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Thiophenol-Mediated 1,5-Hydrogen Transfer for the Preparation of Pyrrolizidines, Indolizidines, and Related Compounds

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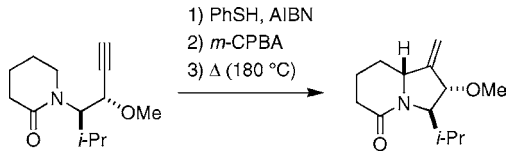
ABSTRACT



The efficient preparation of 1-azabicyclic alkanes is described. Highly functionalized skeletons are prepared in a concise manner using a radical tin-free 1,5-hydrogen transfer−cyclization process. The precursors for the radical reactions are readily assembled either from pyrrolidine/piperidine/hexahydro-1*H*-azepine or via condensation of a properly designed *N*-alkylimine with an allenylzinc species.

Azabicyclic skeletons are important frameworks in natural products. For instance, pyrrolizidines[1] and indolizidines are present in many natural products (Figure 1). Polyhydroxylated alkaloids (azasugars) are of particular interest since their structural analogy with sugars makes them potential inhibitors of the wide range of enzymes involved in biological processes.[2] Therefore, it is not surprising that they represent privileged target structures for organic chemists.[3] Moreover, *Stemona* alkaloids such as, for instance, parvistemonine (Figure 1) possess a related 1-azabicyclo[5.3.0]decane ring and present some interesting biological properties.[4]

Many strategies have been developed by chemists to achieve the formation of the bicyclic skeleton, most of them involve the nitrogen atom in the cyclization step. Strategies involving activation of the position α to the nitrogen atom are known and involve mainly iminium and acyliminium ion chemistry.[5] Several radical approaches to bicyclic alkaloid skeletons have been developed in the last 20 years, but most of them rely on the use of toxic tin derivatives.[6−8]

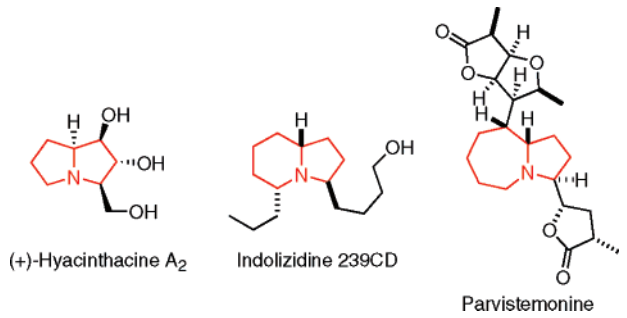


Figure 1. Examples of azabicyclic alkaloids.

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(1) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773−781.
(2) (a) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265−295. (b) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159−2191.
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(4) Pilli, R. A.; Rosso, G. B.; De Oliveira, M. d. C. F. *Alkaloids* **2005**, *62*, 77−173.

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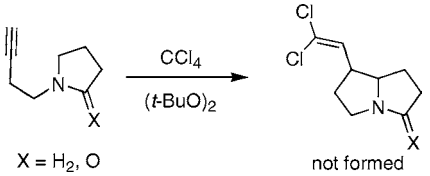
The use of 1,5-hydrogen atom transfer for generating 1-aminoalkyl and 1-amidoalkyl radicals is well-documented.[9] Parsons reported the synthesis of pyrrolizidines using a translocation−cyclization process involving an allylic radical.[10] Robertson has reported the synthesis of pyrrolizidines using a 1,5-hydrogen transfer−5-exo cyclization process starting from alkenyl bromides.[11] Bachi used a related tin-mediated 1,6-hydrogen transfer−7-endo cyclization process to prepare a bicyclic β-lactam starting from a propargyl *N*,*O*-acetal.[12] Ring-fused pyrrolidines were prepared by Wille from alkynylamines via a radical addition−translocation−cyclization process involving nitrate radicals.[13] In an early study, Hart reported a failure to prepare a pyrrolizidine/pyrrolizidinone from the easily available *N*-homopropargylpyrrolidine/pyrrolidinone using Heiba's[14] radical addition−translocation−cyclization process (Scheme 1).[7]

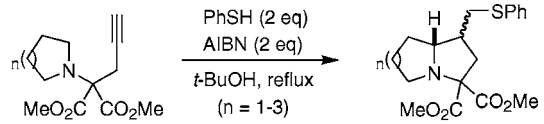
Scheme 1. Early Attempts by Hart to Prepare Pyrrolizidines and Pyrrolizidinones From *N*-Homopropargylpyrrolidine According to Heiba's Procedure[6]

