Efficient Regioselective Synthesis of 4- and 5-Substituted Isoxazoles under Thermal and Microwave Conditions

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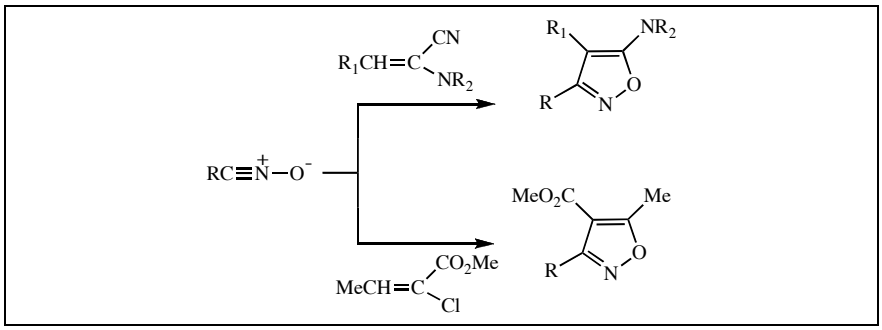
Received February 18, 2008



The [2+3] cycloaddition reaction between nitrile oxides **2** and the captodative olefins **1** or the methyl crotonate derivatives **4** is regioselective and leads to the formation of the 5-substituted amino-isoxazole **3** or the 4-substituted methoxycarbonyl-isoxazole **5** derivatives, respectively. All these reactions are greatly accelerated by microwave irradiation without changing their regioselectivity with respect to the thermal conditions.

J. Heterocyclic Chem., **45**, 1385 (2008).

INTRODUCTION

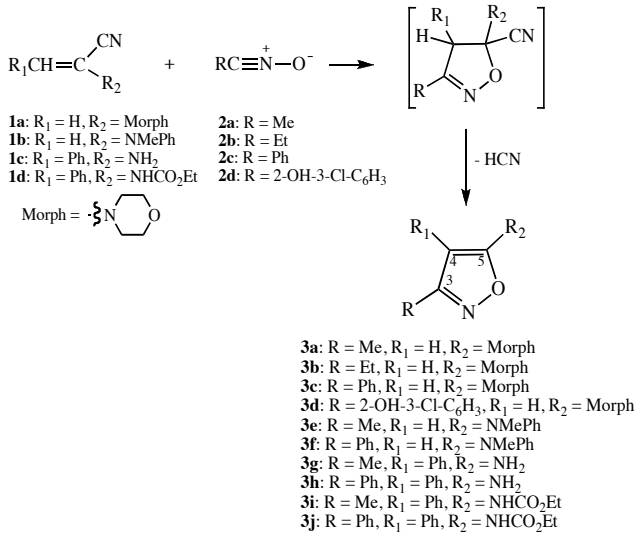
Heterocyclic compounds are of considerable interest because of their extensive use in the design of biologically active molecules and advance organic materials [1]. Isoxazoles are very important class of compounds among them because of their presence in many biologically active systems [2]. Moreover it can be used as a potential synthetic reagent as masked 1,3-dicarbonyl systems due to their ring-opening reactions [3]. Among the several synthetic strategies to isolate isoxazole compounds most of them are based on the high reactivity of the $C\equiv N^{+}\text{-}O^{-}$ group, which reacts with the aliphatic triple bond and double bond to afford the isoxazole and isoxazoline, respectively [4]. Regioselectivity is one of the most interesting features of this type of cycloaddition reactions where the nature of the substituent play an important role in the formation of the final products [5]. Recently, we have reported [6] that microwave irradiation can accelerate the 1,3-dipolar cycloaddition reactions remarkably. Herein we describe one convenient regioselective methodology to obtain 4- or 5-substituted isoxazole derivatives by the action of the nitrile oxides on methyl crotonate derivatives or captodative olefins, respectively, under thermal as well as microwave conditions.

