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A Convenient Method for 3-Pyrroline Synthesis

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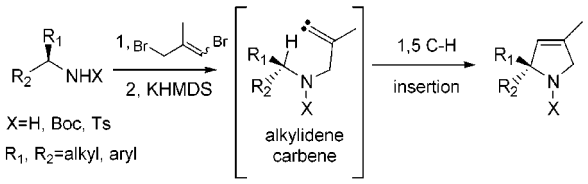
ABSTRACT



The synthesis of a range of 3-pyrrolines has been achieved from primary amine starting materials using a two-step alkylation/alkylidene carbene CH-insertion reaction sequence. We have shown that insertion into a range of CH-bond types is possible, and the formation of nitrogen-bearing quaternary stereocenters is a relatively facile process. The insertion reaction occurs with >95% retention of stereochemistry, but the presence of protecting groups on nitrogen is generally deleterious to the cyclization process.

In 1970, Walsh and Bottini reported the first studies on the formation of 3-pyrrolines via an alkylidene carbene 1,5-CH insertion reaction.[1] In this work the key reactive intermediate was generated by the KO^{t}Bu-mediated 1,1-elimination of HX (X = Br, Cl)[2] from suitably functionalized 1-halo-3-alkylaminopropenes. Although a limited number of 3-pyrrolines were accessed using this chemistry, the maximum yield of the desired heterocycle was a modest 36%. In 1996, Shiori and co-workers reported a significant improvement in this methodology, when they showed that alkylidene carbenes, generated by the action of lithio(trimethylsilyl)diazomethane (LTDM) on a range of 1-alkylamino-2-propanones, cyclized to form the corresponding 3-pyrrolines in good to excellent yields.[3] In this study, however, only tertiary amino-ketone cyclization precursors were examined, and this represents a serious limitation in this methodology. We felt that the alkylidene carbene CH-insertion reaction could be expanded into a very useful general method for 3-pyrroline synthesis if secondary amino-ketone cyclization precursors could also be used.[4]

Our preliminary studies in this area started by trying to apply Shiori's methodology to precursors derived from primary amines. Unsurprisingly, we quickly found that the amino-ketone cyclization precursors **3** (Figure 1) required for the LTDM-mediated carbene generation were generally difficult to prepare and handle, so at this early stage in our studies, an alternative choice of cyclization precursor was examined.

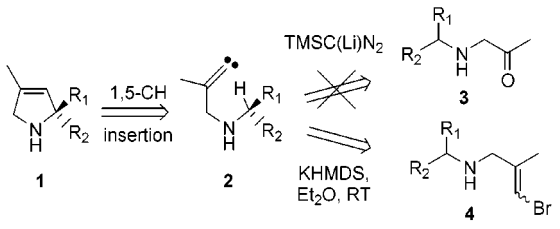


Figure 1.

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(1) Walsh, R. A.; Bottini, A. T. *J. Org. Chem.* **1970**, *35*, 1086.
(2) (a) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745. (b) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1142.
(3) Ogawa, H.; Aoyama, T.; Shiori, T. *Heterocycles* **1996**, *42*, 75.

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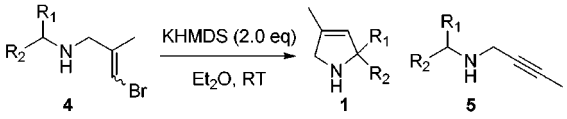
As part of their extensive studies on the synthetic utility of alkylidene carbenes, Taber et al. have shown that cyclopentenes can be produced in high yield by the base-mediated 1,1-elimination of suitably functionalized 1-halo-alkenes.[5] In the course of this work, they found that KHMDS was the most suitable base and that diethyl ether was the most appropriate solvent for the reaction. As these 1,1-elimination and cyclization conditions had worked so well for cyclopentene synthesis, we wondered whether they could be applied to the analogous 3-pyrroline synthesis.

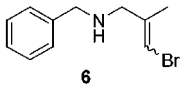
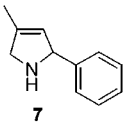
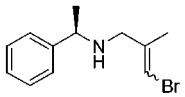
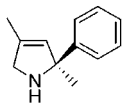
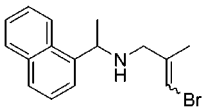
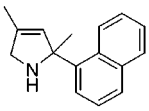
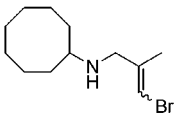
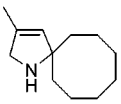
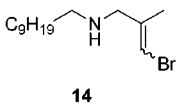
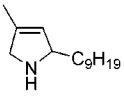
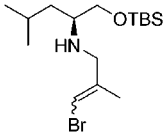
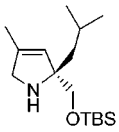
To test this idea, a range of 1-bromo-3-alkylaminopropene cyclization precursors was synthesized by the selective monoalkylation of the corresponding primary amine with 1,3-dibromo-2-methylpropene (40−80% yield).[6] As the alkylating agent was synthesized as a 2.3:1 mixture of *E:Z* isomers,[1] the resulting 1-bromo-3-alkylaminopropenes were produced in a corresponding *E:Z* ratio. These materials were used as mixtures of geometric isomers in the subsequent cyclization reactions.[7]

