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Cyclization of functionalized ketene-*N*,*S*-acetals to substituted pyrroles: applications in the synthesis of marine pyrrole alkaloids

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This paper is dedicated to Professor H. Ila on the occation of her 60th birthday.

Abstract—α-Oxoketene-*N*,*S*-acetals, prepared by the reaction of alkyl glycinates with β-oxodithiocarboxylates followed by alkylation, underwent cyclization in the presence of the Vilsmeier reagent to afford alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates in excellent yields. When the reaction was extended to β-oxodithiocarboxylates derived from deoxyanisoin, 3,4-diarylpyrrole-2-carboxylates, the key intermediates in the synthesis of lukianol A and lamellarin Q were formed.

Recently, several pyrrole-containing bioactive natural products like, lukianol A,[1] lamellarins,[2] ningalins,[3] policitones,[4] halitulin[5] etc., have been isolated and some of them are in clinical trials as antitumor agents. These marine alkaloids are a new class of DNA targeting compounds with considerable cytotoxicity and many of them function as Multi Drug Resistant (MDR) reversal agents.[2,6] They possess in common a 3,4-diarylpyrrole-2-carboxylate skeleton or can be derived from this structural unit. The key step in the synthesis of these alkaloids is the construction of the 3,4-diarylpyrrole-2-carboxylate unit which is often accomplished in a multistep sequence involving metal-catalyzed coupling reactions.[7] Herein we report a convenient and efficient synthesis of highly functionalized pyrroles from readily available starting materials employing a simple iminium ion mediated cyclization. The utility of this protocol in the synthesis of pyrrole-containing marine natural products has been demonstrated by formal total syntheses of lukianol A and lamellarin Q.

The Vilsmeier–Haack reaction has been extensively used for the formylation of various electron-rich aromatic, aliphatic and heteroaromatic substrates.[8] The broad synthetic utility of the halomethyleniminium salts results from initial iminoalkylations followed by cyclizations leading to a variety of heterocyclic compounds.[9] While there are several reports on the cyclization of intermediate iminium salts to six-membered heterocycles such a pyridines[10] and quinolines,[11] formation of substituted pyrroles under Vilsmeier–Haack conditions is less common.[12] Ketene-*N*,*S*-acetals are highly versatile enamines widely used in the synthesis of heterocycles.[13] Junjappa and co-workers have recently reported a synthesis of substituted quinolines by the cyclization of ketene-*N*,*S*-acetals under Vilsmeier–Haack conditions.[14] Kirsch and co-workers have described cyclodehydration of functionalized ketene-*N*,*S*-acetals leading to thiophenes, pyrroles and thienopyrroles.[15] We found that the reaction of suitably substituted ketene-*N*,*S*-acetals leads to substituted pyrrole-2-carboxylates in the presence of the Vilsmeier reagent. The key step is an iminium salt mediated cyclization of α-oxoketene-*N*,*S*-acetals **4** prepared from β-oxodithioesters **1** and alkyl glycinate hydrochlorides **2** followed by alkylation. β-Oxodithioesters **1**, easily prepared[16] by the reaction of enolizable carbonyl compounds with dimethyl trithiocarbonate, are valuable synthetic intermediates[17] and can be transformed to α-oxoketene dithioacetals, *N*,*S*-acetals and *O*,*S*-acetals.[13]

The condensation of β-oxodithioester **1a** with methyl glycinate hydrochloride in the presence triethylamine in methanol proceeded smoothly to afford the β-oxothioamide **3a** in 96% yield. Alkylation of the thioamide **3a** by ethyl iodide using potassium carbonate, as the base, in acetone afforded the *N*,*S*-acetals **4a** in 91%

