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# Direct Synthesis of Monofunctionalized Indolizine Derivatives Bearing Alkoxymethyl Substituents at C-3 and Their Benzofused Analogues

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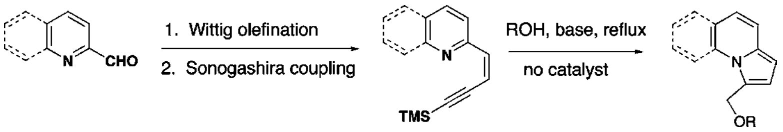
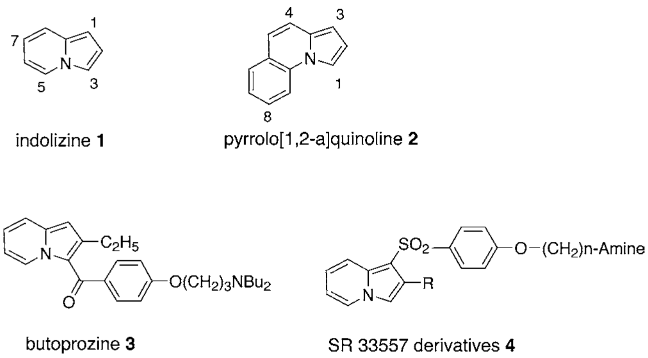
## ABSTRACT



**Treatment of (*Z*)-2-pyridine and quinoline silylated vinylacetylenes at reflux with several alcohols in the presence of a suitable inorganic base (KOH, $K_2CO_3$, CsF, or KF) serendipitously gave 3-alkoxylmethylindolizines and the corresponding 1-alkoxymethylpyrrolo [1,2-*a*]quinolines and not the anticipated desilylated vinylacetylene derivatives. A mechanistic possibility for this unexpected chemical transformation is suggested.**

Indolizine derivatives (Figure 1) have been the subject of a number of biological and theoretical studies because of their intriguing molecular structures[1] and their therapeutic applications.[2−5] Among other uses, synthetic and natural indolizine derivatives have considerable potential as new calcium entry blockers, chemotherapeutics, and cardiovascular agents.[2−4] In addition, several *O*-containing synthetic indolizines have been screened and identified as possessing strong antioxidant effects that prevent the initiation of



indolizine **1**    pyrrolo[1,2-a]quinoline **2**

butoprozine **3**    SR 33557 derivatives **4**

**Figure 1.** Nuclei of indolizine, benzo[*e*]indolizine, and useful synthetic indolizines.

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(1) (a) The Structure, Reactions, Synthesis, and Uses of Heterocyclic Compounds. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vols. 1−8. (b) Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky A. R., Rees C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 443. (c) Swinborne, J. H.; Klinkert, G. *Adv. Heterocycl. Chem*. **1978**, 23, 103. (d) Heterocyclic Systems with Bridgehead Nitrogen Atom (Part 1). In *The Chemistry of Heterocyclic Compounds*; Mosby, W. L., Ed.; Wiley-interscience: New York, 1961; Vol. 1.

(2) (a) Gubin, J.; Lucchetti, J.; Mahaux, J.; Nisato, D.; Rosseels, G.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem*. **1992**, *35*, 981. (b) Gubin, J.; Descamps, M.; Chatelain, P. P.; Nisato, D. Eur. Pat. Appl. EP 235,111, 1988. (c) Gubin, J.; Vogelaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rosseels, G.; Peiren, M.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem*. **1993**, *36*, 1425. (d) Gupta, S. P.; Mathur, A. N.; Nagappa, A. N.; Kumar, D.; Kumaran, S. *Eur. J. Med. Chem*. **2003**, *38*, 867.

(3) (a) Olden, K.; Breton, P.; Grzegorzewski, K.; Yasuda, Y.; Gause, B. L. *Pharmacol. Ther*. **1991**, *50*, 285. (b) Ahrens, P. B,; Ankel, H. *J. Biol. Chem*. **1987**, *262*, 7575. (c) Sasak, V. W.; Ordovas, J. M.; Elbein, A. D.; Berninger, R. W. *Biochem. J*. **1985**, *232*, 759. (d) Dennis, J. W. *Cancer Res*. **1986**, *46*, 5131.

