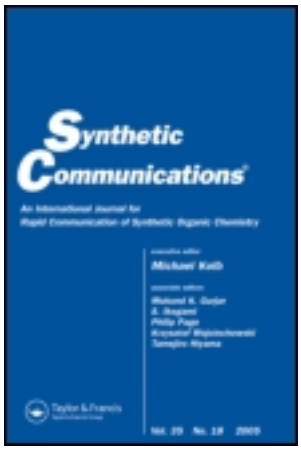


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF ETHYL PYRROLE-2-CARBOXYLATES: A REGIOSELECTIVE CYCLIZATION OF ENAMINONES UNDER KNORR-TYPE CONDITIONS

Ibrahim Elghamry [a]
[a] Division of Organic Chemistry, FB6, Gerhard-Mercator-University Duisburg, Duisburg, D-47048, Germany
Version of record first published: 16 Aug 2006.

To cite this article: Ibrahim Elghamry (2002): SYNTHESIS OF ETHYL PYRROLE-2-CARBOXYLATES: A REGIOSELECTIVE CYCLIZATION OF ENAMINONES UNDER KNORR-TYPE CONDITIONS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:6, 897-902

To link to this article: http://dx.doi.org/10.1081/SCC-120002701

SYNTHETIC COMMUNICATIONS, 32(6), 897–902 (2002)

SYNTHESIS OF ETHYL PYRROLE-2-CARBOXYLATES: A REGIOSELECTIVE CYCLIZATION OF ENAMINONES UNDER KNORR-TYPE CONDITIONS

Ibrahim Elghamry

Division of Organic Chemistry, FB6,
Gerhard-Mercator-University Duisburg,
D-47048 Duisburg, Germany

ABSTRACT

A regioselective formation of ethyl pyrrole-2-carboxylates **4** and **5** is effected by reductive condensation of enaminones **1a–f** and ethyl 2-oximinoacetoacetate **2**. The structures of the products have been delineated by spectroscopic methods.

Ethyl pyrrole-2-carboxylates are versatile precursors for the total synthesis of synthetic model and naturally occurring tetrapyrroles, porphyrins and bilirubins.[1] The Knorr pyrrole synthesis is one of the most widely used reactions for the preparation of pyrrole-2-carboxylates. In its initial form, it involved reductive condensation of 2-oximinoacetoacetate with 1,3-dioxo compounds in the presence of Zn/AcOH and NaOAc.[2,3] Though enaminones are useful starting materials in the synthesis of many heterocyclic compounds,[4,5] pyrrole syntheses rarely make use of them, despite the fact that enaminones as building blocks offer a great variation in the substitution pattern of the pyrrole ring.[6–10]

For synthesis of pyrrole-2-carboxylates with an alkyl substituent at position 3 and an oxoaryl or aryl substituent at position 4, we used enaminones **1a-f** and ethyl 2-oximino acetoacetate **2** as synthons. As is customary for Knorr-type pyrrole synthesis, zinc dust was the reducing agent and acetic acid was the solvent.

Enaminones **1a–f** reacted with 2-aminoacetoacetate (generated in situ from **2** under Zn-Knorr conditions) via dimethylamine elimination to produce enaminones **3**, which cyclize in a regioselective manner. When $R^1 = H$ (enaminones **1a-c**), the α-carbon of the enamininone adds to the acyl group of the acetoacetate and subsequent elimination of water gives pyrrole-2-carboxylates **4a–c** as final products in 30–35% yield.[11] (Route A, Scheme 1).