RESULTS AND DISCUSSION

We have studied the reactions of the captodative alkenes $(R_1)C(H)=C(R_2)(CN)$ **1** with various alkyl/aryl nitrile oxides $RC\equiv N^{+}O^{-}$ **2**. To prevent the dimerization of nitrile oxides they were prepared *in situ* in the presence of dipolarophiles. Generally, the [2+3] cycloaddition reactions between olefins **1** and nitrile oxides **2** are not very fast and it takes 1-3 days depending on the nature of the olefin used under stirring at room temperature or refluxing conditions. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel by elution with hexane/ethyl acetate producing isoxazoles **3** as exclusive products, in moderate to very good yields (98-41%) (Scheme 1). The expected isoxazolines could not be detected most likely due to the evolution of HCN gas, which helps in driving the reaction to give isoxazoles.

These reactions are greatly accelerated by focused microwave irradiation (70 ºC, 300 Watt), taking 1-3 h, whereas conventional heating methods require much longer times. The yields of the isoxazoles **3** synthesized by this way are comparable with the thermal method (see Experimental Section).

Scheme 1

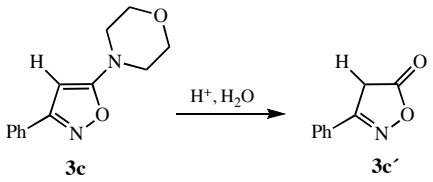


The obtained isoxazoles **3a-j** were characterized by elemental analyses, IR and ^{1}H and ^{13}C{^{1}H} spectroscopies, and FAB-MS. Their IR spectra do not show the typical N≡C band at *ca*. 2240 cm^{-1} and display two strong bands *ca*. 1570 cm^{-1} and *ca*. 1600 cm^{-1} corresponding to N=C and C=C, respectively, due to the isoxazole ring, in agreement with the literature [7]. In the ^{1}H NMR spectrum of the compounds **3a-3f** the ethylenic proton was detected in the range 4.95-5.90 ppm. To ascertain the position of the amino moiety for the di-substituted isoxazoles **3a-3f**, we compare these results with similar compound synthesized earlier. Döpp *et al* [8] reported the synthesis of the 4-(3-phenylisoxazol-5-yl)morpholine **3c** by reacting benzonitrile oxide with 4-ethynylmorpholine. The authors found the signal for the ethylenic proton at 5.30 ppm whereas in our case we observed it at 5.35 ppm confirming that the amino moiety is in position 5. In the ^{13}C{^{1}H} NMR of **3a-3f** the corresponding signals of C-3, C-4 and C-5 are detected in the range of 161.3-169.4, 74.1-81.3 and 169.1-179.2 ppm, respectively and these results are in agreement with those reported in the literature [9].

Moreover, the acid hydrolysis of the isoxazole **3c** gives the lactone **3c´** as exclusive product which has been confirmed by the characteristic IR band of the carboxylic group of lactone at 1805 cm^{-1} [4c,10]. This result also strongly suggests that the initial isoxazole **3c** was substituted by the morpholine in the position 5 (Scheme 2).

Comparison of ^{1}H and ^{13}C{^{1}H} NMR spectroscopic data between the tri-substituted isoxazoles **3g-3j** with the similar compounds reported previously by other groups

Scheme 2

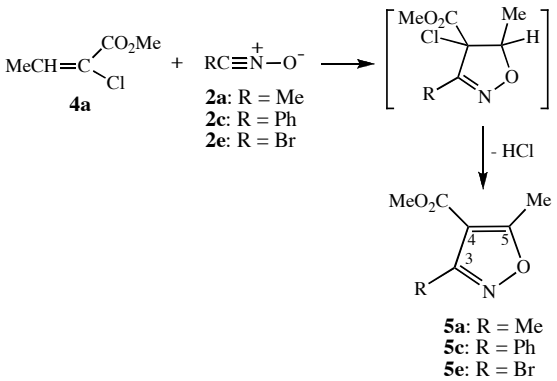


confirm that the isoxazoles are substituted at 5-position by the amino moiety [11].

The [2+3] cycloaddition reaction between nitrile oxides **2** and the captodative olefins **1** is regioselective and leads to the formation of the isoxazoles **3** as unique products substituted in position 5 by the amino moiety instead of the expected isoxazolines, by eliminating HCN gas. The transient existence of the isoxazolines may be explained due to the presence of two groups (cyano and amino) geminal to the α oxygen atom.

