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Base-Promoted Reactions of Dichlorocarbene Adducts of Cyclic Enamines: A New Route to Annulated Pyrroles

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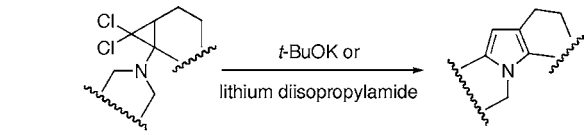
ABSTRACT



gem-dihalogenocyclopropanes
1–5

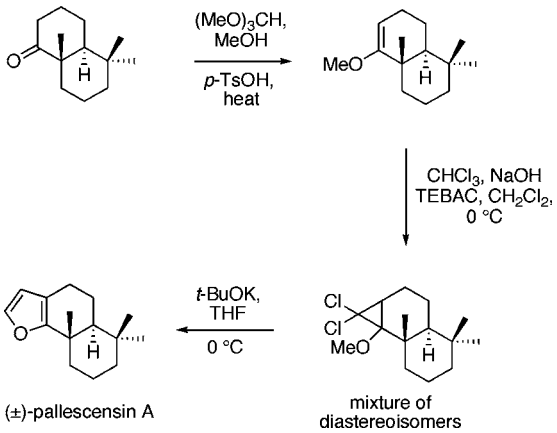
annulated pyrroles
13–17

Treatment of the *gem*-dihalogenocyclopropanes 1–5 with potassium *tert*-butoxide or LDA results in the formation of the corresponding and annulated pyrroles 13–17, respectively.

Recently, we reported that the dichlorocarbene adducts of various alkyl enol ethers react with strong base to give furans.[1] This process thus provides a method for the three-step furannulation of various enolizable ketones, and we have demonstrated the utility of it in the synthesis of the racemic modification of the furanosesquiterpenoid natural product pallescensin A.[1] The relevant reaction sequence is shown in Scheme 1, and the pathway by which the furan-forming step proceeds is the subject of ongoing studies within these laboratories.

In an effort to extend this type of chemistry, we were prompted to examine the base-promoted reactions of the corresponding dihalogenocarbene adducts of enamines. A major motivation for doing so was the expectation that these reactions might lead to pyrroles bearing otherwise difficult to obtain substitution patterns and so provide a useful addition to the repertoire of methods available for preparing these particularly important aromatic heterocycles.[2] Although the dichlorocarbene adducts of enamines are known,[3] we are not aware of any systematic studies of the base-promoted reactions of such compounds. Herein, therefore, we detail

Scheme 1



(±)-pallescensin A

mixture of
diastereoisomers

our preliminary studies of this matter and report on the successful generation of a range of unusual pyrrolic systems.[4]

The adducts **1**−**10** used in the present study were generally prepared (29−85%) by subjecting the relevant enamine to reaction with chloroform or bromoform and sodium hydroxide in the presence of the phase-transfer catalyst triethyl-

(1) Foot, J. S.; Phillis, A. T.; Sharp, P. P.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2006**, *47*, 6817.

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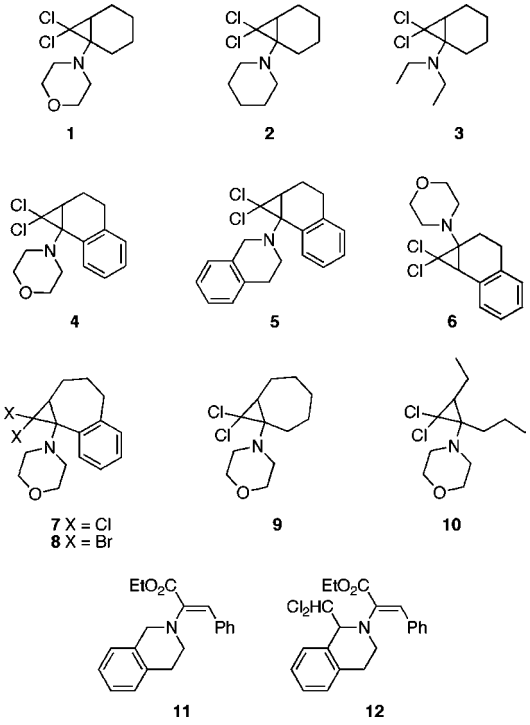
benzylammonium chloride (TEBAC) under conditions first defined by Mąkosza.[5] Despite the propensity of *gem*-dihalogenocyclopropanes carrying electron-donating substituents to undergo facile electrocyclic ring cleavage,[6] these adducts proved to be rather stable and generally crystalline materials. Indeed, the structures of compounds **4** and **6** were confirmed by single-crystal X-ray analysis.[7] In contrast, however, no success was had in efforts to isolate the dichlorocarbene adducts of the morpholino-based enamines derived from indan-1-one and cyclopentanone or the same types of adducts from the pyrrolidine-derived enamines of α-tetralone or cyclohexanone. In each instance only complex mixtures of materials were obtained. Interestingly, attempts to add dichlorocarbene to the double bond of the readily prepared amino-substituted cinnamate **11** delivered, as the only isolable material, what is tentatively identified as the dichlorocarbene insertion product **12** (11%).



