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Tetrahedron
Tetrahedron 63 (2007) 8949–8953

Formation of dihydrouracils via cyclization of *N*-substituted 3-thioureidopropanoic acids and facile desulfurization

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Received 17 March 2007; revised 27 May 2007; accepted 5 June 2007
Available online 20 June 2007

Abstract—Cyclization of *N*-3 substituted 3-thioureidopropanoic acids in isobutyric anhydride at high temperature resulted in the unexpected formation of *N*-3,*N*-1-substituted dihydrouracils, as confirmed by thorough spectroscopic characterization. A mechanism based on the identification of intermediates observed at lower reaction temperatures is proposed.

1. Introduction

Heterocyclic compounds have played an invaluable role in pharmaceutical and agrochemical discovery processes. We have been interested in sulfur containing heterocycles,[1,2] including 2-amino-4,5-dihydro-1,3-thiazine[3] derivatives as potential scaffolds for the synthesis of screening libraries. In particular our attention was drawn to 2-amino-4,5-dihydro-1,3-thiazin-6-ones. The preparation of these compounds has not been extensively reported in the literature.[4–6] During the course of our recent studies[7] to produce thiazinones via the cyclization of *N*-substituted 3-thioureidopropanoic acids (**1**),[4,8] the reactions unexpectedly produced *N*-substituted dihydrouracils (**2**). To our knowledge the conversion of thioureas to dihydrouracyls has not been previously reported.

2. Results and discussions

The *N*-substituted dihydrouracils (**2**) were isolated and spectroscopically characterized. In general, we observed that cyclization of the thioureidopropanoic acids conducted in isobutyric anhydride at high temperature (180 °C) for short times (30 min–3 h) resulted in the formation of the *N*-substituted dihydrouracils in high yield. Reaction at lower temperatures (up to 130 °C) in isobutyric (Table 1, Supplementary data) or other anhydrides (Table 2, Supplementary data) resulted in the formation of compounds without desulfurization or in the formation of reaction product mixtures. Identification of the mixture components, discussed later, suggests the mechanism for the unexpected formation of the biologically interesting *N*-substituted dihydrouracils.

Table 1 shows the *N*-3-substituted 3-thioureidopropanoic acid (**1**), starting material, and cyclization reaction conditions, which resulted in *N*-3,*N*-1-substituted dihydrouracil product formation in high yield (>90% by HPLC). Starting thioureas for the reactions were prepared by coupling the 3-aminopropanoic acid with the corresponding aryl isothiocyanate moiety.

Analytical analysis and thorough spectroscopic characterization were conducted to determine the identity of the products (**2a–j**) isolated from the reactions carried out in isobutyric anhydride at 180 °C (Table 1). For **2b**, the CHNS elemental analysis determined was consistent with the calculated composition of the proposed structure. The high resolution mass spectrum (HRMS) of **2b** indicates that m/z=311.1366 $(M+Na)^+$. This result is consistent with the proposed molecular formula of **2b**, $C_{16}H_{20}N_2O_3$. No reasonable sulfur containing potential structure is consistent with the HRMS result.

To identify **2b**, ^1H, ^{13}C, and $^1H/^{13}C$ heteronuclear 2D NMR spectra were analyzed. The ^1H NMR spectrum of **2b** in $CDCl_3$ displays resonances from carbon bound protons that are very similar to those of starting material plus signals

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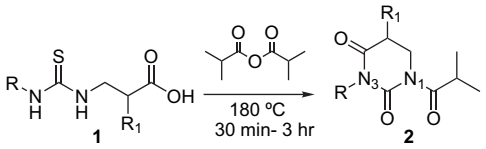
doi:10.1016/j.tet.2007.06.042

Table 1. Cyclization reaction summary



#	R	R_1	Isolated yield[a] (%)	δC_{13} (ppm) of product		
				C_2	C_4	^{i}Bu C=O
a	Benzyl	H	47	152.0	169.3	180.2
b	*p*-Methylbenzyl	H	46	151.9	169.2	180.1[b]
c	*p*-Methylbenzyl	CH_3	53	152.2	172.3	180.9[b]
d	*p*-Methylphenyl	H	49	152.8	170.8	180.2[b]
e	*o*-Methylphenyl	H	60	151.9	169.3	180.4
f	*m*-Methoxyphenyl	H	60	152.3	169.6	180.5
g	*p*-Chlorophenyl	H	N.D.[c,d]	152.3	169.6	180.4
h	*o*-Chlorophenyl	H	N.D.[c,e]			
i	*p*-Nitrophenyl	H	47	151.8	169.3	180.1
j	α-Naphthyl	H	N.D.[c,e]			

