SYNTHESIS AND CONFORMATION OF 3-NITRO-2-[1-(L)-PROLYL]-THIOPHENE DERIVATIVES [a,b]

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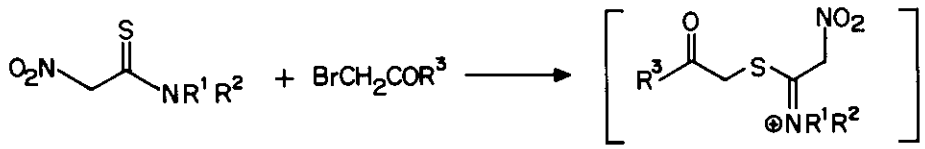
Abstract - Chiral thiophene derivatives with a strong push - pull system (nitroenamine) have been synthesized and their solution conformation has been determined.

Hantzsch synthesis of thiazoles[1] is based on the condensation of α-halogenated carbonyl compounds with thioamides which are either unsubstituted (-$CSNH_2$) or have only one substituent on the nitrogen (-CS-NHR). The obtention of 2-aminothiophenes from thioamides and α-halo ketones is much more difficult. There seem to be only two reports in the literature on such a condensation. *N,N*-Disubstituted thioamides having a methylene group adjacent to the thiocarbonyl group (-CH_2-CS-NRR) on reaction with α-halo ketones undergo *S*-alkylation; subsequent treatment with base leads to the formation of 2-aminothiophenes.[2] The second example is the synthesis of 2-anilino-3-nitrothiophenes by the reaction of the sodium salt of 1-anilino-1-mercapto-2-nitroethylene (enethiolate of a thioamide) with α-halo ketones.[3] We now report the synthesis of several 4-aryl-(or alkyl)-3-nitro-2-[1-(L)-prolyl]thiophenes by the condensation of *N*-nitrothioacetyl (L)-proline with α-halo ketones.

Earlier, we had reported a general method for the synthesis of a variety of nitrothioacetamides, including the *N*-nitrothioacetyl derivatives of (L)-proline ethyl/benzyl ester.[4] The availability of such nitrothioacetamides gave us a unique opportunity of examining their synthetic utility. We were especially

a. Dedicated to Professor A. R. Katritzky, FRS, on his 65th birthday.

b. NCL Communication No. 5785.



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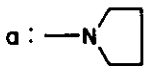
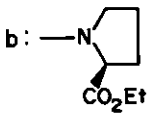
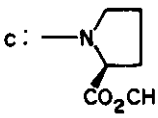
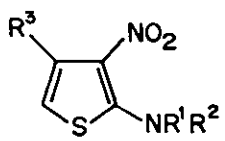
a : 

b : 

c : 



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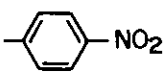
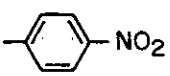
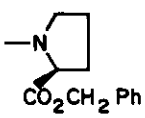
		NR^1R^2	R^3
2a	:		Ph
2b	:	〃	
2c	:	〃	Me
2d	:		Ph
2e	:	〃	
2f	:	〃	Me
2g	:		Ph

