Tetrahedron 65 (2009) 1704–1707

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solvent-free synthesis of penta-substituted pyrroles: one-pot reaction of amine, alkyl acetoacetate, and fumaryl chloride

Abdolali Alizadeh *, Mohadese Babaki, Nasrin Zohreh

Department of Chemistry, Tarbiat Modares University, PO Box 14115-175, Tehran, Iran

ARTICLE INFO

Article history:
Received 28 September 2008
Received in revised form 16 November 2008
Accepted 4 December 2008
Available online 9 December 2008

ABSTRACT

A novel, convenient, and efficient approach to the synthesis of penta-substituted pyrroles has been reported based on the multicomponent reaction. Solvent-free condition for the formation of enaminones from primary amines and alkyl acetoacetates and it's reaction with fumaryl chloride lead to the formation of pyrroles that have halide, CH_2CO_2H, ester functional groups, and two alkyl substitutions.

1. Introduction

Five-membered, nitrogen-containing heterocycles, such as pyrroles, indoles, and carbazoles, are important building blocks in an extensive number of biologically active compounds.[1] Among them, pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes.[2] Some of the recently isolated pyrrole containing marine natural products have been found to exhibit considerable cytotoxicity and function as multidrug resistant (MDR) reversal agents.[3] Many of these biologically active compounds have emerged as chemotherapeutic agents. In addition, polysubstituted pyrroles are molecular frameworks having immense importance in material science.[4] They have been also employed as antioxidants,[5a] antibacterial,[5b,c] ionotropic,[5d,e] antitumor,[5f] anti-inflammatory,[5g,h] and antifungal agents,[5i] P38 kinase,[6a] prolyl-4-hydroxylase,[6b] poly (ADP-ribose) polymerase inhibitors,[6c] estrogen receptor β selective ligands,[6d] AT_1-selective angiotensin II receptor antagonists,[6e] and minor groove recognition elements.[6f,g] Moreover, they are a highly versatile class of intermediates in the synthesis of natural products as well as in heterocyclic chemistry.[7]

Consequently, a large number of methods have been developed for their synthesis, which include: Knorr,[8] Paal–Knorr,[9] Hantzsch syntheses,[10] 1,3-dipolar cycloaddition reactions,[11] reductive coupling,[12] and aza-Wittig reactions.[13] These methodologies typically require the preparation of the precursors prior to cyclization, which can complicate both the synthesis and the structural modification of the substituted pyrroles. This has stimulated significant interest in the design of new synthetic routes to pyrroles, including several efficient multicomponent reactions[14–17] and metal-catalyzed routes.[18]

In spite of many reported methods for the synthesis of pyrroles, it is still challenging to prepare polysubstituted pyrroles with various substituents directly from readily available building blocks. Continuing our efforts in the development of multicomponent reaction for the synthesis of various heterocycles,[19] in this paper, we describe the realization of a one-pot, multicomponent, and solvent-free assembly of highly substituted pyrroles utilizing primary amines, alkyl acetoacetate, and fumaryl chloride.

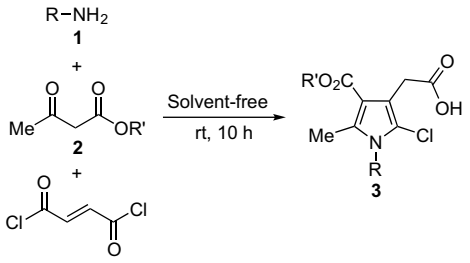
2. Results and discussion

Our research group reported the synthesis of series of heterocycles using the reaction of enamines or enaminones with various electrophiles.[20] Following on from this research, we become interested in the application of fumaryl chloride in multicomponent reaction for first time (which display electrophilic property at the two site of its structure) to synthesize highly functionalized pyrroles. Our strategy to reach this goal is outlined in Scheme 1. The reaction between primary amines **1**, alkyl acetoacetate **2**, and fumaryl chloride under solvent-free conditions at room temperature (the amine and alkyl acetoacetate are mixed first and then fumaryl chloride is added) leads to the formation of penta-substituted pyrroles **3** in 70–85% yields (Scheme 1).