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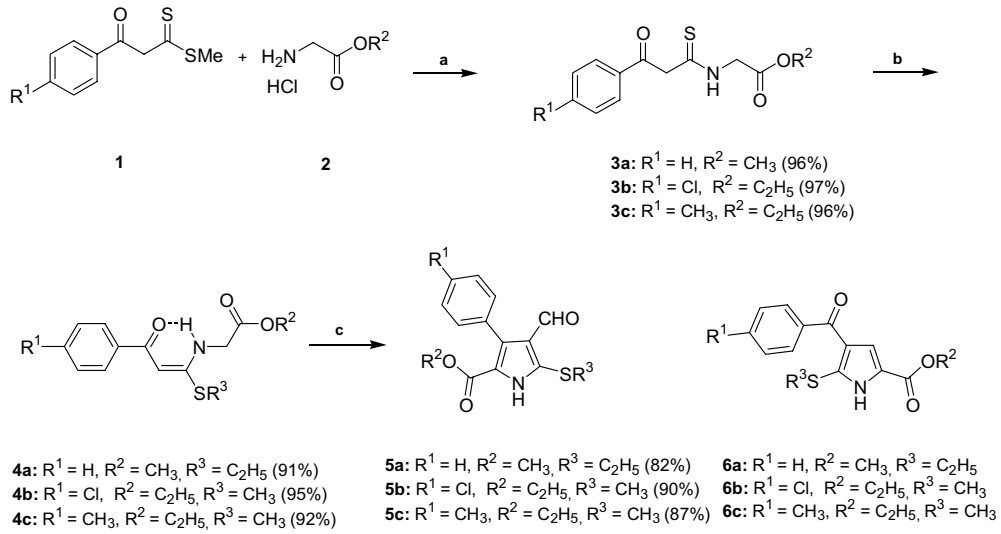
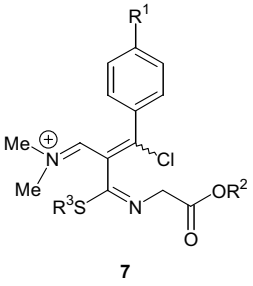
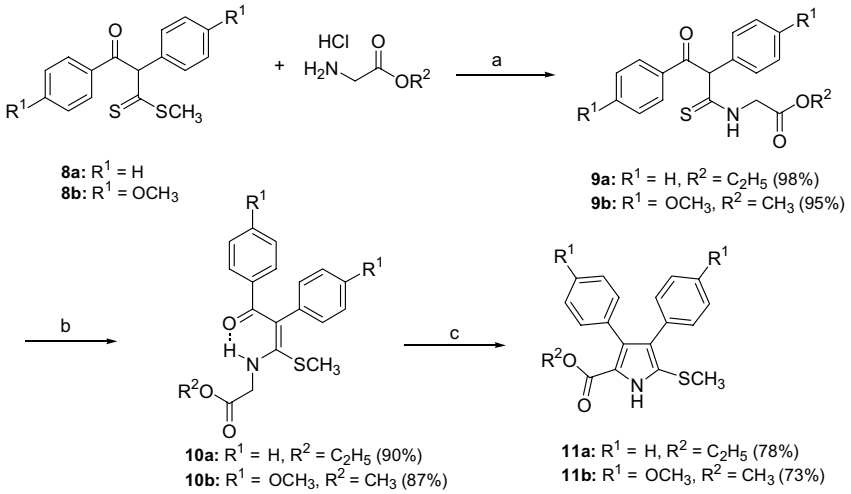


Scheme 1. Reagents and conditions: (a) Et_3N, R^2OH, rt, 5 h; (b) K_2CO_3, acetone, reflux, 0.5 h, cooled to 0 °C, R^3I, 3 h; (c) $POCl_3$, DMF, rt, 6 h, 80 °C, 2 h.

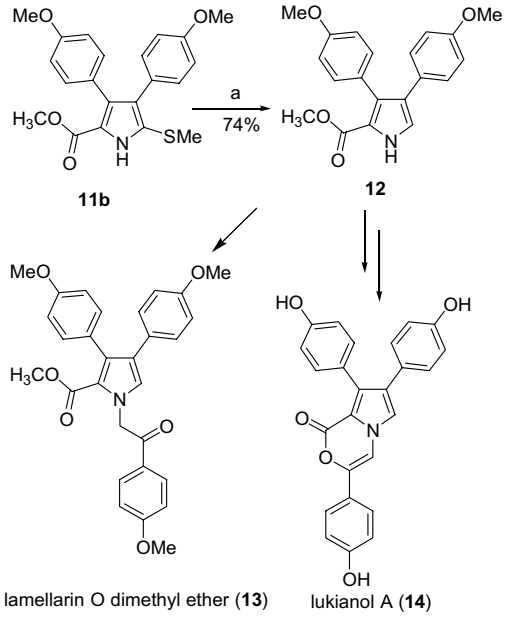


yield. The other ketene-*N*,*S*-acetals **4b** and **4c** were also prepared in a similar fashion employing appropriate dithioesters **1b**–**c**, alkyl glycinates and alkylating agents via **3b**–**c** (Scheme 1).