Scheme 1

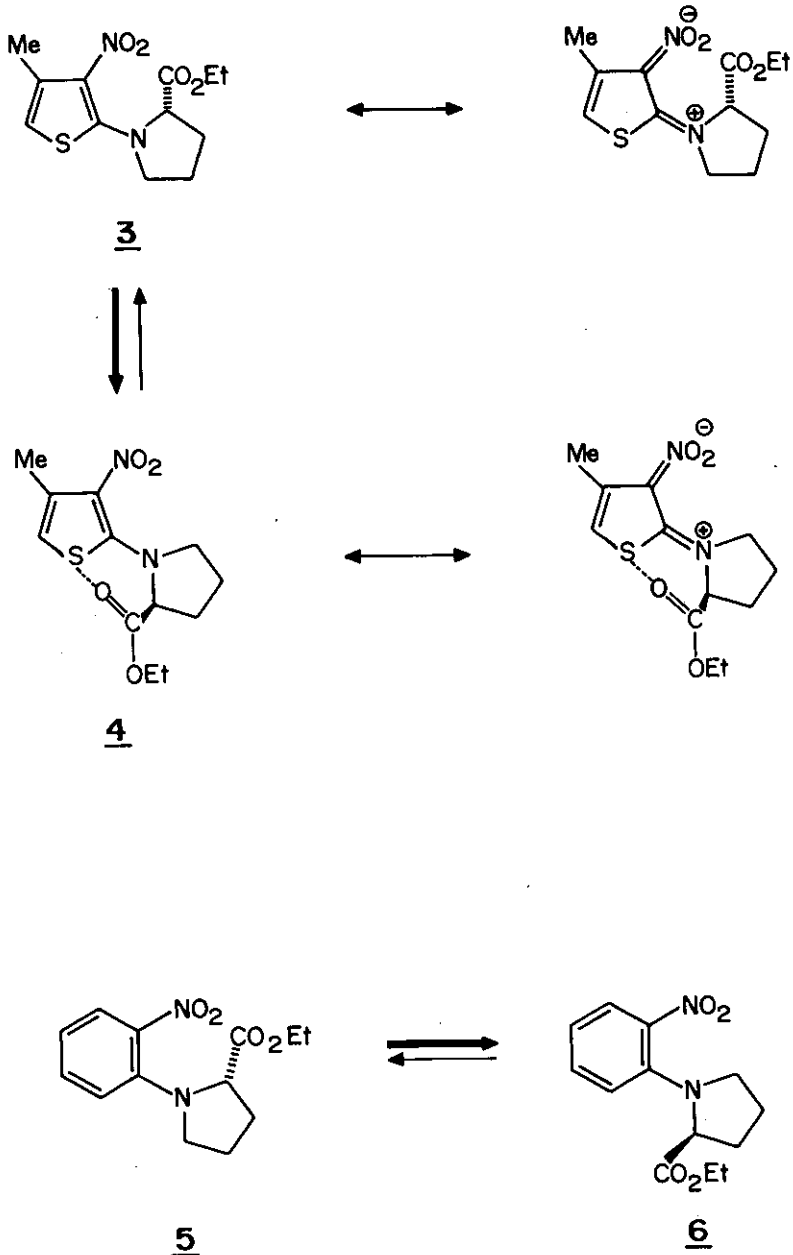
intrigued by the possibility of synthesizing 4-alkyl-(or aryl)-2-amino-3-nitrothiophenes, especially those in which a chiral proline unit is attached at position 2 of the thiophene. We hoped that such compounds would exhibit interesting non-linear optical properties. The reason for this was two-fold: it has been shown recently[5] that substitution of thiophene for benzene in donor - acceptor stilbenes results in significant enhancement of the second order nonlinear optical hyperpolarizability. The molecules that we hoped to synthesize would have a thiophene ring connecting a donor (amine) and an acceptor (nitro). Furthermore, the presence of a chiral unit [(L)-proline] in the molecule would ensure that the compound, if crystalline, would belong to a noncentrosymmetric class.[6]

As a preliminary check on the feasibility of the projected synthesis, *N*-nitrothioacetylpyrrolidine (**1a**) was allowed to react with phenacyl bromide in presence of DBU in benzene (Scheme 1). This gave the thiophene (**2a**) in nearly quantitative yield as a deep yellow solid. The structure was confirmed by the analytical values, mass spectrum (molecular ion at m/z 274), ir and nmr spectra. Thus in the ^{1}H nmr spectrum, there was a sharp singlet at δ 6.1 for the C_5-H of the thiophene ring, and in the ^{13}C nmr spectrum, the carbon atoms of the thiophene ring resonated at 105.10 (C-5), 135.39 (C-2), 137.44 (C-4) and 156.19 ppm (C-3). Compounds (**2b**) and (**2c**) were made similarly by the condensation of **1a** with *p*-nitrophenacyl bromide and bromoacetone respectively.

The method could be easily extended to the synthesis of the thiophenes (**2d** to **g**) bearing an (L)-proline unit at position 2. The requisite *N*-nitrothioacetyl derivatives (**1b** and **1c**) of (L)-proline ethyl ester and benzyl ester respectively were prepared by the procedure outlined earlier.[4] Condensation of **1b** with phenacyl bromide as before led to the thiophene (**2d**). In the uv absorption spectrum, the compound showed an intense absorption band at λ_{max} 405 nm (ε: 1.94×10^5) corresponding to the intramolecular charge transfer (ICT) involving the nitroenamine moiety. In addition to this broad ICT band, an intense band at λ_{max} 234 nm (ε: 1.56×10^6) due to a π - π^* transition was also observed.