The data obtained from elemental analysis, IR, ^1H and ^{13}C NMR, and mass spectra confirmed all of the proposed products. The mass spectrum of **3a** displayed a molecular ion peak at *m*/*z* 287 and more important, an ion peak at *m*/*z* 242 indicated that CO_2 has been lost and thus the presence of CO_2H group on the structure was confirmed. The most important absorption band in IR spectrum is due to the OH stretching frequency of acid group, which appeared as broad band between 2751 and 3384 cm^{-1}. Absorption bands at 1730 and 1698 cm^{-1} are due to the two carbonyl groups. The ^1H

* Corresponding author. Fax: +98 21 88006544.
E-mail addresses: aalizadeh@modares.ac.ir, abdol_alizad@yahoo.com (A. Alizadeh).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.12.011

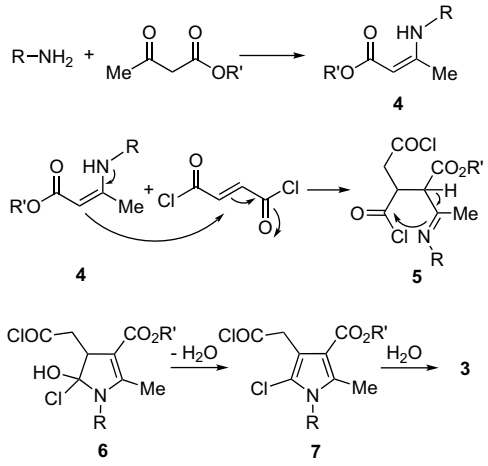


Product	R	R'	Yield % of 3
3a	^{i}But	Me	70
3b	^{i}But	Et	78
3c	*n*-Pr	Me	85
3d	*n*-Pr	Et	85
3e	allyl	Me	73
3f	allyl	Et	70
3g	^{i}Pr	Me	80
3h	^{i}Pr	Et	80

Scheme 1.

NMR spectrum of **3a** exhibited three sharp singlet signals recognized as arising from methyl of pyrrole ring, CH_2, and OMe groups (δ_H=2.49, 3.72, and 3.82 ppm, respectively). One multiplet from 2.06 to 2.10 ppm and two doublet signals at 0.92 and 3.70 ppm ($^3J_{HH}$=5.2 and 7.2 Hz) are due to the ^{i}Bu group. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed 12 distinct signals in agreement with the proposed structure that characteristic carbons of pyrrole ring resonance at 110.6, 112.5, 116.1, and 135.6 ppm. Partial assignment of these resonances for **3** derivatives is given in Section 4.2.

Although we have not established the mechanism of our reaction in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the established chemistry of enaminone synthesis,[21] it is reasonable to assume that enaminone **4** apparently results from the addition of primary amines **1** to the alkyl acetoacetate **2**. Continuing, in the presence of fumaryl chloride, intermediate **4** can attack two electrophile sites of fumaryl chloride (COCl or conjugated double bond). Based on Motherwell and co-worker's report,[22] enaminone **4** attacks the double bond to produce intermediate **5**. Because of kinetic facility, formation of five-membered ring, 1*H*-pyrrol-2-ol **6**, is observed. By loss of a molecule of H_2O, pyrrole **7** is formed, which is converted to the corresponding pyrrole derivatives **3** in 70–85% yield.



Scheme 2.

3. Conclusion

In summery, we reported an efficient method for the synthesis of penta-substituted pyrroles. The advantages of our work are as follows: (1) the reaction is performed under neutral and more important is under solvent-free condition. (2) No catalyst is required for this reaction. (3) Five functional groups are on the product, which is capable to convert to other functional groups. (4) The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

4. Experimental

4.1. General

Primary amines, alkyl acetoacetates, and fumaryl chloride were obtained from Merck (Germany) and Fluka (Switzerland). Melting points were measured on an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-AVANCE spectrometer at 500.1 and 125.7 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel 230–240 mesh.