To orient the regioselectivity of the cycloaddition reaction towards the 4-substituted cycloadducts, we have purposefully taken two geminal groups (CO_2Me, Cl) in the same ethylenic carbon atom. The reaction between α-chloro methyl crotonate **4a** and nitrile oxides **2** furnished the isoxazoles **5** as the exclusive products, in moderate to good yields (63-39%) (Scheme 3). The expected isoxazolines could not be detected also in this case because of the evolution of HCl gas, which helps in driving the reaction to give the final compounds. The presence of chloro substituent geminal to the ester functional group in **4a** reinforces the electron-withdrawing effect of methoxycarbonyl group and helps the nucleophilic attack to occur at β carbon atom. Similar reactions without the chloro substituent furnished mixtures of isoxazolines where the major product is the result of nucleophilic attack at α position [5e].

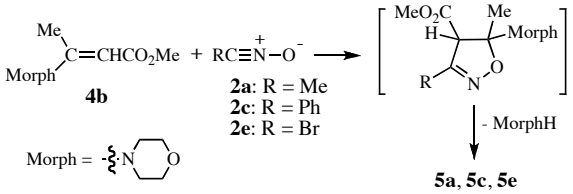
Scheme 3



The obtained isoxazoles **5** were characterized by elemental analyses, IR and ^{1}H and $^{13}C\{^{1}H\}$ spectroscopies, and FAB-MS. Their IR show the typical bands of isoxazole ring along with a strong band at *ca*. 1730 cm^{-1} due to the carbonyl of ester. All the ^{1}H and $^{13}C\{^{1}H\}$ NMR are in agreement with the literature [12].

In another alternative route strategic introduction of electron-donating group containing amino moiety like morpholine at β with respect to the ester makes it possible to synthesize the same isoxazoles **5** starting from methyl 3-morpholinobut-2-enoate **4b** and nitrile oxides **2**. In this case the morpholine could be isolated at the end and no traces of isoxazolines have been observed (Scheme 4). Similar results were reported earlier when pyrrolidine enamine of ethyl acetoacetate reacts with nitroethane to give ethyl 3,5-dimethyl-4-isoxazolecarboxylate in good yields [12a].

Scheme 4



The [2+3] cycloaddition reaction between nitrile oxides **2** and methyl crotonate derivatives **4** is regioselective and leads to the formation of the isoxazoles **5** as exclusive product substituted in position 4 by the methoxycarbonyl group.

Interestingly, sometimes the presence of halo or methylthio atoms in position α or β with respect to the ester of the type (X)(Y)C=C(Z)(CO_2Me) (**6a** X = Me, Y = Cl, Z = H; **6b** X = Me, Y = SMe, Z = H; **6c** X = $CH(OMe)_2$, Y = Br, Z = H; **6d** X = $CH(OMe)_2$, Y = H, Z = Br) inhibits the [2+3] cycloaddition reaction completely and only the starting material was recovered quantitatively. Similar observations were also reported [12a] in the case of β-alkoxyacrylic esters.

CONCLUSIONS

The results of this work show that the [2+3] cycloaddition reaction between nitrile oxides **2** and the captodative olefins **1** or the methyl crotonate derivatives **4** is regioselective and leads to the formation of the 5-substituted amino-isoxazole **3** or the 4-substituted methoxycarbonyl-isoxazole **5** derivatives, respectively, as exclusive products. Microwave irradiation promotes the [2+3] cycloaddition reaction by shortening the reaction time without changing the regioselectivity relatively to conventional heating method.