The reaction of substrates **1**−**5** with base at 0−18 °C for 0.5−5.0 h produced the expected outcomes in that the corresponding pyrroles, **13**−**17** respectively, were obtained in yields ranging from 28−82% (Table 1, entries 1−7). Such studies also revealed that lithium diisopropylamide (LDA) was a superior base to *t*-BuOK. The structures of the products were established by standard spectroscopic methods and confirmed through the single-crystal X-ray analyses of compound **16**[7] and a derivative of congener **17** (vide infra). The selective and efficient formation of the pyrrolo[2,1-*a*]-isoquinoline-type system **17** over its pyrrolo[1,2-*b*]isoquinoline-based isomer is noteworthy.

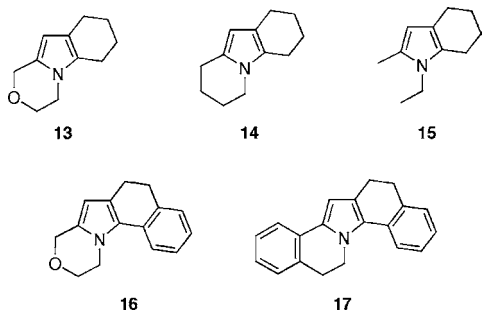


Table 1. Products Derived from Base-Promoted Reactions of Compounds **1**−**10**[a]

entry	substrate	base	temp (°C)	time (h)	product	yield (%)
1	**1**[b,c,d]	LDA	0	3	**13**	82
2	**2**[c,e]	LDA	0	3	**14**[f]	66
3	**3**	LDA	0	3	**15**[g]	54
4	**4**[d]	LDA	0	5	**16**	43
5	**4**	*t*-BuOK	0	0.5	**16**	28
6	**5**	LDA	0	3	**17**	45
7	**5**	*t*-BuOK	18	16	**17**	30−35
8	**6**[d,h]	*t*-BuOK	18	22	**18**	79
9	**7**	LDA	0	8	NR[i]	
10	**8**	LDA	0	3	**19**	81
11	**9**[d]	LDA	0	8	NR	
12	**10**	LDA	0	8	NR	

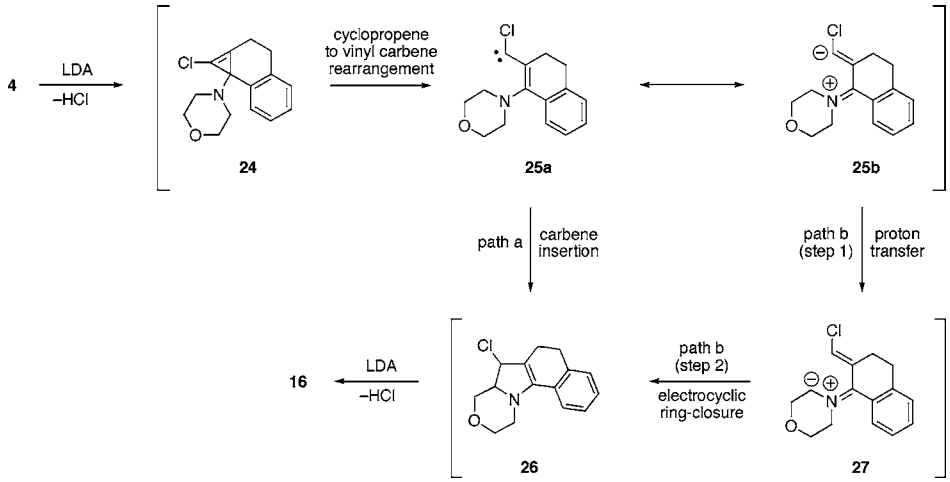
[a] All reactions were carried out using THF as solvent, except for entry 5 where 1:1 v/v THF/DMSO was used. [b] Reference 3a. [c] Reference 3e. [d] Reference 3f. [e] Reference 3b. [f] Reference 8. [g] Reference 9. [h] Reference 3c. [i] NR = no reaction.