4.2. General synthesis procedure (for example, 3a)

To a magnetically stirred 5 mL flat bottom flask containing isobutyl amine (0.07 g, 1 mmol) was added methyl acetoacetate (0.11 g, 1 mmol). After 10 min, fumaryl chloride (0.15 g, 1 mmol) was added to the reaction mixture and was allowed to stir for 10 h. Purification of the crude product by column chromatography [silica gel (Merck 230–240 mesh), *n*-hexane/EtOAc (10:1)] gave the title compound **3a**.

*4.2.1. 2-[2-Chloro-1-isobutyl-4-(methoxycarbonyl)-5-methyl-1H-pyrrol-3-yl]acetic acid (**3a**)*

White powder, mp 80–82 °C, 0.2 g, yield: 70%. [Found: C, 54.31; H, 6.34; N, 4.88. $C_{13}H_{18}ClNO_4$ requires: C, 54.27; H, 6.31; N, 4.87%.] R_f (20% EtOAc/*n*-hexane): 0.30; IR (KBr) (ν_{max}, cm^{-1}): 2525–3345 (OH), 1711 (CO_2Me), 1698 (CO_2H), 1514 and 1453 (Ar), 1230 (C–O); δ_H (500.1 MHz, $CDCl_3$) 0.92 (6H, d, *J* 5.2 Hz, NCH_2CHMe_2), 2.06–2.10 (1H, m, NCH_2CHMe_2), 2.49 (3H, s, C=C*Me*), 3.70 (2H, d, *J* 7.2 Hz, NCH_2CHMe_2), 3.72 (2H, s, CH_2CO_2H), 3.82 (3H, s, O*Me*), 9.50–12.10 (1H, br, CO_2H); δ_C (125.7 MHz, $CDCl_3$) 12.4 (C=C*Me*), 19.6 (NCH_2CHMe_2), 29.3 (CH_2CO_2H), 32.1 (NCH_2CHMe_2), 51.2 (NCH_2), 51.5 (O*Me*), 110.3 (C_{ipso}–CH_2CO_2H), 112.6 (C_{ipso}–CO_2Me), 116.7 (C_{ipso}–Cl), 135.85 (C_{ipso}–Me), 166.6 (CO_2Me), 174.1 (CO_2H); MS (EI, 70 eV): *m*/*z* (%)=289 (M+2, 15), 287 (M^+, 48), 269 (9), 256 (11), 243 (100), 228 (34), 208 (77), 186 (39), 172 (35), 156 (49), 142 (13), 106 (14), 77 (17), 57 (49), 45 (21).

*4.2.2. 2-[2-Chloro-4-(ethoxycarbonyl)-1-isobutyl-5-methyl-1H-pyrrol-3-yl]acetic acid (**3b**)*

White powder, mp 90–92 °C, 0.22 g, yield: 74%. [Found: C, 55.76; H, 6.70; N, 4.65. $C_{14}H_{20}ClNO_4$ requires: C, 55.72; H, 6.68; N, 4.64%.] R_f (20% EtOAc/*n*-hexane): 0.16; IR (KBr) (ν_{max}, cm^{-1}): 2775–3165 (OH), 1725 (CO_2Et), 1696 (CO_2H), 1514 and 1453 (Ar), 1267 (C–O); δ_H (500.1 MHz, $CDCl_3$) 0.92 (6H, d, *J* 8.0 Hz, NCH_2CHMe_2), 1.35 (3H, t, *J* 5.0 Hz, OCH_2Me), 2.04–2.10 (1H, m, NCH_2CHMe_2), 2.50 (3H, s, C=C*Me*), 3.69 (2H, d, *J* 5.0 Hz, NCH_2CHMe_2), 3.73 (2H, s, CH_2CO_2H), 4.30 (2H, q, *J* 5.0 Hz, OCH_2Me), 9.40–12.20 (1H, br, CO_2H); δ_C (125.7 MHz, $CDCl_3$) 11.8 (OCH_2Me), 13.8 (C=C*Me*), 19.3 (NCH_2CHMe_2), 28.8 (CH_2CO_2H), 31.6 (NCH_2CHMe_2), 50.9 (NCH_2), 59.7 (OCH_2Me),