Diethyl ether solutions of each of the 1-bromo-1-alkenes (Table 1) were treated with KHMDS (2.0 equiv, 0.5 M in PhMe) at room temperature, and both TLC and ^{1}H NMR analysis of the crude reaction mixtures showed that the starting vinyl bromides had been consumed in all cases. We were delighted to find that the major product formed in each reaction was the desired 3-pyrroline[8] and that the remaining mass balance was composed largely of the corresponding but-2-ynyl-amine **5**.[9] The isolated yields of the 3-pyrrolines were generally lower than ^{1}H NMR of the crude reaction mixture had indicated, and we believe that this discrepancy to is due to loss of the cyclic amines during column chromatography.

From the examples presented in Table 1, it can be seen that heterocycle formation by insertion into a range of carbon−hydrogen bond types is possible and that insertion into tertiary C−H bonds leads to the formation of quaternary centers. We have shown previously that alkylidene carbenes can be used for the asymmetric synthesis of nitrogen-bearing quaternary stereocenters during cyclopentene formation,[10] and we chose the (*R*)-α-methylbenzylamine **8** and leucinol **16** derived precursors to examine whether the same would be true in the formation of 3-pyrrolines,[11] as this has not been studied previously.

Table 1. 3-Pyrroline Synthesis via Alkylidene Carbene Insertion



starting material	3-pyrroline product	% yield[a] 1 : 5
 6	 7	55 : 8
 8	 9	55 :9
 10	 11	65 : 10[b]
 12	 13	43 : 21
 14	 15	65 : 14[b]
 16	 17	53 : 25

[a] Isolated yields. [b] The respective yields of the 3-pyrroline and the acetylene were determined by ^{1}H NMR.

Although we were unable to determine the enantiomeric excesses of the 3-pyrrolines **9** and **17** directly, we were able to form suitable derivatives on which this analysis could be carried out. Thus, conversion of **9** to its *N*-Boc derivative **23** was achieved by reaction with BOC anhydride, and chiral HPLC (hexane/IPA 99:1) showed this material to have >95% ee. Finding a suitable derivative for the leucinol-derived 3-pyrroline **17** proved to be a little more challenging, but deprotection of the TBS protecting group (HOAc/H_2O/THF 3:1:1, reflux) and Mosher's ester formation[12] provided material that was found to have >95% ee as determined by ^{19}F NMR.[13] These results showed that the key CH-insertion process had proceeded with the same level of stereoselectivity

(4) For further examples of nitorgen heterocycle synthesis using alkylidene carbenes, see: (a) Yagi, T.; Aoyama, T.; Shiori, T. *Synlett* **1997**, 1063. (b) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440. (c) Williamson, B. L.; Tykwinski, R. R.; Stang, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 93. (d) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656.

(5) (a) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. (b) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.*, **2001**, *66*, 143. (c) Taber, D. F.; Meagley, R. P.; Doren, D. J. *J. Org. Chem.* **1996**, *61*, 5723.

(6) For full details see Supporting Information.

(7) Taber et al. have shown that 50:50 mixtures of *E/Z* vinyl chlorides can be used to form cyclopentenes in high yields (90%). See ref 5c.

(8) No evidence for 2-amino-cyclopropene (via 1,3-CH insertion) and/or azetidene (via 1,4-NH insertion) formation was observed.

(9) The observed ratio of the 3-pyrroline **9** and alkyne **5** products produced in the cyclization of **8** was independent of concentration and temperature over the range 0−25 °C.

(10) Gabaitsekgosi, R.; Hayes, C. J. *Tetrahedron Lett.* **1999**, *40*, 7713.

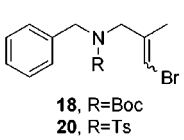
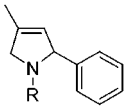
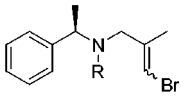
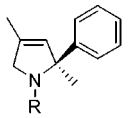
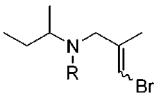
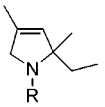
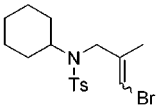
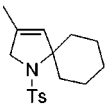
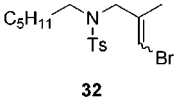
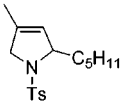
as that observed in previous studies, thus confirming the fact that alkylidene carbenes are excellent synthetic tools for establishing nitrogen-bearing quaternary stereocenters.