Compounds (**2e** to **g**) were prepared similarly and characterized. The yields ranged from 60 - 80%.

<u>Conformational aspects</u>. The presence of a nitroenamine (push-pull) unit in **2** results in the C_2-N bond having partial double-bond character; there will therefore be a significant barrier to the interconversion of the two possible rotamers (**3** and **4**) of **2f** as shown in Scheme 2. The population in each of these would depend on the energy difference between the two conformations. In the event, it turned out that in $CDCl_3$ solution at ambient temperature, we could observe only one set of signals for **2f** leading to the conclusion that the compound existed predominantly in only one conformation. The identification of this conformer as **4** is based on the following evidence : The two protons of the δ CH_2 of the proline unit in **2f** are magnetically nonequivalent due to the chirality at the α-carbon atom. However, as compared to simple proline



Scheme 2 : ROTAMERS OF 2f

derivatives, the two protons in **2f** have significantly different chemical shift values, the difference being about 0.25 ppm (multiplets at δ 3.40 and 3.65). This is because one of them is more deshielded by the nitro group than the other. A similar situation existed with the two γ-CH_2 protons as well; in this case, the chemical shift difference was 0.30 ppm. We feel that in conformation (**3**) in which the γ and δ CH_2 groups are farther removed from the NO_2 group, such significant chemical shift differences would not arise.

This preference for the conformation (**4**) over (**3**) could be due to two possible factors: (i) there could be a lowering of energy in **4** due to the existence of a non-bonded attractive interaction between the sulfur atom of the thiophene ring and the oxygen of the ester group (see dotted lines in **4**), or (ii) conformer (**3**) could be disfavored (increase in energy) due to steric repulsion between the nitro and ester groups. In order to determine the possible role of non-bonded interaction in the preference for **4**, the benzene analog of **2f** was synthesized by the reaction of *o*-chloronitrobenzene with (L)-proline ethyl ester. This compound can exist in either conformation (**5**) or (**6**). The ^1H nmr spectrum of this compound in $CDCl_3$ again proved conclusively that the preferred conformation was **6** in which the two protons of the δ CH_2 group had a chemical shift difference of 0.31 ppm (multiplets at δ 3.18 and 3.49). It is thus clear that the preference for the conformers (**4**) and (**6**) is steric in origin and is unrelated to S...O attraction.

EXPERIMENTAL SECTION

All melting points were determined with a Yanaco micro melting point apparatus and are uncorrected, ^1H nmr spectra were recorded on a Bruker 200 MHz spectrometer. Chemical shifts are given in ppm related to tetramethylsilane. Mass spectra were obtained on a CEC-21-110B spectrometer at 70ev. Ir spectra were recorded with a Perkin - Elmer "Infracord - 137B" using NaCl discs. All optical rotations were measured using JASCO - 181 digital polarimeter.

General procedure for the synthesis of nitrothioacetamides (1)

A solution of amine(10 mmol) in MeCN(15 ml) was added slowly to a suspension of 1,1-bismethylthio-2-nitroethene(1.66 g, 10 mmol) and catalytic amount of *p*-TsOH in MeCN(20 ml) at room temperature. A clear solution was obtained and the evolution of methanethiol was observed by its characteristic odor. The reaction mixture was stirred at ambient temperature for 3-24 h. Solvent was removed under vacuum to get a gum. The unreacted starting material was precipitated by treating the gum with ice cold EtOH, and filtered off; the filtrate was concentrated to get a gum. This was washed twice with hexane or petroleum ether to remove dimethyl disulfide. Final purification was done by column chromatography on a silica gel column with benzene as the eluent to get 1-amino-1-methylthio-2-nitroethene which was dissolved in dry EtOH (deoxygenated by flushing with nitrogen gas) containing acetic acid (2 eq.) and

kept under N_2 atmosphere. Fused Na_2S(1.5 eq.) was added in many portions through a solid addition funnel. This solid addition funnel is designed in such a way that a closed system will be maintained throughout the course of the reaction. The solvent was removed and contents were taken into benzene, undissolved salts were filtered off. The filtrate was concentrated to get a thick gum which was chromatographed on a silica gel column with benzene as the eluent to get pure nitrothioacetamides (**1a - c**).