110.0 (C_{ipso}–CH_2CO_2H), 12.0 (C_{ipso}–CO_2Me), 116.1 (C_{ipso}–Cl), 135.3 (C_{ipso}–Me), 165.5 (CO_2Me), 174.5 (CO_2H); MS (EI, 70 eV): *m*/*z* (%)=303 (M+2, 19), 301 (M^+, 53), 283 (4), 272 (4), 257 (80), 256 (98), 238 (7), 228 (59), 222 (40), 200 (15), 184 (20), 172 (90), 156 (26), 154 (32), 127 (10), 122 (8), 106 (11), 92 (11), 77 (19), 57 (86), 43 (31), 41 (100).

4.2.3. 2-[2-Chloro-4-(methoxycarbonyl)-5-methyl-1-propyl-1H-pyrrol-3-yl]acetic acid (**3c**)

White powder, mp 115–116 °C; 0.22 g, yield: 82%. [Found: C, 52.68; H, 5.90; N, 5.12. $C_{12}H_{16}ClNO_4$ requires: C, 52.66; H, 5.89; N, 5.12%.] R_f (20% EtOAc/*n*-hexane): 20; IR (KBr) (ν_{max}, cm^{-1}): 2940–3315 (OH), 1689 (CO_2Me), 1610 (CO_2H), 1508 and 1446 (Ar), 1247 (C–O); δ_H (500.1 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.4 Hz, $NCH_2CH_2\mathit{Me}$), 1.69–1.73 (2H, m, $NCH_2\mathit{CH_2}Me$), 2.53 (3H, s, C=C*Me*), 3.74 (2H, s, $\mathit{CH_2}CO_2H$), 3.81 (3H, s, O*Me*), 3.86 (2H, t, *J* 7.5 Hz, $NC\mathit{H_2}CH_2Me$), 9.58–12.01 (1H, br, $CO_2\mathit{H}$); δ_C (125.7 MHz, $CDCl_3$) 11.0 ($NCH_2CH_2\mathit{Me}$), 11.9 (C=C*Me*), 23.4 ($NCH_2\mathit{CH_2}Me$), 31.8 ($\mathit{CH_2}CO_2H$), 45.9 (NCH_2), 50.9 (OMe), 110.3 (C_{ipso}–CH_2CO_2H), 112.5 (C_{ipso}–CO_2Me), 116.1 (C_{ipso}–Cl), 135.5 (C_{ipso}–Me), 166.1 ($\mathit{CO_2}Me$), 176.0 ($\mathit{CO_2}H$); MS (EI, 70 eV): *m*/*z* (%)=275 (M+2, 3), 273 (M^+, 10), 229 (45), 228 (52), 194 (32), 172 (29), 156 (55), 92 (8), 65 (30), 41 (100).

4.2.4. 2-[2-Chloro-4-(ethoxycarbonyl)-5-methyl-1-propyl-1H-pyrrol-3-yl]acetic acid (**6d**)

White powder, mp 123–124 °C, 0.24 g, yield: 85%. [Found: C, 54.29; H, 6.33; N, 4.88. $C_{13}H_{18}ClNO_4$ requires: C, 54.27; H, 6.31; N, 4.87%.] R_f (20% EtOAc/*n*-hexane): 0.28; IR (KBr) (ν_{max}, cm^{-1}): 2845–3435 (OH), 1711 (CO_2Et), 1657 (CO_2H), 1551 and 1453 (Ar), 1225 (C–O); δ_H (500.1 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.4 Hz, $NCH_2CH_2\mathit{Me}$), 1.36 (3H, t, *J* 7.1 Hz, $OCH_2\mathit{Me}$), 1.69–1.735 (2H, m, $NCH_2\mathit{CH_2}Me$), 2.53 (3H, s, C=C*Me*), 3.73 (2H, s, $\mathit{CH_2}CO_2H$), 3.87 (2H, t, *J* 7.5 Hz, $NC\mathit{H_2}CH_2Me$), 4.31 (2H, q, *J* 7.1 Hz, $OC\mathit{H_2}Me$), 9.40–12.40 (1H, br, $CO_2\mathit{H}$); δ_C (125.7 MHz, $CDCl_3$) 11.0 ($NCH_2CH_2\mathit{Me}$), 12.0 ($OCH_2\mathit{Me}$), 14.3 (C=C*Me*), 23.4 ($NCH_2\mathit{CH_2}Me$), 32.4 ($\mathit{CH_2}CO_2H$), 45.9 ($OC\mathit{H_2}Me$), 60.3 (NCH_2CH_2Me), 110.5 (C_{ipso}–CH_2CO_2H), 112.6 (C_{ipso}–CO_2Me), 116.2 (C_{ipso}–Cl), 135.5 (C_{ipso}–Me), 166.4 ($\mathit{CO_2}Me$), 174.0 ($\mathit{CO_2}H$); MS (EI, 70 eV): *m*/*z* (%)=289 (M+2, 2), 287 (M^+, 7), 277 (2), 243 (25), 214 (75), 198 (13), 172 (55), 149 (33), 81 (13), 65 (30), 43 (100).