We envisaged that treatment of the ketene-*N*,*S*-acetal **4** with the Vilsmeier–Haack reagent would lead to iminoalkylation followed by cyclization to afford the substituted pyrroles **6**. However when the *N*,*S*-acetals **4** were treated with the Vilsmeier–Haack reagent prepared from $POCl_3$ and DMF,[18] the product mixture after hydrolysis with saturated aqueous potassium carbonate solution gave the substituted pyrroles **5** exclusively in 82–90% yields (Scheme 1).[19] The reaction was carried out at room temperature for 4 h, and then at 80 °C for 2 h. Interestingly the carbonyl group of the aroyl moiety was involved in the cyclization despite an iminoalkylation at the β-position of the ketene-*N*,*S*-acetal moiety. The formation of **5** could have resulted from the cyclization of an intermediate **7**,that could have been easily derived from **4** on treatment with the chloromethyleniminium salt, followed by hydrolysis. The electron-withdrawing nature of the iminium salt moiety in **7** should facilitate the cyclization. The conversion of the enaminoketone moiety to the chlorosubstituted vinamidium intermediate **7** circumvents possible stereochemical constraints on the cyclization process.[13c] Base



Scheme 2. Reagents and conditions: (a) Et_3N, EtOH, rt, 5 h; (b) K_2CO_3, acetone, reflux, 0.5 h, cooled to 0 °C, CH_3I, 3 h; (c) $POCl_3$, DMF, rt, 6 h, 80 °C, 7 h.



Scheme 3. Reagents and conditions: (a) Raney Ni, EtOH, reflux, 3 h.

catalyzed alkylation of ketene-*N*,*S*-acetals has been found to proceed with spontaneous cyclodehydration to pyrroles.[15] However similar cyclization was not observed during the preparation of ketene-*N*,*S*-acetal **4**.

Gupton et al. have utilized reactions of vinylogous iminium salts with α-aminocarbonyl compounds for the synthesis of substituted pyrroles.[20] This protocol has recently been used for the total synthesis such as ningalin B hexamethyl ether and lukianol A.[21] We envisaged that cyclodehydration of ketene-*N*,*S*-acetals **10** derived from readily available substituted deoxybenzoins would lead to a rapid access of 3,4-diarylpyrrole-2-carboxylates which are the key precursors for the synthesis of marine pyrrole alkaloids. The efficient cyclization of **4** to **5** under Vilsmeier–Haack conditions prompted us to employ this reagent for the cyclization of **10** to **11** as well. We found that the cyclization does not proceed effectively in the presence of bases.

The ketene-*N*,*S*-acetals **10** were prepared from the corresponding dithiocarboxylates **8** on treatment with alkyl glycinate followed by alkylation. The ketene *N*,*S*-acetals **10a** and **10b** underwent smooth cyclization to afford the corresponding 3,4-diaryl pyrroles **11a** and **11b** in good yields under Vilsmeier–Haack conditions (Scheme 2). Reductive removal of the alkylsulfanyl group from **11b**using Raney Ni afforded the Fürstner intermediate **12** (lamellarin Q dimethyl ether) in 74% yield which has previously been transformed into lukianol A and lamellarin O dimethyl ether (Scheme 3). [22]

In summary, we have developed a straightforward and simple protocol for highly functionalized pyrrole derivatives. We have also extended the scope of the method for the efficient total synthesis lukianol A and lamellarin Q. We are currently investigating the total synthesis of several other pyrrole-containing marine natural products using this protocol and the results will be published in due course.

