A Novel Pyrrole Synthesis: One-Pot Preparation of Ethyl 5-Methylpyrrole-2-carboxylate

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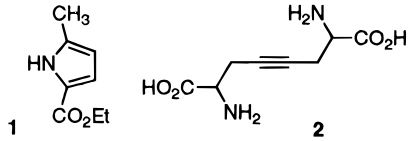
The preparation of ethyl 5-methylpyrrole-2-carboxylate (**1**), a starting material for the synthesis of porphyrin analogs,[1] can be achieved using a number of literature procedures.[2] The various syntheses generally follow well-known routes to pyrroles (like the Fischer−Fink synthesis) and require several steps, either for the preparation of the starting materials or for the actual reaction sequence. This paper reports a one-pot synthesis of **1** from the reaction of commercially available starting materials. An interesting feature of the reaction is its mechanism, which we postulate involves formation and reaction of a butatriene intermediate.



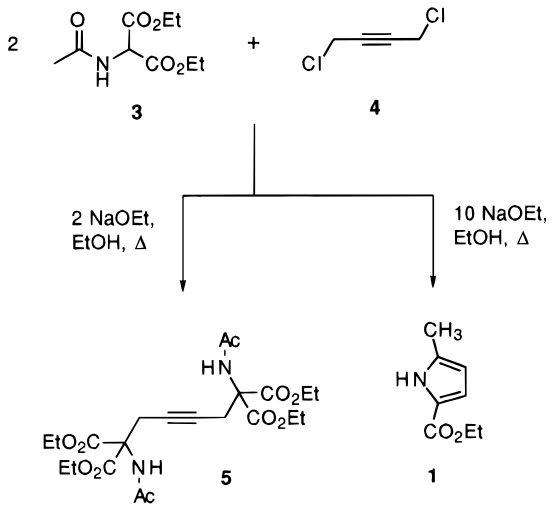
1 **2**

The discovery of this synthesis came about during studies aimed at preparing bis-amino acid **2** following a literature synthesis[3] where the first step calls for reaction of 2 equiv of diethyl acetamidomalonate (**3**) and 1 equiv of 1,4-dichloro-2-butyne (**4**) with 2 equiv of NaOEt in refluxing EtOH to yield **5** (see Scheme 1). In the process of repeating the literature work the reaction was inadvertantly run using 10 equiv of NaOEt; under these conditions the major product obtained following chromatographic purification bore no resemblance spectroscopically to the expected product **5**; rather, the major product was identified by spectroscopic and combustion analysis as the pyrrole **1**.

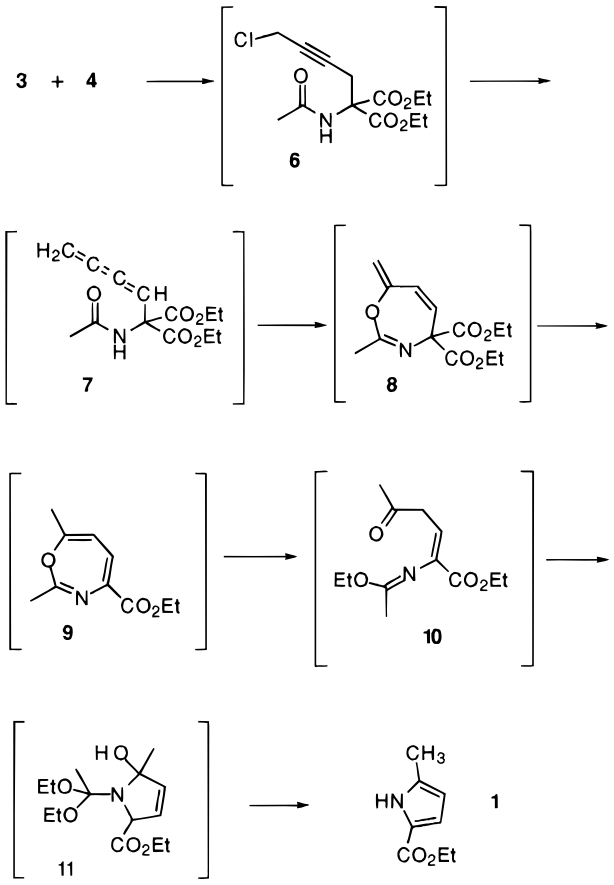
Subsequent studies of this reaction have shown that 1 equiv each of **3** and **4** along with an excess of NaOEt is sufficient to obtain **1**. Both **3** and **4** are needed for formation of **1**, indicating that **1** is derived from the combination of **3** and **4**. Also, heat is required for formation of **1**; when the reaction is run at room temperature none of the pyrrole **1** is formed. Although the yield of pure **1** has been modest (between 30−45%), the ready availability of the starting materials and the ease with which the reaction can be run make this an attractive route for synthesizing **1**.