4.2.5. 2-[1-Allyl-2-chloro-4-(methoxycarbonyl)-5-methyl-1H-pyrrol-3-yl]acetic acid (**3e**)

White powder, mp 135–137 °C; 0.20 g, yield: 73%. [Found: C, 53.08; H, 5.21; N, 5.17. $C_{12}H_{14}ClNO_4$ requires: C, 53.05; H, 5.19; N, 5.16%.] R_f (20% EtOAc/*n*-hexane): 0.14; IR (KBr) (ν_{max}, cm^{-1}): 2520–3060 (OH), 1710 (CO_2Me), 1697 (CO_2H), 1515 and 1411 (Ar), 1276 (C–O); δ_H (500.1 MHz, $CDCl_3$) 2.48 (3H, s, C=C*Me*), 3.80 (3H, s, O*Me*), 3.82 (2H, s, $\mathit{CH_2}CO_2H$), 4.48–4.53 (2H, m, $NC\mathit{H_2}$), 5.84–5.87 (2H, m, C=C$\mathit{H_2}$), 6.84–6.88 (1H, m, C*H*=CH_2), 9.00–11.80 (1H, br, $CO_2\mathit{H}$); δ_C (125.7 MHz, $CDCl_3$) 13.8 (C=C*Me*), 31.7 ($\mathit{CH_2}CO_2H$), 46.2 ($NC\mathit{H_2}$), 50.9 (OMe), 109.3 (C_{ipso}–CH_2CO_2H), 112.6 (C_{ipso}–CO_2Me), 116.2 (C_{ipso}–Cl), 117.0 (CH=$\mathit{CH_2}$), 131.7 (CH=CH_2), 133.5 (C_{ipso}–Me), 165.8 ($\mathit{CO_2}Me$), 176.6 ($\mathit{CO_2}H$); MS (EI, 70 eV): *m*/*z* (%)=274 (M+2, 2), 272 (M^+, 15), 230 (45), 228 (65), 91 (100), 65 (18).

4.2.6. 2-[1-Allyl-2-chloro-4-(ethoxycarbonyl)-5-methyl-1H-pyrrol-3-yl]acetic acid (**3f**)

