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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 1061–1062

Efficient synthesis of 3-carboxylate pyrroles using microwave irradiation

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Received 17 November 2004; revised 17 December 2004; accepted 21 December 2004

Abstract—3-Carboxylate pyrroles are prepared by microwave irradiation of 1,3-oxazolium-5-oxides and various α-acetoxy-acrylic esters in a single synthetic step, in excellent yields and with high regioselectivity.

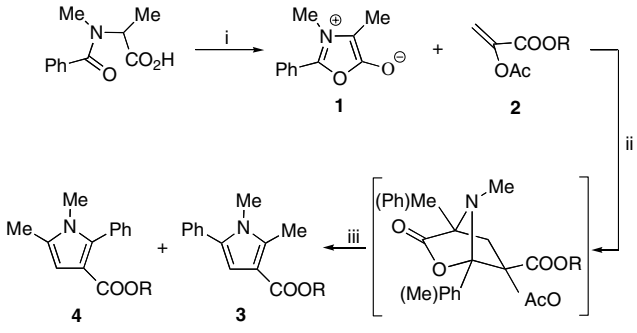
3-Carboxylate pyrroles are a class of products of interest both in applicational terms and because of the biopharmacological properties demonstrated by some derivatives of members of this family.[1] A possible route of access to this kind of molecule is through cycloaddition of 1,3-oxazolium-5-oxides (münchnones)[2] with acetylenic dipolarophiles,[3] but low yields and poor regiochemical control makes this route unattractive.

In view of this, we have developed a new microwave-assisted[4] synthetic methodology, which has given excellent results in terms of both yield (over 90%) and speed and simplicity of execution; regioselectivity[5] is, moreover, high.

Thus the desired pyrroles **3** and **4** were obtained by cycloaddition between münchnone **1** and α-acetoxy-acrylic esters **2** (Scheme 1).[6]

In a typical experiment,[7] mesoionic derivative **1**, prepared in situ using the traditional method[8] of cyclodehydration from the corresponding N-substituted amino acid with acetic anhydride in dioxane, was mixed with olefins and the mixture was irradiated at 100 °C for 10 min. The subsequent work-up produced the results shown in Table 1.

All the compounds synthesised were characterised by their spectral and analytical data.[10]



Scheme 1. Reagents and conditions: (i) Ac_2O/dioxane; (ii) microwave, 10 min; (iii) –AcOH, $–CO_2$.

In particular, their regiochemistry was confirmed on the basis of intramolecular NOE effects. Dipolar interactions in **3** between *H*C-4 and *ortho*-hydrogens of ArC-5, together with the lack of any detectable contact between analogous hydrogens in **4**, are vindication of the structures assigned.

The efficiency of the method and its general applicability were demonstrated by also using a β-substituted olefin such as *Z*- and *E*-ethyl 2-acetoxy-4-oxopent-2-enoate **5** (mixture 1:2.6).

Here again the expected pyrroles **6** and **7** were produced with an overall yield of 91% as indicated in Scheme 2.

Structures **6** and **7** were assigned on the basis of analytical and spectroscopic data[11] and their relative regiochemistry is confirmed by NOE measurements. Thus, irradiation of H_3COCC-4 in **6** resulted in NOE

Keywords: Dipolar cycloaddition; Microwave synthesis; Regioselectivity; Mesoionic compounds.
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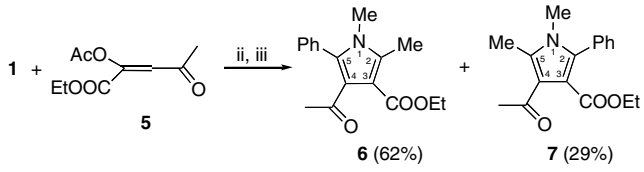
doi:10.1016/j.tetlet.2004.12.102

Table 1. Regioselective synthesis of 3-carboxylate pyrroles

Entry		R	**3** (%)[a]	**4** (%)[a]
1	a	Me	100	—
2[9]	b	Et	92	6
3	c	*n*-Pr	88	4
4	d	*n*-Bu	89	4

[a] Isolated yields.