[a] Isolated product by chromatographic column.
[b] Studies included HMQC and HMBC NMR.
[c] Not determined.
[d] Although, compound was not able to be purified, key NMR signals were able to be assigned.
[e] Identification based on MS and UV. Due to the complexity of the crude, compounds were not able to be purified and NMR data was not obtained.

characteristic of an isobutyryl group; resonances of the three methylene groups and the isobutyryl methyls of **2b** arise from pairs of NMR equivalent protons. Unlike that of starting material, the spectrum of **2b** contains no ^{1}H resonances from exchangeable, non-carbon bound protons. The ^{13}C NMR spectrum of **2b** displays aliphatic and aromatic region signals that are very similar to those of starting material. Resonances from an isobutyryl group are observed here also. Two ^{13}C signals are observed at 169.2 ppm and 151.9 ppm that are not readily identified by comparison to the spectrum of the starting material. These are key to the structure identification.

^{1}H/^{13}C gHMBC NMR spectroscopy provided the additional information needed to determine the chemical structure of **2b** through the spectral observation of two and three bonds, ^{1}H–^{13}C heteronuclear *J* couplings. Figure 1 shows the structure of **2b** along with key HMBC correlations observed and ^{13}C chemical shift assignments.

Strong peaks between the benzylic methylene protons resonance (δ 4.96, s, 2H) and both of the key carbon resonances (δ 169.2, 151.9) are observed. Knowing the chemical shift of the isobutyryl carbonyl carbon resonance to be 180.1 ppm from the HMBC data, the prior observation establishes that **2b** is cyclic. It also rules out potential cyclic isomers consistent with the molecular formula, such as an amino-

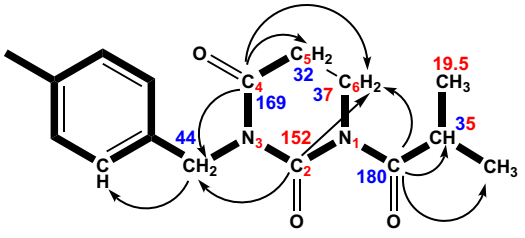


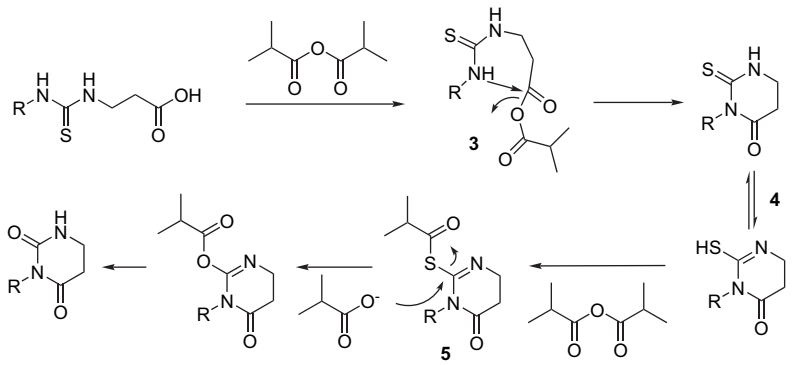
Figure 1. Summary of key ^{13}C chemical shifts (blue) and ^{1}H/^{13}C HMBC correlations observed in an experiment with the magnetization transfer delay, 1/2 J, set to 61 msec for product **2b**.

substituted oxazinone, since correlations from two downfield non-phenyl carbons to the benzyl CH_2 protons are seen. The chemical shifts of the carbons observed at 169.2 ppm and 151.9 ppm agree well with those determined for the carbonyl carbons of dihydrouracyl reference compounds. As shown in Figure 1, N_1 is established as the isobutyryl acylation site, since the isobutyryl carbonyl carbon resonance at 180.1 ppm is correlated with the C_6 methylene proton resonance at 3.91 ppm in the HMBC spectrum of **2b**.