White powder, mp 140–142 °C, 0.21 g, yield: 75%. [Found: C, 54.64; H, 5.63; N, 4.89. $C_{13}H_{16}ClNO_4$ requires: C, 54.65; H, 5.64; N, 4.90%.] R_f (20% EtOAc/*n*-hexane): 0.22; IR (KBr) (ν_{max}, cm^{-1}): 2901–3460 (OH), 1700 (CO_2Et), 1610 (CO_2H), 1500–1399 (Ar), 1259 (C–O); δ_H (500.1 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.0 Hz, $OCH_2\mathit{Me}$), 2.51 (3H, s, C=C*Me*), 3.76 (2H, s, $\mathit{CH_2}CO_2H$), 4.33 (2H, q, *J* 7.0 Hz, $OC\mathit{H_2}Me$), 4.51–4.56 (2H, m, $NC\mathit{H_2}$), 4.81–5.87 (2H, m, C=C$\mathit{H_2}$), 5.84–5.93 (1H, m, C*H*=CH_2), 9.37–12.18 (1H, br, $CO_2\mathit{H}$); δ_C (125.7 MHz, $CDCl_3$) 11.8 ($OCH_2\mathit{Me}$), 14.3 (C=C*Me*), 32.2 ($\mathit{CH_2}CO_2H$), 46.3 ($NC\mathit{H_2}$), 60.5 (OCH_2Me), 110.02 (C_{ipso}–CH_2CO_2H), 112.1 (C_{ipso}–CO_2Me), 112.6 (C_{ipso}–Cl), 117.2 (CH=$\mathit{CH_2}$), 131.6 (CH=CH_2), 135.5 (C_{ipso}–Me), 168.0 ($\mathit{CO_2}Et$), 175.1 ($\mathit{CO_2}H$); MS (EI, 70 eV): *m*/*z* (%)=287 (M+2, 4), 285 (M^+, 16), 279 (6), 256 (7), 243 (10), 241 (30), 224 (5), 212 (36), 196 (11), 192 (4), 178 (18), 167 (25), 149 (40), 132 (10), 113 (6), 99 (6), 85 (6), 71 (18), 57 (31), 43 (48), 41 (100).

4.2.7. 2-[2-Chloro-1-isopropyl-4-(methoxycarbonyl)-5-methyl-1H-pyrrol-3-yl]acetic acid (**3g**)

White powder, mp 100–102 °C, 0.21 g, yield 76%. [Found: C, 52.68; H, 5.89; N, 5.11. $C_{12}H_{16}ClNO_4$ requires: C, 52.66; H, 5.89; N, 5.12%.] R_f (20% EtOAc/*n*-hexane): 0.32; IR (KBr) (ν_{max}, cm^{-1}): 2510–3465 (OH), 1704 (CO_2Me), 1685 (CO_2H), 1515 and 1410 (Ar), 1253 (C–O); δ_H (500.1 MHz, $CDCl_3$) 1.56 (6H, d, *J* 5.0 Hz, $NCH\mathit{Me_2}$), 2.57 (3H, s, C=C*Me*), 3.70 (2H, s, $\mathit{CH_2}CO_2H$), 3.80 (3H, s, O*Me*), 4.64–4.65 (1H, m, $NC\mathit{H}Me_2$), 9.09–11.89 (1H, br, $CO_2\mathit{H}$); δ_C (125.7 MHz, $CDCl_3$) 14.1 (C=C*Me*), 21.4 ($NCH\mathit{Me_2}$), 29.7 ($\mathit{CH_2}CO_2H$), 48.7 (OMe), 51.2 ($NCHMe_2$), 110.2 (C_{ipso}–CH_2CO_2H), 113.1 (C_{ipso}–CO_2Me), 115.7 (C_{ipso}–Cl), 135.3 (C_{ipso}–Me), 166.8 ($\mathit{CO_2}Me$), 173.8 ($\mathit{CO_2}H$); MS (EI, 70 eV): *m*/*z* (%)=275 (M+2, 20), 273 (60), 257 (14), 243 (12), 242 (11), 229 (75), 214 (24), 199 (13), 187(79), 172 (71), 155 (100), 153 (17), 127 (28), 116 (11), 98 (18), 92 (16), 81 (15), 65 (37), 45 (38).

4.2.8. 2-[2-Chloro-1-isopropyl-4-(ethoxycarbonyl)-1-isopropyl-5-methyl-1H-pyrrol-3-yl]acetic acid (**3h**)