N-Nitrothioacetylproline ethyl ester (1b) : Gum, yield: 65%; $[\alpha]_D^{23}$ = -120.2° (c = 1; EtOH); **ir**(neat): 1740, 1570, 1480, 1450, 1370 cm^{-1}; **^{1}H nmr**($CDCl_3$,δ): ***trans conformer***, 1.25(t, J = 8 Hz, 3H, CH_3), 1.8-2.6 (m, 4H, $2CH_2$), 3.65-3.9(m, 2H, NCH_2), 4.18(q, J = 8 Hz, 2H, OCH_2), 4.7-5.1(m, 1H, NCH), 5.53 (dd, J = 1 and 1 Hz, 2H, O_2NCH_2), ***cis conformer***, 1.29(t, J = 8 Hz, 3H, CH_3), 1.8-2.6(m, 4H, $2CH_2$), 3.65-3.9(m, 2H, NCH_2), 4.21(q, J = 8 Hz, 2H, OCH_2), 4.7-5.1(m, 1H, NCH), 5.38(dd, J = 1 and 1 Hz, 2H, O_2NCH_2); **^{13}C nmr**($CDCl_3$): ***trans conformer***, 13.67(CH_3), 24.64(γ-C), 28.92 (β-C), 51.57(δ-C),61.19(α-C), 65.78(O-C), 83.19(O_2N-C), 169.12(C=0), 184.64(C=S), ***cis conformer***, 20.59(CH_3), 22.14(γ-C), 30.92(β-C), 54.45(δ-C), 62.31(α-C), 63.30(O-C), 83.19(O_2N-C),169.04(C=O), 184.85(C=S); **ms**(m/z): 246(M^+), 216(M^+-NO), 200(M^+-NO_2), 173(M^+-CO_2Et), 70(100%); *Anal.* Calcd for $C_9H_{14}N_2O_4S$: C,43.9; H,5.7; N,11.4; S,13.01. Found: C,44.3; H,5.9; N,11.1; S,13.3.

N-Nitrothioacetylproline benzyl ester (1c) : mp 63°C; yield: 65.7%; $[\alpha]_D^{23}$ = -77.2° (c = ; EtOH); **ir**(nujol): 1740, 1560, 1470, 1450, 1380 cm^{-1}; **^{1}H nmr**($CDCl_3$,δ): ***trans conformer***, 2.15-2.45 (m, 4H, $2CH_2$), 3.75-3.85(m, 2H, NCH_2), 5.05(dd, J = 6 and 6 Hz, 1H, NCH), 5.2(d, J = 1.4 Hz, 2H, OCH_2), 5.55(s, 2H, O_2NCH_2), 7.41(s, 5H, Ph), ***cis conformer***, 2.15-2.45(m, 4H, $1CH_2$), 3.75-3.85(m, 2H, NCH_2), 4.85(dd, J = 6 and 6 Hz, 1H, NCH), 5.4(dd, J = 1 and 1 Hz, 2H, O_2NCH_2), 7.39(s, 5H, Ph); **ms**(m/z): 308(M^+), 278(M^+-NO,100%), 262(M^+-NO_2), 91($PhCH_2^+$); *Anal.* Calcd for $C_{14}H_{16}N_2O_4S$: C,54.6; H,5.2; N,9.1. Found: C,54.9; H,5.4; N,8.7.

General procedure for the synthesis of thiophenes 2

Nitrothioacetamide (**1a-c**, 2 mmol) was taken in benzene (8 ml) and DBU (340 mg, 2.2 mmol) was added to the solution. The contents were stirred under nitrogen for 10 min. α-Halo ketone (2.2 mmol) in benzene (7 ml) was added to the flask. The reaction mixture was stirred at 60°C for 12 h. The solvent was removed under reduced pressure and the mixture was chromatographed on a silica gel column with a mixture of benzene and petroleum ether (3:1) as the eluent to get the pure thiophene derivatives (**2a-g**)

3-Nitro-4-phenyl-2-N-pyrrolidinylthiophene (2a): mp 114°C; yield: 98%; **ir**(nujol): 1540, 1460, 1380, 1360 cm^{-1}; **^{1}H nmr**($CDCl_3$): 2.05 (m, 4H, $2CH_2$), 3.35 (m, 4H, $2NCH_2$), 6.1(s, 1H, =CH), 7.28 (s, 5H, Ph); **^{13}C nmr**($CDCl_3$): 25.38, 52.65, 105.10, 127.09, 127.21, 127.46, 127.78, 135.39, 137.44, 156.19; **ms**(m/z): 274 (M^+,100%), 257, 229, 158, 77, 71; *Anal.* Calcd for $C_{14}H_{14}N_2O_2S$: C,61.31; H,5.11. Found: C,60.90; H,4.82.