(2) For useful points of entry into the literature detailing new methods for the synthesis of pyrroles, their biogenesis, and their chemical manipulation, see: (a) Reisser, M.; Maas, G. *J. Org. Chem*. **2004**, *69*, 4913. (b) Agarwal, S.; Knölker, H.-J. *Org. Biomol. Chem*. **2004**, *2*, 3060. (c) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem*. **2005**, *9*, 1589. (d) Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett*. **2006**, *8*, 2043. (e) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett*. **2006**, *8*, 5349. (f) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett*. **2006**, *8*, 5837. (g) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep*. **2006**, *23*, 517. (h) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem*. **2006**, 3043. (i) Tóth, J.; Nedves, A.; Dancsó, A.; Blaskó, G.; Tőke, L.; Nyerges, M. *Synthesis* **2007**, 1003. (j) Pan, Y.; Lu, H.; Fang, Y.; Fang, X.; Chen, L.; Qian, J.; Wang, J.; Li, C. *Synthesis* **2007**, 1242.

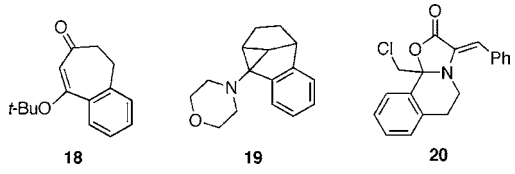
(3) (a) Ohno, M. *Tetrahedron Lett*. **1963**, 1753. (b) Wolinsky, J.; Chan, D.; Novak, R. *Chem. Ind*. (*London, UK*) **1965**, 720. (c) Pandit, U. K.; de Graaf, S. A. G.; Braams, C. T.; Raaphorst, J. S. T. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 799. (d) de Graaf, S. A. G.; Pandit, U. K. *Tetrahedron* **1973**, *29*, 2141. (e) Mąkosza, M.; Kacprowicz, A. *Bull. Acad. Pol. Sci., Chim*. **1974**, *22*, 467. (f) Graefe, J.; Adler, M.; Muehlstaedt, M. *Z. Chem*. **1975**, *15*, 14.

(4) This work was undertaken as part of a program within our group to exploit *gem*-dihalogenocyclopropanes as building blocks for chemical synthesis. For representative publications, see: (a) Banwell, M. G.; Gable, R. W.; Peters, S. C.; Phyland, J. R. *J. Chem. Soc., Chem. Commun*. **1995**, 1395. (b) Banwell, M.; Edwards, A.; Harvey, J.; Hockless, D.; Willis, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2175. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R.; Wu, A. W. *J. Org. Chem*. **2000**, *65*, 4241. (d) Banwell, M. G.; Ebenbeck, W.; Edwards, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 114. (e) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2002. (f) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem*. **2003**, *1*, 296. (g) Taylor, R. M. *Aust. J. Chem*. **2003**, *56*, 631. (h) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem*. **2004**, *57*, 537. (i) See reference 2b. (j) See reference 1. (k) Banwell, M. G.; Vogt, F.; Wu, A. W. *Aust. J. Chem*. **2006**, *59*, 415. (l) Banwell, M. G.; Phillis, A. T.; Willis, A. C. *Org. Lett*. **2006**, *8*, 5341. For a review of certain aspects of our work in this area, see reference 2c.