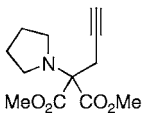
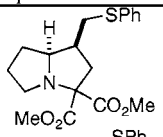
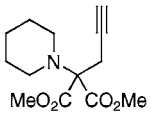
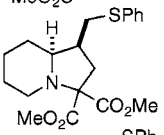
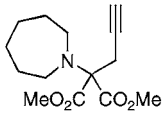
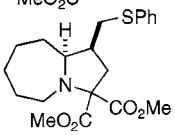


Recently, we reported that thiophenol is a very efficient reagent to generate alkenyl radicals suitable for 1,5-hydrogen transfer−cyclization reactions leading to cyclopentane derivatives.[15−17] This high yielding process was the key reaction for a recent total synthesis of (−)-erythrodiene.[18] The efficiency of the thiophenol-mediated hydrogen transfer−cyclization process prompted us to investigate further the translocation approach of Hart (Scheme 1) for preparing a variety of nitrogen-containing heterocycles. We report here an efficient tin-free cascade reaction leading to polysubstituted pyrrolizidine and indolizidine derivatives as well as related nitrogen-containing bicyclic systems starting from easily available starting materials.

The monocyclic *N*-homopropargylic amines **1**−**3** are easily prepared in two steps from pyrrolidine, piperidine, and hexahydro-1*H*-azepine. The reactions starting from the propargylmalonates **1**−**3** were carried out in refluxing *t*-BuOH using a slow addition of thiophenol over 24 h and afforded the expected azabicyclic derivatives **4**−**6** in moderate to excellent yields (Table 1). Careful GC/MS analysis of the crude reaction mixtures did not show any byproduct. The moderate yield obtained for compound **4** (entry 1) is likely due to purification problems on silica gel. The corresponding [4.3.0] and [5.3.0]bicyclic derivatives **5** and **6** (entries 2 and 3) were both obtained in high yields and in moderate (entry 2) to good (entry 3) diastereoselectivities. The relative endo configuration of the major diastereomers was attributed by analogy with literature precedents[7] and in accordance with the rules for radical cyclization.[19]

Table 1. Synthesis of 1-Azabicyclic Compounds via Thiophenol-Mediated 1,5-Hydrogen Transfer−Cyclization Process Starting from Amino-Substituted Propargylmalonates



alkyne		product[a]		yield	dr
	**1**		**4**	55%	>95:5
	**2**		**5**	90%	78:22
	**3**		**6**	92%	90:10

[a] Only the major diastereomer is shown.

(5) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628.
(6) (a) Ikeda, M.; Sato, T.; Ishibashi, H. *Rev. Heteroat. Chem.* **1998**, *18*, 169−198. (b) Aurrecoechea, J. M.; Suero, R. *ARKIVOC* **2004**, 10−35. (c) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913−926.
(7) Hart, D. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 279−300.
(8) For the use of N-centered radicals, see: Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 407−426.
(9) For selected pioneering works, see: (a) Snieckus, V.; Cuevas, J. C.; Sloan, C. P.; Liu, H. T.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896−898. (b) Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 793−794. (c) Curran, D. P.; Liu, H. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. Reviews: (d) Feray, L.; Kouznetsov, N.; Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 246−278. (e) Cekovic, Z. *J. Serb. Chem. Soc.* **2005**, *70*, 287−318.
(10) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81−82.
(11) Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825.
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(13) Stademann, A.; Wille, U. *Aust. J. Chem.* **2004**, *57*, 1055−1066.
(14) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772−3777.
(15) For the first use of thiophenol in a translocation−cyclization process, see: Burke, S. D.; Jung, K. W *Tetrahedron Lett.* **1994**, *35*, 5837−5840.
(16) (a) Beaufils, F.; Dénès, F.; Renaud, P. *Org. Lett.* **2004**, *6*, 2563−2566. (b) Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4230−4233. (c) Beaufils, F.; Dénès, F.; Becatini, B.; Renaud, P.; Schenk, K. *Adv. Synth. Catal.* **2005**, *347*, 1587−1594.
(17) For the generation of alkenyl radicals by addition of thiyl radicals to alkynes, see also: (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103−2109. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Org. Chem.* **1994**, *59*, 2818−2823. (c) Benati, L.; Calestani, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S. *Org. Lett.* **2003**, *5*, 1313−1316.
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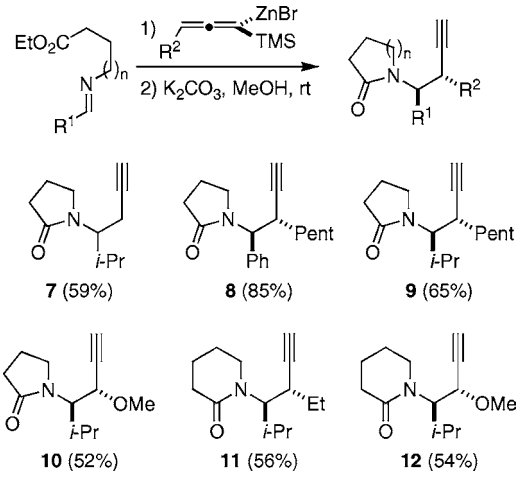
Next, the preparation of functionalized pyrrolizidinones and indolizidinones using a highly modular approach was examined. The precursors **7**−**12** were prepared from simple imines by condensation with various allenylzinc species according to Scheme 2.[20]