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References and notes

1. Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Sceuer, P. J. *Helv. Chem. Acta* **1992**, *75*, 1721–1726.
2. Bailly, C. *Curr. Med. Chem.—Anti-Cancer Agents* **2004**, *4*, 363–378.
3. Kang, H.; Fenical, W. *J. Org. Chem.* **1997**, *62*, 3254–3262.
4. Rudi, A.; Goldberg, I.; Stein, Z.; Frolow, F.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *J. Org. Chem.* **1994**, *59*, 999–1003.
5. Kashman, Y.; Koren-Goldshlager, G.; Gravalos, M. D. G.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997–1000.
6. Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62.
7. (a) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 155–156; (b) Banwell, M.; Flynn, B.; Hamel, E.; Hockless, D. *Chem. Commun.* **1997**, 207–208.
8. (a) Jones, G.; Stanforth, S. P. *Org. React.* **2000**, *56*, 373–384; (b) Marson, C. M. *Tetrahedran* **1992**, *48*, 3659–3726; (c) Jutz, C. In *Advances in Organic Chemistry*; Taylor, E. C., Ed.; John Wiley & Sons: New York, 1976; Vol. 9, pp 225–342.
9. (a) Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539–557; (b) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1–39; (c) Meth-Cohn, O.; Taylor, D. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1463–1464; (d) Jackson, A.; Meth-Cohn, O. *J. Chem. Soc., Chem. Commun.* **1995**, *22*, 1319; (e) Cheng, Y.; Liu, Q.-X.; Meth-Cohn, O. *Tetrahedron Lett.* **2000**, *41*, 3475–3478; (f) Majo, V. J.; Perumal, P. T. *J. Org. Chem.* **1998**, *63*, 7136–7142; (g) Majo, V. J.; Perumal, P. T. *Tetrahedron Lett.* **1997**, *38*, 6889–6892; (h) Amaresh, R. R.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3837–3840; (i) Akila, S.; Selvi, S.; Balasubramaniyan, K. *Tetrahedron* **2001**, *57*, 3465–3469.
10. (a) Thomas, A. D.; Asokan, C. V. *Tetrahedran Lett.* **2002**, *43*, 2273–2275; (b) Thomas, A. D.; Asokan, C. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2583–2587; (c) Thomas, A. D.; Josemin; Asokan, C. V. *Tetrahedron* **2004**, *60*, 5069–5076; (d) Katrizky, A. R.; Denisenko, A.; Arend, M. *J. Org. Chem.* **1999**, *64*, 6076–6079.
11. (a) Amerash, R. R.; Perumal, P. T. *Indian J. Chem.* **1997**, *36B*, 541–544; (b) Meth-Cohn, O.; Narine, B.; Tarnawski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1520–1530.
12. Balasundaram, B.; Venugopal, M.; Perumal, P. T. *Tetrahedron Lett.* **1993**, *34*, 4249–4252.
13. (a) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423–5506; (b) Ila, H.; Junjappa, H.; Mohanata, P. K. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: New York, 2001; Vol. 13, Chapter 1, pp 1–24; (c) Barun, O.; Mohanta, P. K.; Ila, H.; Junjappa, H. *Synlett* **2000**, 653–657; (d) SyamKumar, U. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193–4296.
14. Mahata, P. K.; Venkatesh, C.; SyamKumar, U. K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966–3975.
15. Sommen, G.; Comel, A.; Kirsch, G. *Tetrahedron* **2003**, *59*, 1557–1564.
16. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693–694.
17. (a) Roy, A.; Nandi, S. S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 229–232; (b) Tominaga, Y.; Okuda, H.; Kohra, S.; Mazume, H. *J. Heterocycl. Chem.* **1991**, *5*, 1245–1256; (c)

Curphey, T. J.; Joyner, H. H. *Tetrahedron Lett.* **1993**, *34*, 7231–7234.

18. *General procedure for the synthesis of alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1H-pyrrole-2-carboxylates* **5**: The Vilsmeier reagent was prepared by mixing ice cold, dry DMF (25 mL) and $POCl_3$ (2 mL, 20 mmol). The mixture was then stirred for 30 min at room temperature. The *N*,*S*-acetal **4** (3.25 g, 10 mmol) was dissolved in dry DMF (10 mL) and added over 10 min at 0–5 °C. The reaction mixture was stirred for 6 h at room temperature and heated to 80 °C for 2 h with stirring. The reaction mixture was then cooled and poured into cold, saturated aq K_2CO_3 (200 mL) and extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to afford the crude product, which was chromatographed over silica gel using hexane–ethyl acetate (10:1) as eluent to give alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates **5**.
19. *Spectroscopic data for ethyl 3-(4-chlorophenyl)-4-formyl-5-(methylsulfanyl)-1H-pyrrole-2-carboxylate* **5b**: mp 118–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (t, 3H, J = 7.2 Hz), 2.62 (s, 3H), 4.19 (q, 2H, J = 7.2 Hz), 7.33 (d, J = 8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H), 9.42 (brs, 1H), 9.62 (s, 1H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ = 14.38, 15.56, 61.39, 120.73, 123.01, 128.27, 130.45, 132.28, 133.70, 134.45, 138.91, 160.88, 186.33; EI-MS *m*/*z* (%) = 325 (M^+ + 2, 39) 323 (M^+, 100), 276 (38), 244 (20), 216 (42), 179 (20), 161 (5), 113 (3). Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33. Found: C, 55.60; H, 4.45; N, 4.42.
20. (a) Gupton, J.; Krumpe, K.; Burnham, B.; Dwornik, K.; Petrich, S.; Du, K.; Bruce, M.; Vu, P.; Vargas, M.; Keertikar, K.; Housein, K.; Jones, C.; Sikorski, J. *Tetrahedron* **1998**, *54*, 5075–5088; (b) Gupton, J.; Petrich, S.; Smith, L.; Bruce, M.; Vu, P.; Du, K.; Dueno, E.; Jones, C.; Sikorski, J. *Tetrahedron* **1996**, *52*, 6879–6892.
21. (a) Gupton, J.; Clough, S.; Miller, R.; Lukens, J.; Henry, C.; Kanters, R. P.; Sikorski, J. A. *Teterahedron* **2003**, *59*, 207–215; (b) Gupton, J.; Krumpe, K.; Burnham, B.; Webb, T.; Shuford, J.; Sikorski, J. *Tetrahedron* **1999**, *55*, 14515–14522.
22. Fürstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637–6641.