EXPERIMENTAL

Material and instrumentation. Solvents and reagents were purchased from Aldrich and dried by usual procedures. The captodative olefins **1** [13], the methyl crotonate derivatives **4** [14], the olefins **6** [15] and the nitrile oxides **2a**-**2b** [16], **2c**-**2d** [5e] and **2e** [17] were prepared according to published methods. C, H and N elemental analyses were carried out by the Microanalytical Service of the Instituto Superior Técnico. ^{1}H and ^{13}C NMR spectra (in $CDCl_3$) were measured on a Varian Unity 300 spectrometer at ambient temperature. Positive-ion FAB mass spectra were obtained on a Trio 2000 instrument by bombarding 3-nitrobenzyl alcohol (NBA) matrixes of samples with 8 keV (*ca* 1.28 x 10^{15} J) Xe atoms. ^{1}H and ^{13}C chemical shifts (δ) were expressed in ppm relative to $Si(Me)_4$. Infrared spectra (4000-400 cm^{-1}) were recorded on a Bio-Rad FTS 3000MX and a Jasco FT/IR-430 instruments in KBr pellets and the wavenunbers are in cm^{-1}. The microwave irradiation experiments were undertaken in a focused microwave CEM Discover reactor (10 mL, 13 mm diameter, 300 W) which is fitted with a rotational system and an IR detector of temperature.

Synthesis of isoxazoles 3 and 5.

(i) Conventional method. In a typical experiment, 0.02 mol of nitroethane, 0.04 mol of phenyl isocyanate and 0.02 mol of olefin were dissolved in 30 mL of dry benzene. A solution of 0.02 mol of triethylamine dissolved in 10 mL of benzene was added drop wise with constant stirring. The reaction was carried out for 20 min at room temperature upon which a precipitation of diphenyl urea was observed along with the evolution of carbon dioxide. Then the mixture was refluxed for 2 days. After cooling it was diluted with 10 mL of benzene and the diphenyl urea was filtered off. The solvent of resulting mixture was removed *in vacuo*. The crude residue was purified by column chromatography on silica (Hexane/Ethyl acetate 4:1) followed by evaporation of the solvent *in vacuo* to give the final isoxazole.

(ii) By focused microwave irradiation in solution. The reagents and solvent were added to a cylindrical Pyrex tube which was then placed in a focused microwave CEM Discover reactor (10 mL, 13 mm diameter, 300 W) which is fitted with a rotational system and an IR detector of temperature. After two hours of reaction at 70 ºC, the mixture was allowed to cool down, the solvent was removed *in vacuo* and the crude residue was purified as indicated in (*i*).

Compound **3a**: Method (i) (78% yield), method (ii) (80% yield). Oil. IR (cm^{-1}): 1600 (C=N) and (C=C). ^{1}H NMR ($CDCl_3$), δ: 2.20 (s, 3H, CH_3), 3.10-3.45 (m, 4H, CH_2), 3.50-3.95 (m, 4H, CH_2), 4.95 (s, 1H, CH). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$), δ: 11.7 (CH_3), 46.6 (CH_2), 65.9 (CH_2), 79.5 (CH), 161.3 (C=N), 170.9 (*N*CO). FAB^{+}-MS, m/z: 168 $[M]^{+}$. *Anal*. Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 57.23; H, 7.06; N, 16.57.

Compound **3b**: Method (i) (75% yield), method (ii) (77% yield). Oil. IR (cm^{-1}): 1600 (C=N) and (C=C). ^{1}H NMR ($CDCl_3$), δ: 1.10 (t, J_{HH} 6 Hz, 3H, CH_3), 2.65 (q, J_{HH} 6 Hz, 2H, CH_2), 3.10-3.45 (m, 4H, CH_2), 3.50-3.95 (m, 4H, CH_2), 4.95 (s, 1H, CH). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$), δ: 12.7 (CH_3), 20.0 (CH_2CH_3), 46.8 (CH_2), 65.2 (CH_2), 78.1 (CH), 166.9 (C=N), 170.9 (*N*CO). FAB^{+}-MS, m/z: 182 $[M]^{+}$. *Anal*. Calcd for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.75; N, 15.37. Found: C, 59.34; H, 7.76; N, 15.35.

Compound **3c**: Method (i) (98% yield), method (ii) (97% yield). Mp: 89 °C. IR (cm^{-1}): 1600 (C=N) and (C=C). ^{1}H NMR ($CDCl_3$), δ: 3.20-3.50 (m, 4H, CH_2), 3.65-3.95 (m, 4H, CH_2),

5.35 (s, 1H, CH), 7.20-7.80 (m, 5H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 46.8 (CH_2), 65.9 (CH_2), 76.9 (CH), 126.6-129.8 ($C_{aromatic}$), 169.4 (C=N), 171.4 (N*C*O). FAB^+-MS, m/z: 230 $[M]^+$. *Anal*. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.14; N, 12.17. Found: C, 68.10; H, 6.17; N, 12.34.

