Tetrahedron Letters,Vol.27,No.32,pp 3685-3688,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ALKYLATION OF SUBSTITUTED PYRROLE DIANIONS; SYNTHETIC STUDIES DIRECTED AT THE B/C RING SYSTEMS OF CC-1065

Thomas A. Bryson* and Gary A. Roth

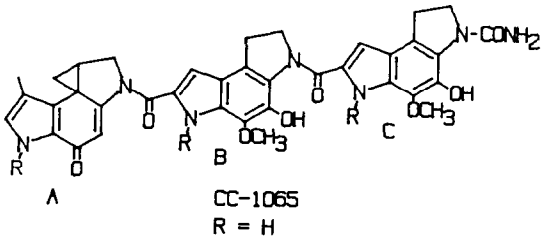
Department of Chemistry
University of South Carolina, Columbia, S.C. 29201

Liu Jing-hau

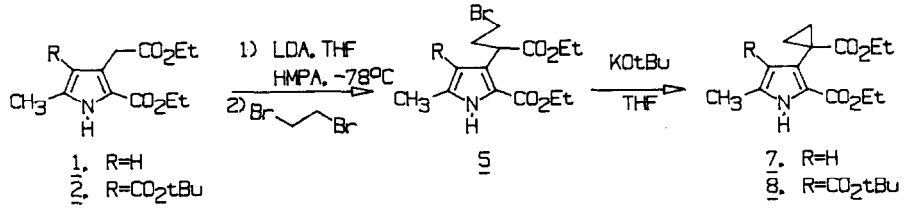
Department of Chemistry
Shanxi University, Taiyuan, Shanxi, Peoples Republic of China

Abstract: The dianion chemistry of pyrroles is investigated using several alkylating agents. Inter-followed by intramolecular alkylation with dibromoethane affords cyclopropylpyrroles 7-10.

The B/C ring systems of CC-1065, a potent antitumor agent[1], have been the target of several synthetic studies[2]. The antitumor activity of CC-1065 has been shown to occur via 1,6-opening of the cyclopropane ring by N-3 of an adenine base in DNA[3]. In light of this, our synthetic strategy directed at the B/C ring systems incorporates a cyclopropane ring early in the synthesis allowing for the preparation of novel and possible biologically active cyclopropane containing heterocycles. In this communication we report the dianion alkylation of several substituted pyrroles and utilize this alkylation to construct simple cyclopropane containing pyrroles. By using a dianion strategy we had hoped to avoid pyrrole or indole nitrogen protection during alkylation and subsequent transformations.



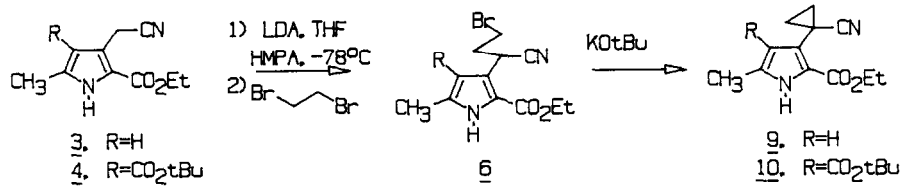
Pyrroles **1-4**, prepared by the Knorr synthesis[4], were treated with 2.2 equivalents of LDA in THF/HMPA (10:1) at −78° C to afford a bright yellow solution of the dianion. Rapid addition of dibromoethane (1.5eq.) followed by warming slowly to room temperature afforded the monoalkylated products **5** and **6** (85-90% after flash chromatography).[5] Exposure of the bromides **5** and **6** to 2.2eq. of LDA in THF lead only to the recovery of starting material. Attempted intramolecular alkylation of **5**