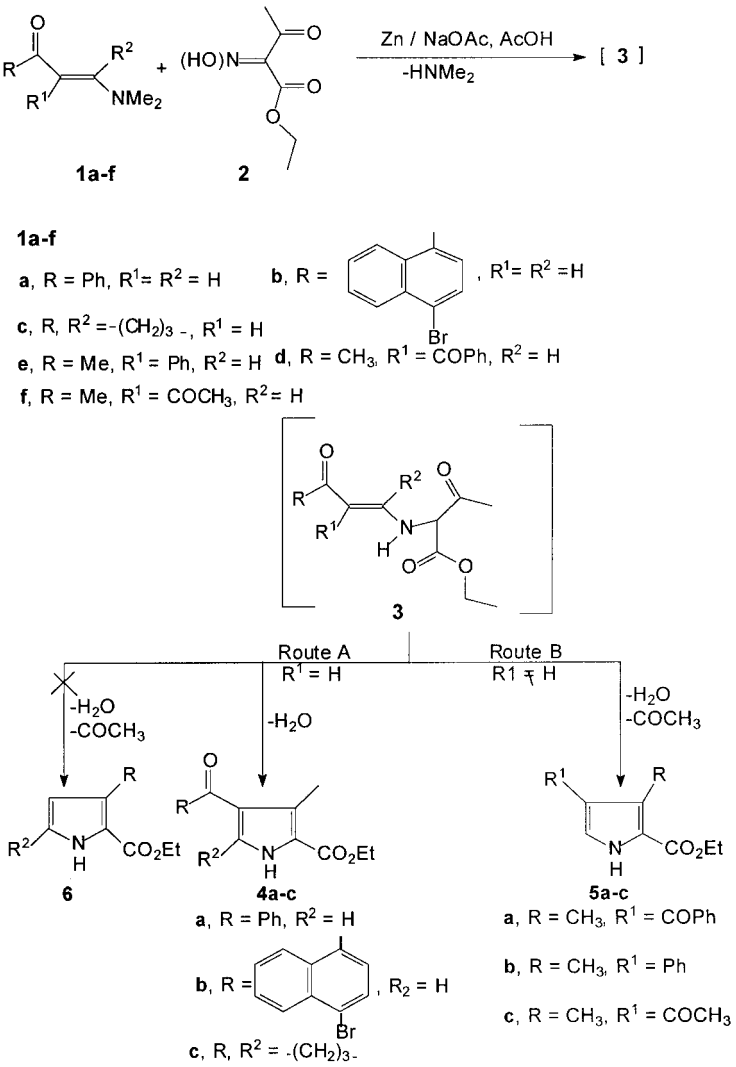
We had initially expected that the products would be the pyrrole-2-carboxylates **6** which are the products of water elimination and deacylation of intermediate **3**, as similar intramolecular cyclization has been reported with analogous intermediates upon treatment with NaOEt in EtOH.[8,12,13] However mass spectra, microanalysis data, IR and $^1H/^{13}C$ NMR were instead consistent with pyrrole-2-carboxylates of Structure **4**.

When R^1 was an electron-withdrawing substituent (as in enaminones **1d–f**) the mechanism for the formation of pyrroles **5** is analogous to the reaction of 1,3-diketo compounds with **2** under similar reaction conditions[15] (Route B, Scheme 1). It involves cyclization and aromatization via dehydration and deacylation (acyl removal is preferred to an alkoxycarbonyl group)[14,15] to afford pyrroles **5a–c** in 52–60% yield. Interestingly, compound **4a** was obtained via both pathways, starting from two different enaminones, from **1a** via route A (30% yield) or from **1d** via route B (55% yield).

It is worth mentioning that the ^1H NMR spectra of all the prepared pyrroles showed a singlet at 2.43–2.75 ppm and a doublet at 7.12–7.32 ppm ($J \cong 3$ Hz) (**4a,b** and **5b,c**) as typical values[8,14] for 3-Me and H-5 in the pyrrole ring respectively.

In conclusion, in this short communication a one pot regioselective synthesis for pyrrole-2-carboxylates **4** and **5** using enaminones has been demonstrated. The use of 4-oxoarylpyrrole-2-carboxylates (type **4a,b**) as synthons for the total synthesis of linearly π-extended porphyrins is in progress.

The NMR spectra were recorded on Bruker 300 or 500 MHz spectrometers using TMS as internal standard and the deuterated solvent as lock. *J* Values are given in Hz. IR spectra were obtained by using a Perkin-Elmer 983 spectrophotometer. Electron impact ionization mass spectrometry (EIMS) was performed on a Varian AMD 604 instrument using 70 eV ionization energy. Melting points (mp) are uncorrected. Enaminones **1a,b,d–f** were prepared by reaction of dimethylformamide dimethyl acetal (DMFDMA) with alkyl ketones. **1c** was prepared following the



Scheme 1.

literature procedure[16] from 1,3-cyclohexanedione and dimethylamine. Ethyl 2-oximinoacetoacetate was prepared as described.[17] All chromatographic separations were performed by column chromatography with ethyl acetate/*n*-hexane (1 : 1) as an eluent.