Scheme 2. Reagents and conditions: (ii) microwave, 10 min; (iii) –AcOH, $-CO_2$.

enhancement for the *ortho*-hydrogens of the aryl at C-5, indicating a close spatial proximity between these protons. Conversely, in compound **7**, irradiation of H_3COCC-4 gives rise to NOE enhancement of H_3C-5.

In conclusion, this microwave-assisted process provided a simple and highly efficient method for the regioselective synthesis of various 3-carboxylate pyrroles.

References and notes

1. Zhang, P.; Johnson, W. T.; Klewer, D.; Paul, N.; Hoops, G.; Davisson, V. J.; Bergstrom, D. E. *Nucleic Acid Res.* **1998**, *26*, 2208–2215.
2. Reviews on münchnones include: (a) *Oxazoles: Synthesis, Reactions and Spectroscopy, Part A*; Palmer, D. C., Ed.; John Wiley & Sons: New Jersey, 2003; pp 473–576; (b) *Synthetic Applications of Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Product*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New York, 2002; pp 681–754.
3. Padwa, A.; Burgess, E. M.; Gingrinch, H. L.; Roush, D. M. *J. Org. Chem.* **1982**, *47*, 786–791.
4. Danks, T. N. *Tetrahedron Lett.* **1999**, *40*, 3957–3959.
5. Gribble, G. W.; Pelkey, E. T.; Simon, W. M.; Trujillo, H. A. *Tetrahedron* **2000**, *56*, 10133–10140.
6. Monnin, J. *Helv. Chim. Acta* **1956**, *39*, 1721–1724.
7. *General procedure*: a mixture of olefin **2** (3 mmol), *N*-methyl-*N*-benzoyl-alanine (621.6 mg, 3 mmol) and acetic anhydride (1 mL) in dioxane (40 mL) was irradiated for 10 min in an open glass vial in a CEM microwave synthesiser at 100 °C. After cooling the reaction to room temperature, the solvent was removed under vacuum and the residue was purified by silica gel flash column chromatography using chloroform to give the regioisomer mixture as a yellow solid or oil. Recrystallisation from 80% petroleum ether/methanol afforded **3** and **4** as colourless crystals or a pale yellow oil.
8. Huisgen, R.; Gotthard, H.; Bayer, H. O. *Angew. Chem., Int. Ed.* **1964**, *3*, 135–137; Bayer, H. O.; Gotthard, H.; Huisgen, R. *Chem. Ber.* **1970**, *103*, 2356–2362.
9. *Selected data*. Compound **3a**: mp 97–98 °C; IR (KBr): 1694, 1523, 1461, 1247, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H), 3.43 (s, 3H), 3.73 (s, 3H), 6.49 (s, 1H), 7.18–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.6, 31.8, 50.6, 109.1, 109.2, 112.4, 127.3, 128.4 (2), 129.0, 133.6, 134.8, 138.1, 166.8. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.49; H, 6.61; N, 6.05. Compound **3b**: mp 85–86 °C (lit.[2] mp 83–85 °C); IR (KBr): 1695, 1524, 1491, 1263, 1202 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7 Hz, 3H), 2.24 (s, 3H), 3.25 (s, 3H), 4.06 (q, J = 7 Hz, 2H), 6.32 (s, 1H), 7.16–7.30 (m, 5H). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.19; H, 6.96; N, 5.85. Compound **4b**: mp 65–66 °C (lit.[2] mp 64–66 °C); IR (KBr): 1699, 1520, 1491, 1253, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3H), 2.61 (s, 3H), 3.45 (s, 3H), 4.26 (q, J = 7 Hz, 2H), 6.51 (s, 1H), 7.18–7.34 (m, 5H). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.21; H, 7.09; N, 5.60. Compound **3c**: mp 48–50 °C; IR (KBr): 1694, 1529, 1409, 1242, 1208 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3H), 1.68 (qt, J = 7.5, 6.6 Hz, 2H), 2.51 (s, 3H), 3.36 (s, 3H), 4.13 (t, J = 6.6 Hz, 2H), 6.32 (s, 1H), 7.16–7.30 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 10.6, 11.5, 22.3, 31.7, 64.8, 109.3, 109.4, 111.8, 127.2, 128.4 (2), 128.9, 132.6, 133.7, 136.9, 165.5. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.79; H, 6.36; N, 5.55. Compound **4c**: oil; IR (KBr): 1697, 1529, 1414, 1245, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (t, J = 7.5 Hz, 3H), 1.51 (qt, J = 7.5, 6.6 Hz, 2H), 2.24 (s, 3H), 3.26 (s, 3H), 3.98 (t, J = 6.6 Hz, 2H), 6.43 (s, 1H), 7.19–7.38 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 9.8, 10.1, 26.2, 31.7, 66.8, 109.3, 109.4, 111.8, 127.2, 128.4 (2), 128.9, 132.6, 133.7, 136.9, 164.7. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.51; N, 5.32. Compound **3d**: oil; IR (KBr): 1690, 1529, 1414, 1246, 1206 cm^{-1}; ^1H NMR($CDCl_3$) δ 0.99 (t, J = 7.2 Hz, 3H), 1.46 (qt, J = 7.2, 6.5 Hz, 2H), 1.70 (tt, J = 6.4, 6.5 Hz, 2H), 2.56 (s, 3H), 3.41 (s, 3H), 4.23 (t, J = 6.4 Hz, 2H), 6.60 (s, 1H), 7.24–7.38 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.4, 13.7, 19.3, 31.0, 31.6, 63.0, 109.3 (2), 111.8, 127.2, 128.4 (2), 128.8, 132.6, 133.6, 136.9, 165.4. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.36; H, 7.91; N, 5.09. Compound **4d**: oil; IR (KBr): 1695, 1529, 1419, 1246, 1206 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, J = 7.2 Hz, 3H), 1.18 (qt, J = 7.2, 6.5 Hz, 2H), 1.40 (tt, J = 6.4, 6.5 Hz, 2H), 2.20 (s, 3H), 3.21 (s, 3H), 4.02 (t, J = 6.4 Hz, 2H), 6.44 (s, 1H), 7.27–7.39 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 10.6, 11.9, 23.2, 31.0, 31.6, 65.0, 109.3 (2), 111.8, 127.2, 128.4 (2), 128.8, 132.6, 133.6, 136.9, 164.6. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.59; H, 7.72; N, 5.28.
10. In this case, the two regioisomers **3b** and **4b** were obtained by the quoted means (Ref. 3) with respective yields of 13% and 16%.
11. *Selected data*. Compound **6**: mp 91–93 °C; IR (KBr): 1690, 1668, 1531, 1456, 1294, 1197 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 2.34 (s, 3H), 2.38 (s, 3H), 3.22 (s, 3H), 3.97 (q, J = 7.2 Hz, 2H), 7.19–7.36 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.3, 13.6, 31.0, 31.5, 60.0, 114.9, 124.2, 128.0 (2), 128.5 (2), 130.5, 131.2, 133.5, 138.3, 166.6, 198.2. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.31; H, 6.64; N, 5.04. Compound **7**: mp 106–108 °C; IR (KBr): 1684, 1660, 1528, 1456, 1258, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 2.06 (s, 3H), 2.42 (s, 3H), 3.24 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H), 7.21–7.38 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.5, 14.1, 31.4, 31.7, 60.3, 111.3, 124.8, 128.5 (2), 128.8 (2), 130.5, 130.9, 133.7, 135.1, 165.3, 189.8. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.68; H, 6.75; N, 5.06.