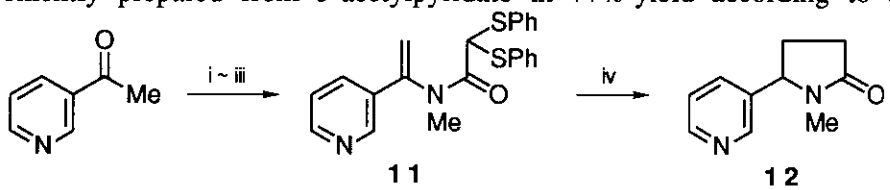
Table 1. Radical Cyclization of *N*-(1-Phenylethenyl)acetamides (**6**–**8**)

	R	R'	Bu_3SnH (equiv.)	Reflux time(h)	% Yield of Products[a] **9**	**10**
6a	Cl	H	2.5	17	17	18[b]
6b	Cl	Cl	3.3	22	c	c[b]
7	I	H	2.5	17	47	12
8	SPh	SPh	3.3	14.5	75	0

[a] Isolated yield. [b] The starting material was recovered (50% for **6a**, 39% for **6b**). [c] Not detected.

The cyclization reaction was found to be highly dependent upon the nature of the radical precursors. Thus, the reaction of the chloride (**6a**) resulted in the formation of only a small amount of the cyclized product (**9**;17%), along with the recovery of a large amount of the starting material. The dichloride (**6b**) failed to cyclize even after the prolonged refluxing time: a complex mixture was obtained from which **6b** was recovered in 39% yield. In contrast, the cyclization of the more reactive iodide (**7**) proceeded smoothly to give **9** in 47% yield. The dithioacetal (**8**) was found to be the radical precursor of choice which gave **9** as a sole product in 75% yield.

Finally, we applied this methodology to a synthesis of cotinine (**12**). The key enamide (**11**) was conveniently prepared from 3-acetylpyridine in 77% yield according to the same



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Scheme 2. *Reagents and conditions:* i, $MeNH_2$, toluene, heat; ii, $Cl_2CHCOCl$, CH_2Cl_2; sat. $NaHCO_3$; iii, PhSNa (2.2 equiv.), EtOH; iv, Bu_3SnH (3.3 equiv.), AIBN, toluene, reflux.

procedure as that described for the preparation of **8**. Treatment of **11** with TBTH (3.3 equiv.) and AIBN afforded (±)-cotinine (**12**)[7,8] in 97% yield as a sole product (Scheme 2). In summary, this study revealed that the 5-*endo*-trig cyclization takes place in a simple system such as *N*-(1-arylethenyl)carbamoylmethyl radicals to give 5-arylpyrrolidin-2-ones. Further application of this method to the synthesis of more complex molecules is in progress.

REFERENCES AND NOTES

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5. Satisfactoty elemental analyses and spectroscopic data were obtained for all new compounds described in this communication.
6. H. Ishibashi, T. S. So, K. Okochi, T. Sato, N. Nakamura, H. Nakatani, and M. Ikeda, *J. Org. Chem.*, 1991, **56**, 95.
7. The ir ($CHCl_3$) and ^{1}H-nmr ($CDCl_3$) spectra of **12** were identical with those of an authentic sample kindly provided by Dr. Hajime Matsushita, Life Science Research Laboratory of Japan Tobacco Inc.
8. For other syntheses of cotinine, see Y. Tsujino, H. Matsushita, A. Saito, K. Kato, T. Kisaki, and M. Noguchi, *Agric. Biol. Chem.*, 1979, **43**, 871; R. Rastogi, G. Dixit, and K. Zutshi, *Electrochim. Acta*, 1983, **28**, 129; R. M. Acheson, M. J. Ferris, and N. M. Sinclair, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 579; E. Wenkert and E. C. Angell, *Synth. Commun.*, 1988, **18**, 1331; R. M. Moriarty, R. K. Vaid, M. P. Duncan, M. Ochiai, M. Inenaga, and Y. Nagao, *Tetrahedron Lett.*, 1988, **29**, 6913.

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