White powder, mp 143–145 °C, 0.23 g, yield: 80%. [Found: C, 54.30; H, 6.32; N, 4.85. $C_{13}H_{18}ClNO_4$ requires: C, 54.27; H, 6.31; N, 4.87%.] R_f (20% EtOAc/*n*-hexane): 0.26; IR (KBr) (ν_{max}, cm^{-1}): 2505–3385 (OH), 1732 (CO_2Et), 1695 (CO_2H), 1512 and 1439 (Ar), 1247 (C–O); δ_H (500.1 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.0 Hz, $OCH_2\mathit{Me}$), 1.50 (6H, d, *J* 7.0 Hz, $NCH\mathit{Me_2}$), 2.62 (3H, s, C=C*Me*), 3.83 (2H, s, $\mathit{CH_2}CO_2H$), 4.31 (2H, q, *J* 7.1 Hz, $OC\mathit{H_2}Me$), 4.42–4.47 (1H, m, $NC\mathit{H}Me_2$), 9.12–12.14 (1H, br, $CO_2\mathit{H}$); δ_C (125.7 MHz, $CDCl_3$) 11.8 ($OCH_2\mathit{Me}$), 14.4 (C=C*Me*), 22.0 ($NCH\mathit{Me_2}$), 30.4 ($\mathit{CH_2}CO_2H$), 49.0 ($NCHMe_2$), 59.7 (OCH_2Me), 110.0 (C_{ipso}–CH_2CO_2H), 112.9 (C_{ipso}–CO_2Me), 120.8 (C_{ipso}–Cl), 135.4 (C_{ipso}–Me), 164.4 ($\mathit{CO_2}Me$), 174.4 ($\mathit{CO_2}H$); MS (EI, 70 eV): *m*/*z* (%)=289 (M^{+2}, 13),287 (M^+, 32), 279 (9), 257 (6), 245 (7), 242 (84), 228 (5), 216 (10), 200 (50), 186 (5), 172 (52), 167 (35), 149 (90), 127 (17), 113 (17), 99 (9), 84(16), 71 (37), 57 (56), 43 (100), 41 (94).

References and notes

1. (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045; (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 615; (c) Nobuyoshi, A.; Akihiko, O.; Chikara, M.; Tatsuya, T.; Masami, O.; Hiromitsu, S. *J. Med. Chem.* **1999**, *42*, 2946; (d) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609; (e) Torok, M.; Abid, M.; Mhadgut, S. C.; Torok, B. *Biochemistry* **2006**, *45*, 5377.
2. Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 119.
3. (a) Tao, H.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5979.
4. (a) Baumgarten, M.; Tyutyulkov, N. *Chem.—Eur. J.* **1998**, *4*, 987; (b) Deronzier, A.; Moutet, J. C. *Curr. Top. Electrochem.* **1994**, *3*, 159; (c) Pagani, G. A. *Heterocycles* **1994**, *37*, 2069.
5. (a) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, *34*, 991; (b) Burli, R. W.; McMinn, D.; Kaizerman, J. A.; Hu, W.; Ge, Y.; Pack, Q.; Jiang, V.; Gross, M.; Garcia, M.; Tanaka, R.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1253; (c) Burli, R. W.; Jones, P.; McMinn, D.; Le, Q.; Duan, J. X.; Kaizerman, J. A.; Difuntorum, S.; Moser, H. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1259; (d) Jonas, R.; Klockow, M.; Lues, I.; Pruecher, H.; Schliep, H. J.; Wurziger, H. *Eur. J. Med. Chem.* **1993**, *28*, 129; (e) von der Saal, W.; Hoelck, J. P.; Kampe, W.; Mertens, A.; Mueller-Beckmann, B. *J. Med. Chem.* **1989**, *32*, 1481; (f) Denny, W. A.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1990**, *33*, 814; (g) Toja, E.; Selva, D.; Schiatti, P. *J. Med. Chem.* **1984**, *27*, 610; (h) Demopoulos, V. J.; Rekka, E. *J. Pharm. Sci.* **1995**, *84*, 79; (i) Del Poeta, M.; Schell, W. A.; Dykstra, C. C.; Jones, S.; Tidwell, R. R.; Czarny, A.; Bajic, M.; Bajic, M.; Kumar, A.; Boykin, D.; Perfect, J. R. *Antimicrob. Agents Chemother.* **1998**, *42*, 2495.
6. (a) de Laszlo, S. E.; Visco, D.; Agarwal, L.; Chang, L.; Chin, J.; Croft, G.; Forsyth, A.; Fletcher, D.; Frantz, B.; Hacker, C.; Hanlon, W.; Harper, C.; Kostura, M.; Li, B.; Luell, S.; MacCoss, M.; Mantlo, N.; O'Neill, E. A.; Orevillo, C.; Pang, M.; Parsons, J.; Rolando, A.; Sahly, Y.; Sidler, K.; Widmer, W. R.; O'Keefe, S. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2689; (b) Dowell, R. I.; Hales, N. H.; Tucker, H. *Eur. J. Med. Chem.* **1993**, *28*, 513; (c) Ferraris, D.; Ficco, R. P.; Dain, D.; Ginski, M.; Lautar, S.; Lee-Wisdom, K.; Liang, S.; Lin, Q.; Lu, M. X. C.; Morgan, L.; Thomas, B.; Williams, L. R.; Zhang, J.; Zhou, Y.; Kalish, V. J. *Bioorg. Med. Chem.* **2003**, *11*, 3695; (d)