Scheme 2. Preparation of Homopropargylic Amines via Addition of Allenylzinc Species to Imines Derived from γ- and δ-Aminoesters

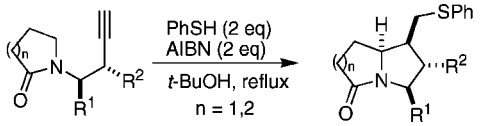


The radical cascade reactions leading to pyrrolizidinones **13**−**16** and indolizidinones **17**−**18** were investigated next, and the results are summarized in Table 2. The substitution of the homopropargylic side chain plays a crucial role in this process.

Monosubstituted homopropargylamine **7** did not afford the expected cyclized product **13** but gave the alkenylsulfide resulting from a simple addition of thiophenol to the alkyne. The presence of vicinal substituents on the homopropargyl moiety increases the rate of hydrogen transfer.[21] For instance, compound **8** gave the desired pyrrolizidine **14** in moderate yield. Analysis of the crude reaction mixture by NMR and GC/MS indicated the presence of two major side products, the reduced alkenyl phenyl sulfide as well as a benzothiophene derivative resulting from the addition of the alkenyl radical intermediate onto the phenyl ring.[22] Cyclization of **9** afforded **15** in high yield (87%, dr = 90:10). A slightly lower diastereoselectivity was observed with **10** which led to **16** in 89% yield (dr = 61:39). Similarly, indolizidinones were prepared using this method. For instance, piperidinones **11** and **12** afforded the corresponding cyclized indolizidinones **17** (87%, dr = 95:5) and **18** (92%, dr = 78:22) in high yields and good to moderate stereoselectivities.

The relative configuration of the four contiguous asymmetric centers was attributed by NOE experiments on **17**. NMR analysis of **18** allowed confirmation the relative configuration of the major diastereomer. However, we were

Table 2. Cyclization of *N*-Homopropargylic Pyrrolidinones and Piperidinones

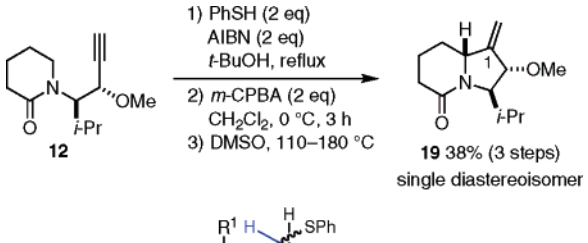


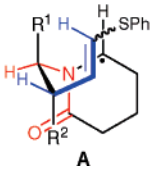
substrate	product	yield	dr
7	**13**	–	–
8	**14**	56%[a]	77:23
9	**15**	87%	90:10
10	**16**	89%	61:39
11	**17**	87%	95:5
12	**18**	92%	78:22

[a] NMR yield, the product is contaminated by the noncyclized reduced product and the benzothiophene derivative.

not able to determine with full confidence the relative stereochemistry of the minor diastereomer. The crude product of this reaction containing **18** as 78:22 mixture of isomers was oxidized to the corresponding sulfoxides with 1 equiv of *m*-CPBA. Heating the sulfoxides at 180 °C afforded the corresponding 1-exo-methylene-substituted indolizidin-5-one **19** in 38% yield from **12** (Scheme 3). The formation of a

Scheme 3. Stereoselective Three-Step Preparation of a 1-Methylene-2,3-disubstituted Indolizidin-5-one





A

(20) Poisson, J. F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889−1891.
(21) Jung, M. E. *Synlett* **1999**, 843−846.
(22) Benzothiophenes are known side products of the translocation−cyclization process involving thiophenol; see ref 16 for details.