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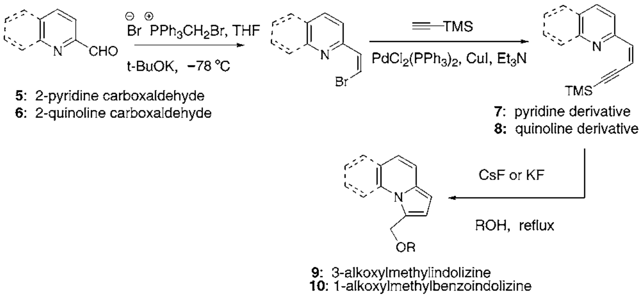
10.1021/ol051860t CCC: $30.25

processes that lead to DNA damage.[5] In this respect, indolizine derivatives represent prime synthetic targets and investigational compounds useful in the development of drugs to treat human diseases such as cancer[6] and HIV infections.[7]

A number of synthetic approaches to these azabicyclic heterocycles have been reported and reviewed in the literature.[1,8] Most previous practical syntheses of the indolizine ring system have employed the Scholtz or Tschitschibabin cyclocondensation reactions.[1,2a,9] In addition to these existing procedures, a number of dipolar cycloaddition reactions of pyridinium ylides with various olefinic and acetylenic precursors appended with electron-withdrawing groups have been developed and proven to be quite valuable in the synthesis of certain indolizine derivatives.[1,10] However, some of the cycloaddition methods are plagued by low-yielding reactions and regioselectivity problems when unsymmetrical, highly functionalized, and sterically demanding alkynes or olefins are used as substrates.[1,8−10] Therefore, an alternate method for the preparation of indolizines that allows functional group variation on the indolizine nucleus is highly desirable for structural and biological activity assessments. In this paper, we wish to report an unprecedented cyclization reaction of the silicon-capped (*Z*)-2-pyridine vinylacetylene with various basic alcohol solutions to give 3-alkoxymethyl-substituted indolizines. Likewise, 1-alkoxymethylpyrrolo[1,2-*a*]quinolines (benz[*e*]indolizine) derivatives were successfully obtained from the cyclization of (*Z*)-2-quinoline vinylacetylene.[11a]

Our laboratory recently described the preparation of silylated vinylacetylene derivatives **7** and **8** from commercially available 2-pyridine and 2-quinoline carboxaldehydes by means of modified Wittig bromoolefination/Sonogashira coupling procedures.[11b] The treatment of silylated conjugated acetylenic derivatives with basic alcoholic solutions or fluoride ions has been known to afford the corresponding terminal acetylenes.[12] However, to our surprise, upon the attempted desilylation of (*Z*)-2-pyridine-silylated vinylacetylenes **7** and **8** under standard basic methanol conditions at room temperature, we observed that the desired terminal vinylacetylenes were relatively unstable under the reaction conditions and were converted to 3-methoxymethylindolizine **9a** and 1-methoxymethylpyrrolo[1,2-*a*]quinoline **10b**, respectively (Scheme 1, Tables 1 and 2). The assigned structures of the products of the reactions are strongly supported by $^1$H NMR, $^{13}$C NMR, and high-resolution mass spectrometry studies. Notably, the $^1$H NMR spectra obtained for all of the indolizine and benz[*e*]indolizine products (except the deuterated compound **10a**) listed in Tables 1 and 2 showed a downfield singlet signal between 4.8 and 4.90 ppm consistent with indolizy-type methylene hydrogens bearing an alkoxyl group.

**Scheme 1.** Synthesis of 3-Alkoxymethylindolizines and 1-Alkoxymethylbenz[*e*]indolizines



**5**: 2-pyridine carboxaldehyde
**6**: 2-quinoline carboxaldehyde
**7**: pyridine derivative
**8**: quinoline derivative
**9**: 3-alkoxylmethylindolizine
**10**: 1-alkoxylmethylbenzoindolizine

Investigations aimed at the optimization of the reaction conditions indicated that the use of KF or CsF along with heating the reaction mixture to reflux in the desired alcohol as solvent resulted in rapid and efficient synthesis of indolizine products. In subsequent reactions, the alcohol was systematically varied to include primary, secondary, tertiary, and cyclic alcohols. In addition, functionalized alcohols such as propargyl, allylic, and benzyl alcohols were used to furnish a library of 3-alkoxymethylindolizines and 1-alkoxymethylbenzo[*e*]indolizine derivatives (Tables 1 and 2). In some cases (Table 1, entries 1−5, and Table 2, entries 1−6), the desired products were simply extracted from the reaction mixture with excellent purity, thereby eliminating the need for further chromatographic purification. It is of interest to note that, when the desilylation reactions were performed at 0 °C (basic methanolic solution or TBAF), the desilylated vinylacetylenes were obtained.[11b] However, when the reac-

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[5] (a) Gundersen, L. L.; Malterud, K. E.; Negussie, A. H.; Rise, F.; Teklu, S.; Østby, O. B. *Bioorg. Med. Chem*. **2003**, *11*, 5409. (b) Nasir, A. I.; Gundersen, L. L.; Rise, F.; Antonsen, Ø.; Kristensen, T.; Langhelle, B.; Bast, A.; Custers, I.; Haenen, G.; Wikström, H. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1829. (c) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem*. **1996**, *39*, 3636.