The structures of **2c** and **2d** were also studied using ^{1}H/^{13}C gHMBC NMR spectroscopy. Correlations observed in the HMBC spectrum of **2d** correspond to those observed in the spectrum of **2b**, aside from the absence of correlations, which is not present in **2d**. C-13 chemical shifts of the key carbonyl carbon resonances C_2 and C_4 of **2d** match those observed for **2b** very well, as shown in Table 1. This establishes the structure of **2d** as a *N*-3,*N*-1-substituted dihydrouracil like **2b**. For **2c**, correlations observed in its HMBC spectrum are analogous to those observed for **2b** aside from additional correlations involving the C_5-methyl group and the now inequivalent H_6 methylene protons. The C_2 and C_4 carbonyl carbon shifts also match those of **2b** very well establishing **2c** as a *N*-3,*N*-1-substituted dihydrouracil.

The *N*-3,*N*-1-substituted dihydrouracil core structure of the remaining products in Table 1 is established by the very close correspondence of their structurally key ^{13}C and ^{1}H chemical shifts to those of the thoroughly examined compounds **2b**, **2c**, and **2d**.

Several experiments were conducted whose results suggest the mechanism for *N*-3,*N*-1-substituted dihydrouracil formation at high temperature, described above. When cyclization reactions were conducted in isobutyric anhydride at lower temperatures, from 80 °C to 130 °C, the *N*-3,*N*-1-substituted dihydrouracils were formed in low reaction yields, typically less than 10% as monitored by HPLC (Table 1, Supplementary data). HPLC indicated that characterizable quantities of



Scheme 1. Rationalization of the formation of dihydrouracils.

reaction product mixture components were present, and they were identified by NMR and/or LCMS analysis. For example, after 15 min at 80 °C in isobutyric anhydride, the 3-(3-*p*-methylbenzylthioureido)-propanoic acid cyclization reaction mixture contained the *N*-3,*N*-1-substituted dihydrouracil reaction product **2b** (5%), an activated cyclization precursor 3-(3-*p*-methylbenzylthioureido)-propanoic-isobutyryl anhydride **3** (R=*p*-methylbenzyl) (9%), compound **5** (R=*p*-methylbenzyl) (10%), an amide decomposition product (11%), unidentified multiple components (12%), and the unacylated thioxo cyclization product 2-thioxo-3-*p*-methylbenzyl-tetrahydropyrimidin-4(1*H*)-one **4** (R=*p*-methylbenzyl) (52%). In a similar reaction, milligram quantities of pure compound **4** (R=*p*-tolyl) were isolated.[7] When suspended in isobutyric anhydride at 180 °C for 90 min, this thioxo compound was converted to the *N*-3,*N*-1-substituted dihydrouracil **2d** quantitatively. These data suggest the mechanism outlined in Scheme 1 for the formation of *N*-substituted dihydrouracils.

3. Conclusions

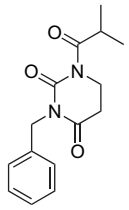
Reaction conditions that readily result in the high yield formation of *N*,*N*-substituted dihydrouracils from easily prepared *N*-3-substituted 3-thioureidopropanoic acid starting materials are found. The identities of these cyclization reaction products were determined using CHNS elemental analysis, high resolution MS, LCMS, and heteronuclear NMR spectroscopies. A cyclization mechanism involving an activated anhydride derivative of the *N*-substituted thioureidopropanoic acid and the desulfurization mechanism has been proposed based on the identification of reaction intermediates. This method should facilitate the preparation of the biologically interesting *N*-substituted dihydrouracils.[9]

4. Experimental part

4.1. General procedure for cyclization of 3-thioureidopropanoic acids

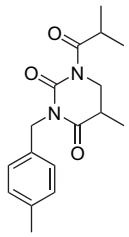
A solution of a 3-thioureidopropanoic acid (5%) in isobutyric anhydride was heated at 180 °C and was then concentrated in vacuo. The crude product was purified by silica gel chromatography.