single diastereoisomer, albeit in modest overall yield (not optimized), was confirmed by GC/MS and ^{1}H NMR analyses. This indicates that the diastereomers of **18** differ by their relative configuration at C1. Interestingly, the stereochemical outcome of the cyclization of compounds **8**−**12** does not fit with a classical chair-like transition state frequently encountered in radical cyclization.[23] Allylic strain ($A^{1,3}$-strain) forces the amide to adopt the conformation depicted in red, whereas the alkenyl sulfide moiety adopts a skew butene conformation depicted in blue. As result, a boat-like transition state is favored that leads to preferential formation of the major diastereomers depicted in Table 2.[19]

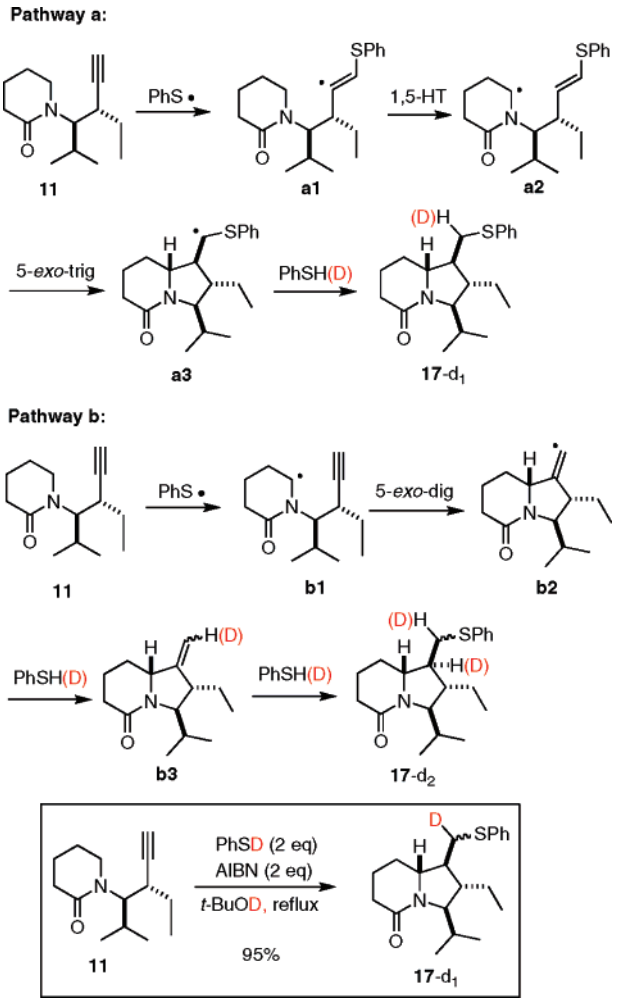
The assumed mechanism of the reaction (Scheme 4, pathway a) involves a radical cascade initiated by addition of a thiyl radical onto the alkyne moiety leading to **a1** followed by an intramolecular 1,5-hydrogen transfer, a 5-exo-trig cyclization of **a2**, and finally a reduction of the cyclized radical **a3** by thiophenol. However, an alternative mechanism (Scheme 4, pathway b) could be envisaged. Direct hydrogen atom abstraction by the thiyl radical could afford the α-aminyl radical **b1** that undergoes a 5-exo-dig cyclization to **b2**, followed by a reduction to the exo-methylene derivative **b3**. Finally, radical addition of thiophenol to **b3** should afford the cyclized product **17**. This second mechanism has to be envisaged since thiyl radicals are known to abstract hydrogen atoms bound to an amino-substituted carbon center.[24] Analysis of the crude reaction mixture did not allow detection of the exo-methylene intermediate **b3**. Moreover, a deuterium-labeling experiment was conducted (Scheme 4), and only the monodeuterated **17**-d_1 was isolated in 95% yield (no bisdeuterated product **17**-d_2 detected). These two experimental results support pathway a over pathway b.

In conclusion, we have reported here a fast access to 1-azabicyclic alkanes such as pyrrolizidine and indolizidine derivatives from easily accessible precursors. This procedure is highly efficient when the *N*-homopropargylic side chain is 1,1-disubstituted or 1,2-disubstituted. This very simple approach allows the preparation of polysubstituted derivatives with a high flexibility. We are currently further investigating the application of this chemistry for the total synthesis of alkaloids.

(23) For related stereocontrol in radical cyclizations, see: Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139−145.

(24) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. *J. Org. Chem.* **2006**, *71*, 7288−7292.

Scheme 4. Mechanistic Investigation



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Supporting Information Available: Experimental procedures, product characterization, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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