1. R=H
2. R=CO_2tBu

5

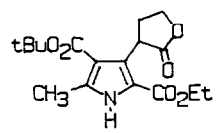
7. R=H
8. R=CO_2tBu



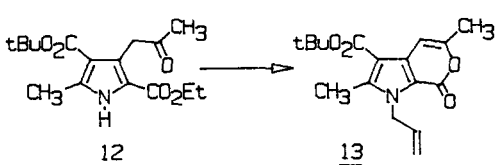
3. R=H
4. R=CO_2tBu

6

9. R=H
10. R=CO_2tBu

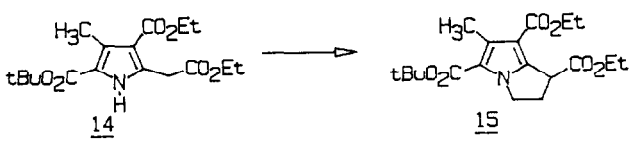


11



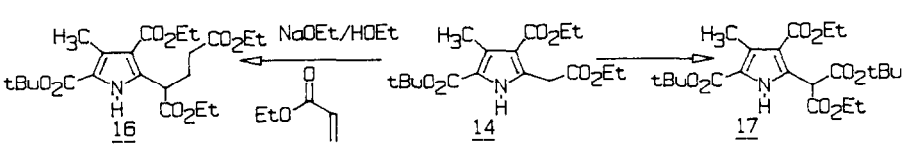
12

13



14

15



16

14

17

(R = CO_2tBu) with KOtBu/tBuOH or NaOEt/EtOH did give the desired product **8**, but also produced substantial quantities of lactone **11**. This by-product could be minimized by treatment of the monobromopyrroles **5** and **6** with 2.5eq. of KOtBu in THF forming the desired cyclopropanes, **7-10**, in 80-90% yields.

The lithium dianions of **1-4** were found to react with a variety of alkylating agents such as epibromohydrin and allylbromide. The cyclopropane ring of pyrroles **7-10** have been found to be resistant to nucleophillic opening under a variety of conditions. Attempted dianion alkylation of the analogous lithium dianion of pyrrole propanone **12** with dibromoethane resulted only in recovery of starting material. Use of allyl bromide as the alkylating agent gave high yields of the N-allylated lactone vinyl ether **13**. It is interesting to note the reversal in the site of alkylation with the dianion of **12** and that the vinyl lactone is seemingly formed only after the stabilized pyrrole anion is quenched by N-alkylation with a good carbon electrophile.[6] Treatment of **12** with 3.2 eq. of LDA followed by introduction of the alkylating agent gave alkylation at the methyl group of the methyl ketone presumably through a tri-anion intermediate.

For comparison, the triester **14** was studied to see if this isomer would undergo similar dianion alkylation. Indeed, following deprotonation of **14** under the usual conditions and introduction of dibromoethane, the C and N alkylation product, **15**, was obtained in 85% yield. In addition to alkylation, **14** undergoes Michael addition to give **16** in 90% yield(1.1eq. NaOEt/EtOH/ethyl acrylate), and C-acylation to **17** (95%) with di-t-butyl dicarbonate.[7]

In conclusion, we have shown that dianion alkylation is an effective method for cyclopropanation of pyrrole acetonitriles and pyrrole acetic acid esters. This method has been used to prepare cyclopropane containing pyrroles which are used as intermediates in a synthesis directed at the B/C ring systems of CC-1065.

Acknowledgements

We wish to thank the American Cancer Society (Grant SIN107) for partial support of this work.

References and Notes

1. (a) D. Martin, C. Biles, S. Gerpheide, L. Hanka, W. Krueger, J. McGovern, S. Mizsak, G. Neil, J. Steward, and J. Visser, *J. Antibiot.*, **1978**, *31*, 1211. (b) C. Chidester, W. Krueger, S. Mizsak, D. Duchamp, and D. Martin, *J. Am. Chem. Soc.*, **1981**, *103*, 7629. (c) D. Martin, C. Chidester, D. Duchamp, and S. Mizak, *J. Antibiot.*, **1980**, *33*, 902.

2. (a) P. Magnus and S. Halazy, *Tetrahedron Lett.*, **1985**, 2985. (b) R. Sundberg and B. Pearce, *J. Org. Chem.*, **1985**, *50*, 425. (c) D. Boger and S. Coleman, *J. Org. Chem.*, **1984**, *49*, 2240. (d) R. Bolton, C. Moody, C. Rees, and G. Tojo, *J. Chem. Soc., Chem. Commun.*, **1985**, 1775. (e) N. Komoto, Y. Enomoto, M. Miyagaki, Y. Tanaka, K. Nitenai, and H. Umezawa, *Agric. Biol. Chem.*, **1979**, *43*, 555.

3. L. Hurley, V. Reynolds, D. Swenson, G. Petzold, and T. Schahill, *Science*, **1984**, *226*, 843.

4. For the preparation of **1** and **2** via the Knorr synthesis see: A. Battersby, E. Hunt, E. McDonald, J. Paine III, and J. Saunders, *J. Chem. Soc. Perkin I*, **1976**, 1008.