4.1.1. 3-Benzyl-1-isobutyryl-dihydropyrimidine-2,4-dione (2a). Prepared according to general procedure from the 3-(3-benzyl-thioureido)-propanoic acid (25.9 mg, 0.1 mmol), isobutyric anhydride (0.6 mL), heating the mixture for 1 h. The crude product was purified by chromatography (hexane/EtOAc, 70/30) to afford a white solid (12.8 mg, 47%).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.27 (m, 5H, aromatic H), 5.01 (s, 2H, PhCH_2), 3.93 (t, J=6.4 Hz, 2H, NCH_2), 3.70–3.64 (m, 1H, CH(CH_3)$_2$), 2.74 (t, J=6.4 Hz, 2H, CH_2), 1.19 (d, J=6.4 Hz, 6H, C(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.2 (C_q, C=O), 169.3 (C_q, C=O), 152.0 (C_q, C=O), 136.9 (C_q, aromatic C_q), 128.6 (CH, aromatic CH), 128.5 (CH, aromatic CH), 127.7 (CH, aromatic CH), 44.2 (CH_2, PhCH_2), 37.0 (CH_2, NCH_2), 35.5 (CH, CH(CH_3)$_2$), 32.0 (CH_2, CH_2), 19.6 (2CH_3, CH(CH_3)$_2$). MS (EI$^+$); *m*/*z* (%) : 274 [M] (100). HRMS [M]$^+$ $C_{15}H_{18}N_2O_3$: calcd 274.1317; found 274.1331.

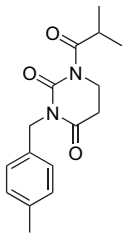
4.1.2. 1-Isobutyryl-3-(4-methylbenzyl)-dihydropyrimidine-2,4-dione (2b). Prepared according to general procedure from the 3-[3-(4-methylbenzyl)-thioureido]-propanoic acid (80 mg, 0.32 mmol), isobutyric anhydride (1.7 mL), heating the mixture for 2 h. The crude product was purified by chromatography (hexane/EtOAc, 75/25) to afford a white solid (42 mg, 46%).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, J=8 Hz, 2H, aromatic H), 7.12 (d, J=8 Hz, 2H, aromatic H), 4.96 (s, 2H, PhCH_2), 3.91 (t, J=6.4 Hz, 2H, NCH_2), 3.70–3.64 (m, 1H,

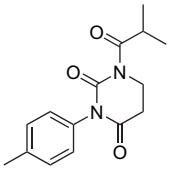
C*H*(CH_3)$_2$), 2.72 (t, *J*=6.4 Hz, 2H, C*H*$_2$), 2.32 (s, 3H, *p*-C*H*$_3$), 1.18 (d, *J*=6.8 Hz, 6H, C(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.1 (C_q, C=O), 169.2 (C_q, C=O), 151.9 (C_q, C=O), 137.3 (C_q, aromatic C_q), 133.8 (C_q, aromatic C_q), 129.0 (CH, aromatic CH), 128.6 (CH, aromatic CH), 43.8 (CH_2, Ph*C*H$_2$), 36.9 (CH_2, N*C*H$_2$), 35.3 (CH, *C*H(CH_3)$_2$), 31.8 (CH_2, *C*H$_2$), 21.0 (CH_3, *p*-*C*H$_3$), 19.5 (2CH_3, CH(*C*H$_3$)$_2$). MS (ESI); *m*/*z* (%): 311 [M+Na] (60), 312 (10), 313 (2), 314 (1). HRMS [M+Na] $C_{16}H_{20}N_2O_3Na$: calcd 311.1372; found 311.1366.

4.1.3. 1-Isobutyryl-5-methyl-3-(4-methylbenzyl)-dihydropyrimidine-2,4-dione (2c). Prepared according to general procedure from 3-[3-(4-methylbenzyl)-thioureido]-butanoic acid (85 mg, 0.32 mmol), isobutyric anhydride (1.7 mL), heating the mixture for 2 h. The crude product was purified by chromatography (hexane/EtOAc, 75/25) to afford a white solid (51 mg, 53%).