[6] (a) Humphires, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res*. **1986**, *46*, 5215. (b) Ostrander, G. K.; Scribner, N. K.; Rohrschneider, L. R. *Cancer Res*. **1988**, *48*, 1091. (c) Bols, M.; Lillelund, V. H.; Jensen, H. H.; Liang, X. *Chem. Rev*. **2002**, *102*, 515. (d) Pearson, W. H.; Guo, L. *Tetrahedron Lett*. **2001**, *42*, 8267. (e) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

[7] (a) Ruprecht, R. M.; Mullaney, S.; Andersen, J.; Bronson, R. *J. Acquired Immune Defic. Syndr*. **1989**, *2*, 149. (b) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; De Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (c) Kaspas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Radamacher, T. W. *Proc. Natl. Acad. Sci. U.S.A*. **1989**, 86.

[8] (a) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209. (b) Behnisch, R.; Behnisch, P.; Eggenweiler, M.; Wallenhorst, T. Indolizine. In *Houben-Weyl*; Thieme: Stuttgart, 1994; Vol. E6b/1, 2a, pp 323−450. (c) Katritzky, A. R.; Qui, G.; Yang, B.; He, H. Y. *J. Org. Chem*. **1999**, *64*, 7618. (d) Zhang, X. C.; Huang, W. *Synthesis* **1999**, 51.

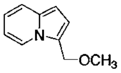
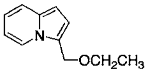
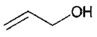
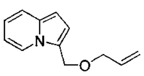
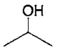
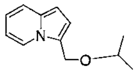
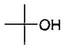
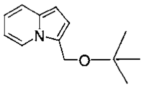
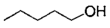
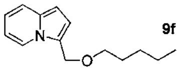
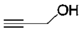
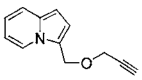
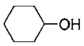
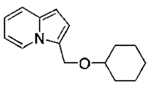
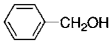
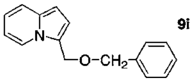
[9] (a) Scholtz, M. *Ber. Dtsch. Chem. Ges*. **1912**, *45*, 734. (b) Boekelheide, V.; Windgassen, R. J. *J. Chem. Soc*. **1959**, *81*, 1456. (c) Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges*. **1927**, *60*, 1607. (d) Jones, G.; Stanyer, J. *J. Chem. Soc*. **1969**, 901. (d) Kostik, E. J.; Abiko, A.; Oku, A. *J. Org. Chem*. **2001**, *66*, 2618.

[10] (a) Padwa, A.; Austin, D. J.; Precedo, L.; Zhi, L. *J. Org. Chem*. **1993**, *58*, 1144. (b) Wei, X.; Hu, Y.; Li, T.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2487. (c) Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem* **2004**, *69*, 3202. (d) Acheson, R. M.; Robinson, D. A. *J. Chem. Soc*. **1968**, 1633. (e) Fang, X.; Wu, Y. M.; Deng, J.; Wang, S. W. *Tetrahedron* **2004**, *60*, 5487.

[11] (a) Hayford, A.; Kaloko, J., Jr. U.S. Pat. Appl. 60/640,369, 2004. (b) Kaloko, J. M.S. Thesis, East Carolina University, Greenville, NC, 2005. (c) Hayford, A.; Kaloko, J., Jr.; El-Kazaz, S.; Bass, G.; Harrison, C.; Corprew, T. *Org. Lett*. **2005**, *7*, 2671.

[12] (a) Halbes, U.; Pale, P. *Tetrahedron Lett*. **2002**, *43*, 2039. (b) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis* **1983**, 312. (c) Konakahara, T.; Takagi, Y. *Synthesis* **1979**, 192. (d) Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem*. **1965**, *4*, 217.

**Table 1.** Array of 3-Alkoxymethylindolizines

| entry | alcohol | products | base | yield (%) | time (hr) |
|---|---|---|---|---|---|
| 1 | $CH_3OH$ |  **9a** | KF | 90 | 1 |
| 2 | $CH_3CH_2OH$ |  **9b** | KF | 92 | 1 |
| 3 |  |  **9c** | KF | 100 | 0.75 |
| 4 |  |  **9d** | KF | 94 | 1.5 |
| 5 |  |  **9e** | KF | 92 | 7 |
| 6 |  |  **9f** | CsF | 37 | 1 |
| 7 |  |  **9g** | CsF | 77 | 2 |
| 8 |  |  **9h** | CsF | 68 | 1 |
| 9 |  |  **9i** | CsF | 82 | 2 |

tions were allowed to warm to room temperature, the indolizine products eventually prevailed. It is also worth noting that the treatment of the desilylated vinylacetylenes with various alcohols also yielded the indolizine products in the absence of base or fluoride ions.