Compound **3d**: Method (i) (51% yield), method (ii) (56% yield). Mp: 92 °C. IR (cm^{-1}): 1600 (C=N) and (C=C). ^1H NMR ($CDCl_3$), δ: 3.20-3.50 (m, 4H, CH_2), 3.65-3.95 (m, 4H, CH_2), 5.90 (s, 1H, CH), 7.00-7.70 (m, 3H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 49.4 (CH_2), 64.0 (CH_2), 74.1 (CH), 125.8-163.3 ($C_{aromatic}$), 163.4 (C=N), 179.2 (N*C*O). FAB^+-MS, m/z: 280 $[M]^+$. *Anal*. Calcd for $C_{13}H_{13}N_2ClO_3$: C, 55.62; H, 4.66; N, 9.98. Found: C, 55.62; H, 4.65; N, 9.96.

Compound **3e**: Method (i) (58% yield), method (ii) (60% yield). Oil. IR (cm^{-1}): 1610 (C=N) and (C=C). ^1H NMR ($CDCl_3$), δ: 2.18 (s, 3H, CH_3), 3.30 (s, 3H, CH_3N), 5.00 (s, 1H, CH), 7.00-8.00 (m, 5H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 11.7 (CH_3), 38.2 (CH_3N), 81.3 (CH), 122.6-144.9 ($C_{aromatic}$), 161.4 (C=N), 169.1 (N*C*O). FAB^+-MS, m/z: 188 $[M]^+$. *Anal*. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.26; H, 6.62; N, 15.01.

Compound **3f**: Method (i) (74% yield), method (ii) (76% yield). Mp: 81 °C. IR (cm^{-1}): 1610 (C=N) and (C=C). ^1H NMR ($CDCl_3$), δ: 3.30 (s, 3H, CH_3N), 5.50 (s, 1H, CH), 7.00-8.00 (m, 10H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 38.3 (CH_3N), 78.7 (CH), 122.9-144.8 ($C_{aromatic}$), 163.7 (C=N), 169.7 (N*C*O). FAB^+-MS, m/z: 250 $[M]^+$. *Anal*. Calcd for $C_{16}H_{14}N_2O$: C, 76.77; H, 5.64; N, 11.20. Found: C, 76.79; H, 5.59; N, 11.48.

Compound **3g**: Method (i) (55% yield), method (ii) (59% yield). Mp: 158 °C. IR (cm^{-1}): 1600 (C=N) and (C=C). ^1H NMR ($CDCl_3$), δ: 2.50 (s, 3H, CH_3), 4.50 (s, br, 2H, NH), 7.20-7.60 (m, 5H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 11.6 (CH_3), 109.1 (*C*Ph), 127.1-128.9 ($C_{aromatic}$), 167.4 (C=N), 174.2 (N*C*O). FAB^+-MS, m/z: 175 $[M+1]^+$. *Anal*. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.78; N, 16.08. Found: C, 68.76; H, 5.78; N, 16.25.

Compound **3h**: Method (i) (72% yield), method (ii) (70% yield). Mp: 160 °C. IR (cm^{-1}): 1600 (C=N) and (C=C). ^1H NMR ($CDCl_3$), δ: 4.60 (s, br, 2H, NH), 7.20-7.80 (m, 10H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 95.3 (*C*Ph), 127.4-136.7 ($C_{aromatic}$), 162.1 (N*C*O), 167.6 (C=N). FAB^+-MS, m/z: 236 $[M]^+$. *Anal*. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.85. Found: C, 76.75; H, 5.26; N, 11.70.