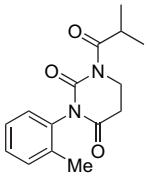
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, *J*=8 Hz, 2H, aromatic H), 7.12 (d, *J*=8 Hz, 2H, aromatic H), 4.95 (d, *J*=3.6 Hz, 2H, PhC*H*$_2$), 4.24 (dd, *J*=13.6, 5.2 Hz, 1H, NCH*H*), 3.74–3.68 (m, 1H, C*H*(CH_3)$_2$), 3.31 (dd, *J*=13.6, 10.4 Hz, 1H, NC*H*H), 2.69–2.64 (m, 1H, C*H*), 2.32 (s, 3H, *p*-C*H*$_3$), 1.28–1.16 (m, 9H, C*H*$_3$, CH(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.9 (C_q, *C*OCH(CH_3)$_2$), 172.3 (C_q), 152.2 (C_q), 138.0 (C_q, aromatic C_q), 134.1 (C_q, aromatic C_q), 128.7 (CH, aromatic CH), 128.4 (CH, aromatic CH), 44.2 (CH_2, Ph*C*H$_2$), 43.5 (CH_2, N*C*H$_2$), 36.2 (CH, *C*H), 35.9 (CH, *C*H(CH_3)$_2$), 21.8 (CH_3, *p*-*C*H$_3$), 20.0 and 19.9 (CH_3, CH(*C*H$_3$)$_2$), 13.6 (CH_3, *C*H$_3$). MS (ESI); *m*/*z* (%): 325 [M+Na] (320), 326 (50), 327 (10). HRMS [M+Na] $C_{17}H_{22}N_2O_3Na$: calcd 325.1528; found 325.1523.

4.1.4. 1-Isobutyryl-3-*p*-tolyl-dihydropyrimidine-2,4-dione (2d). Prepared according to general procedure from 3-(3-*p*-tolyl-thioureido)-propanoic acid (92.7 mg, 0.39 mmol), isobutyric anhydride (2.25 mL), heating the mixture for 0.5 h. The crude product was purified by chromatography (hexane/EtOAc, 75/25) to afford a white solid (52 mg, 49%).



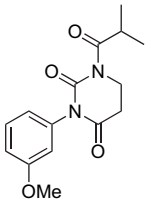
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, *J*=8.0 Hz, 2H, aromatic H), 7.06 (d, *J*=8.0 Hz, 2H, aromatic H), 4.10 (t, *J*=6.4 Hz, 2H, NC*H*$_2$), 3.68–3.60 (m, 1H, C*H*(CH_3)$_2$), 2.88 (t, *J*=6.4 Hz, 2H, C*H*$_2$), 2.39 (s, 3H, *p*-CH_3Ph), 1.2 (t, *J*=6.4 Hz, 6H, C(C*H*$_3$)$_2$). ^{13}C NMR (DMSO, 100 MHz) δ 180.2 (C_q, C=O), 170.8 (C_q, C=O), 152.8 (C_q, C=O), 138.1 (C_q, aromatic C_q), 134.0 (C_q, aromatic C_q), 129.9 (CH, aromatic CH), 129.5 (CH, aromatic CH), 37.7 (CH_2, N*C*H$_2$), 35.3 (CH, *C*H(CH_3)$_2$), 32.17 (CH_2, *C*H$_2$), 21.4 (CH_3, *p*-*C*H$_3$Ph), 20.2 (2CH_3, CH(*C*H$_3$)$_2$). MS (EI$^+$); *m*/*z* (%): 275 [M+1] (20), 274 (100). HRMS [M]$^+$ $C_{15}H_{18}N_2O_3$: calcd 274.1317; found 274.1307.

4.1.5. 1-Isobutyryl-3-*o*-tolyl-dihydropyrimidine-2,4-dione (2e). Prepared according to general procedure from 3-(3-*o*-tolyl-thioureido)-propanoic acid (42.5 mg, 0.18 mmol), isobutyric anhydride (0.90 mL), heating the mixture for 1 h. The crude product was purified by chromatography (hexane/EtOAc, 75/25) to afford a white solid (29.4 mg, 60%).