Chesworth, R.; Wessel, M. D.; Heyden, L.; Mangano, F. M.; Zawistoski, M.; Gegnas, L.; Galluzzo, D.; Lefker, B.; Cameron, K. O.; Tickner, J.; Lu, B.; Castleberry, T. A.; Petersen, D. N.; Brault, A.; Perry, P.; Ng, O.; Owen, T. A.; Pan, L.; Ke, H. Z.; Brown, T. A.; Thompson, D. D.; DaSilva-Jardine, P. *Bioorg. Med. Chem. Lett.* **2005**, *24*, 5562; (e) Bovy, P. R.; Reitz, D. B.; Collins, J. T.; Chamberlain, T. S.; Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Koepke, J. P.; Smits, G. J.; McGraw, D. E.; Gaw, J. F. *J. Med. Chem.* **1993**, *36*, 101; (f) Renneberg, D.; Dervan, P. B. *J. Am. Chem. Soc.* **2003**, *125*, 5707; (g) Marques, M. A.; Doss, R. M.; Foister, S.; Dervan, P. B. *J. Am. Chem. Soc.* **2004**, *126*, 10339.

7. Boger, D. L.; Boyce, C. W.; Labrili, M. A.; Sehon, C. A.; Lin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54.
8. Knorr, L. *Chem. Ber.* **1884**, *17*, 1635.
9. Paal, C. *Chem. Ber.* **1885**, *18*, 367.
10. Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474.
11. Berree, F.; Marchand, E.; Morel, G. *Tetrahedron Lett.* **1992**, *33*, 6155.
12. Furstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637.
13. Katritzky, A.; Jiang, J.; Steel, P. J. *J. Org. Chem.* **1994**, *59*, 4551.
14. Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238.
15. Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427.
16. Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465.
17. Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390.
18. Yadav, J. S.; Subba Reddy, B. V.; Rao, T. S.; Narender, R.; Gupta, M. K. *J. Mol. Catal. A: Chem.* **2007**, *278*, 42.
19. (a) Alizadeh, A.; Zohreh, N.; Rostamnia, S. *Tetrahedron* **2007**, *63*, 8083; (b) Alizadeh, A.; Zohreh, N. *Synthesis* **2008**, 429; (c) Alizadeh, A.; Rostamnia, S.; Hu, M. L. *Synlett* **2006**, 1592; (d) Alizadeh, A.; Rostamnia, S.; Zohreh, N.; Oskueyan, Q. *Synlett* **2007**, 1610.
20. (a) Alizadeh, A.; Movahedi, F.; Esmaili, A. A. *Tetrahedron Lett.* **2006**, *47*, 4469; (b) Alizadeh, A.; Movahedi, F.; Masrour, H.; Zhu, L. G. *Synthesis* **2006**, 3431; (c) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *Tetrahedron* **2008**, *64*, 351; (d) Alizadeh, A.; Rezvanian, A.; Bijanzadeh, H. R. *Synthesis* **2008**, *5*, 725.
21. Bruneau, C.; Kaur Vohra, R.; Renaud, J. L. *Synthesis* **2007**, 731.
22. Motherwell, W. B.; Gray, P. J.; Whiteheadb, A. J. *Synlett* **2007**, 431.