3-Nitro-4(4'-nitrophenyl)-2-N-pyrrolidinylthiophene (2b) : mp 171°C; yield: 76%; **ir**(nujol): 1590, 1540, 1450, 1360, 1300, 1260 cm^{-1}; **^{1}H nmr**($CDCl_3$): 2.09 (m, 4H, $2CH_2$), 3.4(m, 4H, NCH_2), 6.21 (s, 1H, =CH), 7.41 and 8.17 (m, 4H, $PhNO_2$); **ms**(m/z): 319 (M^+), 273, 258, 246, 234, 71(100%); *Anal.* Calcd for $C_{14}H_{13}N_3O_4S$: C,52.65; H,4.10. Found: C,53.1; H,4.32.

4-Methyl-3-nitro-2-N-pyrrolidinylthiophene (2c) : mp 98-100°C, yield: 57%; **ir**(nujol): 1550, 1470, 1390, 1320, 1280 cm^{-1}; **^{1}H nmr** ($CDCl_3$): 2.02 (m,4H, $2CH_2$), 2.31 (d, J = 1 Hz, 3H, CH_3), 3.29 (m, 4H, $2NCH_2$), 5.89 (q, J = 1 Hz, 1H, =CH); **ms**(m/z): 212 (M^+), 178, 166, 127, 124(100%), 71; *Anal.* Calcd for $C_9H_{12}N_2O_2S$: C,50.94; H,5.66. Found: C,51.20; H,5.90.

3-Nitro-4-phenyl-2-[1-(L)-prolyl]thiophene ethyl ester (2d): gum, yield: 65%; $[\alpha]_D^{23}$ = -250.93° (c = 0.85, MeOH); **ir**(neat): 2900 - 3100, 1740, 1680(weak), 1550, 1480 and 1380 cm^{-1}; **^{1}H nmr**($CDCl_3$): 1.22(t, J = 7 Hz, 3H, CH_3), 2.13(m, 4H, $2NCCH_2$), 3.58(m, 2H, NCH_2), 4.11(q, J = 7 Hz, 2H, OCH_2), 4.60(m, 1H, NCH), 6.24(s, 1H, =CH), 7.31(m, 5H, Ph); **^{13}C nmr**($CDCl_3$): 13.74, 23.81, 30.96, 53.68, 61.19, 63.83, 106.61, 127.44, 127.82, 128.12, 128.45, 135.42, 137.64, 154.62, 171.23; **ms**(m/z): 346(M^+), 273, 212, 142, 141, 139(100%), 105, 85, 83, 77, 70; **uv**(MeOH): λ_{max} 405 nm (ε 1.94 × 10^5), 234 nm (ε 1.56 × 10^6); *Anal.* Calcd for $C_{17}H_{18}N_2O_4S$: C,58.96; H,5.20; S,9.25; N,8.09. Found: C,59.03; H,5.32; S,9.27; N,8.12.

3-Nitro-4-(4'-nitrophenyl)-2-[1-(L)-prolyl]thiophene ethyl ester (2e): mp 132°C; yield: 81%; $[\alpha]_D^{23}$ = -320.83° (c = 0.36, EtOH), **ir**(nujol): 1750, 1610, 1560, 1450, 1380 cm^{-1}; **^{1}H nmr**($CDCl_3$): 1.24(t, J = 7 Hz, 3H, CH_3), 2.09, 2.17 and 2.48(m, 4H, $2NCCH_2$), 3.48 and 3.71(m, 2H, NCH_2), 4.17(q, J = 7 Hz, 2H, OCH_2), 4.67(m, 1H, NCH), 6.37(s, 1H, =CH), 7.82(q, J = 8 Hz, 4H, $PhNO_2$); **ms** (m/z) : 391 (M^+), 345, 142, 113; *Anal.* Calcd for $C_{17}H_{17}N_3O_6S$: C,52.07; H,4.35; S,8.18; N,10.74. Found: C,52.45; H,4.55; S,8.35; N,10.95.