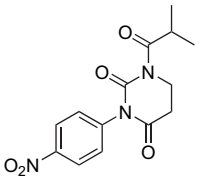
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.08 (m, 4H, aromatic H), 4.14–4.10 (m, 2H, NC*H*$_2$), 3.68–3.62 (m, 1H, C*H*(CH_3)$_2$), 2.89 (t, *J*=6.4 Hz, 2H, C*H*$_2$), 2.15 (s, 3H, C*H*$_3$), 1.20 (d, *J*=6.8 Hz, 6H, C(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4 (C_q, C=O), 169.3 (C_q, C=O), 151.9 (C_q, C=O), 135.9 (C_q, aromatic C_q), 134.2 (C_q, aromatic C_q), 131.3 (CH, aromatic CH), 129.6 (CH, aromatic CH), 128.8 (CH, aromatic CH), 127.4 (CH, aromatic CH), 37.6 (CH_2, N*C*H$_2$), 35.9 (CH, *C*H(CH_3)$_2$), 32.4 (CH_2, *C*H$_2$), 19.9 (2CH_3, CH(*C*H$_3$)$_2$), 17.7 (CH_3, *C*H$_3$). MS (EI$^+$); *m*/*z* (%): 274 [M] (100). HRMS [M]$^+$ $C_{15}H_{18}N_2O_3$: calcd 274.1317; found 274.1305.

4.1.6. 1-Isobutyryl-3-(3-methoxy-phenyl)-dihydropyrimidine-2,4-dione (2f). Prepared according to general procedure from the 3-[3-(3-methoxy-phenyl)-thioureido]-propanoic acid (34.8 mg, 0.14 mmol), isobutyric anhydride (0.70 mL), heating the mixture for 1 h. The crude product was purified by chromatography (hexane/EtOAc, 75/25) to afford a white solid (23.8 mg, 60%).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–6.71 (m, 4H, aromatic H), 4.10 (t, *J*=6.4 Hz, 2H, NC*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 3.67–3.60 (m, 1H, C*H*(CH_3)$_2$), 2.88 (t, *J*=6.4 Hz, 2H, C*H*$_2$), 1.20 (d, *J*=6.8 Hz, 6H, C(C*H*$_3$)$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4 (C_q, C=O), 169.6 (C_q, C=O), 160.6 (C_q, aromatic C_q), 152.3 (C_q, C=O), 136.1 (C_q, aromatic C_q), 130.3 (CH, aromatic CH), 121.0 (CH, aromatic CH), 114.9 (CH, aromatic CH), 114.7 (CH, aromatic CH), 55.6 (CH_3, O*C*H$_3$), 37.5 (CH_2, N*C*H$_2$), 35.8 (CH, *C*H(CH_3)$_2$), 32.4 (CH_2, *C*H$_2$), 19.9 (2CH_3, (*C*H$_3$)$_2$). MS (EI$^+$); *m*/*z* (%): 291 [M+1] (42), 290 (100). HRMS [M$^+$] $C_{15}H_{18}N_2O_4$: calcd 290.1267; found 290.1270.

4.1.7. 1-Isobutyryl-3-(4-nitro-phenyl)-dihydropyrimidine-2,4-dione (2i). Prepared according to general procedure from 3-[3-(4-nitro-phenyl)-thioureido]-propanoic acid (45.7 mg, 0.16 mmol), isobutyric anhydride (0.90 mL), heating the mixture for 1 h. The crude product was purified by chromatography (hexane/EtOAc, 70/30) to afford a white solid (22.7 mg, 47%).



^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (dd, J=9.0, 6.8 Hz, 2H, aromatic H), 7.40 (dd, J=9.0, 6.8 Hz, 2H, aromatic H), 4.14 (t, J=6.4 Hz, 2H, NCH_2), 3.63–3.57 (m, 1H, $CH(CH_3)_2$), 2.93 (t, J=6.4 Hz, 2H, CH_2), 1.21 (d, J=6.8 Hz, 6H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.1 (C_q, C=O), 169.3 (C_q, C=O), 151.8 (C_q, aromatic C_q), 148.0 (C_q, C=O), 140.8 (C_q, aromatic C_q), 130.4 (CH, aromatic CH), 124.8 (CH, aromatic CH), 37.4 (CH_2, NCH_2), 36.0 (CH, $CH(CH_3)_2$), 32.3 (CH_2), 19.8 ($2CH_3$, $CH(CH_3)_2$). MS (EI^+); m/z (%): 306 [M+1] (43), 305 (100). HRMS [M^+] $C_{14}H_{15}N_3O_5$: calcd 305.1012; found 305.1009.

Acknowledgements

The work carried out in Barcelona was partially supported by funds from CICYT (CTQ2006-03794/BQU), the *Generalitat de* Catalunya (2005SGR 00662), the Institut for Research in Biomedicine, and the Barcelona Science Park.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.06.042.

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