Ethyl Pyrrole-2-carboxylates (4) and (5)

General procedure: a mixture of enaminone **1** (0.1 mol), ethyl 2-oximinoacetoacetate **2** (0.1 mol) and sodium acetate (0.3 mol) in glacial acetic acid (200 ml) was heated to 90°C, then Zn dust (16.3 g, 250 mg-atom) was added in small portions such that the pot temperature of the reaction can be controlled between 95 and 105°C by air cooling. Then the reaction mixture was heated at reflux for 3 h. The resulting hot mixture was decanted from the zinc sludge, before zinc acetate crystallized, into ice-water mixture. The resulting precipitate was collected by filtration, washed several times with water air dried and chromatographed on silica gel.

Ethyl 4-Benzoyl-3-methylpyrrole-2-carboxylate (4a = 5a)

Colorless crystals (from *n*-hexane), yield: 30% from **1a** via route A; 50% from **1d** via route B; mp 128–129°C (lit.[18] 127°C). IR (KBr): $\nu = 3300$ (NH), 1710 (CO), 1668 (ester) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.39$ (t, 3H, $J = 7.13$), 2.64 (s, 3H), 4.38 (q, 2H, $J = 7.13$), 7.19 (d, 1H, $J = 3.43$), 7.42 (m, 3H), 7.75 (m, 2H), 9.47 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 11.61$, 14.53, 60.71, 121.60, 124.74, 128.29, 128.56, 128.81, 129.03, 130.12, 131.70, 140.24, 161.73, 191.91. MS: m/z (%) = 258 ($M^+ + 1$, 13.23), 257 (M^+ 75.43), 240 (2.62), 228 (10.82), 210 (100), 182 (17.34), 154 (8.44), 134 (56.42), 105 (55.65). Anal. calcd for $C_{15}H_{15}NO_3$ (257.29): C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 5.76; N, 5.23.

Ethyl 4-[4-Bromo-1-naphthoyl]-3-methylpyrrole-2-carboxylate (4b)

Colorless solid (from *n*-hexane/benzene 2 : 1), (starting material **1b**), yield: 33%; mp 130–131°C. IR (KBr): $\nu = 3310$ (NH), 1690 (CO), 1640 (ester) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.41$ (t, 3H, $J = 7.10$), 2.75 (s, 3H), 4.32 (q, 2H, $J = 7.10$), 7.12 (d, 1H, $J = 3.33$), 7.81 (m, 4H), 8.18 (m, 2H), 8.95 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 11.52$, 14.63, 60.83, 119.52, 122.12, 128.22, 128.51, 129.14, 129.29, 129.54, 129.69, 129.95, 130.34, 130.63, 130.82, 140.11, 140.34, 162.14, 199.29. MS: m/z(%) = 388 ($M^+ + 1$, 0.15), 387 (M^+, 0.10), 345 (59.01), 297 (60.32), 265 (47.43), 235 (8.24), 219 (49.11), 190 (100), 163 (27.23). Anal. calcd for $C_{19}H_{16}NO_3Br$(387.25): C, 58.93; H, 4.16; N, 3.62. Found: C, 58.72; H, 4.03; N, 3.41.

Ethyl 3-Methyl-4-oxo-4,5,6,7-tetrahydro-1H-indole-2-carboxylate (4c)

Colorless solid (from ethanol), (starting material **1c**), yield: 35%; mp 165–166°C (lit.[19,20] 165–167°C). IR (KBr): $\nu = 3165$ (NH), 1690 (CO), 1640 (ester) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.41$ (t, 3H, $J = 7.10$), 2.15 (m, 2H), 2.49 (m, 2H), 2.61 (s, 3H), 2.85 (m, 2H), 4.35 (q, 2H, $J = 7.10$), 9.65 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 11.56$, 14.43, 23.06, 23.39, 38.91, 60.55, 119.64, 120.36, 128.54, 145.46, 162.31, 195.43.

Ethyl 3-Methyl-4-phenylpyrrole-2-carboxylate (5b)

Colorless solid (from *n*-hexane); (starting material **1e**) yield 60%; mp 92–93°C (lit.[10] 94°C). IR (KBr): $\nu = 3310$ (NH), 1645 (ester) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.33$ (t, 3H, $J = 7.1$), 2.51 (s, 3H), 4.35 (q, 2H, $J = 7.10$), 7.15 (d, 1H, $J = 3.19$), 7.51 (m, 5H), 9.14 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 11.51$, 14.53, 60.62, 119.72, 120.44, 121.34, 125.7, 126.84, 127.94, 128.33, 128.76, 130.12, 135.32, 160.43.