4-Methyl-3-nitro-2-[1-(L)-prolyl)thiophene ethyl ester (2f): Orange colored liquid, yield: 70%; $[\alpha]_D^{23}$ = -556.48° (c = 0.67, MeOH); **ir**(neat): 2900-3000, 1750, 1560, 1530 and 1380 cm^{-1}; **^{1}H nmr**($CDCl_3$): 1.16(t, J = 7 Hz, 3H, Me), 2.108, 2.138 and 2.44(m, 4H, $2NCCH_2$), 2.35(d, J = 1 Hz, 3H, =C-Me), 3.40 and 3.65(m, 2H, NCH_2), 4.09(q, J = 7 Hz, 2H, OCH_2), 4.65(m, 1H, NCH), 6.04(m, 1H, =CH); **^{13}C nmr**($CDCl_3$): 13.58, 17.30,

23.74, 30.89, 54.02, 60.96, 63.64, 63.76, 104.25, 132.89, 156.58, 171.01; **ms**(m/z): 284(M^+), 211(100), 193, 177, 165, 151, 139, 126, 71, 66; **uv**(MeOH): λ_{max} 416 nm, (ε 4.1 × 10^5), 256 nm (ε 0.97 × 10^6); *Anal.* Calcd for $C_{12}H_{16}N_2O_4S$: C,50.79; H,5.63; S,11.27; N,9.86. Found: C,50.92; H,5.85; S,11.51; N,9.95.

3-Nitro-4-phenyl-2-[1-(L)-prolyl]thiophene benzyl ester (2g): gum, yield: 60%; $[\alpha]_D^{23}$ = -262.35° (c = 0.25, MeOH); **ir**(nujol): 2950-3100, 1740, 1510, 1370, 1300, 1160 cm^{-1}; **^{1}H nmr**($CDCl_3$): 2.07(m, 4H, $2NCCH_2$), 3.53(m, 2H, NCH_2), 4.58(m, 1H, NCH), 5.07(s, 2H, OCH_2), 6.16(s, 1H, =CH), 7.22(s, 5H, Ph); **^{13}C nmr**($CDCl_3$): 23.76, 30.03, 53.64, 63.79, 66.93, 106.58, 127.40, 127.77, 127.84, 128.04, 128.25, 128.39, 135.07, 135.26, 137.53, 171.06.; **ms**(m/z): 408(M^+), 346, 332, 273, 237, 221, 165, 135, 105, 91, 77; *Anal.* Calcd for $C_{22}H_{20}N_2O_4S$: C,64.71; H,4.90; S,7.84; N,6.86. Found: C,64.95; H,4.97; S,7.92; N,6.95.

2-Nitro-1-[1-(L)-prolyl]benzene ethyl ester (6): Proline ethyl ester (910 mg, 2.5 mmol), *o*-chloronitrobenzene (788 mg, 5 mmol) and excess triethylamine (0.6 ml, 4 eq.) were taken in MeCN (20 ml) and stirred at 60°C for 2 days. Even after 2 days the reaction was not complete. The solvent was evaporated and the product was purified by chromatography on a silica gel column (benzene as an eluent). The product (95 mg) was obtained in 35% yield (calculated from the amount of consumed starting material). **Ir**(neat): 1750, 1610, 1570, 1520, 1380, 1360 and 1190 cm^{-1}; **^{1}H nmr**($CDCl_3$): 1.19(t, J = 7.1 Hz, 3H, CH_3), 1.95, 2.17 and 2.43(m, 4H, $2NCCH_2$), 3.18 and 3.49(m, 2H, NCH_2), 4.13(q, J = 7.1 Hz, 2H, OCH_2), 4.40(m, 1H, NCH), 6.85, 7.40 and 7.69(m, 4H, Ph); **ms**(m/z): 264(M^+), 247, 191(100%), 144, 131, 117, 104, 91 and 77; *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C,59.09; H,6.06; N,10.61. Found: C,59.21; H,6.25; N,10.82.

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