5. All spectral data are in accord with the structure assigned. Only data for 5, 6(R = CO_2tBu), 7 and 10 (R = CO_2tBu) are reported. Data for **5**: mp 63-64°C. PMR($CDCl_3$, 90 MHz, ppm): 1.25(t, 3H, J = 7Hz,ester $C\underline{H}_3$), 1.4 (t, 3H, J = 7Hz, ester $C\underline{H}_3$), 2.25 (s, 3H, ring $C\underline{H}_3$), 2.2-2.7 (m, 2H, $C\underline{H}_2$ CH_2 Br), 3.4 (t*, 2H, J = 7Hz, $C\underline{H}_2$ Br), 4.15 (q, 2H, J = 7Hz, ester $C\underline{H}_2$), 4.3 (q, 2H, J = 7Hz, ester $C\underline{H}_2$), 4.5 (t*, 1H, J = 7Hz, $C\underline{H}$), 5.95 (bd, 1H, J = 3Hz, ring $\underline{H}$), 9.1 (bs, 1H, $N\underline{H}$). Anal. calcd. for $C_{14}H_{20}NO_4Br$: C, 48.57; H, 5.82; N, 4.05. Found: C, 48.66; H, 5.86; N, 4.04. Data for **6** (R = CO_2tBu): mp 127-129°C. PMR ($CDCl_3$, 90 MHz, ppm): 1.4 (t, 3H, J = 6Hz, ester $C\underline{H}_3$), 1.6 (s, 9H, $C(C\underline{H}_3)_3$), 2.45 (s, 3H, ring $C\underline{H}_3$), 2.3-2.9 (m, 2H, $C\underline{H}_2CH_2Br$), 3.5 (t*, 2H, J = 7Hz, $C\underline{H}_2$ Br), 4.35 (q, 2H, J = 6Hz, ester $C\underline{H}_2$), 5.35 (t*, 1H, J = 7Hz, $C\underline{H}$), 9.8 (bs, 1H, $N\underline{H}$). IR($CHCl_3$, cm^{-1}): 2250. Anal. calcd. for $C_{17}H_{23}N_2O_4Br$: C, 51.13; H, 5.76; N, 7.02. Found: C, 51.24; H, 5.85; N, 6.94. Data for **7**: mp 109-110°C. PMR ($CDCl_3$, 90 MHz, ppm): 1.1 (m, 2H, 2 cyclopropane $C\underline{H}$'s), 1.15 (t, 3H, J = 7Hz, ester $C\underline{H}_3$), 1.35 (t, 3H, J = 7Hz, ester $C\underline{H}_3$), 1.6 (m, 2H, 2 cyclopropane $C\underline{H}$'s), 2.3 (s, 3H, ring $C\underline{H}_3$), 4.05 (q, 2H, J = 7Hz, ester $C\underline{H}_2$), 4.25 (q, 2H, J = 7Hz, ester $C\underline{H}_2$), 5.8 (bd, 1H, J = 3Hz, ring $\underline{H}$), 9.3 (bs, 1H, $N\underline{H}$). Anal. calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.25; H, 7.27; N, 5.27. Data for **10** (R = CO_2tBu): mp 151-153°C. PMR ($CDCl_3$, 90 MHz, ppm): 1.2 (m, 2H, 2 cyclopropane $C\underline{H}$'s), 1.4 (t, 3H, J = 6Hz, ester $C\underline{H}_3$), 1.6 (s, 9H, C $(C\underline{H}_3)_3$), 1.7 (m, 2H, 2 cyclopropane $C\underline{H}$'s), 2.4 (s, 3H, ring $C\underline{H}_3$), 4.4 (q, 2H, J = 6Hz, ester $C\underline{H}_2$), 9.7 (bs, 1H, $N\underline{H}$). IR ($CHCl_3$, cm^{-1}): 2250. Anal. calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.05; H, 7.02; N, 8.75.

6. Other combinations of base and alkylating agents failed to yield any vinyl lactone systems; no C-alkylated vinyl lactones or other pyrrole products were formed.

7. L. Grehn and V. Ragnarsson, *Angew. Chem. Int. Ed. Engl.*, **1985**, *23*,296.

* denotes slight broadening due to diastereo topic effects.

(Received in USA 13 May 1986)