Ethyl 4-Acetyl-3-methylpyrrole-2-carboxylate (5c)

Colorless solid (from *n*-hexane); (starting material **1f**), yield: 52%; mp 91–92°C (lit.[10] 94°C). IR (KBr): $\nu = 3210$ (NH), 1685 (CO), 1639 (ester) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 1.41$ (t, 3H, $J = 7.10$), 2.43 (s, 3H), 2.53 (s, 3H), 4.35 (q, 2H, $J = 7.10$), 7.32 (d, 1H, $J = 3.23$), 9.55 (s, 1H). ^{13}C NMR ($CDCl_3$): $\delta = 11.43$, 14.42, 28.45, 60.51, 121.92, 127.28, 127.72, 128.54, 160.53, 192.14.

ACKNOWLEDGMENT

The author is deeply indebted to Alexander von Humboldt Foundation for award of a research fellowship at Duisburg University (Germany).

REFERENCES

1. (a) Paine III, J.B. In *The Porphyrins*. Dolphin, D., Ed.; Academic Press: New York, 1978; *I*, 101–163; (b) Trull, F.R.; Franklin, R.W.;

Lightner, D.A. J. Heterocylic Chem. **1987**, *24*, 1573; (c) Xie, M.; Lightner, D.A. Tetrahedron **1993**, *49*, 2185.
2. Fuhrhop, J.; Penzlin, G. *Organic Synthesis: Concepts, Methods, Starting Materials*, 2nd Ed.; New York, 1994; 150–151.
3. (a) Jones, A.R. *The Chemistry of Heterocyclic Compounds*. Wiley: New York, 1990; *48*, 108–113; (b) Tang, J.; Verkade, J.G. J Org. Chem. **1994**, *59*, 7793.
4. Elnagdi, M.H.; Elghamry, I.; Kandeel, E.; Abdelrahman, A.H.; Al-Naggar, A.A.; Amir, S.; Riad, M. Gazz. Chim. Ital. **1997**, *127*, 791.
5. (a) Lue, P.; Greenhill, J.V. Advances in Heterocyclic Chemistry **1997**, *67*, 209; (b) Greenhill, J.V. J. Chem. Soc. Perkin II **1974**, 164.
6. Jones, M.I.; Froussios, C.; Evans, A.D. J. Chem. Soc. Chem. Commun. **1976**, 472.
7. Walizei, G.H.; Breitmaier, E. Synthesis **1989**, 337.
8. Hombrecher, H.K.; Horter, G. Synthesis **1990**, 389.
9. Williams, P.D.; LeGoff, E. Heterocycles **1984**, *22*(2), 269.
10. Cohnen, E.; Dewald, R. Synthesis **1987**, 566.
11. A Competing Mode of Cyclization of the Amino Acetoacetate Under the Reaction Conditions is Expected. For Example See, (a) Harbuck, J.W.; Rapoport, H. J. Org. Chem. **1971**, *36*, 853; (b) Ref. 3a.
12. Alberola, A.; Andres, J.M.; Gonzalez, A.; Pedrosa, R.; Vicente, M. J. Chem. Soc. Perkin Trans. 1 **1990**, 2681.
13. Kazau, K.; Kuniyoshi, T.; Teiji, K.; Hideyo, N.; JP-Pat. 7033648, 1966, Chem. Abstr. **1971**, *74*, 64204e.
14. (a) Paine III, J.B.; Dolphin, D. J. Org. Chem. **1985**, *50*, 5598; (b) Shrout, D.P.; Lightner, D.A. Synthesis **1990**, 1062.
15. Katritzky, A.R.; Rees, C.W. *Comprehensive Heterocyclic Chemistry*. Pergamon Press, 1984; Vol. 4, 342.
16. Tommaso, A.; Giorgio, S. Gazz. Chim. Ital. **1939**, *69*, 57.
17. Chen, Y.L.; Mariano, P.S.; Little, G.M.; O'Brien, D.; Huesmann, P.L. J. Org. Chem. **1981**, *46*, 4643.
18. Malesic, M.; Karbavcic, A.; Golobic, A.; Golic, L.; Stanovnik, B. J. Heterocyclic Chem. **1997**, *34*, 1757.
19. Clezy, P.S.; Fookes, C.J.R.; Mirza, A.H. Aust. J. Chem. **1977**, *30*, 1337.
20. Schoen, E.K.; Pachter, I.J. US-Pat., 3467755, 1969; Chem. Abstr. **1970**, *72*, 3375y.

Received in the Netherlands April 6, 2001