We were very pleased by these results, and as a corollary we performed a preliminary study on the use of *N*-protected cyclization precursors. We reasoned that if protecting groups were tolerated during the cyclization process, then the isolated yields of the resulting 3-pyrrolines may be improved as these compounds would no longer suffer the handling and purification problems of materials possessing basic nitrogens.

Suitable cyclization precursors were readily synthesized from the corresponding primary amines by protection (Boc or Ts) and subsequent alkylation of the nitrogen with 1,3-dibromo-2-methylpropene.[13] The resulting 1-bromo-1-alkene precursors (Table 2) were then subjected to the alkylidene carbene forming conditions (KHMDS, Et_2O, rt); the results of the cyclization reactions are summarized in Table 2.[14]

In contrast to the results obtained for the free amine versions (Table 1), we observed quite a range of yields for the formation of the 3-pyrroline products. In general, the highest yields were obtained for insertions into methylene C−H bonds, and as for the free amine cases, insertions into aliphatic and benzylic positions appear to occur with equal ease. With the exception of **22** → **23**, the formation of quaternary centers by insertion into tertiary C−H bonds appears to be much less facile than was observed in the free amine examples (cf. Table 1). At first glance, these results seem to be at odds with the accepted order (tertiary > secondary > primary)[15] for the ease of CH-insertion into different bond types, but we believe that steric hindrance in the transition state (due to bulky protecting group) accounts for these apparently anomalous results.

Table 2. 3-Pyrroline Synthesis from *N*-Protected Precursors

starting material	3-pyrroline product[a]	yield[b]
 **18**, R=Boc **20**, R=Ts		**19**, R=Boc, 63 **21**, R=Ts, 64
 **22**, R=Boc **24**, R=Ts		**23**, R=Boc, 59[c] **25**, R=Ts, 29
 **26**, R=Boc **28**, R=Ts		**27**, R=Boc, 27 **29**, R=Ts, 32
 **30**	 **31**	26
 **32**	 **33**	64

[a] Reaction conditions: KHMDS (2.0 equiv), Et_2O, rt. [b] Isolated yields. [c] 3-Pyrroline has >95% ee as judged by chiral HPLC.

In summary, we have shown that the alkylidene carbene 1,5-CH insertion reaction can be used for the synthesis of a range of 3-pyrrolines and that precursors derived from primary amines can be used in this process. It has not escaped our notice that the 3-pyrroline **17** represents the core carbon skeleton of lactacystin, and we are currently examining the application of this methodology to the total synthesis of this natural product.

Acknowledgment. The Authors thank the EPSRC (GR/M74696) and GlaxoSmithKline (CASE for M.P.G.) for generous financial support.

Supporting Information Available: Experimental procedures and characterization data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016603C

(11) For a selection of alternative approaches to 3-pyrrolines, see: (a) Donohoe, T. J.; Harji, R. R.; Cousins, R. P. C. *Tetrahedron Lett.* **2000**, *41*, 1331. (b) Donohoe, T. J.; Ace, K. W.; Guyo, P. M.; Helliwell, M.; McKenna, J. *Tetrahedron Lett.* **2000**, *41*, 989. (c) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (d) Donohoe, T. J.; Guyo, P. M.; Beddoes, R. L.; Helliwell, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 667. (e) Koskinen, A. M. P.; Schwerdtfeger, J.; Edmonds, M. *Tetrahedron Lett.* **1997**, *38*, 5399. (f) Balasubramanian, T.; Hassner, A. *Tetrahedron Lett.* **1996**, *37*, 5755. (g) Boruah, A.; Baruah, B.; Prajapati, D.; Sandhu, J. S.; Ghosh, A. C. *Tetrahedron Lett.* **1996**, *37*, 4203. (h) Huwe, C. M.; Blechert, S. *Tetrahedron Lett.* **1995**, *36*, 1621. (i) Burley, I.; Hewson, A. T. *Synthesis* **1995**, 1151. (j) Baldwin, J. E.; Field, R. A.; Lawrence, C. C.; Lee, V.; Robinson, J. K.; Schofield, C. J. *Tetrahedron Lett.* **1994**, *35*, 4649. (k) Ketcha, D. M.; Carpenter, K. P.; Zhou, Q. *J. Org. Chem.* **1991**, *56*, 1318. (l) Anderson, W. K.; Milowsky, A. S. *J. Org. Chem.* **1985**, *50*, 5423. We thank one referee for supplying useful additional references in this area.

(12) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.

(13) For full details see Supporting Information.

(14) We did not observe the formation of alkyne-containing side products (cf. **5**) in these cyclization reactions (as judged by IR, TLC, and ^{1}H NMR analysis of the crude reaction mixtures). At present we are unable to account adequately for this observation, and further studies are underway to explain these results.

(15) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251.