An obvious question regarding this reaction is the mechanism that generates **1**. Outlined in Scheme 2 is one possible mechanism for the formation of **1** from **3** and **4** based on literature precedents. Initial alkylation of the sodium salt of **3** with **4** generates propargyl chloride **6**, which then undergoes a 1,4-elimination to generate the butatriene intermediate **7**.[4] In the next step, **7** undergoes base-promoted nucleophilic attack by the amide carbonyl oxygen on the central double bond of the butatriene to yield the oxazepine intermediate **8**. Butatrienes are known to be unstable and to undergo addition reactions with a variety of substances at the central double bond.[5] In addition, Williams and Kwast recently discovered a new synthesis of bicyclic piperazine-2,5-diones, and they postulated that the key reaction in the synthesis involved formation and enolate addition to a butatriene.[6]

Scheme 1



Scheme 2



(1) Chang, C. K. *J. Org. Chem.* **1981**, *46*, 4610.

(2) (a) Fischer, H.; Beller, H.; Stern, A. *Chem. Ber.* **1928**, *61B*, 1074. (b) Terry, W. G.; Jackson, A. H.; Kenner, G. W.; Kornis, G. *J. Chem. Soc.* **1965**, 4389. (c) Falk, H.; Hofer, O.; Lehner, H. *Monatsh. Chem.* **1973**, *104*, 925. (d) Elder, T.; Gregory, L. C.; Orozco, A.; Pflug, J. L.; Wiens, P. S.; Wilkinson, T. J. *Synth. Commun.* **1989**, *19*, 763. (e) Lash, T. D.; Hoehner, M. C. *J. Heterocycl. Chem.* **1991**, *28*, 1671.

(3) Schlogl, K. *Monatsh. Chem.* **1958**, *89*, 377.

(4) Schubert, W. M.; Liddicoet, T. H.; Lanka, W. A. *J. Am. Chem. Soc.* **1954**, *76*, 1929.

(5) Fischer, H. Cumulenes. In *The Chemistry of Alkenes*; Patai, S., Ed.; Interscience: London, 1964; Chapter 13, p 1100.

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Decarboxylation of **8** yields the isomeric 1,3-oxazepine monoester **9**. Species like **9** are known to undergo base-promoted fragmentation to yield ketones (like **10**) that then undergo further reaction to yield pyrrolidines (like **11**).[7] In the last step **11** undergoes elimination and then hydrolysis on workup to yield **1**.

This novel pyrrole synthesis and the findings of Williams and Kwast[6] indicate that investigations of the formation and reaction of butatriene intermediates, an area that has not received much attention to date, could yield rapid, new, and/or improved routes to a variety of organic compounds.

Experimental Section

Ethyl 5-Methylpyrrole-2-carboxylate, 1. To 9.0 mL of 1 M NaOEt/EtOH (9 mmol) was added 0.395 g (1.82 mmol) of diethyl acetamidomalonate (**3**) and the resulting solution brought to reflux, and 190 μL (1.94 mmol) of 1,4-dichloro-2-butyne (**4**) was added. After 1 h an additional 190 μL (1.94 mmol) of 1,4-dichloro-2-butyne (**4**) and 0.70 mL (1.8 mmol) of 21 wt % NaOEt in EtOH were added. Reflux was continued for an additional 1 h, after which the EtOH was evaporated. The remaining brown residue was partitioned between 50 mL of EtOAc and 50 mL of water. The aqueous layer was extracted twice with 50 mL portions of EtOAc. The EtOAc layers were combined and washed: three times with 25 mL portions of saturated $NaHCO_3$, three times with 25 mL portions of 1 M HCl, and one time with a 25 mL portion of brine. The organic layer was treated with decolorizing carbon and anhydrous $MgSO_4$ and then evaporated to yield a light yellow oil. On exposure to high vacuum for 16 h the oil crystallized to yield 137 mg (49%, mp 94−98 °C) of **1** as a light orange solid. Flash chromatography (2:1 hexane/ether) yielded 107 mg (38%) of pure **1** as light yellow crystals: mp 98−100 °C (lit. mp 100 °C,[2a] 97−99 °C,[2b] 92−95 °C[2e]); ^{1}H NMR[2e,8] (300 MHz, $CDCl_3$) δ 9.1 (1H, br s), 6.80 (1H, m), 5.91 (1H, m), 4.30 (2H, q, J = 7 Hz), 2.30 (3H, s), 1.35 (3H, t, J = 7 Hz); ^{13}C NMR[2e,9] (75 MHz, $CDCl_3$) δ 161.8, 135.4, 121.3, 116.3 109.0, 60.2, 14.6, 13.2; TLC, R_f 0.3 (2:1 hexane/ether). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.75; H, 7.19; N, 9.15. Found: C, 62.75; H, 7.24; N, 9.00.

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(6) Williams, R. M.; Kwast, A. *J. Org. Chem.* **1988**, *53*, 5787.
(7) Pedersen, C. L.; Buchardt, O. *Acta Chem. Scand.* **1973**, *27*, 271.
(8) Roomi, M. W.; Dugas, H. *Can. J. Chem.* **1970**, *48*, 2303.
(9) (a) Abraham, R. J.; Lapper, R. D.; Smith, K. M.; Unsworth, J. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1004. (b) Cushley, R. J.; Sykes, R. J.; Shaw, C.-K.; Wasserman, H. W. *Can. J. Chem.* **1975**, *53*, 148.