Compound **3i**: Method (i) (41% yield), method (ii) (44% yield). Mp: 150 °C. IR (cm^{-1}): 1730 (CO_2Et), 1600 (C=C), 1570 (C=N). ^1H NMR ($CDCl_3$), δ: 1.20 (t, J_{HH} 7.1 Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.50 (q, J_{HH} 7.1 Hz, 2H, CH_2), 6.50 (s, br, 1H, NH), 7.00-7.60 (m, 5H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 11.5 (CH_3), 14.5 (CH_3CH_2), 61.3 (CH_2), 108.3 (*C*Ph), 128.1-129.6 ($C_{aromatic}$), 153.1 (NH*C*O), 156.4 (C=N), 161.3 (N*C*O). FAB^+-MS, m/z: 246 $[M]^+$. *Anal*. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.46; H, 5.75; N, 11.34.

Compound **3j**: Method (i) (47% yield), method (ii) (50% yield). Mp: 155 °C. IR (cm^{-1}): 1733 (CO_2Et), 1590 (C=C), 1570 (C=N). ^1H NMR ($CDCl_3$), δ: 1.18 (t, J_{HH} 7.0 Hz, 3H, CH_3), 4.18 (q, J_{HH} 7.0 Hz, 2H, CH_2), 7.00-7.60 (m, 10H, aromatic), 9.20 (s, br, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 14.2 (CH_3), 62.7 (CH_2), 107.5 (*C*Ph), 128.1-129.6 ($C_{aromatic}$), 152.5 (NH*C*O), 157.3 (C=N), 162.2 (N*C*O). FAB^+-MS, m/z: 308 $[M]^+$. *Anal*. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.10; H, 5.23; N, 9.08. Found: C, 69.94; H, 5.14; N, 9.23.

Compound **5a**: Method (i) (39% yield), method (ii) (40% yield). Oil. IR (cm^{-1}): 1730 (CO_2Me), 1610 (C=C) and (C=N). ^1H NMR ($CDCl_3$), δ: 2.50 (s, 3H, CH_3CN), 2.75 (s, 3H, CH_3), 3.95 (s, 3H, CH_3O). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 8.2 (CH_3CO), 10.5 (CH_3), 53.9 (CH_3O), 124.3 (CCO_2), 158.8 (C=N), 162.5 (CH_3CO), 165.5 (CO_2CH_3). FAB^+-MS, m/z: 155 $[M]^+$. *Anal*. Calcd for $C_7H_9NO_3$: C, 54.18; H, 5.85; N, 9.03. Found: C, 54.05; H, 5.85; N, 9.01.

Compound **5c**: Method (i) (63% yield), method (ii) (65% yield). Oil. IR (cm^{-1}): 1725 (CO_2Me), 1600 (C=C) and (C=N). ^1H NMR ($CDCl_3$), δ: 2.75 (s, 3H, CH_3), 3.95 (s, 3H, CH_3O), 7.25-7.95 (m, 5H, aromatic). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 8.9 (CH_3), 52.6 (CH_3O), 120.4 (CCO_2), 128.1-131.0 ($C_{aromatic}$), 155.7 (C=N), 158.3 (CH_3CO), 168.9 (CO_2CH_3). FAB^+-MS, m/z: 217 $[M]^+$. *Anal*. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.42; H, 5.10; N, 6.34.

Compound **5e**: Method (i) (39% yield), method (ii) (40% yield). Oil. IR (cm^{-1}): 1750 (CO_2Me), 1598 (C=C) and (C=N). ^1H NMR ($CDCl_3$), δ: 2.70 (s, 3H, CH_3), 3.95 (s, 3H, CH_3O). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 8.8 (CH_3), 52.9 (CH_3O), 122.3 (CCO_2), 144.3 (CH_3CO), 155.7 (C=N), 156.9 (CO_2CH_3). FAB^+-MS, m/z: 219 $[M]^+$. *Anal*. Calcd for $C_6H_6BrNO_3$: C, 32.75; H, 2.75; N, 6.37. Found: C, 32.79; H, 2.73; N, 6.42.

Acknowledgement. This work has been partially supported by the Fundação para a Ciência e a Tecnologia (FCT) and its POCI 2010 program (FEDER funded) (Portugal). S. M. expresses gratitude to FCT for his post-doc fellowship (grant SFRH/BPD/14690/2003) and J. L. to the FCT and the Instituto Superior Técnico (IST) for a research contract (Ciência 2007 program).

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