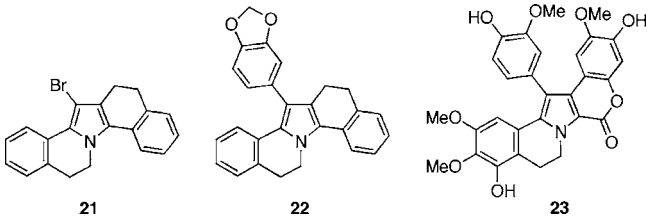
Scheme 2



There are a number of instances in which pyrrole formation is not observed. For example, subjection of compound **6**, the regioisomer of cyclopropane **4**, to treatment with *t*-BuOK failed to give the hoped for pyrrole. Rather, the β-oxygenated cycloheptenone **18**[7] was obtained in 79% yield (Table 1, entry 8). The origin of the divergent behavior of compounds **4** and **6** remains unclear at present. The lack of reaction of the dichlorocarbene adducts **7**, **9**, and **10** when subjected to the sorts of conditions just mentioned (see entries 9, 11, and 12) was also surprising and prompted an examination of the behavior of the *gem*-dibromo analogue **8**, of compound **7**, under the same conditions. Treatment of compound **8** with LDA (entry 10) provided the diquinane **19** in 81% yield. Presumably this compound arises through LDA-promoted lithium-for-bromine exchange at the apical cyclopropyl carbon, and this is followed by loss of the elements of lithium bromide to give the corresponding cyclopropylidene. This last species then undergoes insertion into the remote and *syn*-orientated benzylic C−H bond to give the observed product.[10] On the basis that treatment of the carbene insertion product **12** with base might deliver a pyrrole, this was treated with potassium *tert*-butoxide. However, the product so formed was the oxazolidinone **20** (62%), the structure of which follows from a single-crystal X-ray analysis.[7]



The utility of the pyrrole-forming reaction described above is highlighted by the conversion, using *N*-bromosuccinimde, of compound **17** into the brominated derivative **21** and then Suzuki−Miyaura cross-coupling[11] of the latter material with 3,4-methylenedioxyphenylboronic acid to give compound **22** (40% from compound **5**), the structure of which was secured by single-crystal X-ray analysis.[7] Pyrrole **22** bears some structural resemblance to the pentacyclic ring system associated with certain members of the lamellarin class of marine alkaloids, e.g., **23** (lamellarin K),[12] so the method described here offers considerable potential for the rapid preparation of a range of analogues of these biologically intriguing natural products. Work directed toward such ends is now underway in these laboratories and results will be reported in due course.



At least two distinct reaction pathways can be envisaged for the base-promoted conversion of compounds **1**−**5** into the corresponding pyrroles. Both of these (paths a and b, Scheme 2) would involve dehydrochlorination of the substrate, e.g., **4**, to give the corresponding ring-fused cyclopropene **24**[13] that then engages in ring opening to the

(5) (a) Mąkosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, 4659. For a discussion of the methods available for the generation of dihalogenocarbenes, see: (b) Banwell, M. G.; Reum, M. E. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: London, 1991; Vol. 1, p 19.

(6) Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099.

(7) Details of the single-crystal X-ray analyses carried out as part of this study are provided in Supporting Information.

(8) Kolind-Andersen, H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 543.

(9) Volodina, M. A.; Mishina, V. G.; Terent'ev, A. P.; Kiryushkina, G. V. *Zh. Obshch. Khim.* **1962**, *32*, 1922.

(10) For an example of a related conversion, see: Marquis, E. T.; Gardner, P. D. *Tetrahedron Lett.* **1966**, 2793.

(11) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(12) For useful reviews on the biological properties and synthesis of the lamellarins, see: (a) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363. (b) Handy, S. T.; Zhang, Y. *Org. Prep. Proced. Int.* **2005**, *37*, 411. Also see: (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213.

(13) These types of ring-fused cyclopropenes are readily trapped in Diels−Alder cycloaddition reactions. For example, see: Banwell, M. G.; Corbett, M.; Gulbis, J.; Mackay, M. F.; Reum, M. E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 945.

corresponding vinylcarbene **25a**/zwitterion **25b**.[14] This last species could undergo C−H insertion (path a) to give the chlorinated dihydropyrrole **26**[15] that loses a second equivalent of HCl to deliver the observed and fully aromatic product, e.g., **16**. An alternate pathway (path b, Scheme 2) would involve intramolecular proton transfer within intermediate **25** to give the ylide **27**. Such a species might then be expected to undergo electrocyclic ring closure[2a,16] to give dihydropyrrole **26**, the final intermediate in the reaction sequence and one that is common to both paths a and b. Our recent and soon-to-be published mechanistic studies on the equivalent furan-forming reaction lead us to believe that path a is more likely to be followed.

(14) For a review on thermally-induced cyclopropene to carbene rearrangements, see: Baird, M. S. *Chem. Rev.* **2003**, *103*, 1271.

(15) For a related pathway that has been proposed to account for the formation of an annulated furan, see: Mueller, P.; Pautex, N. *Helv. Chim. Acta* **1988**, *71*, 1630.

(16) These types of ring-closures are well documented. For a review, see: Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947.

(17) CCDC numbers 652972−652977.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support.

Supporting Information Available: Full experimental procedures; crystallographic data and atomic displacement ellipsoid plots and CIFs for compounds **4**, **6**, **16**, **18**, **20**, and **22**;[17] ^{1}H and/or ^{13}C NMR spectra of compounds **1**−**5**, **13**−**20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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