The use of high boiling and/or expensive alcohols such as benzyl alcohol and deuterated alcohols as solvent in the transformation was undesirable. Thus, we have demonstrated that such transformations proceeded smoothly using CsF and 10−20 molar equiv of the alcohol in refluxing anhydrous toluene (Table 1, entries 6−9, and Table 2, entries 7−10).

**Scheme 2.** Proposed Mechanism for Formation of Monosubstituted Alkoxymethylindolizines

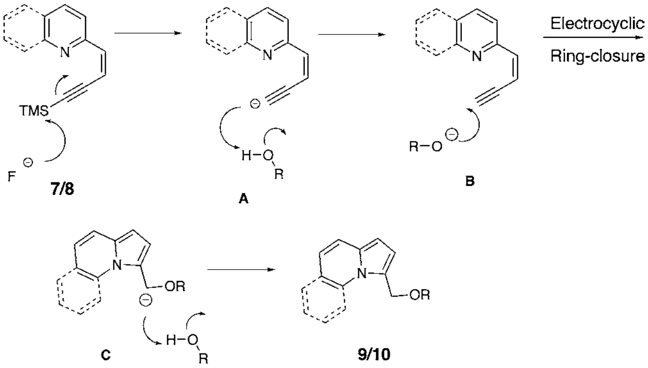
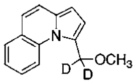
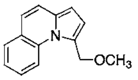
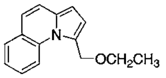
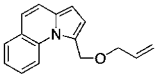
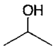
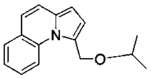
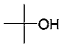
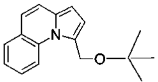
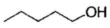
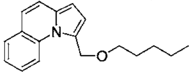
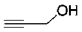
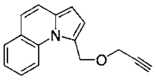
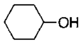
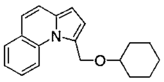
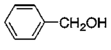
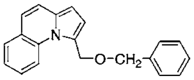


**Table 2.** Array of 1-Alkoxymethylbenz[*e*]indolizines

| entry | alcohol | products | base | yield (%) | time (hr) |
|---|---|---|---|---|---|
| 1 | $CH_3OD$ |  **10a** | KF | 87 | 1 |
| 2 | $CH_3OH$ |  **10b** | KF | 95 | 1 |
| 3 | $CH_3CH_2OH$ |  **10c** | KF | 96 | 1 |
| 4 |  |  **10d** | KF | 100 | 0.75 |
| 5 |  |  **10e** | KF | 86 | 1.5 |
| 6 |  |  **10f** | KF | 97 | 7 |
| 7 |  |  **10g** | CsF | 57 | 1 |
| 8 |  |  **10h** | CsF | 51 | 2 |
| 9 |  |  **10i** | CsF | 77 | 1 |
| 10 |  |  **10j** | CsF | 47 | 2 |

The formation of the observed products could be rationalized by postulating an electrocyclic reaction pathway that begins with the formation of the terminal vinylacetylene **A** via protodesilylation of **7** or **8** upon treatment with fluoride ions (Scheme 2). A 1,6 Michael-type conjugate addition of alkoxide at the acetylenic terminus followed by electrocyclization involving pyridine nitrogen results in the direct formation of 3-alkoxymethyl-substituted indolizine or benz[*e*]indolizine derivatives under mild conditions. On the basis of the proposed mechanism, treatment of **8** with KF in refluxing deuterated methanol ($CH_3OD$) gave the doubly deuterated benzo[*e*]indolizine **10a** in 87% yield (Table 2).

In terms of synthetic value, the protocol unveiled in this paper has proven to be general and very successful in the preparation of a variety of 3-alkoxymethyl-substituted indolizines and 1-alkoxymethylbenzindolizines in moderate to high yields. These compounds not only constitute a new class of C(3)-hydroxymethyl-protected indolizines and C(1)-benz[*e*]indolizine analogues, they are also potential building blocks in the synthesis of biologically relevant C(3)-substituted hydroxymethyl indolizidines and C-1 benz[*e*]indolizidines via suitable protective group removal and traditional hydrogenation methods.

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**Supporting Information Available:** Experimental procedures and spectra data for the preparation of starting materials, **7**, and **8** in addition to the $^{1}$H NMR and $^{13}$C NMR of 3-alkoxymethylindolizines **9a**−**i** and 1-alkoxymethylbenzo[*e*]indolizines **10a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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